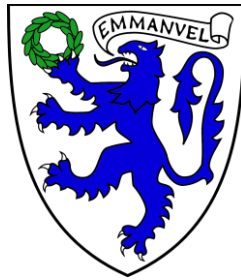


# **An investigation into the prevalence, impact and management of cancer-related fatigue in teenage and young adult patients**



Dr Anna Olga Spathis

Emmanuel College

Department of Public Health and Primary Care

University of Cambridge

*This dissertation is submitted for the degree of*

*Doctor of Medicine (MD)*

*January 2019*

## **MD thesis title**

An investigation into the prevalence, impact and management of cancer-related fatigue in teenage and young adult patients

## **Student name**

Dr Anna Spathis

## **Abstract**

Teenage and young adult (TYA) cancer patients describe debilitating fatigue. The impact of fatigue is particularly detrimental at this age because it hinders key developmental needs, such as independence. Although exercise and psychological treatments are the most effective management approaches in older adults, TYAs have unique healthcare needs and research findings cannot be extrapolated to younger patients. The aim of this programme of research was to increase understanding of cancer-related fatigue (CRF) in TYAs, in order to develop a non-pharmacological fatigue intervention.

Three multimethod studies have been conducted, underpinned by self-efficacy theory. 1) A systematic literature review synthesised existing research evidence. 2) A multicentre electronic survey evaluated the experience of TYA CRF and its current management across the UK. 3) A multiphase, longitudinal, qualitative study, involving patient-parent dyads, has led to the co-design of a fatigue intervention.

This work has confirmed that fatigue is the most prevalent and distressing symptom experienced by TYAs with cancer, and is an independent predictor of poor quality of life. Fatigue persists long after the end of cancer treatment, perpetuated by vicious cycles of emotional and behavioural responses to the symptom. Cognitive fatigue has a particularly negative impact and influences the ability to work, be in education or socialise. Parents also experience adverse consequences, including fatigue-related interpersonal tensions. Despite the enormity of the problem, fatigue is currently inadequately managed. TYAs described extensive, age-related intervention needs, including a preference for videos over written information. The co-designed intervention is predominantly cognitive in approach with, for example, mindfulness techniques being more acceptable than energy conservation. TYAs require structured activity support, given the physical reserve of youth and fear that activity may worsen fatigue.

Young patients have inspired, and helped drive, this programme of work. Engagement with the research process was high, and participants embraced the innovative research methods. Information has been generated that will optimise the design of the future definitive trial to test intervention effectiveness.

## **Declaration**

This dissertation is the result of my own work. It includes nothing which is the outcome of work done in collaboration, except as specified in the text in the following places: section 2.4.4 (page 21), section 2.4.5 (page 22), section 3.4.7.2 (page 55), section 4.4.3 (page 104), section 4.4.4 (page 105) and section 4.4.7.2 (page 107).

It is not substantially the same as any that I have submitted, or is being concurrently submitted, for a degree, diploma or other qualification at the University of Cambridge or any other University or similar institution. I further state that no substantial part of my dissertation has already been submitted, or is being concurrently submitted, for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution.

The word count, excluding preface, tables, figures, appendices and bibliography, is 68,719 words, within the word limit of 70,000 words agreed by the MD Degree Committee.

## Acknowledgements

I acknowledge with gratitude the support from my supervisors, Dr Stephen Barclay and Dr Sara Booth. I am indebted to Stephen for his expert guidance, positivity and encouragement, and dedication to finding sources of research funding; I thank Sara for her influence over many years, nurturing my interest in non-pharmacological symptom intervention with her pioneering work in breathlessness self-management.

I am grateful to the many research and clinical colleagues who have supported this work, including those colleagues whose invaluable roles are listed in the 'methods' section of each study. Dr Helen Hatcher and Laura Abbas endorsed the need for this research and have supported it since its inception. Dr Maria Loades helpfully influenced my understanding of chronic fatigue, and Dr Sarah Hoare and Dr Gemma Clarke provided wise counsel on qualitative data analysis. My clinical consultant colleagues, Dr Rosemary Wade, Dr Sarah Galbraith and Dr Yvonne Cartwright, provided continual encouragement and support (including chocolate motivation). I thank my colleagues in the Breathlessness Intervention Service, Julie Burkin, Catherine Moffat, Rachel Tuffnell and Pauline Kleanthous, for their kindness and patience, and for quietly shouldering more clinical work at times of peak thesis writing – I noticed and appreciated this so much.

I thank the many funders of this work, who provided salary costs to backfill my clinical work for a day each week and other research costs: Macmillan Cancer Support, the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) East of England, the NIHR School of Primary Care Research and Marie Curie Care. I am particularly grateful to Nic Lee and Hannah Pimperton at Macmillan Cancer Support for their belief in this work, for funding much of it and for exemplary generation of impact, including professional production of the videos requested by research participants.

I am immensely grateful to the many research participants; their enthusiastic and enterprising collaboration, when coping with serious illness at a young age or such illness in a child, was deeply humbling. Finally, I thank David, Ella, Maria, my parents and Gillian for their solidarity, support and patience.



## **Personal statement**

This short statement provides a personal explanation for the research context. Apart from this section and a short reflexive account in section 4.5.16.3 (page 194), this thesis is written in the third person.

I have long felt compelled to undertake research in the field of cancer-related fatigue, cognisant of the relative neglect of this particularly common and distressing symptom. My first decade of research activity attempted to evaluate a drug treatment for fatigue, the central nervous system stimulant modafinil. The work culminated in the delivery of a rigorous randomised controlled trial, published in a high impact journal, with an unequivocally negative finding: modafinil is no more effective than placebo.

By this time employed as a palliative care consultant in the Cambridge Breathlessness Intervention Service, I learned from skilled Allied Health Professional and medical colleagues about the value of non-pharmacological approaches for breathlessness and, the closely-related symptom, fatigue. The motivation to focus on the distinct needs of young patients came from my past experience working in the children's and young adults' hospice, Helen and Douglas House in Oxford, and subsequent valuable clinical collaboration with the Cambridge Teenage and Young Adult Cancer Service.

This has been the route to the path now pursued, developing a non-pharmacological fatigue intervention for young cancer patients. My clinical and research experiences have fostered a conviction that non-pharmacological approaches to the management of symptoms, such as breathlessness and fatigue, are not only safer but often more effective than drug treatments, through targeting the root causes and consequences of the symptoms. Such management, however, requires active engagement on the part of both patients and healthcare professionals. I hope that this thesis may serve to illuminate these insights.

## Abbreviations

App	Mobile application
AHP	Allied health professional
AYA	Adolescent and young adult
CBT	Cognitive behavioural therapy
CFS/ME	Chronic Fatigue Syndrome/Myalgic Encephalomyelitis
CNS	Central nervous system
CRF	Cancer-related fatigue
EBCD	Experience-based co-design
FICS	Fatigue Intervention Co-design Study
fMRI	Functional magnetic resonance imaging
GET	Graded exercise therapy
HCP	Healthcare professional
IT	Information technology
MFS	PedsQL™ Multidimensional Fatigue Scale
MRC	Medical Research Council
NCI	National Cancer Institute (USA)
NCRI	National Cancer Research Institute (UK)
NHS	National Health Service
NRS	Numerical rating scale
OT	Occupational therapist
PI	Principal Investigator
PIS	Participant information sheet
PPI	Patient and public involvement
PSEFSM	Perceived self-efficacy for fatigue self-management
PTC	Principal treatment centre
RCP	Royal College of Physicians
RCT	Randomised controlled trial
STA	Sleep, thoughts, activity
TCT	Teenage Cancer Trust
TYA	Teenage and young adult
WHO	World Health Organisation
YP	Young person

Further abbreviations follow as footnotes to a number of tables containing extensive abbreviation.

## Table of contents

Abstract .....	i
Declaration .....	ii
Acknowledgements .....	iii
Personal statement .....	iv
Abbreviations .....	v
Table of contents .....	vi
List of tables .....	xi
List of figures .....	xiii
<b>1 Introduction .....</b>	<b>1</b>
<b>1.1 Context .....</b>	<b>1</b>
1.1.1 Cancer-related fatigue .....	1
1.1.2 Teenage and young adult health .....	5
1.1.3 Teenage and young adult cancer .....	8
1.1.4 Teenage and young adult cancer-related fatigue .....	11
<b>1.2 Research programme rationale .....</b>	<b>13</b>
1.2.1 Brief overview of programme .....	13
1.2.2 Overview of patient and public involvement .....	14
1.2.3 Justification for research .....	15
1.2.4 Theoretical basis .....	16
<b>1.3 Aim and objectives .....</b>	<b>18</b>
1.3.1 Aim .....	18
1.3.2 Objectives .....	18
<b>2 Systematic literature review .....</b>	<b>19</b>
<b>2.1 Title .....</b>	<b>19</b>
<b>2.2 Rationale .....</b>	<b>19</b>
<b>2.3 Aim and objectives .....</b>	<b>19</b>
2.3.1 Aim .....	19
2.3.2 Objectives .....	19
<b>2.4 Methods .....</b>	<b>20</b>
2.4.1 Timeline .....	20
2.4.2 Literature search strategy .....	20
2.4.3 Selection criteria .....	20
2.4.4 Quality assessment and data analysis .....	21
2.4.5 Study team and roles .....	22
<b>2.5 Results .....</b>	<b>23</b>
2.5.1 Description of articles .....	23

2.5.2	Fatigue prevalence .....	25
2.5.3	Fatigue severity .....	31
2.5.4	Impact of fatigue.....	32
2.5.5	Experience of parents.....	34
2.5.6	Fatigue correlates .....	34
2.5.7	Interventions to manage fatigue.....	35
<b>2.6</b>	<b>Discussion .....</b>	<b>39</b>
2.6.1	Overview of evidence .....	39
2.6.2	Contextualizing with related systematic reviews.....	40
2.6.3	Strengths and limitations.....	41
2.6.4	Implications.....	42
<b>2.7</b>	<b>Key points.....</b>	<b>44</b>
<b>3</b>	<b>Fatigue in Focus multicentre survey.....</b>	<b>45</b>
3.1	Title .....	45
3.2	Rationale.....	45
3.2.1	Justification for study .....	45
3.2.2	Justification for electronic survey method .....	45
3.3	Aim and objectives .....	47
3.3.1	Aim .....	47
3.3.2	Objectives .....	47
3.4	Methods.....	48
3.4.1	Study population.....	48
3.4.2	Questionnaire content.....	48
3.4.3	Survey process .....	50
3.4.4	Data management.....	51
3.4.5	Patient and public involvement .....	52
3.4.6	Ethical considerations.....	53
3.4.7	Research governance.....	53
3.5	Results .....	56
3.5.1	Process data .....	56
3.5.2	Characteristics of participants and non-responders.....	58
3.5.3	Fatigue prevalence and severity .....	62
3.5.4	Impact of fatigue.....	70
3.5.5	Management of fatigue .....	72
3.5.6	Qualitative data.....	79
3.6	Discussion .....	80
3.6.1	Fatigue experience.....	80
3.6.2	Fatigue impact.....	83
3.6.3	Fatigue management .....	85

3.6.4	Theoretical underpinning.....	86
3.6.5	Methodological discussion .....	87
3.6.6	Strengths and limitations.....	90
3.6.7	Implications.....	92
<b>3.7</b>	<b>Key points.....</b>	<b>95</b>
<b>4</b>	<b>Fatigue Intervention Co-design Study .....</b>	<b>97</b>
<b>4.1</b>	<b>Title .....</b>	<b>97</b>
<b>4.2</b>	<b>Rationale.....</b>	<b>97</b>
4.2.1	Justification for study .....	97
4.2.2	Justification for research design .....	99
<b>4.3</b>	<b>Aim and objectives.....</b>	<b>102</b>
4.3.1	Aim .....	102
4.3.2	Objectives .....	102
<b>4.4</b>	<b>Methods.....</b>	<b>103</b>
4.4.1	Study population.....	103
4.4.2	Study schedule .....	104
4.4.3	Methodological considerations .....	104
4.4.4	Data management.....	105
4.4.5	Patient and public involvement .....	106
4.4.6	Ethical considerations.....	106
4.4.7	Research governance.....	107
<b>4.5</b>	<b>Results .....</b>	<b>109</b>
4.5.1	Participants.....	109
4.5.2	Process measures.....	110
4.5.3	Framework development .....	112
4.5.4	Relationship between research questions, frameworks and analytical themes.....	113
4.5.5	Overview of analytical themes .....	115
4.5.6	Theme A1: TYA developmental stage compounds the impact of fatigue.....	115
4.5.7	Theme A2: TYA developmental characteristics influence intervention design .....	123
4.5.8	Conceptual model A: Characteristics, Experiences, Needs star model .....	145
4.5.9	Theme B1: TYAs experience pervasive tensions and misunderstandings.....	147
4.5.10	Theme B2: Fatigue-related tensions have a detrimental impact on family .....	154
4.5.11	Conceptual model B: the Concordant Tension Tree.....	160
4.5.12	Theme C1: Fatigue may perpetuate with vicious cycles .....	161
4.5.13	Theme C2: Responses to fatigue relate to outcomes.....	174
4.5.14	Conceptual model C: Sleep, Thoughts, Activity (STA) model of TYA fatigue.....	180
4.5.15	Co-designed intervention .....	182
4.5.16	Trustworthiness of research .....	190

<b>4.6</b>	<b>Discussion .....</b>	<b>199</b>
4.6.1	Integration of themes .....	199
4.6.2	Theoretical underpinning.....	204
4.6.3	Methodological discussion .....	206
4.6.4	Strength and limitations.....	206
4.6.5	Implications.....	207
<b>4.7</b>	<b>Key points.....</b>	<b>211</b>
<b>5</b>	<b>Research synthesis.....</b>	<b>215</b>
<b>5.1</b>	<b>Multimethod integration .....</b>	<b>215</b>
5.1.1	Integration method .....	215
5.1.2	Triangulation of research outcomes .....	217
5.1.3	Discussion .....	221
<b>5.2</b>	<b>Programme research outputs.....</b>	<b>225</b>
5.2.1	Public dialogue .....	225
5.2.2	Educational materials .....	225
5.2.3	University of Cambridge research award .....	225
5.2.4	Dissemination of findings .....	226
<b>5.3</b>	<b>Ten key novel findings from integrated research programme .....</b>	<b>227</b>
<b>5.4</b>	<b>Ten key recommendations .....</b>	<b>229</b>
5.4.1	Recommendations for clinical practice and policy .....	229
5.4.2	Recommendations for future research .....	230
<b>5.5</b>	<b>Concluding comments.....</b>	<b>231</b>
<b>6</b>	<b>References.....</b>	<b>233</b>
<b>7</b>	<b>Appendices.....</b>	<b>269</b>
<b>7.1</b>	<b>Research outputs.....</b>	<b>269</b>
7.1.1	Educational materials .....	269
7.1.2	University of Cambridge research award .....	269
7.1.3	National presentations .....	269
7.1.4	Publications .....	270
<b>7.2</b>	<b>Systematic literature review.....</b>	<b>291</b>
7.2.1	Eligibility criteria .....	291
<b>7.3</b>	<b>Fatigue in Focus multicentre survey .....</b>	<b>292</b>
7.3.1	Priming process .....	292
7.3.2	Survey covering email.....	294
7.3.3	Patient information sheet.....	295
7.3.4	IT process instructions .....	297
7.3.5	Research Ethics Committee approval.....	301

7.3.6	Survey questionnaire .....	303
7.3.7	Non-responder analysis comparative histograms .....	313
7.3.8	Regression diagnostic plots .....	315
7.3.9	Symptom cluster based regression model .....	320
7.3.10	Survey supplementary qualitative data.....	322
<b>7.4</b>	<b>Fatigue Intervention Co-design Study.....</b>	<b>323</b>
7.4.1	Patient information sheet.....	323
7.4.2	Parent information sheet.....	325
7.4.3	Healthcare professional information sheet.....	327
7.4.4	Information for Facebook.....	328
7.4.5	Patient consent form .....	329
7.4.6	Parent consent form .....	330
7.4.7	Research Ethics Committee approval.....	331
7.4.8	Patient interview and focus group schedule .....	334
7.4.9	Parent interview and focus group schedule .....	336
7.4.10	Final node structure.....	338
7.4.11	Intervention prototype guidance for Allied Health Professional .....	339
7.4.13	Framework 1: Participant experiences.....	340
7.4.14	Supplementary qualitative data.....	348
7.4.15	Triangulation of qualitative data between sources, time points and methods.....	370

## List of tables

Table 1.1 Definition of key age-related terms.....	5
Table 1.2 Overview of developmental changes in adolescence .....	6
Table 1.3 Selected global standards for quality health services for adolescents .....	8
Table 2.1 Search terms .....	20
Table 2.2 Roles of other team members in review .....	22
Table 2.3 Summary of key fatigue outcome measures .....	24
Table 2.4 Studies evaluating fatigue prevalence, grouped by relationship to cancer treatment.....	26
Table 2.5 Controlled studies evaluating fatigue severity .....	33
Table 2.6 Studies evaluating fatigue interventions.....	36
Table 2.7 Systematic review key points .....	44
Table 3.1 Roles of other team members in survey .....	55
Table 3.2 Site process data.....	57
Table 3.3 Comparison of responder and non-responder demographic data .....	60
Table 3.4 Symptom prevalence .....	63
Table 3.5 Comparison of demographic data between responders with and without fatigue.....	64
Table 3.6 Relationship between fatigue severity and continuous independent variables .....	68
Table 3.7 Linear model of predictors of fatigue severity in fatigued participants.....	69
Table 3.8 Linear model of predictors of fatigue severity in fatigued participants controlling for gender. 69	
Table 3.9 Linear model of predictors of quality of life in fatigued participants.....	70
Table 3.10 Impact of fatigue on aspects of daily life.....	71
Table 3.11 Interpretation of fatigue cause.....	72
Table 3.12 Other interpretations of the cause of fatigue .....	73
Table 3.13 Comparison of participants according to whether received fatigue treatment .....	75
Table 3.14 Relationship between fatigue treatments, fatigue severity and time after cancer treatment	76
Table 3.15 Perceived successfulness of each treatment.....	76
Table 3.16 Personal view of best fatigue treatment.....	77
Table 3.17 Personal view of best fatigue treatment: free text responses .....	78
Table 3.18 Relationship between receiving and recommending active or rest-focused treatments.....	78
Table 3.19 Fatigue in Focus survey key points in context .....	96
Table 4.1 Roles of other team members in FICS .....	108
Table 4.2 Overview of participant characteristics.....	109
Table 4.3 Overview of study participation .....	111
Table 4.4 Summary of data sources .....	112
Table 4.5 Overview of three framework matrices .....	113
Table 4.6 Research questions, framework categories and analytical themes .....	114



Table 4.7 Overview of analytical themes .....	115
Table 4.8 Summary of relationship between TYA developmental characteristics and fatigue impact ...	116
Table 4.9 Summary of TYA developmental characteristics and influence on intervention design.....	124
Table 4.10 Examples of responses and outcomes .....	174
Table 4.11 Exploratory tabulation of participant approaches, engagement and fatigue outcomes .....	174
Table 4.12 Predominant mediating approach for positive outcomes .....	175
Table 4.13 Overview comparison of intended and delivered features of prototype intervention .....	184
Table 4.14 Features of the 'trial ready' fatigue intervention .....	187
Table 4.15 Techniques to establish the trustworthiness of the research findings .....	188
Table 4.16 Features of CRF and CFS/ME in young patients relative to older adults.....	200
Table 4.17 Fatigue Intervention Co-design Study key points in context.....	212
Table 5.1 Multimethod integration matrix .....	218
Table 7.1 Linear model of predictors of fatigue severity using cluster level mean symptom scores .....	320
Table 7.2 Linear model of predictors of quality of life using cluster level mean symptom scores.....	321

## List of figures

Figure 1.1 Teenage and young adult cancer by diagnostic group 2000-2009 .....	9
Figure 1.2 Overview of research programme and intentions .....	14
Figure 1.3 Theory-based logic model .....	17
Figure 2.1 PRISMA flowchart of included articles .....	22
Figure 3.1 Number of respondents each day .....	58
Figure 3.2 Comparative histogram of time since last treatment for responders and all non-responders	61
Figure 3.3 Comparative histogram of cancer treatment duration with non-responders post-treatment	61
Figure 3.4 Symptom prevalence bar chart .....	63
Figure 3.5 Clustered bar chart of symptom severity.....	64
Figure 3.6 Dendrogram of hierarchical symptom cluster analysis.....	65
Figure 3.7 Histogram of MFS scores .....	67
Figure 3.8 Box plot of fatigue severity according to time after last treatment .....	67
Figure 3.9 Box plot of relationship between time of last treatment and speaking to a healthcarer .....	74
Figure 3.10 Stacked bar chart showing perceived successfulness of each fatigue treatment .....	77
Figure 4.1 Study flow diagram.....	110
Figure 4.2 Characteristics, Experiences, Needs (CEN) star model.....	146
Figure 4.3 Concordant Tension Tree .....	160
Figure 4.4 Sleep, Thoughts, Activity (STA) conceptual model of TYA CRF .....	181
Figure 4.5 Interaction between overarching concepts and perceived self-efficacy .....	205
Figure 7.1 Comparative histogram of age at survey for responders and all non-responders .....	313
Figure 7.2 Comparative histogram of age at diagnosis for responders and all non-responders.....	313
Figure 7.3 Comparative histogram of time since diagnosis for responders and all non-responders .....	314
Figure 7.4 Frequency of standardised residuals.....	315
Figure 7.5 Normal P-P plot of regression standardised residuals .....	315
Figure 7.6 Scatterplot of standardised residuals and predicted values with Loess line .....	316
Figure 7.7 Scatterplot of residuals of MFS and low mood severity with Loess line.....	316
Figure 7.8 Scatterplot of residuals of MFS and lack of appetite severity with Loess line .....	317
Figure 7.9 Frequency of standardised residuals.....	317
Figure 7.10 Normal P-P plot of regression standardised residuals .....	318
Figure 7.11 Scatterplot of standardised residuals and predicted values with Loess line .....	318
Figure 7.12 Scatterplot of residuals of QOL NRS score and low mood severity with Loess line.....	319
Figure 7.13 Scatterplot of residuals of QOL NRS and lack of appetite severity with Loess line .....	319

# **1 Introduction**

## **1.1 Context**

### **1.1.1 Cancer-related fatigue**

#### ***1.1.1.1 Definitions***

Fatigue is recognised to be one of the most common and debilitating symptoms experienced by patients with cancer. Cancer-related fatigue (CRF) has been defined by the National Comprehensive Cancer Network as ‘a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion, in relation to cancer or cancer treatment, that is not proportional to recent activity and interferes with usual functioning’ [1].

Fatigue is a multidimensional symptom, and the range of perceptions may include feelings of weakness, inability to perform tasks, decreased motivation, low mood, and difficulty thinking clearly [2]. It differs from fatigue felt by healthy individuals in that it is more severe and incompletely relieved by rest or sleep [3,4].

Definition of a ‘fatigue case’ is hindered by the symptom’s multidimensional and subjective nature. In clinical practice, a score of 5 or more, in an 11-item fatigue severity numerical rating scale (NRS), has been recommended as a screening tool to define clinically significant fatigue. Scores of 1-3, 4-6 and 7-10 define mild, moderate and severe fatigue respectively [1,5,6]. A plethora of unidimensional and multidimensional fatigue scales have been developed for research purposes and validated in cancer patients [7-10]. They are, however, rarely used in clinical practice due to time limitations and patient burden.

#### ***1.1.1.2 Importance***

Cancer-related fatigue is a significant symptom both because of its high prevalence and its particularly negative impact. Estimates of prevalence vary widely according to the patient population and method of fatigue assessment. However, many surveys suggest a prevalence of over 75%, rising close to 100% during cancer treatment [11-14]. In studies comparing symptom prevalence rates amongst people of any age with cancer, fatigue is almost always the most common symptom, and patients consistently report that fatigue is the symptom with the most negative impact on quality of life [11-13,15]. A survey of almost 400 cancer patients found that virtually all patients reported that fatigue altered their daily routine, and prevented a ‘normal life’. Fatigue hindered social activities and performance of cognitive tasks. Three-quarters of patients and 40% of caregivers had to change their employment status due to the symptom [12].

Although fatigue is typically most severe during cancer treatment, it can persist long after the end of treatment [16]. In studies of breast cancer survivors, between a quarter and a third of patients experience long-term fatigue, even up to 10 years after diagnosis [17,18]. Furthermore, fatigue appears to be a prognostic indicator, predicting lower survival [19,20].

Despite the magnitude of the problem, CRF is a relatively under-investigated symptom. Patients and healthcare professionals have tended to view it as an inevitable and unavoidable consequence of cancer and its treatment. Fatigue is, indeed, prevalent in the community generally, with 20-30% of healthy people reporting that they 'always feel tired' [21]. These factors have led to a degree of scepticism, in both clinical and research terms. More than half of cancer patients do not report the symptom to their doctor, usually because of the perception that no treatment will be offered [22,23]. Healthcare staff, furthermore, underestimate the impact of fatigue. In a large survey of patients and oncologists, while 61% of patients reported that fatigue affected their lives more than pain, only 37% of oncologists believed this was true [11].

Research into the aetiology and management of fatigue has only begun to accumulate over the last decade. The National Cancer Institute (NCI) in the USA has designated CRF as a high-priority research area, and it is one of the five highest priority research areas of the NCI Oncology Research Program [24]. In the UK in 2018, a National Cancer Research Institute (NCRI) James Lind Alliance Priority Setting Partnership has determined that CRF is one of the top ten research priorities [25].

### ***1.1.1.3 Pathophysiology***

Until recently, attempts to understand the causes of CRF have focused on biological mechanisms. Foremost amongst these is the relationship between fatigue and systemic inflammation [14]. There is growing evidence from longitudinal studies that changes in inflammatory markers, particularly the inflammatory cytokines interleukin-1, tumour necrosis factor- $\alpha$  and interleukin-6, are associated with changes in fatigue over time. This relationship has been shown both during the course of cancer treatment [26,27], and also following treatment completion [28]. Both the cancer itself and cancer treatment appear to activate the pro-inflammatory cytokine system [29].

Two other important biological mechanisms are hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) dysregulation. Breast cancer survivors with persistent fatigue have elevated evening cortisol levels with reduced diurnal variation, along with blunted cortisol responses to psychological stress [30,31]. Similar longitudinal relationships have been found in patients with ovarian cancer, with HPA dysregulation following a comparable temporal pattern to that of the fatigue [32]. In relation to the ANS, lower heart rate variability, indicating reduced parasympathetic

activity, has been associated with fatigue in breast cancer survivors [33]. Interestingly, both these mechanisms may be mediated by systemic inflammation, in that inflammatory processes both influence, and are influenced by, the HPA and ANS [34,35].

Biological mechanisms, however, cannot be the only cause of CRF. Fatigue severity varies to an extent that cannot be explained fully by biological factors, such as the degree of systemic inflammation. Indeed, although inflammation consistently associates with fatigue when measured as a category, there tends to be no relationship when evaluated using a continuous measure [14,36]. Important emerging evidence from longitudinal studies suggests that psychological and behavioural factors may influence the experience of fatigue. Depression and anxiety before cancer treatment, for example, have been shown to predict CRF severity [37-40]. In patients with breast and prostate cancer receiving radiotherapy, pre-treatment sleep disturbance is associated with worse fatigue through, and after, treatment [37,39]. Similar outcomes have been found in gynaecological cancers [41]. Furthermore, low activity levels before cancer diagnosis have been shown to predict persistent fatigue [42]. Fatigue, therefore, appears to be a consequence both of biological, and a range of psycho-behavioural, factors.

#### ***1.1.1.4 Management***

The first step in the management of any symptom is to assess for, and reverse, any treatable underlying medical cause, an approach endorsed by multiple guidelines [1,6,43]. Anaemia, electrolyte imbalance, endocrine disorders and infections are examples of the myriad of potential medical problems that could be contributing to fatigue and may be amenable to treatment [1,43].

Concurrent symptom management is also important. In a landmark study, de Raaf and colleagues revealed that careful attention to general symptom management can significantly improve fatigue severity in adults with cancer [44]. Fatigue tends to co-occur with a number of physical and psychological symptoms, including pain, breathlessness, anorexia, nausea, anxiety and depression [45]. Fatigue, depression and pain form a prevalent symptom cluster[46], as do fatigue, insomnia and pain [47]. Although it has not been established whether the symptoms cluster due to causal inter-relationships or shared aetiological pathways such as systemic inflammation, the finding that concurrent symptom management is effective suggests that other symptoms may be contributing to the perception of fatigue [43].

Beyond the management of underlying medical causes and concurrent symptoms, a diverse range of treatment approaches have been used for CRF in adults. These include pharmacological treatments, physical activity and psychological interventions. The lack of an accepted 'gold standard' treatment for CRF has been attributed to the complex and poorly understood nature of this symptom [14].

### Pharmacological treatments

A recent meta-analysis has found that drug treatment does not ameliorate cancer-related fatigue [48]. Central nervous system (CNS) stimulants, such as methylphenidate, are the most evaluated pharmacological approach. Whilst two systematic reviews have found small statistically significant benefits from these drugs [49,50], the changes did not reach a clinically important threshold [51]. Furthermore, a subsequent larger study, not included in the reviews, has found no benefit from methylphenidate [52]. Previous work from Spathis and colleagues has revealed lack of benefit from the CNS stimulant modafinil, and there is no evidence to support the use of antidepressants [53,54]. Given the possible inflammatory basis for CRF, small phase 2 studies have been undertaken evaluating anti-inflammatory drugs, again with little evidence of benefit [14]. One short-term controlled trial, in patients with advanced cancer in a hospice setting, did find benefit from dexamethasone, but this finding has not been replicated [55].

### Non-pharmacological treatments

Unlike drug approaches, there is consistent evidence to support the effectiveness of exercise and psychological approaches. Two meta-analyses have been recently published, comparing a range of approaches. Mustian and colleagues evaluated 113 high quality randomised controlled trials. The weighted effect sizes for the broad treatment categories of exercise, psychological interventions (cognitive-behavioural approaches or education), exercise plus psychological interventions, and pharmacological approaches were 0.30 ( $p < 0.001$ ), 0.27 ( $p < 0.001$ ), 0.26 ( $p < 0.001$ ) and 0.09 ( $p = 0.05$ ) respectively [48]. During primary cancer treatment, exercise was the most effective intervention. In contrast, after cancer treatment, psychological approaches, and combined exercise with psychological approaches, were the most effective.

In a second meta-analysis involving 245 randomised and quasi-randomised controlled trials, Hilfiker and colleagues confirmed the effectiveness of a range of psychological and exercise approaches [56]. Relaxation, massage, and cognitive behavioural therapy (CBT) combined with physical activity were the three most effective approaches during cancer treatment. After treatment, yoga, combined aerobic and resistance training, and CBT combined with physical activity were the three most effective approaches. These findings cannot easily be compared with those of the preceding meta-analysis because individual treatments were evaluated, rather than broad treatment categories.

A systematic review of meta-analyses of exercise for fatigue in adults with cancer has further confirmed the effectiveness of this approach, although recalculations, using random-effects models and prediction intervals rather than confidence intervals, suggest that the benefits may be smaller

than previously reported [57]. Number need to treat (NNT) values are between 3 and 16 [57].

Bennett and colleagues have undertaken a systematic review of educational interventions for CRF in adults, and have found that education alone has a small effect on reducing fatigue severity, impact and distress [58].

## **1.1.2 Teenage and young adult health**

### **1.1.2.1 Terminology of age**

Numerous terms have been used to describe young people in the transition between childhood and adulthood. A summary of definitions is provided in table 1.1.

**Table 1.1 Definition of key age-related terms** (adapted from [24])

<b>Term</b>	<b>Age</b>	<b>Details</b>
Child	< 18	Defined by the Convention of the Rights of a Child; can have a younger threshold in countries where majority is attained below 18.
Adolescence	10-19	Defined by the World Health Organisation; ‘adolescents’ means ‘growing up’ in Latin, and ‘adultus’ means ‘grown up’.
Teenager	13-19	Term first used in the USA in 1920s, and widely used in popular culture after the second World War.
Youth	15-24	United Nations definition developed in the lead up to the International Youth Year of 1985.
Young people	10-24	Less formally defined term, used by the WHO.
Adolescent and young adult (AYA)	10-24	Less formally defined term, with a range that varies according to context; the age range for AYA oncology in the USA is 15-39 [59].
Teenage and young adult (TYA)	13-24	Term used predominantly in the UK in oncology [60].

The definition of ‘adolescence’ has been controversial. Adolescence is viewed as the phase during which transition from childhood to adulthood occurs, encompassing changes in physical, psychological and social development; it lasts from puberty to the age when mature social roles are undertaken [61]. Puberty is, however, occurring increasingly early, with the average age of menarche now 12-13 in high income countries [62]. Furthermore, transitions to mature roles, such as marriage, completion of education, and parenthood, are increasingly delayed to well into the third decade of life. It has, therefore, been recently argued, both in healthcare literature and in the media, that the term ‘adolescence’ should be expanded beyond the ages of 10-19, to include those up to the age of 24 [63].

The term ‘teenage and young adult’ (TYA) will be used in relation to the cohort of young patients involved in the research described in this thesis, as it is the prevailing term used for young cancer patients in the UK. However, much of the research conducted in a non-oncology setting, and virtually all work conducted outside the UK, uses other terms, particularly ‘adolescent and young adult’ (AYA)

and ‘young people’. Therefore, a broader range of terms will be needed in the discussion sections of this work.

#### **1.1.2.2 Importance of this age**

The current generation of young people is the largest in history. There are 11.7 million young people aged 10-24 in the UK, one in five of the population; the 1.8 billion across the world comprise a quarter of the global population [64,65]. Any attempt to meet the needs of this cohort has, therefore, immense potential for impact.

The transition between childhood and adulthood is one of the most rapid phases of human development. Extensive changes in physical, cognitive, emotional, social and behavioural development occur, as summarised in table 1.2.

**Table 1.2 Overview of developmental changes in adolescence** (adapted from [64,66] and [67])

Developmental area	Key changes
Physical	<ul style="list-style-type: none"><li>• Growth spurt</li><li>• Puberty and maturation of reproductive organs</li><li>• Development of secondary sex characteristics, and menarche (girls)</li></ul>
Cognitive	<ul style="list-style-type: none"><li>• Increasing abstract thought</li><li>• Increased capacity for setting goals</li><li>• Interest in moral reasoning</li></ul>
Emotional	<ul style="list-style-type: none"><li>• Intense self-involvement</li><li>• Developing self-identity</li><li>• Emotional reactivity and conflict</li></ul>
Social	<ul style="list-style-type: none"><li>• Seeking independence and responsibility</li><li>• Distancing from parents and seeking relationships outside family</li><li>• Influenced strongly by peer group</li></ul>
Behavioural	<ul style="list-style-type: none"><li>• Regression to child-like behaviour when under strain</li><li>• Seeking out novel experiences and making risky choices</li><li>• Establishing life-long behaviours</li></ul>

Young people form a group with substantial and distinct needs that differ both from those of younger children and from older adults. The characteristics of young people are not simply those that would be expected if there was a smooth continuum from child to adulthood. At a neurodevelopmental level, the changes of adolescence are non-linear [66]. In a widely accepted neurobiological model of adolescence, the features of this age can be explained by the differential rates of development of the limbic system and prefrontal cortical regions of the brain. The subcortical limbic system matures early, a part of the brain involved in emotional reactivity, reward seeking and behavioural motivation. In contrast, the controlling prefrontal cortex, involved in executive function, planning and impulse control, develops relatively slowly, only reaching full maturation towards the middle of the third decade of life [66].



The mismatch between limbic and prefrontal cortical development, along with overproduction of axons and synapses before the rapid pruning that occurs in late adolescence, results in a unique stage of brain functioning [68]. In recent years, rather than viewing this period as a negative phase of suboptimal decisions and inappropriate risk-taking, it has been recognised that such programming of the adolescent brain may indeed be advantageous in evolutionary terms [66,69]. It has been convincingly argued that high-risk behaviour is needed, in order to leave the parental home and take the steps necessary to find a partner. Increased emotional reactivity enhances scanning for, and responses to, threats as adolescents move from a safe to a novel environment [66].

Nonetheless, this stage of young life is undeniably a period of vulnerability, this being particularly evident with respect to health [65,70]. Impulsive and emotionally-driven decisions, influenced by the modern unprecedented social forces of electronic media and marketing, can impact negatively on health. In 2015, an estimated 1.2 million adolescents worldwide died from largely preventable causes, more than two-thirds of adolescent deaths being due to injuries, both unintentional such as road traffic accidents and drowning, and intentional such as homicide and suicide [71]. Moreover, adolescence is associated with a surge in mental health disorders, with half of lifetime mental disorders starting by the age of 14; such disorders are considered to be the single largest contributor to the non-fatal disease burden experienced by young people [64]. Emerging evidence suggests that inadvertent consequences of social media, such as increased potential for comparison with peers, may be contributing significantly to the increasing incidence of depression and anxiety in the young [72].

Whereas childhood mortality has declined by more than 80% in the last half century, that of adolescents has improved only marginally [67,73]. The mortality of adolescents aged 10-19 is greater than that of children aged 1-4 years [74]. In the UK, healthcare outcomes for patients aged 10-24 are amongst the worst in Europe, and the number of emergency presentations of older adolescents to hospital has increased more than three-fold over the last decade [75-77].

Adolescence is a formative age; the changes in adolescence have health-related consequences with an impact, not only during adolescence, but also lifelong [71]. Many of the unhealthy behaviours that tend to start in adolescence, such as smoking, alcohol use and physical inactivity, are believed to be contributing to the so-called 'epidemic of non-communicable disease' occurring in modern adult society [78]. Young people become parents and, in turn, influence the health and health-related attitudes of the next generation. Improvements in adolescent health, therefore, impact not only

directly on this large cohort of vulnerable people, but also have the potential to improve global health across every generation [71].

It is unsurprising, therefore, that promotion of adolescent health is a key international healthcare priority [65]. Over the last five years, the World Health Organisation (WHO) has been driving global accelerated action to improve health in adolescents [71]. The unique nature of adolescence mandates specific and explicit age-focused healthcare policy and services. Eight global standards have been created to define the required level of quality in the delivery of adolescent healthcare; those most relevant to this work are summarised in table 1.3 [79].

**Table 1.3 Selected global standards for quality health services for adolescents** (adapted from [79])

Adolescents' health literacy	<b>Standard 1.</b> Systems are needed to ensure that adolescents understand their own health, and know how to access health care services.
Appropriate services	<b>Standard 3.</b> Services need to fulfil the needs of all adolescents.
Quality improvement	<b>Standard 7.</b> Service data is collected, analysed and used to support quality improvement.
Adolescents' participation	<b>Standard 8.</b> Adolescents are involved in the planning and evaluation of health services, as well as in certain appropriate aspects of service provision.

In the UK, national policy now recognises the comparatively poor outcomes in adolescents, and the need for age-appropriate care [80]. In 2014, the Royal College of Physicians (RCP) issued a position statement on the care of adolescent and young adult patients, expressing commitment to 'developmentally appropriate care, tailored to reflect the unique needs of patients during adolescent and young adulthood' [81]. Importantly, the RCP also advocates 'further research to improve our understanding of young adults' and adolescents' health, their experiences of care and their health outcomes' [81]. Evidence is mounting for improved outcomes and cost-effectiveness with specialist age-appropriate support, as increasing numbers of adult and paediatric services attempt to adapt to the specific needs of adolescents [82,83]. In the UK, 10% of adolescents, irrespective of diagnosis, receive healthcare in specialist adolescent units, and report receiving better care than in either paediatric or adult healthcare settings [84].

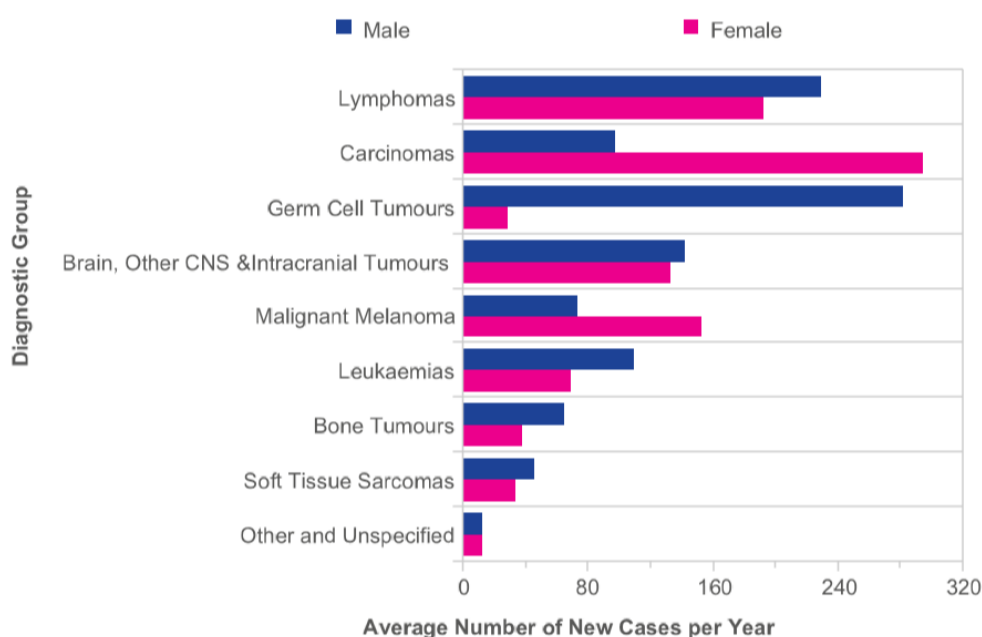
### **1.1.3 Teenage and young adult cancer**

Adolescents living with chronic illness are globally recognised to be a particularly vulnerable group [71]. Young people living with long-term conditions are exposed to a major psychosocial burden and to social marginalisation [85]. At a neurobiological level, it is known that the developing adolescent brain is adversely affected by such stressors, with cognitive regression and even more limited recruitment of the relatively immature pre-frontal cortex [86]. Furthermore, enforced changes to plans and expectations challenge the adolescent developmental needs of autonomy and self-identity

[87]. Risk-taking behaviour appears to be even greater in young people with, rather than without, chronic conditions[88], and such behaviour may manifest as poor adherence to treatment [89,90].

Teenage and young adult cancer is relatively rare, with less than 3000 new cases each year, accounting for less than 1% of the total number of cancer cases in the UK (2013-15) [91]. However, the 5-year survival is over 80%, meaning that large numbers of TYAs are living with, and beyond, cancer. At the end of 2013, it was calculated that there were approximately 33,000 people living in the UK who had been diagnosed with a cancer aged 15-24 [92]. This number is set to grow steadily, as both the incidence of cancer and its survival are increasing [91,93]. Crucially, over two-thirds of TYA cancer survivors suffer from at least one additional chronic health problem, including detrimental long-term sequelae from cancer treatment, such as cardiovascular disease and osteoporosis [94,95].

**Figure 1.1 Teenage and young adult cancer by diagnostic group 2000-2009 (UK, age 15-24)[91]**



The experience of TYAs with cancer differs both from that of older adults and from children, and is recognised to be particularly challenging [60,96]. The cancer profile is different; young people experience late onset paediatric cancers, early onset adult cancers and so-called ‘true adolescent cancers’ (figure 1.1) [91,97]. The latter cancers include Hodgkin’s lymphoma, germ cell tumours, and soft tissue sarcomas, many requiring particularly long and intensive treatment regimens. The prognosis for some cancers, including sarcoma, is less good than that for children or older adults for reasons that are, as yet, not well understood [91]. Many TYAs experience pervasive despair. The

inevitable distress of a cancer diagnosis is compounded by the threat of young death and by parents' understandable anguish, along with the many challenges to adolescent developmental needs, including altered self-image and isolation from peers [98]. Young people with cancer are recognised as being 'uniquely vulnerable', experiencing a 'dual crisis' when the 'normative developmental stressors derived from the tasks of transitioning from adolescent to young adulthood combine with the challenges associated with an unexpected cancer diagnosis' [60].

Unsurprisingly, given the significant challenges, TYAs with cancer experience considerable unmet healthcare needs [99]. In parallel with the global drive to improve adolescent health, there have been international efforts to develop specific and age-appropriate cancer services, initiated in the UK in 1995 with the Calman Hine Report [100-103]. The National Institute of Health and Care Excellence (NICE) subsequently published the 'Children and Young People's Improving Outcomes Guidance' in 2005, requiring the development of national TYA Principal Treatment Centres that every young person with a cancer diagnosis must be able to access [104]. The Teenage Cancer Trust (TCT), a charity dedicated to supporting and advocating for TYAs with cancer, has opened 28 specialist TCT units throughout the UK, staffed by healthcare professionals with specific expertise in the management of young cancer patients [105].

Along with recognition of the need for age-appropriate cancer services, there has been a national drive to increase research in this young patient group [104]. Evidence relating to TYA cancer is considerably less robust than that for paediatric and for adult cancer; neither the TYA age-bracket, nor the types of cancers experienced by TYAs, fit neatly into the agendas of the established cancer research groups for children and older adults [60].

The UK NCRI TYA Clinical Studies Group was established in 2005, to promote research specifically in TYAs with cancer. However, this group has tended to focus on the biology of TYA cancer, on cancer registration and on clinical trials of cancer treatments, with evaluation of patient experience and quality of life tending to lag behind [106]. Of note, in a recent TCT and James Lind Alliance Priority Setting Partnership, young people themselves have convincingly demonstrated that their research priorities relate more to their quality of life, with a desire for research evaluating psychosocial support, management of cancer treatment-related adverse effects and facilitation of return to education and work [107].

#### **1.1.4 Teenage and young adult cancer-related fatigue**

Even without a cancer diagnosis, young people are particularly susceptible to fatigue. It is a prevalent subjective symptom, and studies evaluating fatigue in the general population suggest that 15-30% of adolescents experience fatigue [108-110]. The prevalence is particularly high in females and, in longitudinal studies, fatigue onset tends to be preceded by depression or anxiety [111]. Only a minority, less than 3% of young people, meet criteria for diagnosis with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). This illness is characterised by severe and disabling fatigue lasting at least six months, and accompanied by a range of rheumatological and neuropsychiatric symptoms; no unifying aetiology has yet emerged [112]. Although the prevalence of CFS/ME is slightly higher in adolescents than in older adults, the prognosis is better, with 75% recovering within 2-3 years [113-115].

Young people appear to be particularly prone to fatigue for both developmental and behavioural reasons. During this important phase of brain maturation, the developmental need for longer sleep is hindered by circadian rhythm shifts, with later melatonin secretion and sleep phase delay limiting sleep, in the context of early rise times for school or work [116,117]. Further, young people may develop unhelpful sleep habits, such as alcohol and caffeine consumption, and late evening social commitments. Over the last decade, blue light emitting electronic devices in the bedroom appear to be compounding the problem, by delaying melatonin secretion and sleep onset [118,119].

In the context of cancer, a meta-synthesis of literature evaluating TYA experiences has revealed that fatigue is the symptom featuring most prominently [98]. This is unsurprising given that fatigue is the most prevalent and debilitating symptom in older adults with cancer, and young people have an inherent propensity to develop fatigue. It seems that the dual risk factors for fatigue, cancer and young age, combine to create a particularly significant problem. Studies suggest a TYA CRF prevalence of well over 50%, rising to 90-100% during cancer treatment [120,121].

TYAs appear to experience worse CRF than both older adults [122] and children [123]. Even within a cohort of older adults, there is an inverse correlation between fatigue and age [124]. Not only is the fatigue itself severe at the TYA age, its impact appears to be particularly detrimental, hindering many key adolescent developmental needs, such as autonomy and development of peer-relationships [125,126].

Research focusing on CRF in young people has only begun to emerge in the last 15-20 years. Hinds and colleagues, in the USA, undertook much of the original work defining and starting to assess the

problem [127-129]. Using evidence from qualitative research, they have generated the following conceptual definition of cancer-related fatigue in 13-18 year olds:

‘Fatigue is a complex, changing state of exhaustion that at times seems to be a physical condition, at other times a mental state, and still other times to be a combination of physical and mental tiredness. It is influenced by environmental, personal/behavioural, and treatment-related factors, and results in the adolescent not being able to maintain usual involvement with friends, academics, or sports, experiencing negative emotions like anger, preferring not to be bothered by others, and strong desire to lie down or rest. This changing state of exhaustion can be acute, episodic, or chronic and is relieved by changing the environment, rest, distraction, and medical/pharmacological interventions’ [130].

Subsequently, a number of researchers have continued this work, investigating the prevalence and impact of this debilitating symptom [125,131-134]. Nonetheless, despite the international drive to try to meet the unique needs of adolescents, research evaluating TYA CRF lags far behind that relating to fatigue in older adults [127].

## **1.2 Research programme rationale**

### **1.2.1 Brief overview of programme**

This thesis describes a programme of research investigating the prevalence, impact and management of cancer-related fatigue in teenagers and young adults. Three sequential and closely-related studies have been undertaken, involving multiple methods.

#### **Study 1 A systematic literature review of teenage and young adult cancer-related fatigue**

This broad and comprehensive review provides a systematic overview of existing research. Studies evaluating any aspect of fatigue were included. The work was undertaken between November 2013 and March 2014, and was published in 2015. It was subsequently updated in April 2018, and is described in chapter 2.

#### **Study 2 Fatigue in Focus survey: a multicentre electronic survey evaluating the prevalence, impact and management of teenage and young adult cancer-related fatigue**

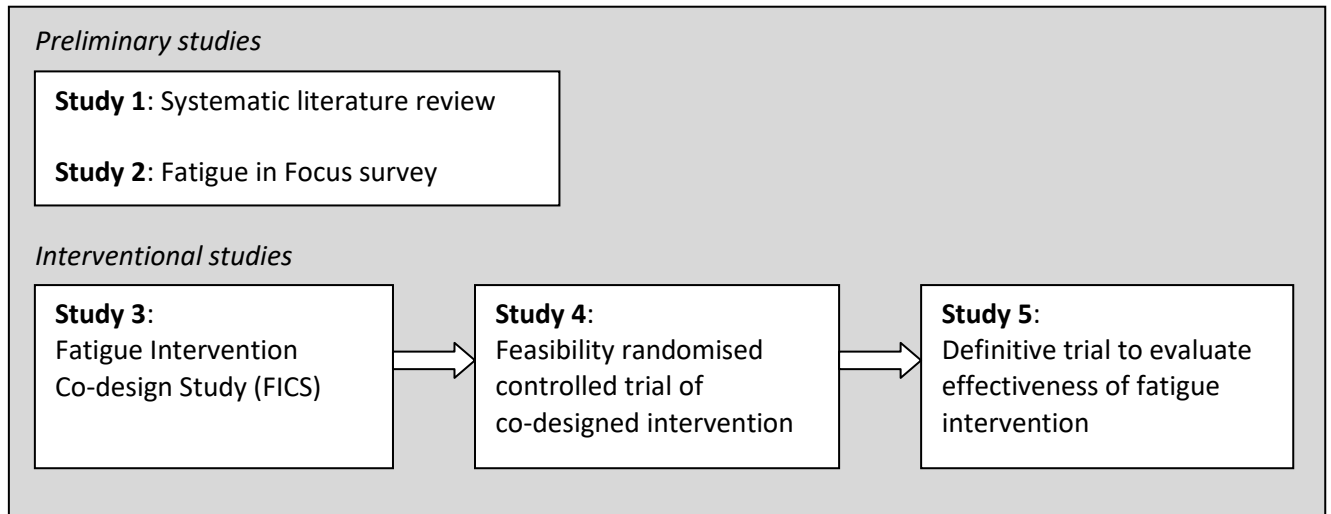
An electronic survey was undertaken, recruiting young participants from three of the thirteen TYA cancer Principal Treatment Centres in the UK. It evaluated the experience of current patients, focusing on the prevalence and severity of fatigue, the impact of fatigue on TYAs and their carers, and existing fatigue management approaches. This predominantly quantitative survey was conducted between December 2014 and October 2015, and published in 2017. It is detailed in chapter 3.

#### **Study 3 Fatigue Intervention Co-design Study (FICS) in teenagers and young adults with cancer**

A multiphase, multi-perspective, qualitative study was undertaken in one centre, to develop a 'trial ready' complex intervention that meets the needs of fatigued TYAs and their parents. Individual interviews and focus groups were conducted involving patient-parent dyads. Participants then received a prototype intervention, and subsequently provided feedback, allowing further intervention development. This longitudinal study commenced in March 2016, with data analysis ending in March 2018. It is described in detail in chapter 4.

The intention is for the three studies to lead towards the development of an intervention that can be tested in future feasibility and definitive randomised controlled trials, as summarised in figure 1.2. Studies 1, 2 and 3 form the basis of this thesis, with studies 4 and 5 expected to occur during 2019-2024.

**Figure 1.2 Overview of research programme and intentions**



The interventional studies 3, 4 and 5 represent the three phases of research defined in the Medical Research Council (MRC) Framework of Complex Interventions as ‘intervention development’, ‘feasibility assessment’ and ‘intervention evaluation’ respectively [135]. The final study described in this thesis, study 3, therefore represents the first phase of intervention development.

### **1.2.2 Overview of patient and public involvement**

This programme of research has been inspired, and indeed driven, by young cancer patients, since its inception. The topic importance was identified in 2010, at a Cambridge TYA cancer service review focus group. Participants ranked ‘fatigue management’ as their top priority. The TYA service lead consultant therefore ran Fatigue Workshops during 2011; every participant rated the workshop with the highest score of 5/5 for usefulness and relevance, and reported improved coping with fatigue.

Laura Abbas (name used with consent) is a former TYA cancer patient who has experienced severe fatigue. She has been the patient and public involvement (PPI) lead for this programme of work. Until 2015, she was the Cambridge TCT Youth Support Co-ordinator, putting her in an ideal position to provide advice from a patient perspective, as well as co-ordinate and support PPI. She reported receiving weekly emails from patients wanting help with fatigue, and has been a dedicated proponent of this programme of work. Her roles in studies 2 and 3 are described in sections 3.4.7.2 (page 55) and 4.4.7.2 (page 107).

A TYA research programme Focus Group, involving five TYA cancer patients, provided strong endorsement and detailed design advice. An ‘e-Focus Group’ corresponded by email to give specific advice in relation to study materials for participants. Patients and parents at a TYA service Family Day



in June 2013 also validated the proposed research approach, and provided advice. The service consultant lead undertook pre-pilot work and found that 16 of the 18 patients she consulted during outpatient clinics would have wanted to know more about fatigue and would, on principle, be prepared to take part in interventional research.

Young people are particularly keen to take an active part in research, to influence and to provide advice [136-138]. The Fatigue Intervention Co-design Study (FICS) was, in itself, an exercise in patient involvement (and led to a University of Cambridge Vice-Chancellor's Public Engagement with Research Award: section 7.1.2, page 69). Participants were able to guide the content of the interview and focus group discussions, as well as fundamentally influence the design of the intervention prototype and subsequent 'trial ready' intervention. It has been well-established that co-production work with patients reaps benefits in terms of the value and usefulness of the research, and also in terms of patient satisfaction [138].

### **1.2.3 Justification for research**

The rationale for this programme of research has already been considered in relation to the research context and the patient involvement, as described in sections 1.1 and 1.2.2 respectively. However, the salient points are summarised below for clarity:

#### Cancer-related fatigue appears to be particularly problematic in TYAs

Fatigue is established as the commonest symptom in adults with cancer. Healthy TYAs experience more fatigue than adults for developmental and behavioural reasons. The combination of a cancer diagnosis and TYA age may, therefore, be a dual risk factor for fatigue, making TYAs particularly vulnerable to the development of CRF. The impact of CRF appears to be magnified by young age. The symptom appears to directly hinder TYA developmental needs and may influence life course through its impact on education, employment and relationships. Behaviours learned at this age tend to form a life-long pattern. TYAs potentially have more of their life ahead of them than older adults, increasing the duration of impact and compounding the fatigue burden.

#### Research outcomes cannot be extrapolated from older adults to TYAs

Over the last five years the WHO has been driving action to improve adolescent health, mandating age-focused healthcare policy, services and standards, underpinned by specific research. There is an international imperative to undertake age-appropriate research for TYAs with cancer. Although there is an emerging evidence base to support the effective treatment of CRF in older adults, such evidence cannot be directly applied to TYAs with their distinct needs.

#### TYAs with cancer want this research to happen so that fatigue can be effectively treated

Cambridge TYA cancer patients have identified fatigue treatment as their healthcare priority. They have initiated, driven, supported and influenced this research. On a national level, young cancer patients' research priorities relate to reversing cancer treatment adverse effects, psychosocial support and facilitating return to education and work. Given that fatigue is a predominant treatment effect, and that the main adverse impact of fatigue is psychosocial, there is clear alignment of regional and national research priorities.

#### **1.2.4 Theoretical basis**

This work is underpinned by Bandura's Self-Efficacy Theory, and two subsequent conceptual models that apply this theory to the field of cancer-related fatigue. Bandura was an eminent psychologist from the USA who introduced the concept of 'self-efficacy' in a highly influential article published in 1977 [139]. He is considered an early 'cognitivist', with interest in cognitive processes such as perception, information processing, reasoning and direction of attention, rather than a 'behaviourist', focusing on determinants and change of behaviour. Bandura defined 'self-efficacy' as 'people's beliefs about their capabilities to produce effects' [140]. It is a measure of confidence in the ability to achieve specific goals, high self-efficacy being associated with being prepared to make a greater effort and persist despite obstacles [141]. He identified self-efficacy as a key mediator of health-promoting behaviours, such as symptom self-management, a finding that has since been extensively corroborated across many fields of healthcare [142-144].

Hoffman and colleagues have subsequently developed a middle-range Theory of Symptom Self-Management, derived in part from Bandura's Self-Efficacy Theory, and applied to the self-management of cancer-related fatigue [145]. Fatigue was the symptom chosen because of the central importance of active self-care within fatigue management, there being no effective pharmacological or other 'passive' approaches. Worse CRF was found to be associated with low self-efficacy for fatigue self-management, and perceived self-efficacy mediated the relationship between the fatigue severity and functional status [146,147]. A 6-item measure of Perceived Self-Efficacy for Fatigue Self-Management (PSEFSM) was developed, with the intention of facilitating development of interventions to increase self-efficacy [148].

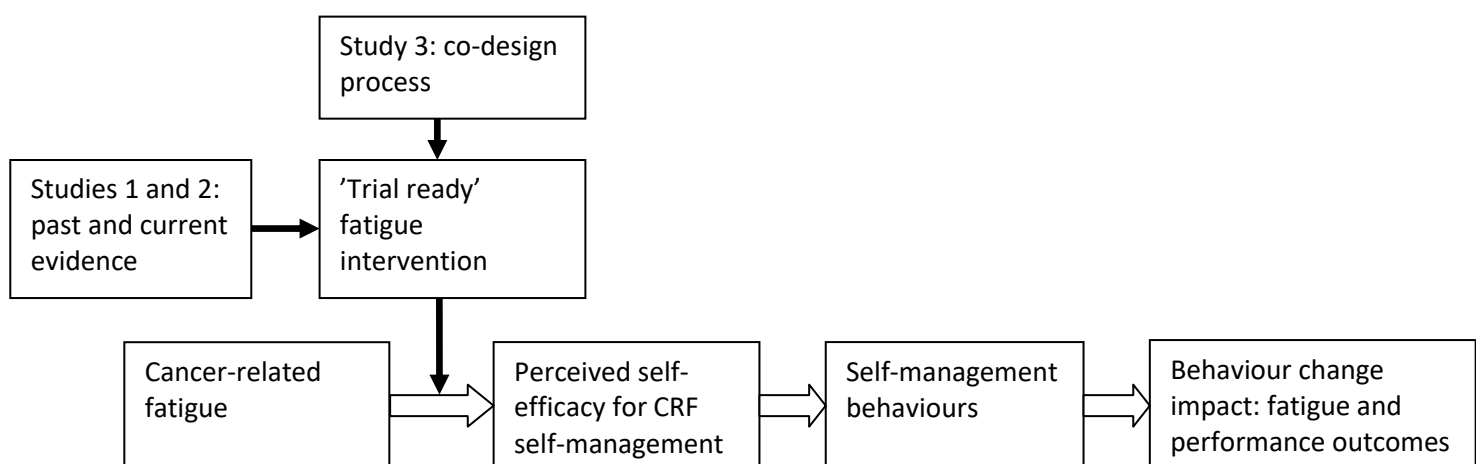
Foster and Fenlon have subsequently developed a conceptual framework for the recovery of health and wellbeing following primary cancer treatment [149]. Cancer-related self-efficacy is central to the framework, mediating successful self-management and subjective recovery. Of note, self-efficacy for fatigue management was the lowest across a range of self-management tasks, in a survey of patients who had completed cancer-treatment in the past 12 months [150].

Overall, therefore, Bandura’s Self-Efficacy Theory and the two related conceptual models suggest that perceived self-efficacy is an important mediator of self-management behaviours, and a concept of relevance to CRF. Patients with long-term conditions consider self-efficacy to be a valuable outcome and, interestingly, would be prepared to trade a substantial reduction in health-related quality of life in return for an improvement in self-efficacy [151]. Research in adolescents with diabetes and juvenile rheumatoid arthritis has shown that the concept of self-efficacy is a relevant concept to young patients with chronic disease, and high self-efficacy for self-management is associated with improved quality of life [152].

Of particular importance given the intention to develop a fatigue intervention, self-efficacy does appear to be amenable to change. A number of studies evaluating self-management or psychological interventions have demonstrated the potential to increase domain-specific self-efficacy, with self-efficacy, in turn, mediating improved health outcomes [153-155]. In the context of adult CRF, recent feasibility studies, involving a web-based intervention and a post-surgical exercise intervention to support fatigue self-management, suggested improvement in self-efficacy and outcomes [156,157].

A final justification for underpinning this work in Self-Efficacy Theory is that self-efficacy has the potential to alter rapidly over days, mediating the subsequent behaviour change and the impact of such change [158]. The Theory of Change is a design and evaluation tool that has been integrated into the MRC Framework of Complex Interventions to try to enhance the likelihood of developing an effective complex intervention [159]. This tool requires specification of intermediate outcomes, in order to facilitate achievement of the desired long-term outcomes. Perceived self-efficacy is an ideal candidate for this intermediate step because of its mediating role. A theory-based logic model for the proposed research is provided below.

**Figure 1.3 Theory-based logic model**



## **1.3 Aim and objectives**

### **1.3.1 Aim**

The overall aim of this programme of research was to increase understanding of the cancer-related fatigue in teenagers and young adults, in order to be able to develop an effective non-pharmacological fatigue intervention.

### **1.3.2 Objectives**

The specific objectives of each of the three studies described in this thesis are stated in each chapter introduction. However, the broad objectives of this work, as a whole, were as follows:

- 1) To review existing literature evaluating any aspect of TYA cancer-related fatigue, providing a synthesis of current research knowledge in this field.
- 2) To survey current TYA patients with cancer to gain a national overview of current fatigue prevalence, impact and management.
- 3) To work with young TYA cancer patients and their parents to co-design an acceptable non-pharmacological fatigue intervention that meets the needs of this age group.

## **2 Systematic literature review**

### **2.1 Title**

A systematic literature review of teenage and young adult cancer-related fatigue

### **2.2 Rationale**

Despite the apparent high prevalence and adverse impact of TYA CRF, at the time of review initiation in 2013, there had been only one previous attempt to synthesise the relevant literature.

In 2004, Erickson reviewed the literature relating to fatigue in adolescents with cancer, using a systematic search strategy, although without considering unpublished work or other 'grey' literature [160]. Using very broad search terms, one being that the studies simply needed to include one or more patients aged 12-19, fifteen studies were incorporated in the review. Nine of these evaluated adolescent symptoms generally; the remaining six focused on fatigue. All generated qualitative data, other than one study demonstrating the properties of the PedsQL™ Multidimensional Fatigue Scale (MFS) [161]. No interventional studies were found. The review concluded by suggesting that clinicians assess for the presence of fatigue, support patients with this symptom and, importantly, work with researchers to 'promote the most coordinated and efficient research to... test specific interventions for fatigue management' [160].

In this context, and given the number of relevant papers published since 2004, it was clear that a further systematic review of the literature was required. Broad eligibility criteria for inclusion were used to ensure a comprehensive overview of existing literature.

### **2.3 Aim and objectives**

#### **2.3.1 Aim**

The aim of this literature review was to provide a systematic review and synthesis of existing research knowledge concerning TYA cancer-related fatigue.

#### **2.3.2 Objectives**

To undertake a systematic review and narrative synthesis of existing evidence in relation to:

1. The prevalence of cancer-related fatigue in TYA patients a) during treatment, b) after treatment.
2. The impact of fatigue on the quality of life of TYA patients.
3. The experience of parents of fatigued TYA patients.
4. Correlates of cancer-related fatigue in TYA patients.
5. The effectiveness of interventions to manage the symptom.

## 2.4 Methods

### 2.4.1 Timeline

The review was initiated in November 2013, completed by March 2014, and published in the *Journal of Adolescent and Young Adult Oncology* (appendix 7.1.4, page 271). The work was subsequently updated in April 2018, and this chapter presents the revised literature review and synthesis.

### 2.4.2 Literature search strategy

MEDLINE, EMBASE, PsycINFO, and CINAHL databases were searched for relevant literature, from 1981 through to October 2013, and subsequently to May 2018. Preliminary searches revealed no literature of relevance published prior to 1981. The search strategy is detailed in table 2.1.

Reference and citation searches were also undertaken, with manual searching of all issues of a key journal, the *Journal of Adolescent and Young Adult Oncology* (volume 1 issue 1 to volume 7 issue 2), and the proceedings of the 2012, 2014 and 2016 Teenage Cancer Trust International Conferences. Related systematic reviews were searched, including reviews evaluating symptoms experienced by teenagers with cancer, fatigue in lymphoma patients, and interventions for fatigue in children and adults [162-165]. Experts in the field of TYA cancer-related fatigue were also contacted.

**Table 2.1 Search terms**

#1	exp fatigue/
#2	fatigue* or tire* or exhaust* or lethargy* (title or abstract)
#3	exp neoplasm/
#4	neoplasm* or cancer* or carcinoma* or lymphoma* or leukaemia* or leukemia* (title or abstract)
#5	1 or 2
#6	3 or 4
#7	5 and 6
#8	limit 7 to 'adolescent' or 'young adult'
#9	tya* or teenage* or "young adult"* (title or abstract)
#10	7 and 9
#11	8 or 10

### 2.4.3 Selection criteria

The key inclusion criteria were that all study participants had malignant disease, and that either the majority were aged 13–24 years-old at the time of cancer diagnosis or treatment, or that the results for this age subgroup were presented separately. Included studies could investigate any aspect of CRF, use any outcome measure, and employ quantitative or qualitative methods. Exclusion criteria included non-English language publication, absence of original empirical data, phase I/II clinical trials, trials involving fewer than 10 patients, case reports and retrospective case note reviews. Studies of TYA-aged survivors of paediatric cancer were not included.

#### **2.4.4 Quality assessment and data analysis**

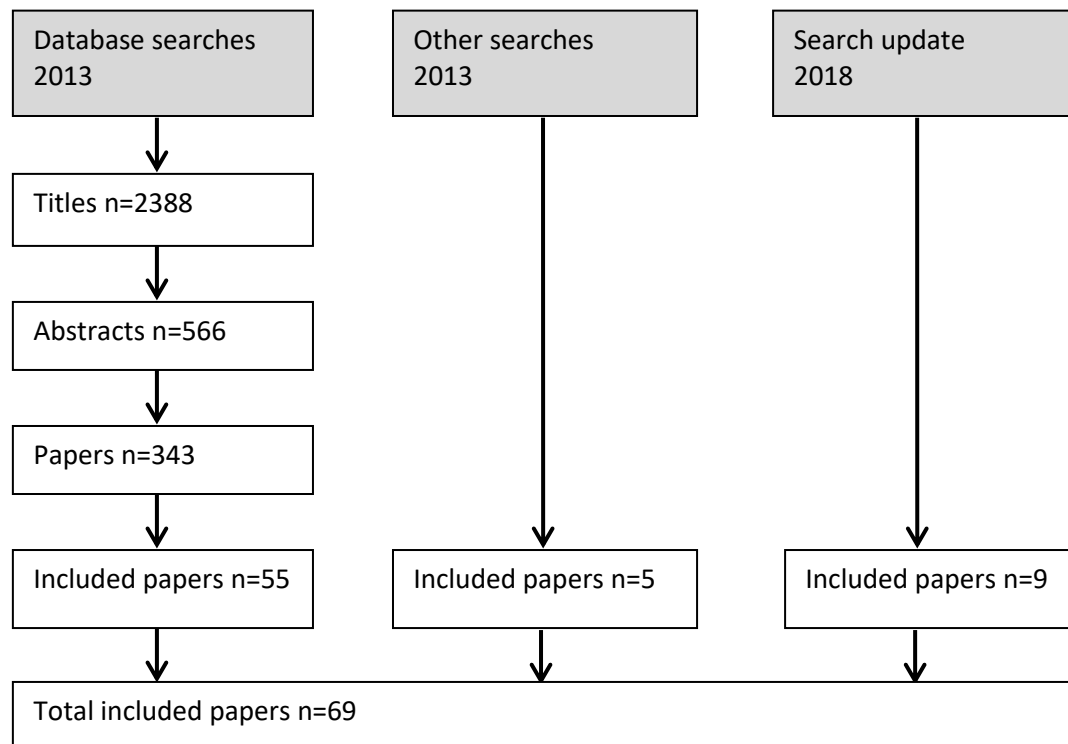
Gough's Weight of Evidence Framework was employed to assess article quality, relevance, and bias, and to generate an overall judgment about contribution [166]. This framework includes analysis of 'fitness for purpose' and relevance to the research question, providing a more applied synthesis of evidence than simply assessing the generic quality of each article. Scores of 'low', 'medium' or 'high' are given for each of the following:

- Weight of Evidence A: integrity of the evidence on its own terms.
- Weight of Evidence B: appropriateness of method for answering the review questions.
- Weight of Evidence C: appropriateness of the focus or relevance for answering the review questions.
- Weight of Evidence D: overall rating generated by combining the A, B, and C scores.

All articles, irrespective of relevance and quality, were included in the review. However, those rated 'medium' and 'high' were given greater weight in the synthesis.

The searches conducted in 2013 produced 2388 unique titles that were initially screened by one researcher (Anna Spathis). After 566 abstracts were reviewed by two researchers (Anna Spathis and Sarah Grove), 343 full articles were read by one researcher (Anna Spathis), who excluded many of them on the basis of the participants' ages. Two researchers (Anna Spathis and Sara Booth) read the remaining articles, with disagreements resolved by discussion. The final number of included articles was 69 (figure 2.1). The updated search in 2018, conducted by one researcher (Anna Spathis), added nine of these papers. A narrative synthesis was undertaken in relation to each of the review questions.

**Figure 2.1 PRISMA flowchart of included articles**



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

#### 2.4.5 Study team and roles

Anna Spathis led this work and every step of the study conduct including: responsibility for study design, writing protocol, all literature searches and data analysis. Stephen Barclay and Sara Booth, MD supervisors, provided regular guidance and advice throughout the study. Sara Booth read some of the papers from the 2013 search, as described in the preceding section. In addition, a number of other colleagues made specific contributions as shown below.

**Table 2.2 Roles of other team members in review**

Sarah Grove	Specialty Trainee in Palliative Medicine, Cambridge University Hospitals	Abstract review to assess eligibility
Helen Hatcher	Consultant Medical Oncologist, TYA service lead, Cambridge University Hospitals	Contribution to review design
Isla Kuhn	Medical Librarian, University of Cambridge	Guidance and support in relation to optimising search strategy



## **2.5 Results**

### **2.5.1 Description of articles**

Forty-three of the 69 included articles were from the USA or Canada, eight were from Norway, Sweden or Germany, three were from the UK, and one each from Taiwan and Australia. All were published between 1992 and 2017. The 69 articles encompassed a total of 61 separate studies, as four pairs of articles [125,132,167-172] and two groups of three articles [134,173-177] were publications describing different aspects of the same study's data set. It was decided to handle these as different studies, because of their distinct areas of focus. Therefore, for the purposes of this review, the 69 articles were viewed as 69 separate studies.

Forty-one studies were cross-sectional and observational. Of the 28 prospective longitudinal studies, seven were interventional clinical trials. Most studies involved only quantitative methods, though seven were qualitative and ten employed a mixed-methods design. Most were rated as medium or poor on Gough's Weight of Evidence Framework. Although 16 were of high quality on Weight of Evidence A (integrity of the evidence on its own terms) [168,176,178-191], only three were judged to be of high overall quality by Weight of Evidence D [168,178,184].

All participants, aside from those in some of the control groups, had a cancer diagnosis. Seven studies only recruited patients with lymphoma and/or leukemia [132,169,182,190-193], and one involved only patients with extremity bone tumors [194]. All the remaining studies investigated more than one cancer type. The majority of participants were in the 13–24 age range in 52 studies; subgroup data for this age range was presented separately in the remaining 17 papers. The number of patients within each study ranged from eight [195] to 1202 [191], and the median or mean time since diagnosis ranged from two months [196] to 20 years [132].

Fatigue was the study focus and the first outcome measure described in the results for only 20 studies [123,125,129-132,134,168,169,172,179,183,184,187,194,197-201]. Two of these involved validating symptom measures [129,183] and none were interventional. Across the 69 included studies, the most commonly used fatigue outcome measures were the Fatigue Scale-Adolescent (FS-A) [129], the Multidimensional Fatigue Scale (MFS) [161], and the Memorial Symptom Assessment Scale (MSAS 10-18) [202], used in 16, 15 and nine studies, respectively. Thirteen studies used a range of other validated fatigue measures: the Chalder Fatigue Questionnaire, Piper Fatigue Scale, Functional Assessment in Chronic Illness Therapy (FACIT) fatigue scale, Edmonton Symptom Assessment Scale and the EORTC CQC-C30. Nine studies used unvalidated measures, and the remaining seven studies were entirely qualitative in design. Table 2.3 provides further detail on the more commonly used measures.

**Table 2.3 Summary of key fatigue outcome measures**

<b>Name of measure</b>	<b>Description</b>
Chalder Fatigue Questionnaire [7]	11-item multidimensional fatigue scale developed for use in adult epidemiological studies of patients with chronic disease, and to find fatigue 'cases.' It is scored using a 4-point verbal rating scale, with a case defined as a score of $\geq 4$ with dichotomized bimodal scoring.
Edmonton Symptom Assessment Scale [203]	A series of ten numerical rating scales (each 0-10) evaluating nine symptoms, one being 'tired'. It was developed for use in cancer patients in a palliative care context, but is not widely used in different conditions and contexts.
EORTC CQC-C30 [204]	This scale was developed for the assessment of the quality of life of cancer patients in international clinical trials. The scale includes five functional scales, three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality of life scale.
Fatigue Scale-Adolescent [129]	14-item multidimensional scale developed specifically to assess CRF in adolescents aged 13-18. It is scored using a 5-point verbal rating scale, and parent and staff proxy versions have been developed.
Functional Assessment in Chronic Illness Therapy fatigue scale [10]	Initially developed as a multidimensional measure of fatigue in adult oncology patients with anaemia, its use has been widened to include fatigue assessment in chronic illness. It is a standalone scale within the wider FACIT measurement system. It has 13 items, scored using a 5-point verbal rating scale.
Memorial Symptom Assessment Scale [178]	32-item scale developed to assess the frequency, severity, and associated distress of 32 common symptoms, including fatigue, in adult cancer patients. Each symptom is measured with 4-point (frequency and severity) or 5-point (distress) numerical rating scales. It has been modified for use in patients aged 10-18 (30-item) and aged 7-12 (8-item); a number of other revised versions also exist.
Multidimensional Fatigue Scale [161]	18-item scale developed to measure fatigue in paediatric cancer patients and now used as a generic multidimensional measure in all paediatric patient populations. It is a module of the PedsQL™ measurement model, which assesses paediatric quality of life. Versions are available for patients aged 5-7, 8-12, 13-18 and 18-24, with associated parent proxy versions. It provides general (physical), cognitive and sleep/rest fatigue subscale scores.
Piper Fatigue Scale [8]	Multidimensional fatigue scale developed for use in adult cancer patients. A number of versions exist, including the original 40-item scale and a revised 22-item scale. Each item is scored with a 0-10 numerical rating scale. It assesses four domains of fatigue: behavioural/severity, affective meaning, sensory and cognitive/mood; it generates a score for each domain as well as a total score.
Symptom Distress Scale [205]	11-item scale that measures distress related to symptoms, including fatigue, scored using a 5-point verbal rating scale. It was developed specifically to identify the concerns of adult patients receiving cancer treatment.

### 2.5.2 Fatigue prevalence

Twenty-seven studies investigated the prevalence of TYA CRF (table 2.4). Fatigue was measured during treatment in 15 studies, after treatment in five studies, and in a mixed population of patients both during and after treatment in six studies. In one study, the treatment status of the patient population was not defined [206]. A 'fatigue case' was most commonly defined as fatigue being scored as 'present' using the MSAS, a score of anything other than 'no fatigue' on a 5-point Likert scale, or a dichotomized score of  $\geq 4$  on the Chalder Fatigue Scale [7].

The heterogeneity of study populations, outcome measures, and definitions of 'fatigue case' hindered comparison of prevalence data between studies and prevented meta-analysis. Fatigue prevalence ranged from 7% [184] to 100% [207] during treatment, 9% [187] to 67% [120] after treatment, and between 31% [208] and 100% [209] in mixed populations. As detailed in table 2.4, the prevalence of fatigue and other symptoms were compared on 22 occasions in 12 studies; it was the most prevalent symptom on 11 occasions [121,170,171,178,207,210-212] and the second-most prevalent on seven occasions [178,206,212-214].

Two studies, both evaluating survivor populations, included a healthy control group; non-contemporaneous controls were used in both studies. Aksnes and colleagues found a fatigue prevalence of 14% in extremity bone tumor survivors, which was not significantly different from that of age- and gender-matched cases from healthy population surveys ( $p=0.30$ ) [194]. In contrast, Hamre and colleagues reported a fatigue prevalence of 34% in survivors of Hodgkin's lymphoma, compared to 8% in an unmatched healthy control population ( $p<0.001$ ) [132].

**Table 2.4 Studies evaluating fatigue prevalence, grouped by relationship to cancer treatment**

Study	Aim(s)	Participants (mixed tumors unless stated)	Study design and fatigue assessments	Definition of fatigue 'case'	Fatigue prevalence (rank compared to other symptoms)	Weight of Evidence D
<b>During treatment</b>						
Ameringer and colleagues. 2013 [196]	Examine the trajectory of symptoms across a chemotherapy cycle	•n=9 •Mean age: 15.3 years •Mean since diagnosis: 2.6 months	•Longitudinal observational pilot •FS-A	Not described	•All participants experienced some fatigue at every time point	Low
Ameringer and colleagues. 2015 [189]	Examine symptom experiences, clusters and perceived causes	•n=70 •Mean age: 18.5 years •Mean since diagnosis: 3 months	•Cross-sectional observational •MSAS 10-18	Presence of 'lack of energy' in last week on MSAS	•55.6% (4 of 31)	Medium
Atay and colleagues. 2012 [214]	Determine symptom prevalence 1, 2, and 3 months after diagnosis	•n=54 •61% 13-18 years	•Longitudinal observational •MSAS 10-18	Presence of 'lack of energy' in last week on MSAS	•Month 1: 66.7% (5 of 30) •Month 2: 75.9% (2 of 30) •Month 3: 63% (joint 2 of 30)	Medium
Baggott and colleagues. 2010 [212]	Describe changes in symptoms at weekly intervals from D1	•n=66 •Mean age: 14.8 years •Mean since diagnosis: 16.3 months	•Longitudinal observational •Revised MSAS 10-18	Presence of 'lack of energy' in last week on MSAS	•Week 0: 75.8% (1 of 31) •Week 1: 70.5% (2 of 31) •Week 2: 57.4% (2 of 31) •Significant linear decrease over time	Medium
Baggott and colleagues. 2012 [207]	Describe the usefulness of eDiary to record symptoms over a 3-week trial	•n=10 •Mean age: 18.2 years •Mean since diagnosis: 12.2 months	•Longitudinal observational •2 questions from FS-A in a VAS format	VAS >30 on 0-100 scale on at least 1 day	•Reported fatigue-physical and fatigue-mental: 100% (1 of 11) •% days that VAS >30 on 0-100 scale, 64% and 62%, respectively (1 of 11)	Low
Baggott and colleagues. 2012 [121]	Evaluate symptom clusters	•n=131 •Mean age: 14.8 years •Median since diagnosis: 3.3 months	•Cross-sectional on D0 of ≥cycle 2 of chemotherapy •Revised MSAS 10-18	Presence of 'lack of energy' in last week on MSAS	•75.6% (1 of 31)	Medium

Study	Aim(s)	Participants (mixed tumors unless stated)	Study design and fatigue assessments	Definition of fatigue 'case'	Fatigue prevalence (rank compared to other symptoms)	Weight of Evidence D
Corey and colleagues. 2008 [208]	Describe the relationship between support and symptom distress	•n=72 (ARM 2) •Mean age: 14.8 years (ARM 2) •Mean since diagnosis: 3.75 years (ARM 1, 2)	•Secondary analysis of data from two studies •Symptom Distress Scale	3-5 on 1-5 Likert scale	•ARM 2 (recent diagnosis): 42.5%	Medium
Enskar and colleagues. 2007 [120]	Evaluate distress, coping support, and care	•n=54 •Mean age: 16.0 years •32 were <3 months of diagnosis	•Cross-sectional •LSS-A	Anything other than 'not at all' / 'do not agree at all' on 1-5 VRS	•For 15 patients on treatment: 93%; significantly more than patients off treatment (p<0.05)	Medium
Erickson and colleagues. 2010 [125]	Describe fatigue patterns during month of chemotherapy	•n=20 •Mean age: 16.1 years •Mean since starting chemotherapy: 8.71 weeks	•Longitudinal mixed methods •Daily fatigue NRS, MFS	>0 on 0-10 NRS	•Experienced fatigue at some point, including during 'days immediately following chemotherapy': 100%	Medium
Erickson and colleagues. 2011 [172]	Describe relationship between fatigue and sleep-wake disturbances	•n=20 •Mean age: 16.1 years •Mean since starting chemotherapy: 8.71 weeks	•Longitudinal observational •Weekly MFS from D1 for 5 weeks	'Feeling tired' 'sometimes,' 'often,' or 'almost always'	•At some point over study period: 75%	Medium
Hedstrom and colleagues. 2005 [176]	Investigate perceptions of distress amongst recently-diagnosed adolescents	•n=56 •Age (years): 13-15, n=35; 16-19, n=21	•Cross-sectional, mixed methods •Fatigue assessed as an aspect of distress using Likert scale	3-5 on 0-5 Likert scale	•62% (4 of 20)	Medium
Mandrell and colleagues. 2011 [184]	Calculate the revised FS-A score that defines a fatigue 'case' meriting clinical intervention	•n=138 •Mean age: 14.83-16.27 years across all studies	•Analysis of data from 9 studies •FS-A and FS-P	>31 on scale of 13-65	•ALL: 15%; 7-14%/26-33% (ALL off/on DXM) •Solid tumor or AML: 10% (D1), 28% (D2), 50% (D3-4) •Mixed diagnoses: 36% (D1); 56% (final day); 54% (1 week after end)	High

Study	Aim(s)	Participants (mixed tumors unless stated)	Study design and fatigue assessments	Definition of fatigue 'case'	Fatigue prevalence (rank compared to other symptoms)	Weight of Evidence D
Miller and colleagues. 2011 [213]	Describe prevalence, frequency, severity, and distress of multiple symptoms	•n=39 •Mean age: 13.5 years	•Longitudinal observational •MSAS 10-18 daily for 5 days evaluating symptoms from 'past day'	Presence of 'lack of energy' in last week on MSAS	•49.6% (2 of 31)	Medium
Walker and colleagues. 2010 [210]	Describe symptoms before (T1) and 1 week after (T2) chemotherapy	•n=51 •Mean age: 14.2 years •Mean since diagnosis: 6 months	•Longitudinal observational in 2 centers •MSAS 7-12	Presence of 'tiredness' in last week on MSAS 7-12	•T1: 54.3% (1 of 9) •T2: 67.4% (1 of 9)	Medium
Williams and colleagues. 2012 [211]	Calibrate the Therapy-Related Symptom Checklist-Children	•n=163 •Subgroup of 385 participants in age range 12-17 years	•Cross-sectional •TRSC-C	Severity of 'feeling sluggish' of more than 0 on 0-4 Likert	•81% (1 of 31)	Medium
<b>After treatment</b>						
Adams and colleagues. 2004 [192]	Evaluate cardiovascular function after mediastinal RT	•n=48 HD survivors •Median age at diagnosis: 14.2 years •Median since diagnosis: 14.3 years	•Cross-sectional •General Health Survey (unvalidated tool)	≥1 on 0-4 Likert scale of fatigue severity	•67%	Medium
Aksnes and colleagues. 2007 [194]	Examine fatigue, mental distress, and QOL in EBT survivors compared to matched controls	•n=57 EBT survivors •Mean age at diagnosis across subgroups: 16-25 years •Mean since diagnosis: 9-14 years	•Case-control (non-contemporaneous controls HD, TC, NORMS) •CFQ	Sum of ≥4 using dichotomized (0, 0, 1, 1) 4-point Likert scale	•EBT survivors: 14% •HD survivors: 21% •TC survivors: 16% •NORMS: 10%; p=0.3 EBT vs. NORMS	Medium
Enskar and colleagues. 2007 [120]	Evaluate distress, coping support, and care	•n=54 •Mean age: 16.0 years •32 were <3 months of diagnosis	•Cross-sectional •LSS-A	Anything other than 'not at all' on 1-5 VRS	•For 39 patients after treatment: 67%, less than on treatment (p<0.05)	Medium

Study	Aim(s)	Participants (mixed tumors unless stated)	Study design and fatigue assessments	Definition of fatigue 'case'	Fatigue prevalence (rank compared to other symptoms)	Weight of Evidence D
Hamre and colleagues. 2013 [132]	Determine prevalence of chronic fatigue in leukemia/lymphoma survivors	•n=92 (subgroup of 290); all HD •Mean age diagnosis: 14.6 years •Mean age at survey: 35.0 years	•Cross-sectional •CFQ	Sum of $\geq 4$ using dichotomized (0, 0, 1, 1) 4-point Likert scale	•35% vs. 8% in control group (note control group age, 19-50 years) •Adjusted odds ratio of fatigue in HD vs. control: 5.9	Low
Mulrooney and colleagues. 2008 [187]	Describe prevalence and risk factors for fatigue and sleep disturbance	•n=631 (subgroup of 1897) •Diagnosed age: 15-21 years •>5 years from diagnosis	•26-center cohort study •FACIT-fatigue	Score below 10th percentile for sibling cohort	•8.6%	Medium
<b>Mixed during and after treatment</b>						
Collins and colleagues. 2000 [178]	Determine symptom prevalence, characteristics, and distress	•n=160 •70 had chemotherapy within last 2-4 weeks, 58 >4 months ago •Mean age: 14.0 years	•Cross-sectional •MSAS 10–18	Presence of 'lack of energy' in last week on MSAS	•Overall: 49.7% (1 of 30) •CNS tumor: 66.7% (1 of 30) •Lymphoma: 50% (1 of 30) •Leukemia: 43.8% (2 of 30) •Solid tumor: 53.7% (3 of 30)	Medium
Corey and colleagues. 2008 [208]	Describe relationship between distress and three sources of support	•n=127 (ARM 1) •Mean age: 16.4 years (ARM 1) •Mean since diagnosis: 3.75 years (ARM 1 and 2)	•Secondary analysis of data from 2 studies •Symptom Distress Scale	3-5 on 1-5 Likert scale	•ARM 1 (mixed population): 31.4% •1-year increase in age increased odds of fatigue by 1.23-1.25	Medium
Enskar and colleagues. 1997 [209]	Evaluate adolescents' experience of areas of life affected by the disease	•n=10 •Age 13-16 years at diagnosis n=8 •Age at interview: 15-20 years	•Cross-sectional observational •5-point NRS (non-validated questionnaire)	$\geq 2$ on 1-5 NRS	•100%	Medium
Nunes and colleagues. 2015 [200]	Investigate and compare fatigue and sleep patterns in adolescents and children	•n=18 •Age 13-17 years •Subgroup of 35 hospital patients being discharged home	•Cross-sectional observational •MFS	MFS score < 75	•54%	Medium

Study	Aim(s)	Participants (mixed tumors unless stated)	Study design and fatigue assessments	Definition of fatigue 'case'	Fatigue prevalence (rank compared to other symptoms)	Weight of Evidence D
Ream and colleagues. 2006 [197]	Investigate impact of fatigue on adolescents	•n=22 •Age: 13-20 years	•Longitudinal, mixed methods •Daily diary entry and completion of fatigue NRS	Mention of fatigue in diary entries	•Mentioned fatigue during treatment: 32; 30% in early remission (1-2 years after treatment), 10% in late remission (>5 years)	Medium
Yeh and colleagues. 2008 [170], 2009 [171]	Assess symptoms in older Taiwanese children	•n=144 •Mean age: 14.2 years •For 108 on treatment, mean since diagnosis: 21.2 months	•Cross-sectional observational •MSAS 10-18	Presence of 'lack of energy' in last week on MSAS	•52% (1 of 30) •On/off treatment: 52.8%, 50.0% •Leukemia: 57.3% •Lymphoma: 46.2% •Solid tumor: 46.5%	Medium
<b>Relationship to treatment unstated</b>						
Hughes and colleagues. 2015 [206]	Evaluate symptoms on referral to palliative care	•n=33 •Age: 15-25 on diagnosis	•Cross-sectional observational •Two palliative non-contemporaneous controls •ESAS	Score of $\geq 1$ in 0-10 NRS	•75% (2 of 9) •Palliative care controls matched by gender and cancer type (not age): 76% •Unselected palliative care controls: 72%	Medium

ALL, acute lymphatic leukemia; AML, acute myeloid leukemia; ARM 1, Adolescent Resilience Model study 1; ARM 2, Adolescent Resilience Model study 2; CFQ, Chalder Fatigue Questionnaire; CNS, central nervous system; D1, D2, etc., day 1, day 2, etc.; DXM, dexamethasone; EBT, extremity bone tumor; ESAS, Edmonton Symptom Assessment Scale; FACIT-fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; FS-A, Fatigue Scale-Adolescent; FS-P, Fatigue Scale-Parent; HD, Hodgkin disease; LSS-A, Life Situation Scale for Adolescents; MFS, Multidimensional Fatigue Scale; MSAS (7–12, 10–18), Memorial Symptom Assessment Scale (for 7–12 and 10-18 age range); NORMS, healthy controls; NRS, Numerical Rating Scale; QOL, quality of life; RT, radiotherapy; T1, T2, etc., time point 1, time point 2, etc.; TC, testicular cancer; TRSC-C, Therapy-Related Symptom Checklist-Children; VAS, Visual Analogue Scale; VRS, Verbal Rating Scale



### 2.5.3 Fatigue severity

The severity of fatigue was measured in 38 studies: 21 during treatment, seven after treatment, eight with a mixed cohort of patients both during and after treatment, and one that provided data on two separate patient cohorts during and after treatment, respectively. A further study did not state the treatment status of participants. Ten studies reported relative severity of fatigue in comparison to other symptoms; fatigue was most severe in five [171,191,192,210,211], second in two [121,206], third in one [213] and fourth most severe in two [176,209]. Fourteen different outcome measures were used across these 38 studies. The most commonly used outcome measures were the FS-A, MFS and MSAS, in ten, ten and four studies, respectively. Comparison and synthesis of severity scores was again not possible due to heterogeneity of study populations, methods of reporting the data (for example, absolute score or percentage with score above a defined value), or measures used.

Three studies incorporated a control group for comparison of fatigue severity with healthy individuals of a similar age (table 2.5). Controls ranged from contemporaneous recruits to unmatched reference data. All three studies showed significantly greater fatigue severity in the TYA cancer groups compared to the controls.

Eleven studies compared fatigue severity between younger children and adolescents treated for cancer, of which six measured fatigue with both the Fatigue Scale-Adolescent (FS-A) and the Fatigue Scale-Child (FS-C) [123,173,193,201,215,216]. The FS-A and FS-C [217] each use 14 age-appropriate questions and are validated for 13-18 and 7-12 year olds, respectively. Fatigue was reported as being more severe in adolescents than in younger children in all but one of the eleven studies [193].

Many of the studies that used the FS-A outcome also measured parent reports of fatigue [128,173,174,184,186,187,215,216], but patient and parent scores are not directly comparable using this measure. One study, using the MFS, was able to directly compare the fatigue scores of TYA patients with proxy scores from their caregivers, and found that caregivers tended to overestimate their fatigue severity [168].

Fatigue severity was assessed over time in 13 longitudinal studies. All except for one [190] involved participants currently receiving chemotherapy [123,125,128,133,172,173,196,201,210,212,216,218]. In general, fatigue scores were worse in the two weeks after receiving chemotherapy and then improved until the next cycle. One longitudinal study investigated fatigue severity in TYAs with Hodgkin's lymphoma from the end of treatment over a three year period; there was no significant change in fatigue scores over this time [190]. A small cross-sectional, observational study of three

groups of adolescents during treatment (n=8), 1–2 years after treatment (n=6), and five or more years after treatment (n=8) found that fatigue scores were highest during treatment, lowest during early remission, and higher again during late remission [197].

Although studies using the MFS outcome measures could use subscale scores to determine the differential severity of general, sleep/rest and cognitive fatigue, only five studies reported the subscores. Four found cognitive fatigue to be less severe than the other dimensions, although no studies tested the differences for statistical significance [168,172,186,200]. In the only one of these studies recruiting patients after cancer treatment, Keats and colleagues found cognitive subscores that were of comparable severity to the other two subscales [218].

#### **2.5.4 Impact of fatigue**

Twenty-two studies reported the impact of fatigue on patients [125,131,170,171,173,175-180,185,195,197,210,213,214,219-223]. Distress caused by fatigue was the most commonly described impact, reported in 11 studies. The MSAS, a scale that allows comparison of the level of distress caused by each symptom, was used in six of these studies [170,171,178,210,213,214]. When symptoms were ranked in order of distress, fatigue was in the top half with only one exception [178]. One study reported that distress was correlated with the frequency and severity of fatigue [171]. The remaining five studies used diverse measures of distress [176,180,195,221,222], and fatigue was one of the top four most distressing conditions in four of these studies [176,180,221,222].

The second-most frequently described impact of fatigue was that it was a barrier to physical activity or exercise, which was reported in six studies [125,179,197,219,220,223]. Fatigue was the first [219] and second most [223] significant barrier in one study each. Being unable to take part in exercise led to frustration and loss of confidence, with parents becoming 'over-protective' and preventing their adolescents from taking part in activities that demanded energy [179]. Four studies reported fatigue as a barrier to other social activities [125,179,185,197], including returning to school [185]. A negative impact on affective state, mood, or anxiety was described in three studies [125,131,173].

**Table 2.5 Controlled studies evaluating fatigue severity**

Study	Aim(s)	Participants (mixed tumors unless stated)	Study design and fatigue assessments	Fatigue severity	Weight of Evidence D score
Aksnes and colleagues. 2007 [194]	Examine fatigue, mental distress, and QOL in EBT survivors compared to matched controls	<ul style="list-style-type: none"> <li>•n=57 EBT survivors</li> <li>•Mean age at diagnosis within different cancer type subgroups: 16-25 years</li> <li>•Mean since diagnosis: 9-14 years</li> </ul>	<ul style="list-style-type: none"> <li>•Case-control (non-contemporaneous age- and gender-matched controls HD, TC, NORMS)</li> <li>•CFQ</li> </ul>	<ul style="list-style-type: none"> <li>•Mean total fatigue:</li> <li>•EBT survivors: 13.2</li> <li>•HD survivors: 13.4</li> <li>•TC survivors: 13.4</li> <li>•NORMS: 11.8</li> <li>•EBT survivors had significantly more fatigue than NORMS (<math>p=0.003</math>), but not more than other survivor groups</li> </ul>	Medium
Daniel and colleagues. 2013 [168]	Compare adolescent and parent reports of fatigue in patients with and without cancer	<ul style="list-style-type: none"> <li>•n=102 with cancer on treatment</li> <li>•Mean age: 15.75 years</li> <li>•Mean since diagnosis: 20.4 months</li> <li>•n=97 controls; mean age: 15.55 years</li> </ul>	<ul style="list-style-type: none"> <li>•Cross-sectional observational (contemporaneous controls)</li> <li>•MFS</li> </ul>	<ul style="list-style-type: none"> <li>•MFS score in cancer and control groups, respectively (lower score representing worse fatigue): 58.54 and 71.72 (<math>p&lt;0.001</math>)</li> <li>•Total fatigue, general fatigue, and sleep/rest fatigue worse, but not cognitive fatigue</li> </ul>	High
Smith and colleagues. 2013 [188]	Examine HRQOL of AYA patients and associated health-related characteristics	<ul style="list-style-type: none"> <li>•n=159</li> <li>•Age: 15-25 years</li> <li>•Subgroup of large AYA HOPE study with 523 cancer patients aged 15-39 at diagnosis</li> <li>•Since diagnosis at survey: 6-14 months</li> <li>•80% not on treatment</li> </ul>	<ul style="list-style-type: none"> <li>•Cross-sectional observational (compared to age-range matched population norms)</li> <li>•MFS</li> </ul>	<ul style="list-style-type: none"> <li>•Mean MFS scores:</li> <li>•Ages 18-25: 61.3, significantly worse than reference healthy population score of 71.0 (<math>p=0.001</math>)</li> <li>•Ages 15-17: 59.8, not significantly different from ages 18-25 (no reference data for this age range)</li> </ul>	Medium

AYA, adolescent and young adult; AYA HOPE, Adolescent & Young Adult Health Outcomes & Patient Experience study; CFQ, Chalder Fatigue Questionnaire; EBT, extremity bone tumor; HD, Hodgkin disease; HRQOL, health-related quality of life; MFS, Multidimensional Fatigue Scale; NORMS, healthy controls; QOL, quality of life; TC, testicular cancer

### **2.5.5 Experience of parents**

Although 11 studies collected parent proxy reports of fatigue severity [123,128,129,168,173,174,184,186,215,216,224], none investigated the experiences of parents of TYAs with CRF. Parent proxy reports of fatigue severity correlated more closely with those of their children for parents of cancer patients than for parents of healthy controls, which was attributed to the cancer patients' parents being 'physically closer' and 'more attuned to the needs' of their children [129,168,199]. However, cancer patients' parents appeared to be less adept than the patients themselves at perceiving changes in fatigue over time [123,128]. One study collected staff proxy reports of patient fatigue as well as parent proxy reports [129], and found that staff reports correlated less closely with patients' self-reported fatigue, than parents' reports.

### **2.5.6 Fatigue correlates**

Factors correlating with the presence or severity of fatigue were reported in 30 studies, including five of the six scoring highest on the Gough's Weight of Evidence Framework [168,174,184,186,188].

Thirteen studies highlighted an association between fatigue and physical symptoms, including poor sleep [172,173,196,199,200,215,216], being part of a symptom cluster [121,170,189,214], and nausea [167,199]. Almost all participants in the four studies that examined symptom clusters were receiving chemotherapy [121,170,189,214]. Although there was no consistency in the specific symptoms found to cluster with fatigue, the symptoms tended to be chemotherapy-related. While receiving chemotherapy [120,123,125,134,181,184] or dexamethasone [182] both correlated with increasing fatigue, the evidence for a correlation between fatigue and hospital admission [123,184,213] or anaemia [123,183] was conflicting. Even though patients associated fatigue with 'doing too many things' or 'being too active' [125,130], two studies revealed a correlation between improved performance status and lower fatigue scores [133,183].

Depression or low mood correlated with fatigue in five studies [129,168,174,199,225]. Negative affect [167], global distress [213], anxiety [170,214] and non-specific psychological conditions [181,213] were identified as correlates in a further five studies. Consistent with the link with physical and psychological symptoms, a high correlation with poor quality of life or satisfaction with life was reported in five studies [120,125,168,225,226].

Although some of these correlations might be intuitively considered likely to represent causal relationships, such as the relationship between fatigue and poor sleep quality, no studies specifically assessed causality. A longitudinal study that observed a predictable fluctuation in fatigue during chemotherapy regimens of varying frequency [125] and a study involving planned periods on and off

dexamethasone [182] both suggested causal relationships with fatigue. One further study asked participants to describe their own views as to the causes of symptoms, and 34/37 free text responses suggested that chemotherapy or other medication was considered the main cause of fatigue [189].

### **2.5.7 Interventions to manage fatigue**

Table 2.6 details the seven interventional trials for TYA cancer patients in which fatigue was used as an outcome measure [180,215,224,227-229]. Fatigue was not stated to be the primary outcome measure in any of the seven. Four studies were uncontrolled [218,224,227,228] and five were feasibility studies [215,218,224,227,229].

Four of the studies involved evaluation of a structured activity intervention, and the remaining three investigated a self-care coping intervention, massage therapy and yoga. All of the interventions were standardized with a degree of individualisation in accordance with each patient's exercise capacity. Two uncontrolled trials found a statistically significant benefit from their interventions [218,228], which both involved intensive structured exercise in a gymnasium at weekly intervals for more than two months. The remaining two physical activity intervention studies involved bringing portable gym equipment to patients' hospital rooms and did not find any significant effect [215,227]. No evidence was generated to suggest that the self-care coping, yoga or massage interventions were effective [180,224,229].

**Table 2.6 Studies evaluating fatigue interventions**

<b>Study</b>	<b>Aim(s)</b>	<b>Participants (mixed tumors unless stated)</b>	<b>Study design and intervention</b>	<b>Fatigue assessments</b>	<b>Results</b>	<b>Weight of Evidence D</b>
Atkinson and colleagues. 2012 [228]	Determine the impact of a structured exercise intervention	•n=55 •Age: 15-25 years	•Uncontrolled trial •2–3 sessions/week individual structured exercise in a hospital/private gymnasium with an exercise physiologist over 10 weeks	•Assessed pre- and post-intervention •Revised PFS, Ferrans and Powers QLI, measures of functional fitness	•Improvement in fatigue ( $p \leq 0.0001$ ), as well as QOL and functional assessments •PFS scores decreased by 32%	Medium
Diorio and colleagues. 2015 [224]	Determine the feasibility of yoga for inpatients receiving chemotherapy	•n=11 •Median age: 14.0 years	•Uncontrolled trial •3 yoga sessions/week for three weeks •Individualised sessions including relaxation, breathing and poses of strengthening, flexibility and balance	•Assessed pre- and post-intervention, days 0 and 21 •Outcomes included parent proxy reports of fatigue using MFS	•No change in proxy reports of fatigue	Low
Hinds and colleagues. 2000 [180]	Evaluate effects of an educational intervention designed to facilitate self-care coping	•n=78 •Mean age: 16.0 years	•Two-centre randomized controlled trial •40-minute intervention between T1 (1-12 days after diagnosis) and T2 (5-7 weeks after): information on self-care coping, video with strategies, and rehearsal of strategies •Control had equal time to discuss any topic	•Assessed at T1, T2, 3 months, and 6 months after diagnosis •Six outcome measures, including SDS (includes 5-point fatigue severity VRS)	•No difference in SDS score between groups at any time point •Fatigue 1 of 4 most distressing symptoms at every time point	Low
Hinds and colleagues. 2007 [215]	Evaluate the feasibility of using an enhanced physical activity intervention	•n=11 •Subgroup age: 13-18 years	•Two-centre pilot randomized controlled trial •Pedaling a stationary bicycle exerciser for 30 minutes twice daily for 2-4 days of hospitalization with equipment brought to hospital room •Control spent equal time with researcher	•Assessed daily on days 1, 2, and 3 •Patient, parent, and staff fatigue reports (FS-C, -A, -P, -S), wrist actigraphy, parent sleep diary, hemoglobin	•No difference between groups	Medium

Study	Aim(s)	Participants (mixed tumors unless stated)	Study design and intervention	Fatigue assessments	Results	Weight of Evidence D
Jacobs and colleagues. 2016 [229]	Evaluate the feasibility of conducting a massage intervention	•n=34 •Age: 12-21 years	•Single-centre pilot randomized controlled trial •20-30min massage session on 2-3 consecutive evenings during hospital admission •Waitlist control	•Fatigue assessed daily •Patient, parent, fatigue reports (FS-A, -P), actigraphy, measures of anxiety and mood	•No difference between groups	Medium
Keats and colleagues. 2008 [218]	Assess feasibility of a physical activity intervention	•n=10 •Age: 14-18 years •Mean since diagnosis: 62.5 months	•Uncontrolled feasibility study •Weekly 90 minutes of group education and training for 8 weeks in gymnasium, then variety of non-competitive activities over 16 weeks	•Assessed at baseline, week 8, week 16, 3 months, and 1 year •PedsQL, MFS, Leisure Score Index, FitnessGram (a physical fitness test)	•Improvement in fatigue between baseline and 3 months ( $p=0.01$ ), but post-intervention benefits not sustained at 3 months and 1 year	Medium
Rosenhagen and colleagues. 2011 [227]	Investigate feasibility and acceptability of sports therapy	•n=13 •Mean age: 15.3 years	•Uncontrolled feasibility study (control group gave acceptability data only) •Individualized exercise using ergometer in hospital room during isolation phase of SCT	•Assessed on days 1 and 14 and on discharge after SCT •QOL self-assessment, MFS	•Non-significant trend for fatigue improvement pre- and post-intervention	Low

FS-A, Fatigue Scale-Adolescent; FS-C, Fatigue Scale-Child; FS-P, Fatigue Scale-Parent; FS-S, Fatigue Scale-Staff; MFS, Multidimensional Fatigue Scale; PedsQL, Paediatric Quality of Life Inventory; PFS, Piper Fatigue Scale; QLI, quality of life index; QOL, quality of life; SDS, Symptom Distress Scale; SCT, stem cell transplant; T1, T2, etc., time point 1, time point 2, etc.; VRS, Verbal Rating Scale





## **2.6 Discussion**

### **2.6.1 Overview of evidence**

This systematic literature review and narrative synthesis provides evidence that supports the rationale for this programme of research. It confirms that fatigue is one of the most prevalent and severe symptoms experienced by TYA cancer patients, occurring in the majority of patients and particularly prevalent during cancer treatment. This finding is consistent with systematic review evidence evaluating symptom prevalence in adults with cancer, revealing fatigue to be the most prevalent symptom in older patients [13].

Fatigue was found to be consistently more severe in TYA cancer patients than in younger children with cancer. This concurs with evidence from healthy teenagers, who have a propensity to develop fatigue and daytime sleepiness for developmental and behavioural reasons (section 1.1.4, page 11). Although none of the studies eligible for this review compared TYA CRF levels with that in older adults with cancer, there have been a number of recent studies, incorporating a wider definition of the 'young adult' age range (15-39), that are generating such evidence. Singer and colleagues found worse fatigue in young cancer patients below 40 years, compared to those over 60 years [230]. Two further studies have found equivalent outcomes, when comparing younger and older cancer patients with gynaecological cancers [231] and with breast cancer [232]. Overall, therefore, it does appear that CRF in TYAs is more severe than in both younger and older age groups, at this time of particular vulnerability to fatigue.

This review provides some evidence for long-term persistence of fatigue well beyond the end of cancer treatment, both from cross-sectional studies involving cancer survivors and from a single longitudinal study. A number of other studies, evaluating cancer survivors falling just outside the age criteria for this review, provide further confirmation of persistent fatigue [233-235]. Given high TYA cancer survival rates (section 1.1.3, page 9), large numbers of young people are contending with long-term morbidity while attempting to rebuild their lives after a cancer diagnosis.

Not only is fatigue prevalent, severe, and persistent in TYAs, this review provides strong evidence that the symptom causes significant distress, with a negative impact on quality of life. Fatigue impacts on the ability to exercise, on socialization and on school attendance, all consequences that could contribute to the reported distress. However, none of the studies focused on trying to understand the causes of the distress.

This systematic review has highlighted important 'gaps' in the existing literature. Although many

studies have revealed associations between fatigue and its correlates, there has been little effort to try to understand the aetiology of fatigue in TYAs by trying to assess causality. There has, for example, been little longitudinal research investigating the temporal pattern of fatigue and its correlates over time beyond the end of cancer treatment. There is a complete dearth of literature on the perspectives of parents or others living closely with these young patients. Given the profound impact of fatigue on TYA cancer patients, it would be reasonable to hypothesise that parents may well also be suffering indirect adverse consequences.

It is concerning that, despite the robust evidence base confirming the magnitude of the problem, there have been no published interventional studies with the primary aim of treating TYA CRF. The few interventional studies to date are mostly uncontrolled or feasibility studies investigating physical activity. Exercise is recognized as an effective treatment in adults with CRF. Although two of the four physical activity interventional studies did report significant findings, both were uncontrolled. Given the well-established placebo effect that occurs with subjective symptoms such as fatigue [236], the existing evidence for intervention effectiveness in the TYA age group is, as yet, extremely limited.

An important finding of this review is that fatigue itself is a key barrier to activity. Qualitative studies, both included in this review and closely related, provide anecdotal suggestions from participants that 'being too active' or 'doing too many things' may worsen fatigue [125,130], that parents encourage rest [179], and that in a mixed population of teenagers and younger children, healthcare professionals' most commonly recommended treatment for fatigue was rest and relaxation [237]. Healthy adolescence tends to involve a decline in activity due to conflicting priorities, fear of injury and embarrassment [238]. Cancer-related fatigue, in combination with these normal teenage inhibitions, appears to present a formidable barrier to activity, paradoxically the very intervention that evidence from older adults suggests has the greatest potential to ameliorate fatigue.

## **2.6.2 Contextualizing with related systematic reviews**

In the one systematic review that had been published at the time of initiation of this review, Erickson and colleagues found 15 relevant articles in 2004, using particularly broad eligibility criteria [160]. Although many more studies were included in the current review, and there were only two articles incorporated in both reviews [178,209], it is noteworthy that the key findings were not dissimilar: fatigue is prevalent and distressing in this young age group and research is needed to test intervention. The current review builds on the earlier one, by providing more detail, particularly in relation to the correlates and impact of fatigue.

Since 2013, there have been four related systematic reviews, although none focusing on the TYA age range of 13-24 years. In 2016, Tomlinson and colleagues published a synthesis of qualitative research

to evaluate the 'lived experience' of fatigue in children and adolescents with cancer aged 6-19 [239]. Nine of the 19 studies incorporated in that review were included in the current one, and the review unsurprisingly found similar evidence of the impact of fatigue, again concluding that interventional research is needed.

Using the broader definition of adolescent and young adult (AYA) in oncology in the USA (aged 15-39), Nowe and colleagues recently reviewed quantitative studies [122]. Only one study was eligible for both this and the current review [188]. Their review confirmed that fatigue was more severe in AYAs than older adults. Three small and uncontrolled interventional studies in adults under 40 years were described, two testing a rehabilitation intervention and one an internet-based physical activity intervention, with two of the three leading to a reduction in fatigue.

Two studies have systematically reviewed non-pharmacological interventions in children up to 18 years. Chang and colleagues (2013) analyzed six pilot and feasibility studies. Three led to an improvement in fatigue, but with a suggestion that only 'general', and not 'sleep/rest' or 'cognitive', fatigue was helped; two of the three were physical activity interventions [165]. Lopes-Junior and colleagues (2016) found nine small pilot and feasibility studies, of which only four led to benefit. Three of the four involved a physical activity intervention, again leading to the suggestion that physical activity may have a role in paediatric fatigue management [240]. In both of these studies, limited conclusions could be drawn because of the very low quality and heterogeneity of the included studies. Two studies included in the current review were also included in the Chang and Lopes-Junior reviews [215,218]; the other studies in these reviews involved younger participants.

Overall, therefore, the current review reinforces and builds on the conclusions of the main previous review from 2004. A number of recent systematic reviews have evaluated CRF in adolescents, but their focus, either on children up to 18 or on young adults up to 40 years, has limited the comparability of the findings. Nevertheless, the findings were broadly similar, confirming the prevalence and negative impact of the symptom, and emphasising the need for future high quality interventional studies.

### **2.6.3 Strengths and limitations**

The main strength of this review is its breadth. Studies were eligible if they investigated any aspect of CRF in TYA-aged patients, and even those presenting data from a subgroup of patients aged 13–24 were included. This has led to this review being particularly comprehensive, evaluating a total of 69 articles, considerably larger than all other related reviews of this subject.

The included studies, however, were heterogeneous and of relatively low quality, limiting the

strength of the findings. Furthermore, the symptom was often not the primary focus of the research. Although experts in the field were contacted, literature not published in the form of journal articles or conference abstracts ('grey' literature) may have been missed. Exclusion of non-English articles may also have led to the omission of relevant articles.

## **2.6.4 Implications**

### **2.6.4.1 Clinical practice and policy**

Confirmation of the prevalence of TYA CRF, and the significant distress it causes, should raise awareness of this symptom amongst clinicians. In older adult CRF, a degree of therapeutic scepticism has developed due the lack of clearly effective pharmacological interventions [54,241]. This may also be occurring in younger cancer patients. Simply enquiring about the presence of fatigue in each clinical encounter may in itself be helpful, as this can openly acknowledge the problem and provide the possibility for peer and professional support. Clinical trials suggest that fatigue is amenable to the placebo effect; a recent proof-of-concept trial has confirmed that even non-deceptive open-label placebo can lead to a 30% improvement in fatigue [242]. It may that the placebo effect, at least in part, is gained simply from the focus and support inherent in research involvement, and it is therefore conceivable that simple acknowledgement of the symptom in clinical practice could also be of therapeutic value [54].

Although the evidence base for exercise interventions is very limited, it is likely that encouragement of physical activity would be helpful. In adults, it is already well-established that exercise improves CRF [243,244]. The wider benefits of keeping active during, and after, cancer treatment include increased well-being, functioning, and quality of life, as well as reduced cancer recurrence and mortality [245-248].

### **2.6.4.2 Future research**

This review has clearly revealed a number of neglected topics that require future research. Future prevalence studies need to be controlled, using concurrent, rather than non-contemporaneous, controls. Long-term longitudinal cohort studies are needed, to evaluate changes in fatigue from the time of cancer treatment through to long-term survivorship. This, along with experimental interventional studies and insights from qualitative research, would help elucidate the directionality of the complex relationships between fatigue and its correlates. There is already sufficient research establishing that many factors correlate with fatigue; future work needs to determine causality, to understand the factors contributing to the fatigue and to support effective symptom management.

Fatigue causes significant distress in TYAs. However, there is has been little work to date to establish the mechanisms for this distress. The review has generated suggestions, for example, the impact on

being able to exercise and on socialization. Further research, particularly with a qualitative design, would increase insight.

The complete lack of research evaluating the perspectives of parents, and others close to these young patients, also needs addressing. Over the last decade, there has been recognition of the importance of addressing the needs of family carers. Support from carers can impact positively on patient outcomes, but carers equally experience considerable physical, psychological, social and economic burden from their role [249]. Evaluating and addressing the unmet needs of carers of those with cancer, 'caring for the carers', has become a healthcare priority [250,251]. Recent work has begun to consider the needs of parent carers of TYA cancer patients [99]. However, the impact of specific problems, such as fatigue, has not yet been evaluated.

This review evidences the need to develop a specific TYA fatigue intervention. Definitive interventional research is required, with a rigorous controlled trial design, suitable power to determine meaningful outcomes, and a primary focus on ameliorating fatigue. Preliminary research to support intervention development will be described in the following chapters.

## 2.7 Key points

This review has confirmed that TYA cancer-related fatigue is prevalent, persistent and distressing. It has highlighted many areas requiring further research, the overall research priority being to develop an acceptable, effective treatment for fatigue.

The key findings are summarised in tabular form below. This approach will be taken with each subsequent study within this thesis, in order to demonstrate the sequential building and synthesis of knowledge.

**Table 2.7 Systematic review key points**

<b>TYA CRF topic</b>	<b>Study 1: Systematic review</b>
<b>Prevalence</b>	The prevalence range was 9-67% after cancer treatment; fatigue was the first and second most prevalent symptom in 11 and 6 of 20 studies respectively.
<b>Temporal pattern</b>	Only one longitudinal study has evaluated fatigue beyond the end of cancer treatment.
<b>Symptom correlates</b>	Physical and psychological symptoms most commonly associated with fatigue were poor sleep and low mood respectively.
<b>Impact</b>	The most commonly reported impact was 'distress', followed by fatigue being a barrier to physical and to social activities.
<b>Parents' perspectives</b>	No past research has evaluated the perspectives of parents or other carers.
<b>Management</b>	No studies have evaluated an intervention with a fatigue related primary outcome; current clinical practice, in terms of symptom management, is also unknown.

## **3 Fatigue in Focus multicentre survey**

### **3.1 Title**

The Fatigue in Focus survey: an exploratory multicentre electronic survey of the prevalence, impact and management of fatigue in teenage and young adult cancer patients

### **3.2 Rationale**

#### **3.2.1 Justification for study**

The preceding systematic literature review has established the size of the problem of TYA cancer-related fatigue and the need to develop an effective fatigue intervention. Before developing such an intervention, preliminary work is needed to investigate current TYA fatigue experience and clinical management in the UK.

Building on the review's overview of the *past* literature, a description of the *current* position is needed, in order then to develop an appropriate *future* fatigue intervention. The review established that the main impact of fatigue is distress, with qualitative studies describing the impact on exercise and socialising (section 2.5.4, page 32). However, there has been no previous quantitative evaluation of the impact of fatigue and therefore no prioritisation of the needs of fatigued TYAs. Current clinical management of CRF in the TYA age group has not been previously described in the literature.

Stone and colleagues undertook a UK survey almost two decades ago to investigate the experience, impact and management of CRF in adult patients (median age 59 years) [23]. Fatigue was the most prevalent symptom and the one most affecting adults' daily lives, particularly in relation to the ability to work and enjoy life; only 14% had received fatigue management support. This seminal study raised the profile of cancer-related fatigue. Within a few years, many studies were subsequently published evaluating CRF treatments in adults (section 1.1.1.4, page 3).

A national clinical snapshot of fatigue experience and management is needed to address the unique needs of younger cancer patients. This survey is the first such study to be undertaken.

#### **3.2.2 Justification for electronic survey method**

Healthcare surveys generally collect a relatively small amount of data from a large sample of individuals across the population of interest. Well-suited for descriptive studies, with careful sampling a survey can provide a cross-sectional account that allows a degree of generalisation to the wider population [252].

Only three studies have previously used survey methods in the field of TYA CRF, all of which were included in the literature review. Mulrooney and colleagues examined the prevalence and correlates of fatigue and sleep disturbance in almost two thousand adult survivors of childhood cancer, as part of the national Childhood Cancer Survivor Study in the USA [187]. Only one third of the participants were aged 15-21 at the time of diagnosis, although fatigue and sleep disturbance data were analysed separately for this subset. Two subsequent recent studies have used survey methods for follow-up in cancer treatment trials; fatigue evaluation was not a primary outcome [190,191]. This survey is therefore the first to focus primarily on TYA CRF.

Recent years have seen a rise in the use of electronic survey methods in healthcare research. To date the majority of patient electronic surveys have been service evaluations or quality improvement initiatives, rather than research. Research electronic surveys have largely involved healthcare professionals, rather than patients.

Electronic surveys are recognised to have a number of advantages over traditional paper-based surveys [253]. Principal amongst these is the lower cost; a randomised trial of the effect of survey response mode on completion of a survey by doctors found that on-line methods reduced costs by about one third [254]. This increases the feasibility for large-scale surveys, so increasing outcome validity [255]. Further advantages include the increased ease of data analysis and improved data integrity, with lower rates of illegible data and reduced transcription errors [253]. Simple programming, such as skip logic where the answer to one question determines subsequent questions, can speed up questionnaire completion and reduce participant burden.

A potential disadvantage of electronic survey methods is that they generate unrepresentative participant samples with better access to, or familiarity, with electronic devices [255]. However, internet use has, in recent years, become virtually universal across all age groups; electronic survey methods have been found to be acceptable and feasible even in the elderly [256,257].

A further concern is that electronic surveys tend to generate lower response rates than paper-based methods [253,254]. In the Adolescent and Young Adult Health Outcomes and Patient Experience (AYA HOPE) study, participants (aged 15-39) were given a choice between paper, electronic and telephone survey mode [258]. Three quarters (76%) of participants chose the paper survey version, with only 22% and 2% choosing the online and telephone mode respectively. Two systematic literature reviews evaluating factors impacting on survey response rates, albeit with doctor rather than patient participants, have shown improved response rates with paper, over electronic, methods [259,260]. Factors that improve electronic survey response rates include non-monetary incentives,



personalised and short e-questionnaires, and avoidance of the word 'survey' in the email subject header [261].

Despite these potential concerns, it was decided that the survey would be undertaken electronically, following extensive consultation with current and former TYA cancer patients; they provided clear advice that an electronic survey would be preferable to postal questionnaire (section 1.2.2, page 14). Teenagers and young adults, so called 'digital natives', are very familiar with an electronic environment; mobile technology use is virtually ubiquitous amongst young people, and at least 98% access the internet 'on the go' [262,263]. One of the methodological objectives of this exploratory study was examination of the feasibility of using electronic surveys in this patient group.

### **3.3 Aim and objectives**

#### **3.3.1 Aim**

The aim was to undertake a national survey of current TYA cancer patients concerning their experience of fatigue and its clinical management in practice.

#### **3.3.2 Objectives**

1. To establish the prevalence and severity of fatigue in TYA cancer patients.
2. To evaluate the impact of fatigue in this group.
3. To investigate the current management of fatigue and TYA cancer patients' perception of the effectiveness of such management.
4. To examine the feasibility of using electronic survey methods with TYA cancer patients.

## **3.4 Methods**

### **3.4.1 Study population**

Cancer patients were recruited from three TYA cancer Principal Treatment Centres (PTCs). In the UK, all TYAs with cancer are known to one of the thirteen NHS Trusts in England with PTC status. The three participating PTCs (Cambridge, Manchester and Southampton) cover close to a quarter of the national TYA population.

#### **3.4.1.1 Inclusion criteria**

- Care provided by a regional PTC in the UK
- Email address recorded within the PTC patient database with consent given to use it
- Diagnosed or treated with cancer aged 13-24
- Aged 16-27 at the time of completing the survey.

Eligibility was not influenced by cancer treatment status; both those receiving, and having completed, cancer treatment were eligible for recruitment. All participants were aged 16 or over at the time of survey, as it would not have been feasible to gain parental consent for younger patients within this study design.

#### **3.4.1.2 Exclusion criterion**

- Known to be near the end of life AND the site Principal Investigator believed it would be unacceptable to send the survey.

Patients meeting this exclusion criterion were identified in advance to ensure they were not emailed about the survey; the number excluded were recorded. People receiving the survey who had insufficient English language comprehension, or who did not wish to participate, were self-excluding by failing to complete the survey.

### **3.4.2 Questionnaire content**

The questionnaire collected demographic data, data from two validated outcome measures, and responses to a number of additional questions.

#### **3.4.2.1 Demographic data**

Age, gender, cancer type, month of diagnosis and treatment status were collected from each participant and from the clinical records of all non-responders.

#### **3.4.2.2 Multidimensional Fatigue Scale**

The PedsQL™ Multidimensional Fatigue Scale (MFS) was chosen as the main measure of fatigue severity, as it is the only fatigue scale validated in both teenagers and in young adults [161]. The

PedsQL™ instrument is a commonly used quality of life measure used within NCI Children's Oncology Group studies in the USA. The MFS, one of the subscales of the PedsQL™, is widely used internationally. The scale consists of three subscales of 6 questions: general (physical) fatigue, sleep/rest fatigue and cognitive fatigue. The responses to the 18 questions are marked on a 5-item Likert-type verbal rating scale and scored 0-4, with 4 being the most severe. Items are then reverse-scored and linearly transformed to a 0-100 scale, and the overall score computed as the sum of the item scores divided by the number of items answered. Lower scores represent worse fatigue.

#### ***3.4.2.3 Quality of life visual analogue scale***

The survey questionnaire included a single-item measure of quality of life, a quality of life visual analogue scale (QOL-VAS). There is evidence from cancer patients that information from a single-item measure of quality of life is comparable to that from multiple-item global measures, and that QOL-VAS more readily captures clinically significant changes in quality of life than multiple-item measures [264,265]. The scale was scored in integer increments between 0 and 10.

#### ***3.4.2.4 Additional questions***

The remaining questions were simple, non-validated, questions relevant to the study objectives and generated by the research team. The severity of 11 symptoms (anorexia, anxiety, constipation, diarrhoea, fatigue, low mood, mucositis, nausea and vomiting, pain, weight gain, weight loss), the impact of fatigue on a range of aspects of life and the impact on patients' carers were quantified using a 5-item Likert-type verbal rating scale, 'not at all', 'a little bit', 'somewhat', 'quite a bit' and 'very much'. The successfulness of each treatment received for fatigue was rated using a 4-item scale: 'entirely successful', 'somewhat successful', 'helped only a little' and 'no effect'. Selection of single or multiple best responses was used for a number of further questions, including defining the two symptoms most affecting daily life, participant perception of the cause of fatigue, views on whether fatigue can be treated, and fatigue treatments received. The full questionnaire is at appendix 7.3.6 (page 303).

The wording of three questions, relating to perceived cause of fatigue, views on whether fatigue can be treated, and dialogue with healthcare team, was influenced by the questions used in an earlier survey of adult cancer patients undertaken by Stone and colleagues, in order to allow comparison between TYA and adult findings [23]. The design and detail of the questionnaire were significantly influenced by patient feedback (section 1.2.2, page 14).

The survey incorporated skip logic; questions were included or excluded based on the replies given to earlier questions. Only the first two questions were made compulsory: the severity of the 11 symptoms and selecting the two symptoms most affecting daily life. Without completing these two

questions, the survey could not be submitted. Any participants answering 'not at all', when asked how much fatigue had affected them over the past month, were only able to answer questions about the severity of the 11 symptoms, the two symptoms most affecting daily life, quality of life score and demographic information.

### **3.4.3 Survey process**

The survey was built electronically using QuestionPro online survey software. It was cloned using individual NHS Trust logos for use at each site. At each site, the study involved a three-step process as outlined below. Sites started the process at a time that suited them but, once initiated, a strict procedure on a fixed timeline was followed.

#### ***3.4.3.1 Step 1: priming contact***

Pre-notification to raise awareness of a survey is known to increase response rates [261]. Priming was undertaken in three ways at each site: a standardised email to potential participants, a survey poster and posting of the same information on the TYA cancer service Facebook page (appendix 7.3.1, page 292). Priming was undertaken by potential participants' usual clinical healthcare team members, not the research team. Staff at each site were at liberty to adapt the wording slightly, as long as the content was fundamentally unchanged.

#### ***3.4.3.2 Step 2: survey email***

Seven to fourteen days after the priming contact, an email was sent to all potential participants by a member of their usual clinical healthcare team, or an administrator within the team. Good Clinical Practice in healthcare research stipulates that the initial approach to recruit research participants must be from staff already involved in their clinical care, not from researchers [266]. Using a mail merge process, each participant received a single personalised covering email explaining the purpose of the survey, an invitation to take part and instructions, the electronic link to the survey, a participant's unique token number and a link to the Participant Information Sheet (PIS). The covering email and PIS are in appendices 7.3.2 (page 294) and 7.3.3 (page 295). After clicking on the survey link, participants were required to enter their token number and tick a box confirming informed consent, before completing the survey electronically.

#### ***3.4.3.3 Step 3: reminder to non-responders***

Non-responders were established by noting which tokens had not been used seven days after the initial survey email had been sent. Unused token numbers were sent to the administrator at each site, who sent a single reminder email to each non-responder.

Detailed instructions to support this process were created for each site (appendix 7.3.4, page 297). Submitted survey data was collated on the QuestionPro platform. Data entry was locked three weeks

after the final site had sent out the first survey email. The token numbers of all participants were entered into a prize draw. Four prize-winners were randomly selected and received an iPad or one of three sets of £50 Amazon vouchers.

### **3.4.4 Data management**

#### ***3.4.4.1 Data handling and confidentiality***

All study data were in electronic format, and a number of steps were taken to ensure preservation of patient confidentiality. A firewall was set up between the site and the central study team. The site teams knew the names of the survey recipients and their corresponding token numbers but, importantly, had no access to any participant responses. Conversely, the central research team had access to patient responses linked to token numbers, but had no way of identifying participants from their token numbers.

The mail merge process involves sending multiple individual emails, rather than copying a single email, eliminating the risk of participants being able to view others' email addresses. Electronic data were encrypted in transmission via HTTPS (Hypertext Transfer Protocol Secure), and captured on the QuestionPro questionnaire survey servers in a pseudo anonymised form. The QuestionPro company has an extensive privacy policy and a data security policy, and complies with the USA-EU 'safe-harbour framework'.

The participant responses were downloaded and fully anonymised prior to data analysis. Data were stored on University of Cambridge servers on a secured network requiring password-authentication to access the data server. The University data servers are physically protected in a data centre within card-access only buildings. In addition to survey responses, demographic data (age, gender, diagnosis, time since last cancer treatment) from non-responders were collated at each site, anonymised and emailed by secure NHS mail to the central research team.

#### ***3.4.4.2 Statistical methods***

IBM SPSS software (version 22) was used for all analyses. Non-responder analysis compared demographic data of responders and non-responders. Between group differences were evaluated by an independent samples t-test for normally distributed continuous variables, or the non-parametric equivalent, the Mann-Whitney U test, for variables not normally distributed. Fisher's Exact Test was used with categorical variables. Differences were considered statistically significant where  $p < 0.05$ . Normality was assessed by visually inspecting the data in the format of a histogram, and by calculation of z-scores; scores for either skewness or kurtosis of greater than 3.49 were used to define a significant departure from normality [267].

The response data were analysed using descriptive statistics. The prevalence of each symptom was calculated by excluding only those patients responding with 'not at all'. This is consistent with prevalence calculations within the Memorial Symptom Assessment Scale, a widely used scale validated in cancer patients [202].

Associates of fatigue were examined using correlations for continuous variables and analysis of variance (ANOVA) for categorical variables. When calculating correlation coefficients, all data were plotted to check for linearity (Pearson's and Spearman's coefficients being calculated for linear and non-linear relationships respectively) and to check absence of non-monotonic relationships.

A symptom cluster analysis was performed using Ward's method [268]. A hierarchical agglomerative method was chosen because of the relatively small sample size, and Ward's method was selected as it is considered robust, produces clusters of approximately equal size and is relatively sensitive to outliers. This method involves examining all possible pairs of clusters and calculating the sum of the squared Euclidian distances within each cluster. This is then summed over all clusters, and the combination that gives the lowest sum of squares is chosen.

Linear regression analyses were undertaken using either fatigue severity or quality of life as the dependent variable, and using linear regression methods to evaluate the degree to which these variables could be predicted by symptom severity scores. The rule of thumb of ten cases per predictor was used, to determine the number of variables entered into a regression model [269]. Bootstrap confidence intervals and significance values were used to give an accurate estimate of the true population value of each B-value, without relying on assumptions of normally distributed residuals or homoscedasticity (homogeneity of variance). Regression diagnostics plots were generated to look for evidence of bias in each model, and are available in appendix 7.3.8 (page 315).

A 'successfulness score' for fatigue treatment was generated by attributing 0, 1, 2 and 3, to the ratings 'no effect', 'helped only a little', 'somewhat successful' and 'entirely successful' for each treatment received, and calculating a mean score. The former two ratings defined an unsuccessful treatment and the latter two a successful one.

### **3.4.5 Patient and public involvement**

The survey benefited from PPI advice in a number of ways. One member of the central study team is a former TYA cancer patient and provided feedback on the survey design, questionnaire content, patient information sheet and the survey covering email. The survey was also discussed in outline in a face-to-face focus group convened in April 2014; six TYA cancer patients provided advice on the

content of the survey and terminology. This group, along with three further patients, were emailed the near-final version of the electronic survey to gain further feedback.

The decision to make the survey electronic only, without a concurrent paper version, was an important outcome of the PPI process. During the focus group meeting, there was a consensus that the survey needed to be relatively short, consistent with existing evidence that short questionnaires improve response rates [261]. Advice was given that potential participants needed to know in advance that the survey would be short, and there needed to be an option to save progress part way through completion. Many other valuable ideas were proffered, including the importance of using the word 'fatigue', rather than 'tired' (the latter being considered such an understatement that it would risk people 'feeling angry'), and the value of clarifying how often the fatigue occurred, its relationship to cancer treatment and its impact on daily functioning ('what it stops you from doing').

### **3.4.6 Ethical considerations**

In line with PPI feedback, the survey was kept as short as possible to avoid burdening vulnerable and potentially fatigued participants. During initial testing, it took 5-10 minutes to complete. Inconvenience was further limited by ensuring that it could easily be completed on a mobile electronic device.

All participants were aged 16 or over, and could therefore give informed consent to taking part in the survey. The chair of the regional research ethics committee advised that completion and submission of the survey would be sufficient implicit evidence for consent. However, to achieve absolute clarity, the first page of the survey included an electronic tick box confirming consent.

The ethics of using a prize draw as an incentive was considered extremely carefully. Non-monetary incentives are known to be effective in increasing survey participation [261]. The fact that any individual's chance of winning was small, limited the risk of coercion. Both the covering email and patient information sheet included explicit statements that not taking part in the survey would have no impact on care.

### **3.4.7 Research governance**

#### ***3.4.7.1 NHS and ethical approvals***

This work was jointly sponsored by the Cambridge University Hospitals NHS Trust and the University of Cambridge, the former providing NHS approval and the latter providing insurance and indemnity. Research ethics committee approval was provided through a Proportionate Review process by the NRES Committee East of England – Cambridgeshire and Hertfordshire (REC reference: 15/EE/0037;

appendix 7.3.5, page 301). The other research sites, Manchester and Southampton, were designated as Participant Identification Centres (PICs) as there was no face-to-face recruitment process.

#### ***3.4.7.2 Study team and roles***

Anna Spathis was the Chief Investigator overall, and the Principal Investigator for the Cambridge NHS site. She was involved in every step of the study conduct including: responsibility for study design, writing protocol and all study related documents, gaining research approvals, recruitment of sites, PPI, all communication with site teams including visiting sites, the survey process, IT support and all data analysis.

Stephen Barclay and Sara Booth, MD supervisors, provided regular guidance and advice throughout the study. In addition, a number of colleagues made specific contributions as detailed in table 3.1.



**Table 3.1 Roles of other team members in survey**

Laura Abbas	Former TYA cancer patient, former TCT Youth Support Co-ordinator, Cambridge University Hospitals	Provided PPI; and co-ordinated PPI from other current/former patients
Matt Barclay	Statistician, University of Cambridge	Support with statistical methods and use of SPSS software
James Brimicombe	Data Manager, Department of Public Health and Primary Care, University of Cambridge	Created the survey within QuestionPro; generated tokens, support with data management
Rachel Campsey	Clinical research nurse, Christie Hospital, Manchester	Principal Investigator, Manchester; identified eligible patients
Faith Gibson	Professor of Children and Young People's Cancer Care, Great Ormond Street Hospital	Support with study design and questionnaire content
Helen Hatcher	Consultant Medical Oncologist, TYA service lead, Cambridge University Hospitals	Support with survey design; identified eligible patients
Louise Hooker	Lead nurse TYA cancer service, University Hospital Southampton	Principal Investigator, Southampton; identified eligible patients
Martin McCabe	Clinical senior lecturer in paediatric oncology, University of Manchester	Supported involvement of Manchester; facilitated approvals
Wendy Moss	TYA service administrator, Cambridge University Hospitals	Created database of eligible patients; undertook study processes
Stephanie Manning	Clinical trials administrator, Christie Hospital, Manchester	Created database of eligible patients; undertook study processes
Jane Robson	Lead nurse TYA cancer service, Cambridge University Hospitals	Identified eligible patients in Cambridge
Paddy Stone	Professor of Palliative Medicine, University College London	Support with study design and questionnaire content
Pia Thiemann	Research Associate, University of Cambridge	Support with statistical methods and use of SPSS software
Melanie Williams	Research Administrator, University Hospital Southampton	Created database of eligible patients; undertook study processes

## **3.5 Results**

### **3.5.1 Process data**

The Principal Investigator (PI) and administrator at each site created a site-specific database of potentially eligible participants. Different methods were used in each site, reflecting the diverse administrative arrangements for each service. Priming of potential participants also differed slightly.

In Cambridge, an electronic database of all patients known to the service had already been in use since 2009. Data from a separate small database held by the service Youth Support Co-ordinator was merged with the main database, increasing the number of patients for whom an email address was known. Potential participants were selected by applying the eligibility criteria. Priming used all three available methods: poster, information on Facebook and email to potential participants.

In Southampton, all patient data had been held on paper index cards since 2008, the inception of the TYA service support team. The PI and administrator transferred data on all potentially eligible participants from these cards to a study database. Priming was undertaken by poster and email only, as the Facebook page of the TYA service was temporarily unavailable.

In Manchester, although many patients had given their email address to their TYA service, the local healthcare team felt that, for all but five patients, consent to use these addresses applied only to use for clinical, rather than research, purposes. Therefore, only five patients fulfilled the study eligibility criteria and could be sent a priming email. This reduced the number of potential participants considerably, and meant that the site relied on patients proactively contacting the clinical team to express interest in taking part, having seen study information on Facebook or on a poster. Because participants emailed the local PI in this way, it was possible to ascertain the mode of recruitment; of the 17 people who expressed an interest, 12 had responded to the Facebook information, four to email contact, and one to the poster.

The table below summarises the number of patients involved at each step of the study process across the three sites. Only eight potential participants across the three sites were considered ineligible because of the single exclusion criterion. The number of patients who were ineligible because of not having an email address recorded with consent to use it, but who would otherwise have been eligible, was only recorded at Cambridge: 47 out of 193 otherwise eligible patients.

**Table 3.2 Site process data**

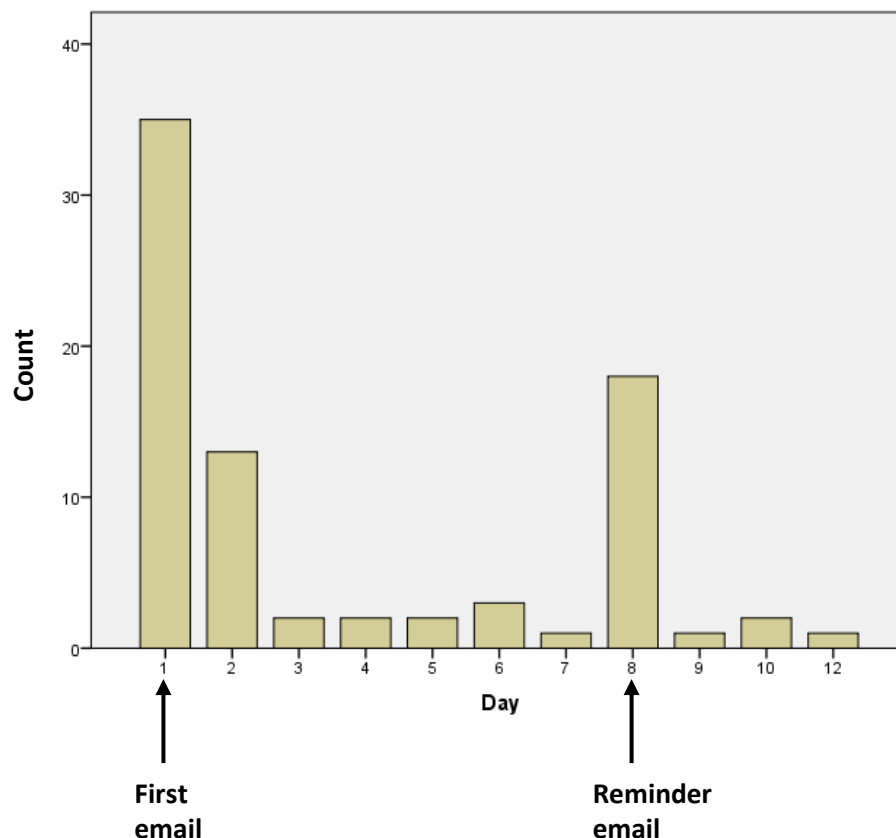
	<b>Cambridge</b>	<b>Southampton</b>	<b>Manchester</b>
Number fulfilling inclusion/exclusion criteria	143/3	69/5	17/0
Number of emails sent containing survey link	140	64	17
Number of emails 'undeliverable'	12	12	0
Number sent survey	128	52	17
Number responders (responding to initial email/reminder email)	51 (36/15)	13 (12/1)	16 (10/6)

Overall, across all three sites, the survey link was sent to 197 eligible participants (excluding the 24 times that the email was returned as 'undeliverable'). Eighty responses were received, equating to a response rate of 41%.

The single reminder email had a clear impact on recruitment, with 22 of the 80 participants responding on or after the day of the reminder email, as demonstrated in figure 3.1. Fifty-four out of the 80 participants responded on the day of receiving either the initial or reminder email.

Participants took a mean of 11.4 minutes (median 8.4) to complete the survey. Those with fatigue who completed the whole survey (n=68) took a mean of 12.4 minutes (median 9.1, range 3.1-61.3) and those without fatigue who only completed part of the survey (n=12) took a mean of 7.7 minutes (median 3.0, range 2.1-52.9). There was no relationship between fatigue severity and the time taken to complete the survey. Forty-six participants used a smart phone to access and complete the survey, 25 a desktop or laptop and nine a tablet.

**Figure 3.1 Number of respondents each day**



There were a total of 4892 potential data entry points amongst the 80 participants, excluding those that were explicitly optional (for example, 'What treatment, if any, was recommended') or become unavailable due to skip logic. Eighty-six data entry points were missing (1.8%).

During data analysis, it was found that two of the options within survey question 13 were associated with ambiguous response categories. In response to the question 'What effect do you feel your fatigue has had on this person?' participants were mistakenly asked to rate 'No effect' and 'Not sure' with the five item verbal rating scale 'not at all', 'a little bit', 'somewhat', 'quite a bit', 'very much' (see appendix 7.3.6, page 311). Excluding these data points, only 51 out of 4758 data entry points involved missing data (1.1%).

### **3.5.2 Characteristics of participants and non-responders**

Demographic data relating to responders and non-responders are summarised in table 3.3.

Continuous data are displayed in comparative histograms (figures 3.2-3.3, with further comparative data presented in appendix 7.3.7, page 313).

There were two main differences between responders and non-responders. First, more females than males responded to the survey email, with 67% of responders and 47% of non-responders being female ( $p=0.004$ ). Second, none of the patients currently receiving cancer treatment responded. The

survey was sent to 23 patients on treatment and 173 patients off treatment; none of the 23 receiving treatment responded.

The median and interquartile range (IQR) of the 'months since last treatment' data were virtually identical (table 3.3). However, visual inspection of the non-responder data revealed: a) a peak of patients still receiving treatment and b) a longer time since treatment than the responders (figure 3.2). The combination of these two opposing factors served to generate the similar median values between the groups.

A second analysis comparing responders with non-responders, excluding those patients in the non-responder group still receiving treatment, was therefore undertaken. This confirmed the longer time since last treatment between responders and non-responders off treatment, although this finding was of only borderline statistical significance ( $p=0.05$ ). There was no longer a gender difference between the two groups, as the non-responders still receiving treatment were predominantly male (18 male, 5 female). The non-responders who had completed treatment had a significantly shorter cancer treatment duration than the responder group (table 3.3, figure 3.3).

**Table 3.3 Comparison of responder and non-responder demographic data**

	<b>Responders (n=80)</b>	<b>All non- responders (n=116)</b>	<b>p *</b>	<b>Non-responders excluding those on treatment (n=93)</b>	<b>p *</b>
Off /on treatment n (missing data)	70/0 (10)	90/23 (3)	<b>&lt;0.001<sup>a</sup></b>	90/0 (3)	NA
Age at survey Mean (SD, range)	22.1 (2.7, 17-27)	21.3 (2.7, 16-27)	0.06 <sup>b</sup>	21.5 (2.6, 16-27)	0.21 <sup>b</sup>
Age at diagnosis Mean (SD, range)	19.0 (3.1, 12-24)	18.2 (3.3, 9-24)	0.12 <sup>b</sup>	18.0 (3.2, 12-24)	0.06 <sup>b</sup>
Months since diagnosis Median (IQR)	31 (18 to 49)	31 (14 to 58)	0.8 <sup>c</sup>	37 (21 to 61)	0.19 <sup>c</sup>
Months since last treatment Median (IQR)	18 (10 to 32)	18 (5 to 46)	0.50 <sup>c</sup>	27 (11 to 52)	<b>0.05<sup>c</sup></b>
Months treatment duration Median (IQR)	8 (4 to 25)	NA	NA	6 (4 to 9)	<b>0.006<sup>c</sup></b>
Gender n male (%)	26 (33)	62 (53)	<b>0.005<sup>a</sup></b>	44 (47)	0.06 <sup>a</sup>
Diagnosis, n (%)					
Leukaemia	20 (25)	20 (17)	0.44 <sup>a</sup>	12 (13)	0.11 <sup>a</sup>
Lymphoma	35 (44)	53 (46)		50 (54)	
Osteosarcoma or Ewing's sarcoma	6 (8)	9 (8)		3 (3)	
Brain neoplasm	1 (1)	8 (7)		6 (6)	
Other**	18 (23)	26 (22)		22 (24)	

\*p values comparing preceding column of non-responders with responders; significant p values in bold

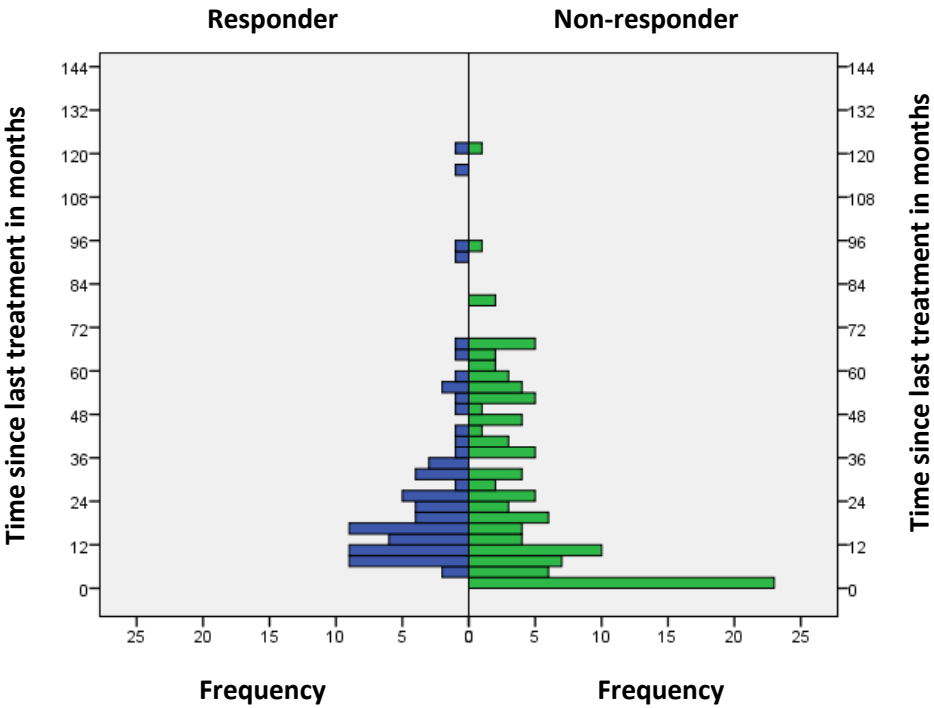
\*\* Other diagnosis were as follows: aplastic anaemia (underlying haematological malignancy not specified) (1), breast (1), cervical cancer (2), germinoma (2), insulinoma (1), melanoma (1), soft tissue sarcoma (3), testicular malignancy (3), teratoma (1), thyroid malignancy (3)

<sup>a</sup> Fisher's Exact Test

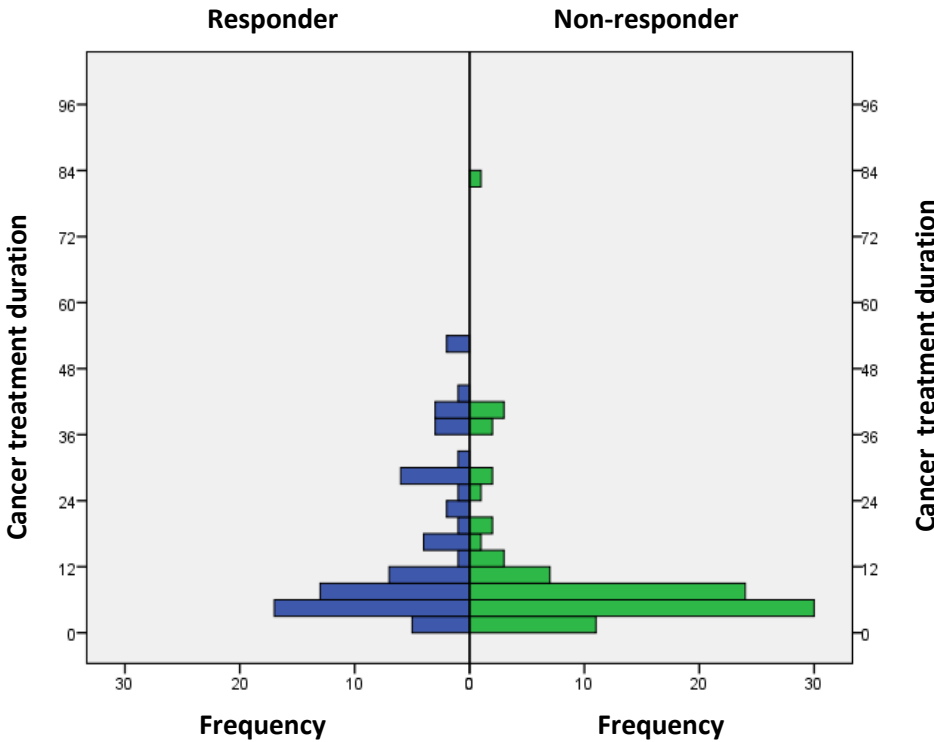
<sup>b</sup> Independent samples t-test

<sup>c</sup> Mann-Whitney U test

**Figure 3.2 Comparative histogram of time since last treatment for responders and all non-responders**



**Figure 3.3 Comparative histogram of cancer treatment duration between responders and non-responders who had completed treatment**



### 3.5.3 Fatigue prevalence and severity

#### 3.5.3.1 Symptom verbal rating scales (VRS)

Fatigue was the most prevalent symptom and was experienced by 85% of participants in the preceding month (table 3.4, figure 3.4). As described in section 3.3.4.2 (page 51), prevalence was calculated by omitting only those participants who had experienced fatigue 'not at all'.

An alternative way of defining prevalence involves only including those patients with a score that reaches a threshold of 'caseness'. This threshold has not been determined for symptom severity verbal rating scales, but has been calculated for 10-item numerical rating scales; scores  $\geq 4$  for pain,  $\geq 5$  for fatigue, anxiety and depression and  $\geq 6$  for appetite loss, have been found to identify patients who report that some relief of the symptom would significantly improve their life [5]. Although these findings cannot be directly extrapolated to the five-item VRS used in this survey, a pragmatic alternative prevalence of symptom 'caseness', counting only the three most severe items in the five-item scale, is also displayed in table 3.4.

There were no significant differences in the demographic characteristics of those with fatigue (68/80), and those without (12/80), as shown in table 3.5.

Bar charts of symptom severity are shown in figure 3.5. Fatigue was ranked as more severe than any of the other symptoms experienced by the survey respondents (Wilcoxon matched pairs signed rank test;  $p < 0.001$  for all symptoms paired with fatigue, except anxiety where  $p = 0.007$ ).

Using a hierarchical symptom cluster analysis, two symptom clusters were found. Fatigue was found to cluster most closely with anxiety and low mood. The remaining symptoms formed a second cluster. Figure 3.6 represents this as a dendrogram, with rescaled distance (0-25) on the x-axis. As smaller distances represent greater degrees of similarity, this cluster analysis represents relatively strong clustering, given the small within-cluster distances and large between-cluster distance. A further hierarchical clustering analysis was undertaken using the complete linkage (furthest neighbour) method, to confirm that the results of the cluster analysis were not sensitive to the choice of clustering algorithm. The results were very similar, with two clear clusters, and fatigue again clustering with anxiety and low mood.



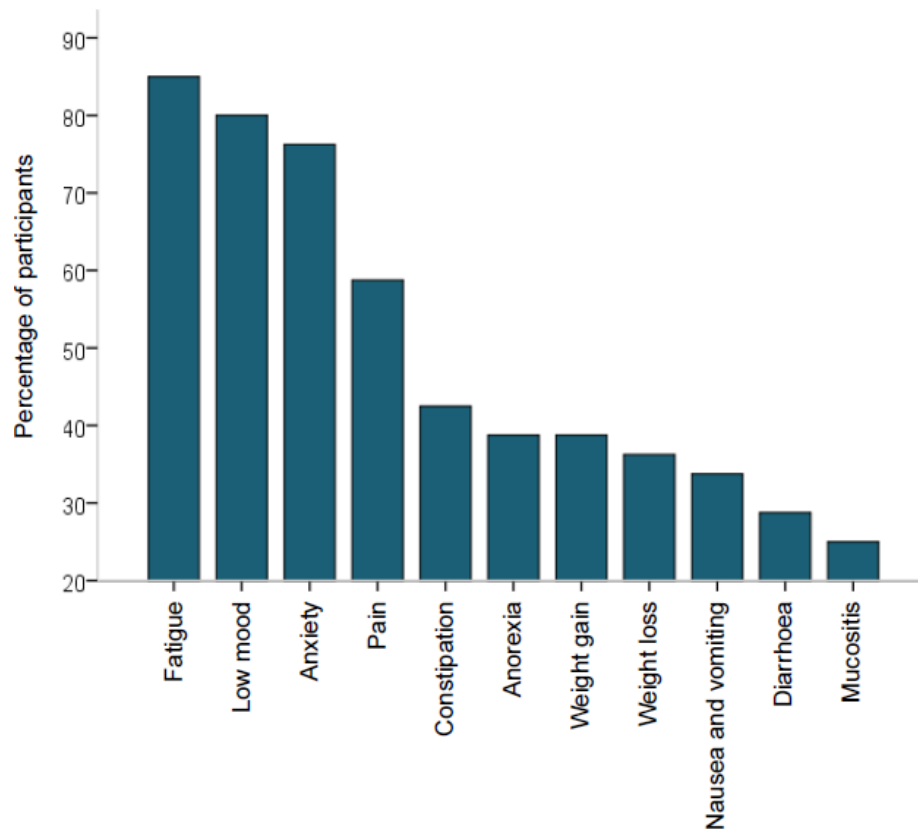
**Table 3.4 Symptom prevalence**

Symptom	Prevalence (%)*	Prevalence of symptom 'case' (%)**
Fatigue	85.0	65.0
Low mood	80.0	48.7
Anxiety	76.2	50.0
Pain	58.7	32.5
Constipation	42.5	18.7
Lack of appetite	38.7	21.2
Weight gain	38.7	17.5
Weight loss	36.2	12.5
Nausea and vomiting	33.7	13.7
Diarrhoea	28.7	20.0
Mucositis	25.0	8.7

\*Counting four most severe scores in five-item verbal rating scale

\*\*Counting three most severe scores in five-item verbal rating scale

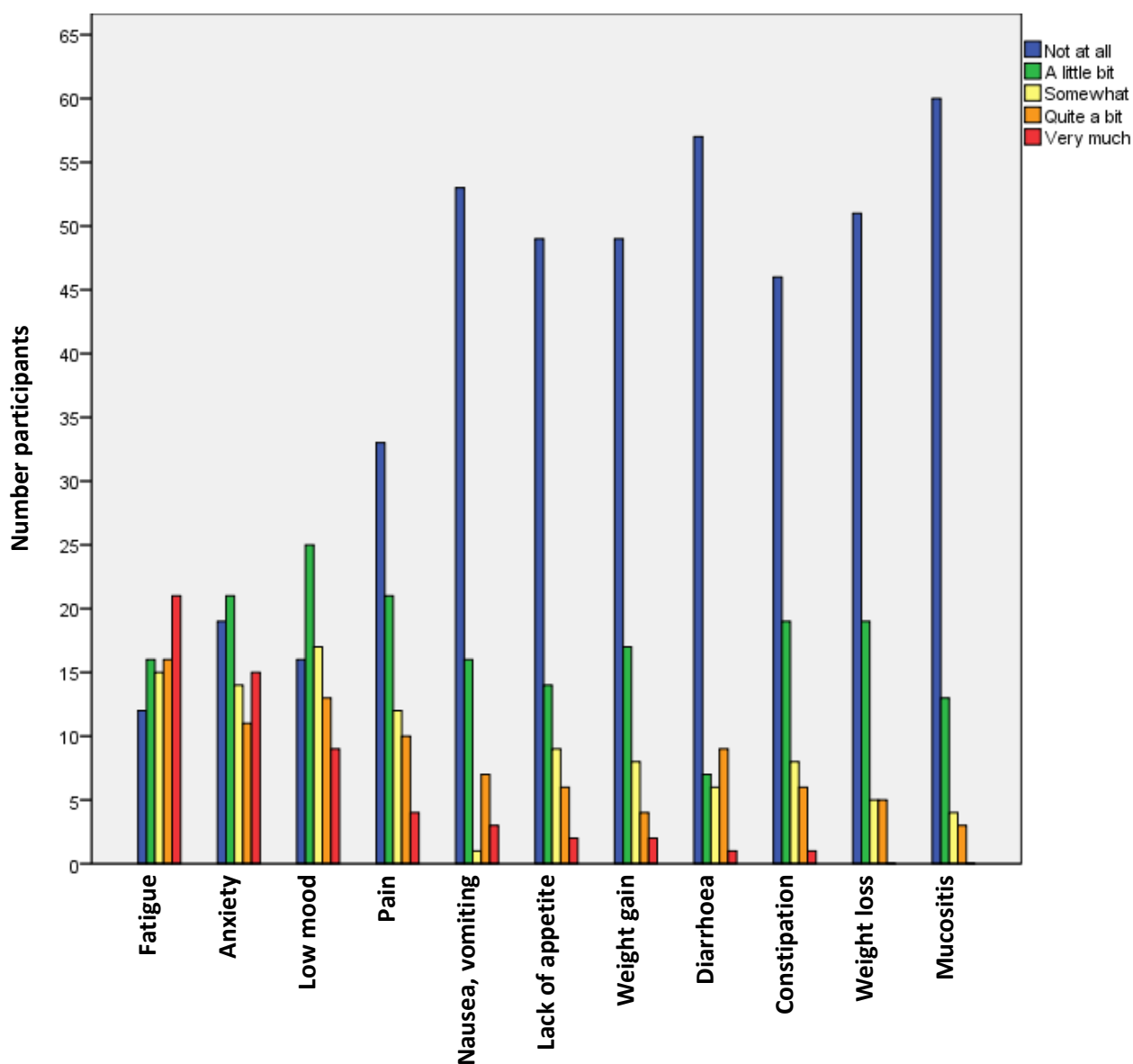
**Figure 3.4 Symptom prevalence bar chart**



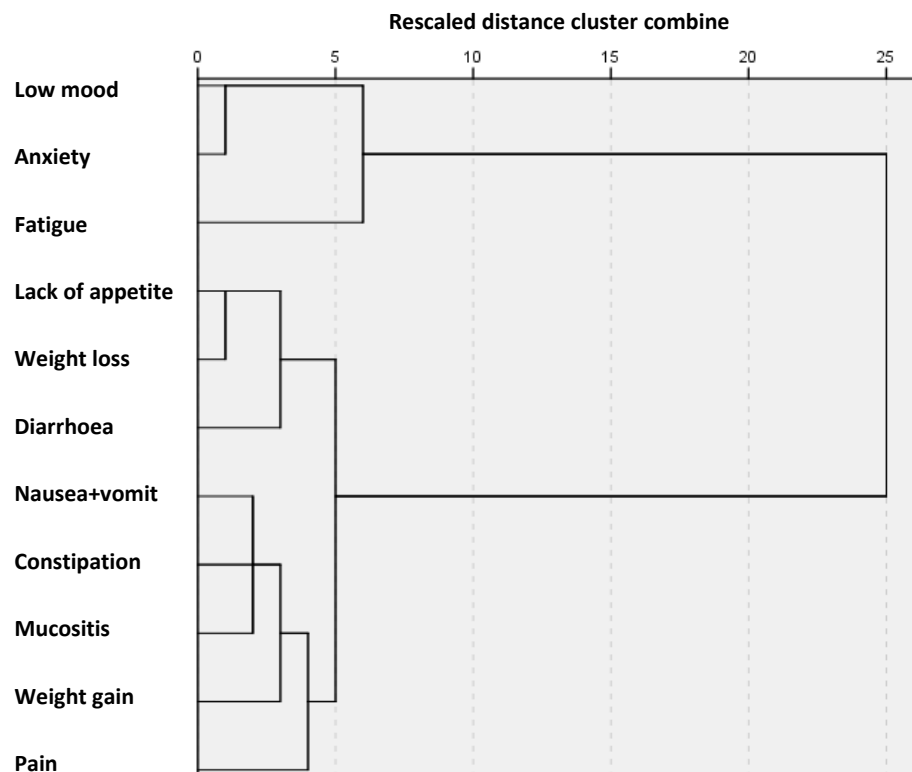
**Table 3.5 Comparison of demographic data between responders with and without fatigue**

	<b>Fatigue present (n=68)</b>	<b>Fatigue absent (n=12)</b>	<b>p</b>
Age at survey Mean (SD, range)	22.0 (2.8, 17-27)	22.5 (2.7, 18-26)	0.61
Age at diagnosis Mean (SD, range)	19.0 (3.2, 12-24)	18.7 (2.9, 14-24)	0.81
Months since diagnosis Median (IQR)	28.5(25)	60.0 (53)	0.06
Months since last treatment Median (IQR)	16.5 (21)	24.0 (36)	0.34
Months treatment duration Median (IQR)	6.5 (19)	12.0 (31)	0.12
Gender n male (%)	20 (29)	6 (50)	0.20

**Figure 3.5 Clustered bar chart of symptom severity**



**Figure 3.6 Dendrogram of hierarchical symptom cluster analysis (Ward's method)**



### **3.5.3.2 Multidimensional Fatigue Scale (MFS)**

The 68/80 participants who had experienced fatigue in the last month completed the MFS. The mean MFS fatigue severity was 44.3 (SD 20.5), and there was little variation between the mean general (physical) fatigue, sleep/rest fatigue and cognitive fatigue subscores: 42.4 (SD 23.1), 45.5 (SD 21.2), 44.9 (SD 28.0) respectively. Fatigue severity was normally distributed (figure 3.7).

Fatigue severity was greater more than one year ( $M=39.0$ ,  $SD=19.7$ , 95% CI 32.3 to 45.6) after last oncological treatment, rather than less than one year ( $M=53.8$ ,  $SD=19.7$ , 95% CI 45.0 to 62.5) after the last oncological treatment [ $t(56)=2.8$ ,  $p=0.007$ ] (figure 3.8). Fatigue was significantly more severe in females ( $M=39.6$ ,  $SD=19.3$ , 95% CI 34.1 to 45.2) than males ( $M=55.6$ ,  $SD=19.6$ , 95% CI 46.4 to 64.7) [ $t(66)=3.1$ ,  $p=0.003$ ]. No statistically significant difference in fatigue severity was found according to diagnosis [one-way ANOVA,  $F(5,62)=0.41$ ,  $p=0.84$ ]. Fatigue severity was also unrelated to any of the other demographic variables: age at survey, age at diagnosis, time since diagnosis or cancer treatment duration (table 3.6).

Fatigue severity (MFS score) correlated significantly with the severity (VRS) of all the other symptoms, except mucositis, with worse fatigue associated with more severe other symptoms (table 3.6). The six variables with highest correlations were entered into a multiple linear regression

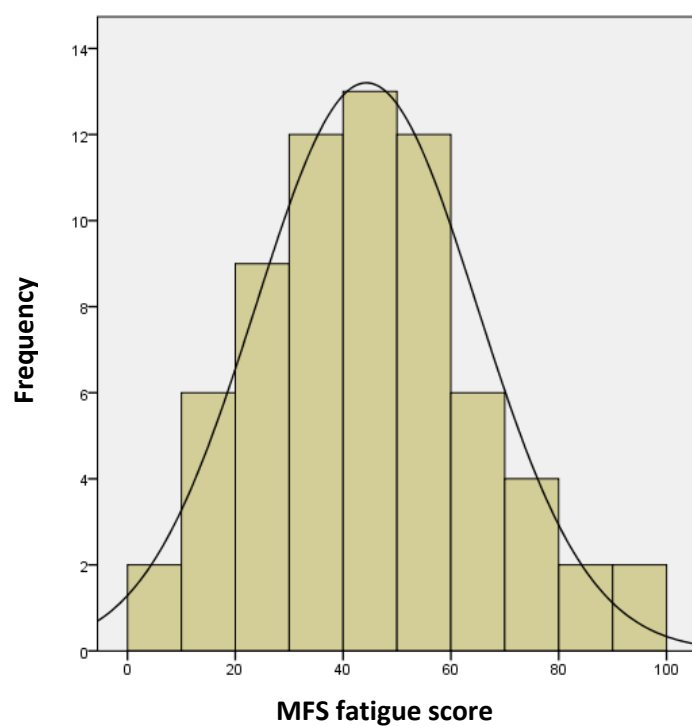
analysis. Variables with low beta coefficients that did not differ significantly from zero were removed from the model, leaving low mood, lack of appetite and pain.

Lack of appetite and low mood predicted 50% of the variation in fatigue severity. Addition of pain contributed a small, although statistically significant, change with the model explaining 53% of the variation (table 3.7). The final model included just low mood and lack of appetite as predictors of fatigue severity. Residuals plots and partial regression plots are in appendix 7.3.8.1 (page 315). There were no major departures from normality in the residuals, and as the partial regression plots could fit a linear line, this confirmed that it was reasonable to treat the 5-item verbal rating scales of symptom severity as continual rather than ordinal data.

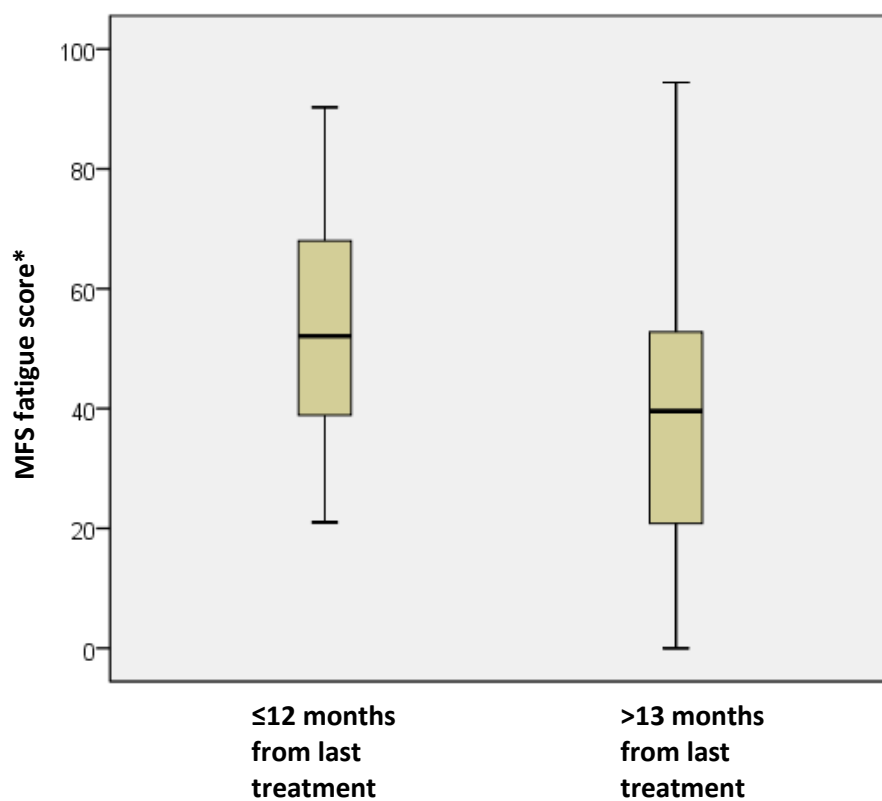
Given that low mood and lack of appetite both correlate with gender (worse symptoms in females), as well as fatigue, a further linear regression analysis was undertaken controlling for gender as a confounding variable. The beta coefficients of low mood and lack of appetite remained significantly different from zero, and the  $R^2$  change was 0.40 (see table 3.8). As well as showing that lack of appetite and low mood still predict fatigue severity after controlling for gender, the model also showed that gender no longer had a statistically significant relationship with fatigue after adjusting for lack of appetite and low mood. While these results do not rule out an independent gender effect, the association between experiencing fatigue and being female appears to be explained by symptoms associated with fatigue – lack of appetite and low mood – being more common in females.

Having noted that the model best able to predict fatigue severity involved one symptom from each of the three symptom clusters (figure 3.6), a further exploratory regression analysis was undertaken using cluster level mean scores. The rationale for doing this was to be able to include all symptom data in the analysis, without risking too many predictors and collinearity. This model generated comparable findings to the analyses using individual symptom predictors, with the lack of appetite and low mood symptom clusters predicting 52% of the variation in fatigue severity (appendix 7.3.9, page 320).

**Figure 3.7 Histogram of MFS scores (n=68)**



**Figure 3.8 Box plot of fatigue severity according to time after last treatment**



\*Note that higher MFS scores represent lower fatigue severity

**Table 3.6 Relationship between fatigue severity (MFS) and continuous independent variables**

	Spearman's rho	Significance (p)
<b>Demographic variables</b>		
Age at survey	-0.075	0.54
Age at diagnosis	-0.052	0.68
Months since diagnosis	-0.074	0.55
Months since last cancer treatment	-0.216	0.10
Months cancer treatment duration	0.030	0.83
<b>Symptom variables</b>		
Low mood	-0.59	<0.001
Lack of appetite	-0.56	<0.001
Anxiety	-0.56	<0.001
Pain	-0.49	<0.001
Diarrhoea	-0.42	<0.001
Nausea and vomiting	-0.30	0.013
Weight loss	-0.29	0.016
Weight gain	-0.29	0.017
Constipation	-0.26	0.035
Mucositis	-0.22	0.079

**Table 3.7 Linear model of predictors of fatigue severity (MFS) in fatigued participants**

	B	Beta	p	Tolerance	VIF
<b>Step 1</b>					
Lack of appetite	-10.57 (-14.18, -6.97)	-0.59	<0.001	-	-
Constant	63.91 (56.09, 71.73)	-	-	-	-
<b>Step 2</b>					
Lack of appetite	-7.12 (-10.60, -3.78)	-0.40	<0.001	0.83	1.20
Low mood	-7.65 (-10.79, -4.51)	-0.46	<0.001	0.83	1.20
Constant	79.25 (70.02, 88.47)	-	-	-	-
<b>Step 3</b>					
Lack of appetite	-5.28 (-9.03, -1.53)	-0.29	0.007	0.65	1.54
Low mood	-7.30 (-10.37, -4.23)	-0.44	<0.001	0.83	1.21
Pain	-3.59 (-6.90, -0.28)	-0.22	0.034	0.71	1.41
Constant	82.89 (73.31, 92.49)	-	-	-	-

Step 1 adjusted  $R^2$  0.34, Step 2 adjusted  $R^2$  0.50 (F change=23.7,  $p<0.001$ ), Step 3 adjusted  $R^2$  0.53 (F change=4.67,  $p=0.034$ )

95% bias corrected and accelerated confidence intervals reported in parenthesis

Confidence intervals and standard errors based on 1000 bootstrap samples

VIF: Variance Inflation Factor

**Table 3.8 Linear model of predictors of fatigue severity (MFS) in fatigued participants, controlling for gender**

	B	Beta	p	Tolerance	VIF
<b>Step 1</b>					
Gender	-15.91 (-26.19, -5.63)	-0.36	0.003	-	-
Constant	55.55 (46.91, 64.19)	-	-	-	-
<b>Step 2</b>					
Gender	-3.53 (-12.00, 4.92)	-0.079	0.407	0.83	1.20
Lack of appetite	-6.96 (-10.42, -3.51)	-0.39	<0.001	0.81	1.23
Low mood	-7.24 (-10.54, -2.93)	-0.43	<0.001	0.76	1.32
Constant	80.15 (70.65, 89.64)	-	-	-	-

Step 1 adjusted  $R^2$  0.11, Step 2 adjusted  $R^2$  0.50 (F change=26.60,  $p<0.001$ )

95% bias corrected and accelerated confidence intervals reported in parenthesis

Confidence intervals and standard errors based on 1000 bootstrap samples

VIF: Variance Inflation Factor

### 3.5.4 Impact of fatigue

#### 3.5.4.1 Impact on quality of life

Fatigue (MFS) was associated with poor quality of life among patients who had experienced fatigue in the last month (Pearson  $r=0.62$ ). Fatigue severity alone therefore predicted 38% of the quality of life ( $r^2=0.38$ ). The strength of correlation between fatigue severity and quality of life was broadly similar across MFS subscales; the correlation coefficients for the general (physical), sleep/rest and cognitive subscales were 0.67, 0.46 and 0.46 respectively. There was also a correlation between fatigue severity measured with the unidimensional five-item verbal rating scale and quality of life, although the strength of the correlation (Spearman's  $\rho=0.50$ ) was smaller than that with the multidimensional MFS (Spearman's  $\rho=0.62$ ).

Given that low mood and anorexia were both associated with poor quality of life (Spearman's  $\rho=0.52$  and  $0.52$  respectively) as well as with fatigue severity, a linear regression analysis was performed to adjust for these potential confounding factors (table 3.9). Fatigue severity was an independent predictor of quality of life, after adjusting for low mood and anorexia. Residuals plots and partial regression plots are in appendix 7.3.8 (page 317). In a linear regression model using data from all the symptoms in the form of the three symptom cluster mean scores, fatigue remained an independent predictor of quality of life (appendix 7.3.9, page 321).

**Table 3.9 Linear model of predictors of quality of life (QOL VAS) in fatigued participants**

	B	Beta	p	Tolerance	VIF
<b>Step 1</b>					
Lack of appetite	-0.79 (-1.25, -0.34)	-0.37	0.001	0.83	1.20
Low mood	-0.72 (-1.14, -0.30)	-0.37	0.001	0.83	1.20
Constant	11.28 (10.05, 12.52)	-	-	-	-
<b>Step 2</b>					
Fatigue severity (MFS)	0.042 (0.011, 0.074)	-0.36	0.010	0.48	2.07
Lack of appetite	-0.49 (-0.98, 0.003)	-0.23	0.051	0.65	1.53
Low mood	-0.40 (-0.86, 0.075)	-0.20	0.098	0.61	1.64
Constant	7.92 (5.14, 10.70)	-	-	-	-

Step 1 adjusted  $R^2$  0.36, Step 2 adjusted  $R^2$  0.42 (F change=7.13,  $p=0.01$ )

95% bias corrected and accelerated confidence intervals reported in parenthesis

Confidence intervals and standard errors based on 1000 bootstrap samples

VIF: Variance Inflation Factor



### 3.5.4.2 Impact on daily life relative to other symptoms

All participants, including those without fatigue, were asked which two out of the 11 symptoms most affected daily life. Fatigue was chosen by 79% of all participants, followed by anxiety (31%), low mood (30%), pain (21%), weight gain (11%), constipation (8%), nausea and vomiting (6%), diarrhoea (4%), weight loss (4%), mucositis (3%), and lack of appetite (1%). Fatigue was chosen significantly more often than any other symptom (Wilcoxon signed ranks tests,  $-7.87 < Z < -4.99$ , all p values  $< 0.001$ )

### 3.5.4.3 Impact on aspects of daily life

Fatigue was experienced by 65% of the fatigued participants either every day (n=21) or most days (n=23). Fatigue frequency correlated strongly with fatigue severity (Spearman's  $\rho = 0.74$ ). The greatest impact of fatigue was on the ability to exercise (table 3.10). Fifty of the 68 fatigued participants (74%) responded that fatigue affected the ability to exercise 'somewhat', 'quite a bit' or 'very much'. The size of the impact on exercise was significantly greater than all the other impacts considered, except for the impact on being able to attend school/study/work. The size of every impact correlated significantly with the fatigue severity score (MFS), with worse fatigue (lower MFS score) being associated with a greater impact (higher impact VRS). It also correlated with the unidimensional 5-item fatigue VRS, although the strengths of the correlations were less strong.

**Table 3.10 Impact of fatigue on aspects of daily life**

	Impact VRS response 'somewhat' / 'quite a bit' / 'very much' (n=68)	Paired comparison with ability to exercise (Z statistic p value)**	Correlation impact VRS and MFS fatigue severity (Spearman's $\rho$ )*	Correlation impact VRS and fatigue VRS (Spearman's $\rho$ )*
Ability to exercise, n (%)	50 (74)	-	-0.53	0.50
Ability to attend school/study/work, n (%)	44 (65)	-1.24, 0.22	-0.69	0.46
Relationship with friends, n (%)	38 (56)	-3.67, $< 0.001$	-0.59	0.37
Ability to socialise, n (%)	38 (56)	-3.43, $< 0.001$	-0.70	0.54
Ability to enjoy life, n (%)	36 (53)	-3.85, $< 0.001$	-0.65	0.45
Ability to be independent, n (%)	34 (50)	-4.20, $< 0.001$	-0.49	0.29
Relationship with family, n (%)	29 (43)	-5.02, $< 0.001$	-0.57	0.35

\*All Spearman's  $\rho$  values significant to the 0.05 level (two-tailed)

\*\* Wilcoxon matched pairs signed rank test

#### **3.5.4.4 Impact on other people**

The person most closely involved in participants' care was a parent (85%, 58/68), another relative (9%, 6/68), or a friend (1%, 1/68); 4% (3/68) had no-one closely involved in their care. 45% of participants (29/64) felt their fatigue made the person most involved in their care 'somewhat', 'quite a bit' or 'very much' upset and 42% (27/64) had the perception that it caused frustration. Two-fifths (41%, 26/64) felt that it limited this person's rest time 'somewhat', 'quite a bit' or 'very much'. Only 13% (8/64) of participants thought there was no impact at all on this person, in terms of causing upset, frustration or limiting rest time. There was a moderate, significant correlation between the severity of the fatigue and the degree of impact for 'frustration' (Spearman's  $\rho = -0.43$ ) and 'upset' (Spearman's  $\rho = -0.38$ ), with worse symptom scores being associated with a greater impact. This relationship with fatigue severity was not found for the impact of 'limiting rest time'.

In response to the question 'Do you think the effect of fatigue on your life is understood by the people around you?', 64% (43/67) indicated 'not at all' or 'a little bit' for friends, with the corresponding proportion for healthcare professionals and family being 28% (19/68) and 33% (22/67) respectively. There was a significant correlation between the fatigue severity and the extent to which friends understood it (Spearman's  $\rho = 0.33$ ,  $p = 0.007$ ); friends were perceived as being less likely to understand, the worse the participants' fatigue severity. No such relationship existed between symptom severity and the degree of family or healthcarer understanding.

### **3.5.5 Management of fatigue**

#### **3.5.5.1 Interpretation of fatigue cause**

The first step in symptom management is understanding its cause. Participants were asked whether they thought their fatigue was caused by 'mainly your illness', 'mainly your treatment' or a 'combination of both'. A fourth 'other' option led to space for a free text entry. The results are tabulated below.

**Table 3.11 Interpretation of fatigue cause**

<b>Cause</b>	<b>Data entered into survey (n=68)</b>	<b>Recategorised 'other' data (n=68; 72 responses)</b>
Mainly illness (n)	4	4
Mainly treatment (n)	16	24
Combination of both (n)	30	33
Other (n)	18	11

Of the 18 participants who indicated 'other', 11 of the 18 free text responses could be recategorised into one of the three main categories: 'mainly your illness', 'mainly your treatment' or a 'combination

of both'. As well as the seven that were not recategorised, four of the 11 free text responses that were recategorised also included another interpretation of the cause of fatigue, beyond illness or treatment. In total, recategorisation of free text data led to 11 'other responses' (table 3.12).

**Table 3.12 Other interpretations of the cause of fatigue**

<i>Doing a lot in one day</i>
<i>Not getting enough physical exercise</i>
<i>Unsure. Maybe also lack of exercise...</i>
<i>Sleeping patterns is terrible... also occasionally smoke weed...</i>
<i>Diagnosed with chronic fatigue syndrome afterwards...</i>
<i>Weight gain</i>
<i>University exams</i>
<i>Studies</i>
<i>Osteoporosis in my knees... I don't now feel like exercising at all, gets me down</i>
<i>It's hard to pinpoint the cause</i>
<i>Not sure</i>

All text is verbatim; some non-contributory words have been omitted

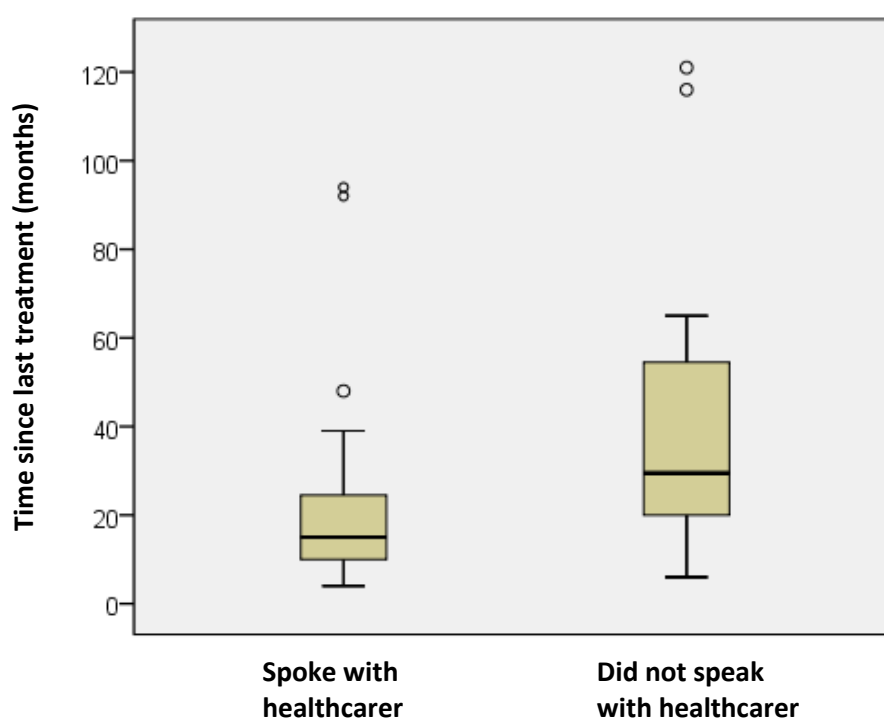
### **3.5.5.2 Belief about whether fatigue can be treated**

Only 19% of fatigued participants (13/68) believed that 'something could be done' about fatigue. 38% (26/68) believed it to be a symptom one 'has to live with' and 43% (29/68) were not sure. No relationship was found between the response to this question and the MFS fatigue severity score (independent t-test,  $t=0.54$ ,  $p=0.60$ ), participants' interpretation of the fatigue cause (Fisher's exact test,  $p=0.28$ ), gender (Fisher's exact test,  $p=0.11$ ), diagnosis (Fisher's exact test,  $p=0.78$ ), age (independent t-test,  $p=0.73$ ), time since diagnosis (Mann-Whitney U test,  $p=0.80$ ) or time since last treatment (Mann-Whitney U test,  $p=0.09$ ).

### **3.5.5.3 Talking to healthcare team about fatigue**

65% of participants (44/68) had talked to a healthcarer about feeling fatigued and 13% (9/68) could not remember doing so. Participants were significantly more likely to have talked to a healthcarer if they were closer to the time of last treatment (Mann-Whitney U test,  $p=0.007$ ), as demonstrated in figure 3.9. Speaking to a healthcarer was not influenced by interpretation of the cause of the fatigue (Fisher's exact test,  $p=0.41$ ), gender (Fisher's exact test,  $p=0.79$ ), diagnosis (Fisher's exact test,  $p=0.15$ ), age (independent t-test,  $t=-0.35$ ,  $p=0.73$ ), time since diagnosis (Mann-Whitney U test  $p=0.66$ ), or duration of cancer treatment (Mann-Whitney U test  $p=0.95$ ).

**Figure 3.9 Box plot of relationship between time of last treatment and speaking to a healthcarer**



The 15 participants who had not talked to a healthcare professional could choose any number from a list of seven potential reasons. The most common reason for not talking was believing nothing could be done (9/15 participants); 6/15 were never asked, 5/15 believed the symptom to be inevitable, 4/15 did not think the fatigue was important enough, 3/15 did not want to bother the healthcarer and 3/15 thought people may consider them 'lazy or complaining'.

#### **3.5.5.4 Treatments given**

Two fifths of participants (41%, 28/68) had had no treatment for fatigue recommended. The remaining participants had received a range of 1-7 treatments (median 2.5).

Compared to those who had received fatigue treatment, those who had not were much less likely to have talked with a healthcarer (table 3.13). All the 40 participants who had talked with a healthcarer had received fatigue treatment, whereas only 4 participants who talked with a healthcarer did not receive treatment (Fisher's Exact Test,  $p < 0.001$ ). In addition, they were significantly more likely to believe healthcarers had limited understanding of the effect of fatigue ( $p = 0.004$ ), and were significantly further from the time of their last cancer treatment ( $p = 0.023$ ). There was no difference in fatigue severity (MFS) between the two groups, nor any difference in any demographic variables, other than the time since last cancer treatment.

**Table 3.13 Comparison of participants according to whether received fatigue treatment**

	No fatigue treatment received	Fatigue treatment received	p value
Fatigue severity (MFS)	46.6	42.7	0.45 <sup>a</sup>
Age at survey (years)	21.9	22.1	0.86 <sup>a</sup>
Age at diagnosis (months)	18.3	19.4	0.16 <sup>a</sup>
Months since diagnosis	44.2	31.8	0.69 <sup>b</sup>
Months since last cancer treatment	37.1	19.1	<b>0.023</b> <sup>b</sup>
Cancer treatment duration (months)	28.2	28.7	0.90
Gender (male)	8/28	12/40	0.56 <sup>c</sup>
Diagnosis	-	-	0.10 <sup>c</sup>
Belief that 'something can be done' about fatigue	3/28	10/40	0.33 <sup>c</sup>
Did talk with healthcarer about fatigue	4/28	40/40	<b>&lt;0.001</b> <sup>c</sup>
Perceived low understanding of fatigue by healthcarer	11/28	8/40	<b>0.004</b> <sup>c</sup>
Perceived low understanding of fatigue by family	11/28	11/40	0.47 <sup>c</sup>
Perceived low understanding of fatigue by friends	19/28	24/40	0.75 <sup>c</sup>

Significant p values highlighted in bold

\*'low' defined as understanding 'not at all' or 'a little bit' in 5-item verbal rating scale

<sup>a</sup> Independent t-test

<sup>b</sup> Mann-Whitney U test

<sup>c</sup> Fisher's exact test

For those who did receive treatment for fatigue, the most common was exercise (27/40) followed by rest/relaxation (22/40). Diet/nutrition (15/40), blood transfusion (14/40) and naps/sleep (14/40) were the next most often received treatments, followed by physiotherapy (6/40), complementary therapies (6/40) and attendance at a fatigue group (2/40). Seventeen of the 22 people recommended rest and relaxation, were also recommended exercise. There was no significant relationship between the number of treatments recommended and fatigue severity (Spearman's rho=-0.15, p=0.21).

For the five most common treatments, an exploratory analysis was undertaken to examine relationships with the severity of fatigue and the time since last treatment. Exercise and rest/relaxation were significantly more likely to be recommended in those with more severe fatigue, whereas blood transfusion was more likely to be recommended a shorter interval after the last treatment (table 3.14).

**Table 3.14 Relationship between fatigue treatments, fatigue severity and time since last cancer treatment**

Fatigue treatment		Fatigue severity (MFS), mean	P value <sup>a</sup>	Months since last cancer treatment, mean	P value <sup>b</sup>
Exercise	Received	37.0	<b>0.017</b>	20.7	0.31
	Not received	49.1		30.7	
Rest/relaxation	Received	36.8	<b>0.035</b>	19.7	0.22
	Not received	47.9		30.3	
Diet/nutrition	Received	40.1	0.37	17.5	0.44
	Not received	45.5		28.8	
Blood transfusion	Received	52.7	0.13	13.3	<b>0.036</b>
	Not received	42.2		29.3	
Naps/sleep	Received	43.0	0.78	17.3	0.43
	Not received	44.7		28.6	

P values compare values between those who did or did not receive each fatigue treatment

Significant values highlighted in bold

<sup>a</sup> Independent t-test

<sup>b</sup> Mann-Whitney U test

### 3.5.5.5 Management effectiveness

Participants rated their perception of the successfulness of fatigue treatments they had received.

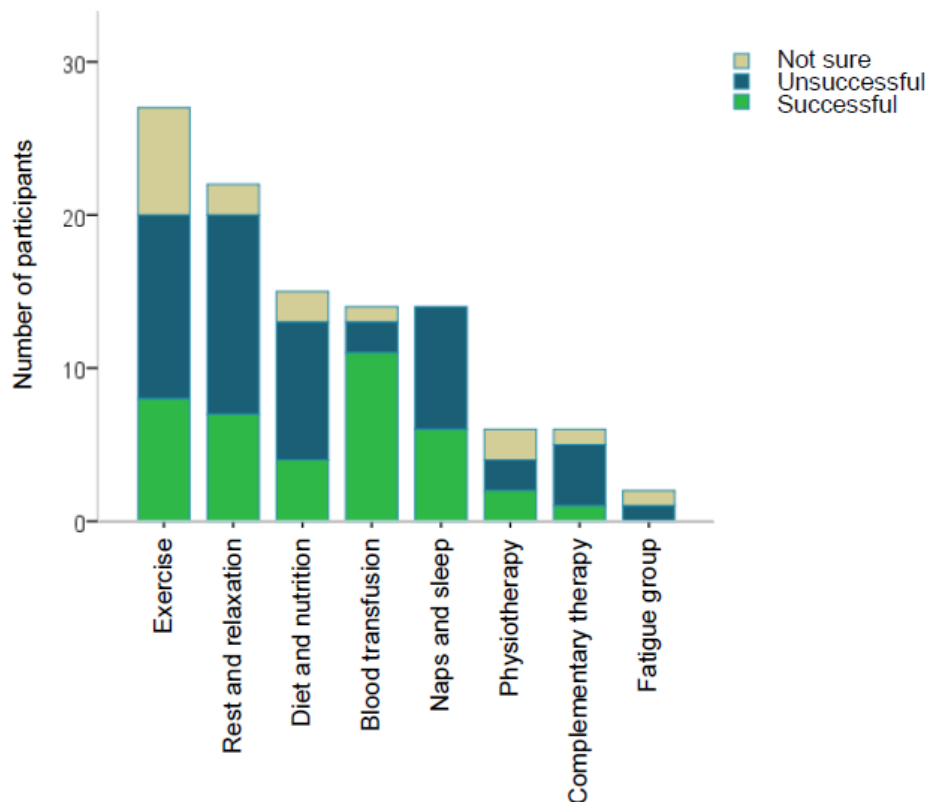
Only blood transfusion was described as successful more often than unsuccessful (table 3.15, figure 3.10). The mean successfulness score across all participants was 1.3 (SD 0.82), a score of 0

representing treatment with 'no effect' and 3 representing an 'entirely successful' treatment. The perceived success of fatigue treatment was highly correlated with fatigue severity ( $r=0.71$ ,  $p<0.001$ ), with higher success being associated with less severe fatigue scores. Successfulness of fatigue treatment was significantly lower in participants more than one year from last cancer treatment, compared to those less than one year from treatment [ $t(30)=-2.93$ ,  $p=0.006$ ].

**Table 3.15 Perceived successfulness of each treatment**

Fatigue treatment	Successful	Unsuccessful	Unsure
Blood transfusion, n (%)	11 (79)	2 (14)	1 (7)
Naps / sleep, n (%)	6 (40)	9 (60)	0
Physiotherapy, n (%)	2 (33)	2 (33)	2 (33)
Rest / relaxation, n (%)	7 (32)	13 (59)	2 (9)
Exercise, n (%)	8 (30)	12 (44)	7 (26)
Diet / nutrition, n (%)	4 (27)	9 (60)	2 (13)
Complementary therapy, n (%)	1 (17)	4 (67)	1 (17)
Fatigue group, n (%)	0	1 (50)	1 (50)

**Figure 3.10 Stacked bar chart showing perceived successfulness of each fatigue treatment**



### **3.5.5.6 Personal view of best treatment(s) for fatigue**

All participants, irrespective of whether they had received fatigue treatment, were asked what they personally thought was the single best treatment for fatigue. Most participants chose exercise, followed by diet/nutrition, rest/relaxation and naps/sleeping (table 3.16). 6/58 participants indicated that they could not answer this question as they had not been given any treatment for fatigue, and 7/58 provided free text information (table 3.17).

**Table 3.16 Personal view of best fatigue treatment**

	Proportion viewing as best fatigue treatment	Number of those recommending a treatment having received that treatment
Exercise	14/58	11/14
Diet/nutrition	7/58	2/7
Rest/relaxation	7/58	2/7
Naps/sleeping	6/58	1/6
Blood transfusion	4/58	3/4
Complementary therapies	3/58	1/3
Physiotherapy	2/58	2/2
Fatigue group	2/58	1/2

**Table 3.17 Personal view of best fatigue treatment: free text responses**

*Getting to the bottom of the cause and treating that*

*End of treatment*

*Pacing/support groups/resting when needed/changing medication*

*Time*

*Health combination of rest/relaxation and exercise*

*I have no idea*

*I really don't know*

All text is verbatim

Thirteen of the 16 participants who recommended an active treatment (exercise and physiotherapy), had received an active treatment themselves; participants who had received an active treatment were significantly more likely to recommend an active treatment as being better than a rest-focused treatment for fatigue (Fisher's Exact Test,  $p=0.001$ ). However, no evidence was found that those who had received a rest-focused treatment (rest/relaxation, naps/sleeping and complementary therapy) were more likely to recommend a rest-focused treatment ( $p=0.62$ ).

**Table 3.18 Relationship between receiving and recommending active or rest-focused treatments**

	Recommend active 'best treatment'	Recommend rest- focused 'best treatment'	p value
Received active treatment	13	3	0.001
Received rest-based treatment	8	5	0.62

p values calculated using Fisher's exact test

The mean MFS fatigue score for those recommending an active treatment was 50.1, whereas that for those recommending a rest-focused treatment was 42.8. This difference was not statistically significant (independent t-test,  $p=0.29$ ).



### **3.5.6 Qualitative data**

Participants were given free text space at the end of the survey to respond to the question 'Is there anything else you would like to tell us that we did not ask?' Fourteen of the 68 participants provided comments, too few for formal qualitative analysis, although all 14 fell within five loose themes. Examples are provided below, and the remaining quotes are in appendix 7.3.10, page 322.

#### ***3.5.6.1 Lack of understanding***

Four participants described a perception of a lack of understanding of others, in relation to their fatigue. Family, friends, teachers and hospital staff were all implicated.

'It's difficult to express to friends or teachers that the fatigue isn't something you're choosing to let effect you. As an 18 year old with cancer many of my friends could spend all night out and were surprised when even after treatment and the all clear I was very tired. Even if there was nothing that could be done about fatigue, to make it a well known fact that the fatigue can continue would make life easier, both in a friendship environment and a professional one.'

#### ***3.5.6.2 Emotional impact***

Several quotes alluded to the emotions such as anger, depression, anxiety and guilt, in relation with fatigue.

'Fatigue is accompanied by low mood and this makes getting angry very easy which is then reflected in how you behave towards everything you do in life.'

#### ***3.5.6.3 Impact on work***

Two of the 14 participants described the impact of, and on, work.

'I get up and go to work but after work I'm so tired and mid week I start to tire.'

#### ***3.5.6.4 Perception activity is helpful***

A few participants suggested that activity was helpful for fatigue. None gave the opposite perspective, in favour of rest, although there was a suggestion that healthcare staff may encourage rest.

'I have found the tiredness doesn't go away day to day, but on occasion if I push through the tiredness while walking etc I feel better and more alert the next day.'

#### ***3.5.6.5 Requests for more research***

Two requests for further research were made.

'More research definitely needs to go into this, as it has completely ruined my life :( '

## **3.6 Discussion**

This survey provides evidence that fatigue is the most prevalent symptom experienced by TYA cancer patients, and it persists long after cancer diagnosis and treatment. It has a highly negative impact, being an independent predictor of poor quality of life, with the greatest adverse impact being on the ability to exercise. It is therefore unsurprising that most did not find advice to exercise helpful, despite exercise being the most evidence-based intervention for fatigue in older adults with cancer [56]. Two out of five fatigued participants (41%) had received no fatigue management support.

These key findings are discussed in detail below in the context of the prior systematic review and other literature of relevance.

### **3.6.1 Fatigue experience**

#### **3.6.1.1 Prevalence**

Fatigue was the most prevalent of eleven symptoms, experienced by 85% of the survey participants in the preceding month. As described in the preceding systematic review, only five previous studies have evaluated fatigue prevalence after cancer treatment alone, as in this survey. Comparison of findings is hindered by heterogeneity in definition of a fatigue 'case'. However, two of the five studies did use the same definition as in this survey (>1 in a 1-5 NRS, or equivalent), both – coincidentally – revealing prevalence rates of 67% [120,192]. The alternative definition of a 'case' described in the survey results (>2 in a 1-5 NRS, or equivalent) has not been used by any preceding studies.

While the fatigue prevalence in this survey appears to be consistent with existing literature, this finding is limited by the potential for selection bias, and the lack of a control group, as discussed in section 3.6.5.2 (page 88).

#### **3.6.1.2 Fatigue type**

Fatigue is a multidimensional symptom, with physical, cognitive, emotional and sleep-related components. The primary fatigue measure used in this survey, the MFS, disaggregates fatigue by generating three subscores for general (physical), cognitive and sleep/rest fatigue. Survey participants' responses indicated that all three dimensions were of comparable severity (general, cognitive, sleep/rest subscores were 42.4, 44.9, 45.5 respectively). In contrast, most evidence to date has suggested that the cognitive component of fatigue is less severe than the other fatigue dimensions in young patients.

Amongst the 15 studies in the systematic review using the MFS measure, only five reported subscores, with four reporting cognitive fatigue to be less severe than the other dimensions [168,172,186,200]. Daniel and colleagues, for example, revealed subscores of general, cognitive and sleep/rest fatigue of 55.8, 69.2, 51.1 respectively [168]. Only one of the five studies produced similar findings to this survey; Keats and colleagues recorded MFS scores in a small study enrolling TYAs to a physical activity intervention after cancer treatment, and revealed cognitive subscores that were of comparable severity (general, cognitive, sleep/rest subscores: 68.8, 69.4, 62.9 respectively) [218].

In considering potential reasons for these differing findings, it is noteworthy that the two studies revealing comparable cognitive fatigue to the other dimensions, this survey and Keats [218], have been the only studies involving only those patients who were *after* completion of cancer treatment. The other four studies involved patients during, or predominantly during, cancer treatment. Daniel and colleagues hypothesised that the apparently less severe cognitive fatigue during cancer treatment may represent 'reduced cognitive demands given reduced school attendance and overall expectations for productivity' [168]. Compared to during cancer treatment, cognitive fatigue could become more apparent after the end of treatment, due to the need to reintegrate with education or work.

An important difference between the survey fatigue scores and all the other studies described above is that the survey only scored MFS fatigue in those who had experienced some fatigue in the last month; the other studies scored fatigue in the whole research cohort, irrespective of whether or not participants were experiencing fatigue. As well as providing a potential explanation for why the symptom severity subscores appear to be worse in the survey than other studies, it is conceivable that the lack of data from the potentially healthier non-fatigued participants could have contributed to the worse cognitive fatigue scores in this survey, given that cognitive fatigue is known to be the least severe dimension of fatigue in healthy adolescents [168]. Equally, though, Keats and colleagues did find significant cognitive fatigue in patients not selected for the presence of fatigue. This, along with the notable difference in cognitive fatigue between studies with participants during, compared to after, treatment, suggests that the marked cognitive fatigue after cancer treatment found in this survey could be a true finding.

### **3.6.1.3 Persistence**

An unexpected and interesting finding was that fatigue scores appeared to be worse in those more than one year after the end of cancer treatment, compared to those less than one year after treatment. As described in the preceding review, cross-sectional studies in cancer survivors have suggested that fatigue remains prevalent in patients long after the end of cancer treatment. Only one longitudinal study in TYA patients has attempted to investigate the temporal pattern of fatigue

beyond the end of cancer treatment; Macpherson and colleagues found that fatigue persisted in survivors of Hodgkin's lymphoma, with no significant changes in fatigue scores between the end of treatment and three years later [190].

This survey is the first research in the TYA population to suggest that fatigue levels after the end of cancer treatment could worsen over time. In a longitudinal study, Andrykowski and colleagues evaluated fatigue in a large cohort of breast cancer patients with a mean age of 55 years; the prevalence of fatigue was 9% at 4 months after the end of cancer treatment and rose to 13% at 42 months [270]. Although the concordance with the survey findings is compelling, the validity of the survey outcome is limited by low study power and the risk of increasing selection bias for more fatigued patients further from treatment, as will be discussed in section 3.6.6.2 (page 90). Although it has therefore not been established that fatigue worsens over time, this survey does provide evidence for fatigue persisting long after the end of cancer treatment in TYAs.

Why might it be that fatigue persists long term? Although the survey was not attempting to answer this question, the finding that the main impact of fatigue was on the ability to exercise could be of relevance, given that physical activity is an effective intervention for CRF in older adults [243,271]. It is conceivable that the TYA fatigue is preventing the main approach that could ameliorate it, leading to its persistence.

Another possibility, given that fatigue is a subjective and self-reported experience, is that it is perceived to persist, because of expectations that it should improve after the end of cancer treatment. Again, the survey did not attempt to explore this aspect. However, the survey finding that virtually all participants believed fatigue was caused by the cancer and/or its treatment could be consistent with this hypothesis. Furthermore, in the free text responses, a few participants referred to the lack of understanding that fatigue may persist longer term.

#### **3.6.1.4 Correlates**

The strength of correlation between the severity of fatigue and that of a wide range of physical and psychological symptoms was another noteworthy survey finding. Low mood, lack of appetite and anxiety were the three symptoms with the strongest correlation with fatigue severity. The close correlation between fatigue and other symptoms is consistent with recent data from the large AYA HOPE study, involving 523 adolescents and young adults aged 15-39, that revealed that the strongest correlates with fatigue were concurrent symptoms [188]. Furthermore, the psychological symptoms, low mood and anxiety, were the two symptoms found to cluster most closely with fatigue in the hierarchical symptom cluster analysis. A meta-analysis of correlates of fatigue in adults with cancer

has revealed congruent findings, with fatigue correlating more closely with psychological than physical symptoms [45].

These findings are of interest for two reasons. First, they support the view of fatigue as a symptom with a significant non-physical dimension. Both anxiety and low mood have previously been shown to be independent predictors of the development of CRF in older adults [272,273]. An effective fatigue intervention is, therefore, likely to require a psychological component. This is consistent with evidence from older adults for the effectiveness of psychological interventions for CRF; indeed, Mustian and colleagues found that psychological approaches were the single most effective treatment for fatigue after the end of cancer treatment [48,56].

Second, the close relationship between fatigue and other symptoms could suggest that, if there is a causal link, control of the other symptoms might also help ameliorate fatigue. De Raaf and colleagues' randomised older adults with CRF to a complex intervention that involved careful management of nine physical symptoms; intervention was found to lead to a significant improvement of fatigue [44]. This supports the possibility of causal relationships between fatigue and other symptoms in older adults; for example, pain may impact on sleep and therefore lead to fatigue. However, the survey findings can only demonstrate an association between symptoms in TYAs, not causality.

### **3.6.2 Fatigue impact**

#### ***3.6.2.1 Impact on quality of life and daily living***

This survey has confirmed the highly detrimental impact of fatigue, including a strong relationship with poor quality of life. Although, as described in the systematic review, previous studies have revealed a correlation between fatigue and poor quality of life, these findings build on existing knowledge in two ways. First, the survey is the first to reveal that fatigue is an independent predictor of quality of life in TYA cancer patients. Second, the two previous studies attempting to quantify the relationship between fatigue and quality of life used the PedsQL™ measurement system to assess both parameters, which could potentially inflate the strength of correlation [168,225]. This survey has been the first to measure fatigue and quality of life using separate validated measures.

Furthermore, this survey is the first to quantify the impact of fatigue on daily living. Participants revealed that fatigue is the single symptom with the greatest impact on daily life in TYAs. Previous research, described in the review, has been qualitative, participants describing the impact on exercise and socialising. Quantitative evidence from this survey has allowed ranking of the impact of fatigue on the different activities of daily living; the effect on the ability to exercise is the single

greatest impact, followed by the impact on the ability to attend school/work, on relationships with friends, and on the ability to socialise, enjoy life and be independent. These findings provide insight into the unexplained review finding that the main impact of fatigue was distress. Given the developmental importance for TYAs of socialising with peers and autonomy (section 1.1.2.2), it is perhaps not surprising that fatigue leads to distress in this young patient group.

These findings are not unique to the TYA age range. The distress caused by CRF in older adults has also been established [274], as well as its impact on the activities of daily living [23]. In a survey of older adults with CRF, Stone and colleagues revealed fatigue to be the symptom with the greatest negative impact on daily life, and quantified the impact of fatigue on aspects of daily living [23]. Their results are not directly comparable to those of the survey because the questions differed to reflect age-related needs: older adults were most concerned about the impact on being able to work, on the ability to enjoy life, on sex life, on hope of fighting the illness, and on the ability to take care of family.

Although the survey was predominantly quantitative, the free text data gave some limited qualitative data on the impact of fatigue. Several participants described their perception of lack of understanding of fatigue, the emotional impact and the impact on work, providing further insight into the detrimental effects of fatigue on quality of life and daily activities.

### ***3.6.2.2 Parents' perspectives***

Parents were, unsurprisingly, reported to be the people most closely involved in caring for TYA cancer patients, and this work has provided the first, albeit proxy, evidence for a negative impact on parents. Only 13% of participants perceived that the fatigue had no impact on the person closest to them, with the remainder indicating that fatigue led to the carer experiencing frustration, upset, or limited rest time. Although over the last decade considering the needs of carers of those with long term conditions, including cancer, has become highly topical, there has, as yet, been little work evaluating the impact of specific symptoms on carers [275,276]. Only one previous study has considered the impact of caring for those with CRF; a small study evaluating the needs of spousal caregivers of older cancer patients suggested increased depression and strain, and an impact on the ability to work [277].

Approximately one third of participants considered that fatigue was not understood by family. Although the effect of this perceived misunderstanding was not investigated, it is possible that this contributes to the frustration reported to be experienced by parents. Misunderstandings in relation to CRF have not previously been described in the literature, in relation to older or younger adults.

### **3.6.3 Fatigue management**

#### **3.6.3.1 Current practice**

This survey provides the first description of current UK clinical practice in TYA fatigue management, revealing therapeutic scepticism and under-management. Less than one in five participants (19%) believed that ‘something could be done’ about their fatigue. Stone and colleagues, in their survey of older adult CRF almost two decades ago, found similar levels of scepticism, with only 22% believing something could be done to improve fatigue [23]. There has been no equivalent survey evaluating current older adult fatigue management since then.

Nonetheless, there has been some evidence of progress in the intervening years. In the current survey, although only two in five participants (41%) had received fatigue management support, the equivalent figure in the Stone survey was substantially lower with only 14% receiving help with fatigue [23]. Two thirds (65%) of the fatigued survey participants had talked to a healthcarer about fatigue and, of those receiving fatigue treatment, 68% had received advice to exercise (the respective figures in older adults being 48% and 4%) [23]. It is encouraging that exercise was found to be the approach most commonly recommended by healthcare professionals, given that it is the most evidence-based treatment, albeit in older adults [56]. Furthermore, most (17/22) of those participants encouraged to rest were also encouraged to exercise.

Overall, however, it is concerning that a significant minority of TYA cancer patients (41%) report having received no fatigue management support at all. Compared with some cancer-related symptoms, such as pain, fatigue appears to be neglected. While evidence from both young and older cancer patients suggests that at least 90% receive adequate support for pain management [99,278], support for fatigue appears to be more in line with other relatively neglected symptoms, such as constipation, depression and insomnia. A large pan-European study, for example, found that 40-80% of older adults self-reporting these symptoms disclosed not having received symptom management support [279]. Rates of inadequate control of these other neglected symptoms have not been reported in the TYA cancer literature.

#### **3.6.3.2 Perceived successfulness of current approaches**

The perceived successfulness of most fatigue treatments was low, with only blood transfusion reported to be more often successful than unsuccessful. Participants reported that most treatments were ineffective for fatigue and most believed that fatigue could not be treated.

Interestingly, exercise was recommended as the best fatigue treatment, despite most participants finding exercise unhelpful for fatigue. Those who had received active treatments, such as exercise or

physiotherapy, were significantly more likely to recommend an active treatment to others, whereas there was no evidence that those who had received rest-focused treatment were more likely to recommend a rest-focused approach to others. The survey finding, that the single greatest impact of fatigue was on the ability to exercise, illuminates this apparent paradox.

The successfulness of fatigue management appeared to be lower in respondents further from the end of cancer treatment. Selection bias may limit the validity of this finding; people could be more likely to participate in the survey, long after the end of treatment, if their fatigue remains severe, and the survey has shown that those with worse fatigue perceived treatment to be less successful. Alternatively, this finding might represent a perception caused by an increasing mismatch between expectations and reality the further a patient is from the end of fatigue treatment. A third possibility is that fatigue management is, indeed, less successful later after the end of cancer treatment. Given that fatigue hinders the exercise that has the potential to ameliorate it, it is conceivable that inactivity may lead to loss of fitness that, in turn, worsens the fatigue and makes it harder to manage. As discussed in section 3.6.6.2 (page 93), further research is needed to investigate this hypothesis.

The successfulness of current fatigue management for TYA cancer patients cannot be compared with that of older patients, as this survey is the first to evaluate the successfulness of fatigue management in routine clinical practice in cancer patients of any age. Research to date in older adults has involved evaluation of the effectiveness of experimental fatigue interventions, rather than observational assessment of the perceived successfulness of existing fatigue management.

#### **3.6.4 Theoretical underpinning**

Although the survey did not explicitly question participants on their self-efficacy for fatigue self-management, several findings suggested self-efficacy was low. [148] Four out of five participants did not believe fatigue could be treated. Furthermore, participants considered current management approaches to have limited successfulness; this included exercise, the most evidence-based approach for CRF management, and the approach participants most recommended to others.

This suggestion of low perceived self-efficacy has implications for future research, both in terms of optimising adherence and promoting engagement with a non-pharmacological intervention, as will be discussed in section 3.6.7.2 (page 93).



### **3.6.5 Methodological discussion**

The findings discussed so far relate to the first three objectives of this study, establishing the prevalence, severity, impact and current management of fatigue. The fourth objective was a methodological one: to examine the feasibility of using an electronic, rather than paper, survey methodology in TYA cancer patients.

As discussed in section 3.2.2 (page 45), an electronic, rather than paper, survey was undertaken following advice from young patients; advantages include the low cost, ease of analysis, high data integrity and reduced participant burden, while anticipating potential limitations from lower response rates and selection bias. As electronic surveys of patients remain rare in research contexts, rather than service evaluations, appraisal of the feasibility of this approach was an integral part of this study.

#### **3.6.5.1 Advantages**

Many of the known benefits of electronic survey methods were confirmed. Data integrity was extremely high, with only 1.8% missing data. This compares favourably with postal surveys; a review of 285 randomised controlled trials collecting patient reported outcomes, many by postal questionnaire, found that 36% of studies reported more than 11% missing data [280].

In this survey, the first two questions were made compulsory, an approach known to reduce missing data. Equally, there is evidence that such an approach can reduce response rates, so a pragmatic compromise was taken with only the first two questions being mandatory [281]. Data analysis was facilitated by direct transfer of electronic data from the QuestionPro platform to the database for analysis, without the need for time-consuming, and potentially inaccurate, data transfer from paper to electronic format.

The burden of the survey on all parties was low. The survey cost a total of £1568 (travel expenses to sites: £240; prizes: £448; site administration costs: £880), excluding the PI salary costs. The extra costs of paper, postage and a data manager salary would have rendered a paper questionnaire considerably more expensive. Perhaps more importantly, there was indirect evidence of low participant burden; participants took a median of eight minutes to complete the survey and no-one withdrew part way through. The conditional branching programmed into the questionnaire meant that those participants who were not fatigued were able to complete the survey in only three minutes. Most participants (46/80) used a smart phone, with associated ease of access. 54/80 participants responded on the day of the initial or reminder email, suggesting that the electronic approach allowed a spontaneous and rapid response, potentially with less of a sense of burden.

The participating sites gained a further unanticipated benefit. Clinical staff at the Southampton and Cambridge sites gave unsolicited descriptions of the benefit of the research process having required them to update their patient database, particularly in relation to ensuring the recording of email addresses with consent to use them.

### ***3.6.5.2 Disadvantages***

The two main concerns about using an electronic survey were the potential for selection bias, due to the necessity for access to the internet, and the risk of a low response rate. In this young population, the risk of the former, although not measurable in this study, was considered to be low due to the ubiquitous access to mobile technology; 99% of 16-34 year olds in the UK are recent internet users [263]. However, there was still potential for selection bias. Twenty four of the initial 221 emails sent from all three sites were returned as 'undeliverable'; it is possible that those individuals who had changed email address differed in some way to those with an unchanged address. This rate is not dissimilar to a previously reported 'bounce rate' of 10% in a survey of healthcare professionals [253].

Furthermore, not all patients had given their email address to their cancer service; in Manchester, uncertainty over whether patients had given consent for their emails to be used for research, led to an unknown proportion of patients not being contacted. In Cambridge, this proportion was known: 47 out of 193 otherwise eligible patients had not given their email address or had not given consent to use it. Those patients without recorded email addresses, or without consent to use them, may have differed from the population as a whole in unknown ways, giving further potential for selection bias.

The potential for non-response bias was considerable, given the response rate of 41%. Response rates reported in the literature vary considerably: published postal surveys are often 50-70%, whereas electronic surveys are lower at 20-50% [259,282-285]. The latter figures relate largely to electronic research surveys of healthcare professionals, patient satisfaction surveys and evaluation of education; electronic research surveys of patients are much less common.

Many of the strategies known to improve response rates were incorporated into the survey design, including priming, reminders and incentives [259-261]. There was a suggestion that priming was helpful in that the site with most limited priming (Southampton) achieved by far the lowest response rate. The loss of service Facebook access in Southampton, combined with the evidence from Manchester that 12/16 participants were recruited through Facebook, suggests that social media may provide a particularly useful priming platform in this young age range. This is perhaps unsurprising, given that social media are increasingly recognised to be highly influential on choices, particularly those made by young people [286].

In terms of reminders, a pragmatic decision was made to limit this to a single reminder in non-responders, in order to limit the burden on this potentially vulnerable patient group. As shown in figure 3.1 (page 58), the single priming email had a marked impact, appearing to trigger 22 of the 80 participants to respond. Consistent with this, the literature suggests that the odds of response increases by more than a quarter when there is follow up contact, and that response rates increase further with each of three successive contacts [287,288]. However, benefit appears to diminish incrementally after the first contact, with evidence that second and third reminders do not significantly change the overall characteristics of respondents or study outcomes [289]. The balance of benefit against burden can be argued therefore to be in favour of one reminder in potentially vulnerable patient groups, although in other populations more than one reminder may be reasonable.

The survey response rate of 41% does potentially compromise its generalisability. Traditionally, response rates of over 50% have arbitrarily been considered acceptable, with corresponding influence on potential for publication. However, a change in perspective has occurred in recent years, in parallel with declining response rates in healthcare research. Morton and colleagues have argued that, in light of recent evidence that lower response rates have little, if any, impact on the accuracy of study findings, there should no longer be a defined 'acceptable response rate' [290,291]. Instead, study validity should be assessed by describing attempts to increase response rates and by comparing the characteristics of non-respondents and respondents.

It was possible to gather demographic data concerning non-responders in this survey; fatigue levels however could not be determined, meaning that selection bias according to fatigue severity could not be excluded. The demographic characteristics of responders and non-responders were broadly comparable (section 3.5.2, page 58), supporting survey validity despite the relatively low response rate. The key difference between the two groups was that no patients responded to the survey while receiving cancer treatment. However, once the data of responders were compared with that of those non-responders also off treatment, it was apparent that there were few demographic differences between the groups. It is noteworthy that there was no longer a gender difference, given the known increased prevalence of CRF in females revealed in this survey (section 3.5.3.2, page 65) and already established in the literature [230]. The two remaining differences between the two groups, median time since last treatment and treatment duration, were relatively small and unlikely to bias the findings significantly.

Overall, therefore, electronic survey methods have been shown to be feasible in this young patient group. As well as the many apparent benefits of this approach, efforts to improve the response rate, along with undertaking a non-responder analysis, partially mitigated the potential negatives. The implications of these findings for future research will be described in section 3.6.7.2 (page 93).

### **3.6.6 Strengths and limitations**

#### **3.6.6.1 Strengths**

The main strength of this survey was its focus on the specific gaps in the literature identified in the systematic review, including the lack of evaluation of parents' perspectives and limited interventional research. The sequential nature of the studies, with the survey being able to build on the review findings, has optimised the usefulness of the survey, despite the many limitations that will be discussed in detail below.

In statistical terms, a further strength is its relatively large size, recruiting 80 patients across the UK from a cohort that is not only relatively small but also particularly vulnerable, due both to young age and the serious nature of a cancer diagnosis. Only 17 of the 69 studies in the systematic review recruited more participants than this survey. Furthermore, a validated and multidimensional fatigue scale was used as the primary outcome, on which a large proportion of the statistical analyses were based. This makes the findings more robust, given the controversy over whether it is acceptable for data from Likert-type scales to be considered continuous, rather than ordinal [292].

#### **3.6.6.2 Limitations**

Survey validity and generalisability have been limited by a number of factors. The two most important limitations are the risk of response bias and the likelihood of type 1 errors occurring.

Although selection bias was possible in relation to internet access and email address availability, of greater concern is the risk of response bias from fatigued people being more interested in taking part in the survey. It is well established that people are more likely to respond to a survey if interested in the topic in question [293]. The main way to have mitigated this risk would have been to avoid the word 'fatigue' in the survey title and information, and to have described the survey as evaluating symptom management more generally. This was considered, but not pursued, due to ethical concerns about loss of transparency, as well as practical matters, such as avoiding a lengthy and burdensome questionnaire. Response bias towards more fatigued patients may have exaggerated several of the study findings, particularly the data on fatigue prevalence and impact. Furthermore, as discussed in sections 3.6.3.2 (page 84) and 3.6.1.3 (page 82), increasing selection bias further from the time of the last cancer treatment could have led to the finding that fatigue was worse, and its treatment less successful, in those more than a year after the end of treatment.

Another significant limitation is the risk of type 1 errors having occurred, given the large number of statistical tests undertaken. A type 1 error occurs when a null hypothesis is true but is rejected, leading to a false positive outcome. Setting a significance level of  $p = 0.05$  means that it was decided that it would be acceptable to have a 5% probability of a false positive result. The more tests that are undertaken, the more likely it is that a true negative finding would appear to be positive by chance. Given that this was an exploratory survey, rather than an attempt to give a definitive answer to a specific question, it was considered more important to minimise type 2, than type 1 errors. No attempt was therefore made to make statistical adjustments, such as a Bonferroni correction to compensate for the multiple comparisons [294]. Overall, therefore, it is possible that some of the statistically significant findings in this survey arise from chance alone. Further research, as described in section 3.6.7.2 (page 93), is needed to confirm the findings.

Although it was argued above that the size of the study population was relatively large, given the small and vulnerable population with a relatively rare problem, the statistical power of the study was low, particularly when analysing data from participant subgroups. Post-hoc power calculations were undertaken, confirming the relatively low power. The survey found a 14-point worsening of MFS fatigue score in those participants more than one year from the end of cancer treatment, compared to those within the year after the end of treatment; Varni and colleagues undertook a similar comparison, in children aged 2-18 rather than the TYA population, and found a 7-point reduction in fatigue (MFS) across the same timescale [161]. A power calculation, using  $\alpha$  and  $\beta$  values of 0.05 and 0.2 respectively, suggested that the survey had only a 27% power to detect a 7-point change in MFS. Other survey calculations appear however to have been more robust; the post-hoc power calculation, using reference data from a study evaluating MFS scores in young adults with a chronic health condition [295], suggested that the survey had 80% power to detect a correlation of 0.31.

In addition to selection and response bias, a further limitation of the survey was the potential for recall bias. Participants were asked to remember fatigue therapy over a period, at times, of years. Recall bias may have led to some apparently spurious findings, such as more blood transfusions having apparently been received by those closer to the end of cancer treatment.

Several other limitations need to be considered. Poor sleep was an important correlate of fatigue in the systematic review, and its inclusion in the survey questions would have been valuable. Generalisability is hindered by all participants having completed cancer treatment, meaning that findings can only be generalised to the post-cancer treatment population. Furthermore, the response rate data from Manchester were unreliable. The lack of prior consent to use email addresses for

research meant that patients were asked by their clinical team whether they were happy for their email address to be used for the survey, which is likely to have increased the apparent response rate. However, as Manchester recruited relatively few participants, this is unlikely to have changed the overall response rate markedly.

### **3.6.7 Implications**

#### ***3.6.7.1 Clinical practice and policy***

Although this survey was an exploratory study, there are multiple implications for clinical practice and policy, as well as for future research.

Building on the clinical implications of the literature review (section 2.6.4.1, page 42), this survey has generated evidence that reinforces the importance of healthcare professionals proactively raising the topic of fatigue during clinical consultations. Participants who did speak with a healthcare professional were much more likely to receive support with fatigue management; all of the 15 patients who did not talk with a healthcarer did not receive fatigue support, whereas 40 of the 44 who did talk received support. The survey revealed a high level of scepticism that fatigue could be treated, and at least a third reported that they felt that healthcare professionals misunderstood their fatigue. These data suggest that, while talking with healthcare professionals is valuable, therapeutic scepticism may inhibit patients from raising the subject.

A solution could be for healthcare staff to raise the topic of fatigue proactively. Fatigue is highly prevalent, so proactive questioning is likely to be productive. Such brief intervention would lead to fatigue affirmation, reducing the perception of being misunderstood. As discussed in section 2.6.4.1 (page 42), interventional studies for older adult fatigue have found clinically relevant benefits from placebo, suggesting that simply talking about fatigue can be therapeutic in itself [54].

The evidence for correlation between fatigue and concurrent symptoms is consistent with the evidence in adults that careful management of other symptoms can improve CRF [44]. Rigorous control of concurrent symptoms should be an existing part of good patient management and may, inadvertently but usefully, have a positive impact on fatigue.

The survey has revealed, for the first time, albeit with proxy reporting, the impact on parents, and the perception of poor family understanding of fatigue. In this context, it is likely that family involvement in clinical discussions about fatigue would be valuable, both for young patients and for family members. This could support family insight into the experience of fatigue, and may potentially reduce the perceived 'frustration' and 'upset' reported by young patients.

### **3.6.7.2 Future research**

This survey has provided extensive information on valuable areas of future research. Attempts to answer a small number of research objectives have inevitably led to generation of a plethora of further questions. As an exploratory study, all outcomes need to be supported by further research powered specifically to confirm each finding.

Although a key outcome of the survey has been the high prevalence of TYA CRF, this needs confirmation in a study designed to reduce the risk of response bias; for example, a survey could evaluate many symptoms, rather than explicitly focusing on fatigue, and could incorporate a control group of healthy age-matched young people. A large number of participants would be needed for the study to have the power to generate valid findings in relation to just one symptom, fatigue.

The persistence of fatigue, and its apparent worsening further from the end of cancer treatment, requires a longitudinal, rather than cross-sectional, study design, in order to evaluate temporal patterns. Prospective data collection would reduce the risk of recall bias. Although one such study has now been undertaken, Macpherson and colleagues only evaluated fatigue in patients with Hodgkin's lymphoma, and in the three year period from the end of cancer treatment. A longer-term study, including the period during cancer treatment, with larger patient numbers and a range of diagnoses would provide invaluable information. Furthermore, such a study could explore further the hypothesised mechanisms for fatigue perpetuation; fatigue expectations could be tested as predictors for symptom perpetuation, and the temporal pattern of fatigue and activity changes could infer causality. Qualitative research is needed to provide further insight into participants' views on causality, for example the direction of the relationships between fatigue and activity, and between fatigue and other symptoms.

Although this survey has provided novel and valuable data quantifying the impact of fatigue, qualitative research is also needed to generate insight into the mechanisms of impact. For example, this work has suggested that the cognitive impact of fatigue is particularly problematic after the end of cancer treatment. Qualitative research would help clarify the relative impact of the different fatigue dimensions of fatigue and could explore a potential mechanism, such as the hypothesis that cognitive demands increase after cancer treatment [168].

Parents' perspectives have been assessed for the first time in this survey, although only by proxy. Direct investigation of parents' views is needed. Given the evidence that misunderstandings may occur, qualitative research could usefully generate insights into the causes and impact of misunderstandings, and whether they contribute to TYA perceptions of parental frustration.

This survey, by providing an overview of current (inadequate) fatigue management in the UK, has firmly established the need for future interventional research. Further, it has highlighted the need for such research to evaluate fatigue treatment beliefs and needs in TYAs, to optimise adherence to, and engagement with, fatigue intervention. Treatment adherence can be more problematic at a young age (section 1.1.3, page 9); a review of adherence in adolescents and young adults with cancer estimated treatment non-adherence rates of 27% to 60% [90]. The survey findings of therapeutic scepticism and fatigue impacting on activity, raise concerns that intervention adherence may be low; health-related beliefs, including perceptions of low therapy efficacy and of obstacles to adherence, are known to be important predictors of poor adherence [89,296,297]. Future research needs to consider how to promote self-efficacy for fatigue management and, specifically, to determine how best to initiate exercise when fatigued. Low intervention engagement is a key barrier to successful non-pharmacological symptom self-management [298]. Engagement can only be achieved with an acceptable intervention that meets the needs of young people.

The persistence of fatigue, along with its apparent increase in fatigue further from the time of the end of cancer treatment, suggests that early fatigue intervention may be valuable, to avoid the symptom becoming entrenched and worsening. Future studies need to determine the optimal timing of fatigue intervention. Given the significant cognitive and affective impact of the symptom, specific research efforts are needed to find out how best to mitigate this component of fatigue, at an age when cognitive function at school, college or work can impact considerably on life direction.

Finally, the novel methodological aspects of this survey have research implications. Electronic surveys, without concurrent paper or telephone contact, appear to be feasible in TYAs. Further research is needed involving patient groups with a lower propensity for mobile technology use. Given that all participants had finished cancer treatment, research is needed to find out how best to reach those currently receiving cancer treatment. It could be, for example, that supplying electronic tablets in hospital could broaden access. The suggestion that priming with social media was particularly productive needs further exploration, not only in TYAs, but also at other patient ages.



### **3.7 Key points**

This survey has provided a valuable contemporaneous overview of the experience of fatigue and its clinical management amongst current TYA cancer patients in the UK. The symptom is, as suggested by the systematic review, prevalent and persistent. The novel findings in relation to the impact on young patients and their parents provide insight into the distress caused by fatigue. The survey has established the need for interventional research. Intervention development needs to focus on supporting treatment adherence, on promoting self-efficacy despite therapeutic scepticism, and on initiating activity when hindered by fatigue.

The key findings from this study are summarised in table 3.19. The table includes findings from the systematic review, to demonstrate the sequential building and synthesis of research findings.

**Table 3.19 Fatigue in Focus survey key points in context**

<b>TYA CRF topic</b>	<b>Study 1: Systematic review</b>	<b>Study 2: Fatigue in Focus survey</b>
<b>Prevalence</b>	The prevalence range was 9-67% after cancer treatment; fatigue was the first and second most prevalent symptom in 11 and 6 of 20 studies respectively.	Fatigue was the most prevalent symptom experienced by 85% of participants after the end of cancer treatment. Cognitive fatigue was particularly prevalent, compared to previous studies evaluating patients during cancer treatment.
<b>Temporal pattern</b>	Only one longitudinal study has evaluated fatigue beyond the end of cancer treatment.	Fatigue severity was higher more than one year after the last cancer treatment, compared to during the year after treatment ends. Further research is needed to gain insight into the cause(s) of fatigue persistence.
<b>Symptom correlates</b>	Physical and psychological symptoms most commonly associated with fatigue were poor sleep and low mood respectively.	Significant correlation was found between fatigue and other symptoms, fatigue forming a symptom cluster with low mood and anxiety. It could not be determined whether this represents association or causal relationships.
<b>Impact</b>	The most commonly reported impact was 'distress', followed by fatigue being a barrier to physical and to social activities.	Fatigue was the symptom with the worst impact on daily life, and an independent predictor of poor quality of life. The greatest impact was on exercise, school/work attendance and socialising, potentially suggesting some sources of fatigue-related distress.
<b>Parents' perspectives</b>	No past research has evaluated the perspectives of parents or other carers.	Parents were the main carers. Only 13% of participants perceived no negative impact on carers, with 'upset' and 'frustration' occurring commonly. A third of parents were perceived to misunderstand the symptom, although the causes and impact of this have not been established. Direct parent views are needed in future research.
<b>Management</b>	No studies have evaluated an intervention with a fatigue related primary outcome; current clinical practice, in terms of symptom management, is also unknown.	Most participants, almost 3 out of 5, had been recommended a fatigue treatment, most commonly advice to exercise. Participants themselves recommended active treatments more than rest-focused ones. However, therapeutic scepticism prevails with no treatments apart from blood transfusion perceived to be successful. Interventional research is needed, with a design that promotes adherence.

## **4 Fatigue Intervention Co-design Study**

### **4.1 Title**

Fatigue Intervention Co-design Study (FICS) in teenagers and young adults with cancer

### **4.2 Rationale**

#### **4.2.1 Justification for study**

##### ***4.2.1.1 Feedback from scrutiny of an early unsuccessful grant application***

From its inception, the overall aim of this programme of research has been to develop an effective fatigue intervention for TYAs with cancer. While the systematic literature review was being undertaken in 2014, Anna Spathis led a research team through an application to NIHR Research for Patient Benefit for funding of a feasibility interventional trial. The intention, at that time, had been to model the intervention on an evidence-based approach for fatigue management in older adults.

Although, as described in section 1.1.1.4 (page 4), recent systematic reviews have shown that exercise and psychological approaches are the most effective treatments for older adult CRF [48,56], in 2014 the strongest evidence was for exercise, education and activity management, the latter also being known as energy conservation [243,299]. This led to the research group developing an intervention called the '3 Es': Exercise, Education and Energy conservation. A qualitative process evaluation was included in the mixed-methods study to gain feedback on the intervention, as well as on trial process, in order to optimise intervention acceptability in a subsequent definitive trial [300].

The application for funding was not approved. The main concern of the funding panel was the 'insufficient detail... about the likely content of the intervention'. It was therefore decided that, before seeking funding for a feasibility trial, it was necessary and important to set up a study focused entirely on intervention development. This chapter describes that study.

##### ***4.2.1.2 Increasing emphasis on complex intervention development***

A non-pharmacological fatigue intervention fits within the definition of a 'complex intervention'. Complex interventions are defined as interventions having several interacting components, with dimensions of complexity including the range of 'behaviours required by those delivering or receiving the intervention' and the degree of permitted intervention flexibility [135]. The MRC published seminal guidance on the evaluation of complex interventions in 2000, which was subsequently updated in 2008 [135].

A key change in the updated guidance has been the increased weight given to the intervention development phase. The guidance suggests that such development needs to be not only underpinned by current evidence and appropriate theory but also, if necessary, ‘supplemented by new primary research’. Such research may include interviews with ‘stakeholders’, and ‘modelling of the intervention’. The development process is further strengthened by understanding *how* the intervention might work [135]. Despite the increasing emphasis on the importance of intervention development, it is striking how rarely researchers provide formal descriptions of how this process occurred, and there have been calls in literature to increase publication of the intervention development process [301,302].

Careful intervention development may be particularly important in young patients; low treatment adherence may be a consequence, at least in part, of failure to recognise their distinct needs [99]. Approaches recognised to increase adherence include customising treatments to meet such needs, and empowering young people to take control of, and responsibility for, their adherence [296].

#### **4.2.1.3 *Building on preceding studies***

The two studies described in the preceding chapters have strengthened further the rationale, both for the need for an intervention for fatigue in TYAs and for the need for age-appropriate intervention development. The systematic literature review established that there have been no previous interventional studies in TYA cancer patients using fatigue as a primary outcome, and the survey confirmed inadequate current management of the symptom in the UK.

The need for intervention development has been highlighted by the paradoxical survey findings that, although participants were most likely to recommend exercise as a fatigue treatment, few considered exercise to be helpful; fatigue is itself a barrier to the approach most likely to help it. Motivating young people to be physically active is likely to be challenging given that activity tends to decline in healthy adolescents [303], activity is particularly low in young people with cancer [304], and there is evidence that activity declines significantly during cancer treatment [305]. With fatigue further hindering activity, it is clearly vital that young people are involved in intervention development, in order to best overcome the many barriers to physical activity.

Beyond the focus on intervention development, several findings from the survey could be usefully explored further with qualitative research, as discussed in section 3.6.7.2 (page 93). The survey provided preliminary pointers to why fatigue may be so distressing in this young group, including the relatively high prevalence of cognitive fatigue after cancer treatment and the negative impact on aspects of daily living; qualitative evaluation of experiences could provide further insight into the mechanisms of the negative impact of fatigue. Fatigue severity closely correlated with that of other

symptoms; qualitative research has potential to determine the direction of causal relationships. The survey provided proxy evidence from TYA patients of the impact of fatigue on parents; parents' perspectives could be explored qualitatively while involving them in intervention development.

## **4.2.2 Justification for research design**

### **4.2.2.1 *Co-design of complex intervention***

Implementation science is a rapidly developing field that is interested in applying research evidence into practice [306]. At the start of its development, a decade ago, the focus was on bridging 'research to practice gaps' [307]. Increasingly, however, the concept of co-creation is being promoted in order to 'deliver health with integrity of purpose' [308]. 'Co-creation' covers two terms that are sometimes used interchangeably: 'co-design' involves working collaboratively with stakeholders to define problems and solutions, whereas 'co-production' involves working collaboratively to implement the proposed solutions [309]. The stakeholders are the patients who will receive the healthcare; their involvement in the co-creation process is vital [306,308].

Experience-based co-design (EBCD) has evolved as a key facet of implementation research [310]. It draws on patients' experiences to innovate and improve the quality of healthcare services, and interest in this approach is growing internationally [311]. A review in 2014 revealed over 80 projects using, or intending to use, EBCD with increasing evidence of its capacity to improve healthcare outcomes [312,313]. Although used initially to improve the quality of services, in recent years a number of examples have emerged of EBCD being used in the development of complex interventions [314].

The process of working with users to develop complex interventions is highly variable and still evolving. In 2011, Lowes and colleagues co-designed a complex intervention, DEPICTED, for young people with diabetes [138]. Young patients, parents and healthcare professionals collaborated to develop the intervention during three, day-long, Stakeholder Action Group meetings. All views were gathered in a workshop environment, and stakeholders did not receive the intervention themselves.

Ream and colleagues used EBCD to co-design a complex intervention, 'Take Care', to enhance the role of carers in outpatient chemotherapy [315]. This multiphase study included interviews with stakeholders, followed by co-design events that established priorities for intervention components and further refined the intervention. The outcome was the development of an intervention prototype for testing in a subsequent feasibility trial. Although multiphase in design, the stakeholders again did not receive the intervention themselves [316].

Building further on this approach, Foster and colleagues co-created a web-based self-management intervention to support adult patients living with CRF [302]. Not only did this work apply co-design methods to the symptom of fatigue, the innovative multiphase study design incorporated two phases of user testing of the intervention, with subsequent further refinement of the prototype. User testing involved different participants and a range of methods of qualitative data collection. Having seen the utility of this approach in a relevant, albeit older, population of patients with CRF, it was decided to use a multiphase iterative approach to co-design, including a phase of user testing and feedback to enhance further intervention acceptability.

#### **4.2.2.2 *Qualitative methods***

When developing a complex intervention, the MRC advocates that ‘wherever possible, evidence should be combined from a variety of sources that do not share the same weaknesses’ [135]. Having already generated quantitative data in the survey, it was decided that predominantly qualitative data would be collected in the Fatigue Intervention Co-design Study (FICS).

Qualitative research provides insight into subjective experiences, illuminates causal explanations for associations, and is valuable in complex intervention design. There is increasing recognition of the role of qualitative research in increasing the depth of understanding of healthcare research, particularly in the complexity of real life with the existence of multiple perspectives, different types of causal pathways and multiple types of outcomes [306,317-319].

This programme of research is underpinned by Self-Efficacy Theory (section 1.2.4, page 16). The survey demonstrated therapeutic scepticism and little confidence that exercise could help the fatigue among TYA cancer patients. It is, therefore, important to understand the factors limiting perceived self-efficacy, and to establish approaches that improve confidence in the ability to self-manage fatigue. Qualitative research methods are best able to generate insight into the complexity of the experience of fatigue and into participant perspectives on improving perceived self-efficacy in fatigue self-management.

It was decided to conduct both interviews and focus groups, to increase the range of insights. Interviews tend to produce a broader range of unique and relevant views, whereas focus groups increase elaboration of ideas and debate [320]. A pragmatic view was taken that individual interviews would be preferable in the context of discussing potentially personal and sensitive information, particularly given adolescent predilection for embarrassment. Equally though, a recent study in which participants were randomised between individual interviews and focus groups, found that more sensitive themes emerged in the focus groups [320]. Either way, using both methods of

data collection was thought to be likely to increase data richness and variety, providing potential for triangulation and thus enhancing the validity of the qualitative research process [321].

The inclusion of parents led to this becoming a multi-perspective qualitative study. Although posing potential challenges, in terms of recruitment and data complexity, multi-perspective research leads to a deeper understanding of the experiences, perceptions, relationships and needs of all participants [322]. It allows the integration of perspectives and optimises recommendations for service improvement in a 'real world' setting, where young people are embedded in social contexts.

Longitudinal qualitative research has emerged in recent years as a valuable approach [323]. It has the capacity to identify trajectories and 'turning points', and deepens the interpretative potential of the research. Although it gives potential for attrition and further increases data complexity, it was decided that a multiphase longitudinal approach would be used, as it would allow the intervention prototype to go through a second stage of refinement, enhancing its validity.

Given the potentially large data set from a multiphase, multimethod and multi-perspective study, it was decided that the Framework Method would be used for data analysis. Developed by Ritchie and Lewis in the 1980s initially for large-scale social policy research, this method has since been increasingly used in medical research [324]. The approach is a form of thematic analysis that has, as its defining feature, a framework matrix output, with a row for each case and a column for each code, and data summarised within each cell. Several features of the Framework Method justify its choice [325]. First, it supports the management of large data sets by providing a descriptive overview of the entire data set within the generated frameworks. Further, it provides a structure that is well suited to semi-structured interviews and focus groups, as these are relatively homogenous in nature, and it facilitates inter-case comparison. Finally, the inherent flexibility of the method allows a mixed deductive and inductive approach. Although much of the analysis was likely to be deductive, testing hypotheses generated from the preceding studies in this programme of research, the freedom to induce new concepts and codes iteratively during data analysis was retained.

## **4.3 Aim and objectives**

### **4.3.1 Aim**

The aim of this study was to co-design a non-pharmacological fatigue intervention with teenagers and young adults with cancer, which can subsequently be tested in a controlled trial to evaluate its effectiveness in increasing perceived self-efficacy in fatigue self-management.

### **4.3.2 Objectives**

1. To investigate the views of TYA cancer patients and their parents on factors that help and worsen fatigue and their perception of self-efficacy
2. To understand the experiences of parents of TYA cancer patients with fatigue
3. To ascertain the views of TYA cancer patients and parents on optimal intervention design
4. To evaluate the experience of receiving the prototype intervention, and to amend the intervention accordingly.



## **4.4 Methods**

### **4.4.1 Study population**

Participants were recruited from one centre, the TYA cancer service at Cambridge University Hospital NHS Foundation Trust, the regional PTC for TYA cancer patients.

#### **4.4.1.1 Eligibility criteria**

##### Patients

- Aged 16-27 with a diagnosis of cancer
- Currently or previously known to the Cambridge TYA cancer service
- Primary cancer treatment completed within one year of recruitment OR on maintenance treatment for leukaemia.
- A screening score of  $\geq 5$  in a 10-item NRS of fatigue severity over the last month
- Able to give informed consent.

##### Parents

- A parent of a patient participant, or of a patient who is not participating but would be eligible to participate
- Patient consent to the parent being approached about the study
- Parent able to give informed consent.

The only exclusion criterion for patients and parents was current active participation in another clinical trial.

#### **4.4.1.2 Sampling and recruitment strategy**

Purposive sampling was used to obtain a maximum variety sample of participants, including age (16-21/22-27), diagnosis (solid/haematological malignancy) and gender (M/F). Recruitment continued until data saturation occurred, with no new themes emerging.

Potential participants were identified and approached by members of their usual clinical team. Study information was also made available on the TYA service Facebook page (appendix 7.4.4, page 328). Participants could be recruited from any setting including outpatients, inpatient ward, day therapy and the Oasis Centre (a non-clinical facility providing support to young cancer patients on the hospital site). Recruiting clinicians were aware of the purposive sampling strategy and were continually updated on the state of recruitment. Interested patients were contacted by Anna Spathis and given information about the study. Patients had at least 24 hours after receiving the Participant Information Sheet (PIS), before making a decision about participation (appendix 7.4.1, page 323).

All young participants were asked if they consented to one or two of their parents being approached to participate. It was made clear that not wishing to give consent to their parents being approached did not preclude their own involvement in the study. Parents could be recruited alone with the consent of a non-participating young patient, if insufficient parents had been recruited once patient recruitment has ceased. The parent PIS and study information for healthcare staff are at appendices 7.4.2 (page 325) and 7.4.3 (page 327).

#### **4.4.2 Study schedule**

##### **Phase A: Pre-intervention**

- Individual interviews with patients and with parents.
- Two focus groups, one for patients and one for parents.

##### **Phase B: Intervention design and delivery**

- Development of prototype intervention, informed by data from phase A.
- Participants receive the intervention from an allied health professional (AHP).

##### **Phase C: Post-intervention**

- Further individual interviews with patients and with parents, to explore their experience of receiving the intervention and to discuss further adaptation.
- Interview with therapist who provided intervention.

#### **4.4.3 Methodological considerations**

Interviews were scheduled for the time and place of the participants' choosing. Patient and parent interviews were conducted separately, both in order to respect confidentiality and also to provide insight into their potentially differing perspectives. Anna Spathis conducted all interviews, apart from eight occasions in phase A, when young participants and parents found it logistically easier to be interviewed concurrently; two researchers (Anna Spathis and Amy Chapman) then conducted the interviews, in separate rooms. The two focus groups were conducted at the same time, in different rooms within one venue, to make it easier for patients and parents to travel together. They were undertaken by Anna Spathis and Amy Chapman (parents and patients respectively). Refreshments were made available.

The interviews and focus group discussions were semi-structured. They followed a topic guide with questions on patient and parent experiences, and participant views about the content, setting and delivery of the fatigue intervention (appendices 7.4.8, page 334; 7.4.9, page 336). The topic guide was developed predominantly from the research objectives, and also influenced by the literature

review and survey findings. The intervention co-design process was necessarily iterative, with questions adapted accordingly through the course of the study.

In anticipation of slow recruitment, as is often encountered in research involving vulnerable patient populations such as TYA cancer patients [326], several minor amendments were made prior to starting the research, to enhance recruitment. Patients with leukaemia on long-term maintenance chemotherapy were allowed to be eligible, and the option was provided for the second interview to be via telephone to reduce participant burden.

#### **4.4.4 Data management**

##### ***4.4.4.1 Data handling and confidentiality***

Interviews and focus groups were digitally audio-recorded, with the electronic audio files stored on a secure, password-protected NHS computer. Audio files were encrypted prior to sending to TypeOut, a professional transcription service; a confidentiality agreement was signed. The verbatim transcripts were returned in encrypted form, which Anna Spathis checked to decipher inaudible words and to fully anonymise the transcript, including respondent quotations.

Each participant was allocated a unique study number and identified by that number throughout the course of the study and data analysis. All data transfer was undertaken according to the NHS Code of Practice on Confidentiality. Personal contact details were kept by the research team because participants' home addresses were potential research sites. These and all other personal information, including the recruitment and screening log, were kept in electronic format on a secure, password-protected, NHS computer. The paper consent forms were stored in a locked filing cabinet in a secure office on an NHS site.

##### ***4.4.4.2 Data analysis process***

Anonymised transcripts were imported into the qualitative data analysis software, NVivo 11, which facilitated management and analysis of the large volume of data.

Patients were assigned numerical codes with the prefix 'TYA' (Teenage and Young Adult). Parents were given codes with the prefix 'PAR' (parent). Healthcare professionals and the research team were assigned as 'HCP' or as 'RES', according to their primary role in the study; the primary role for those involved in recruitment and for the AHP delivering the prototype intervention was as 'HCP'.

Initial transcripts were double-coded to support development of the coding frame. Anna Spathis coded four transcripts (two patients, two parents) and generated an initial coding frame. Two of these transcripts were independently coded by a non-clinician research assistant, who amended the

initial coding frame. Differing views were resolved in a face-to-face meeting. Anna Spathis then coded four further transcripts, with the research assistant double coding two. The final coding frame was agreed in a second meeting, and subsequently applied by Anna Spathis to all remaining transcripts.

#### **4.4.5 Patient and public involvement**

As a former cancer patient with personal experience of fatigue, the PPI representative within the research team, Laura Abbas, provided invaluable support for the study, including providing feedback on the design and process, Participant Information Sheets and interview topic guides. A TYA fatigue research focus group met in person on one occasion, and undertook further communication, when required, by email.

Importantly, as a co-design study, this work was in itself an extensive exercise in patient involvement. Recruited participants were both able to guide the content of the interviews and focus groups, as well as the design of the prototype and subsequent interventions.

#### **4.4.6 Ethical considerations**

Beyond participant confidentiality (page 105), a key ethical concern was limiting participant burden. Significant effort went into reducing any potential negative impact from taking part including:

- Participants could choose home-based interviews.
- Patients could elect to receive the prototype intervention at home.
- The intervention was safe and highly unlikely to cause distress as it was co-designed with participants.
- Other than patients on leukaemia maintenance treatment, only participants who had completed primary cancer treatment were recruited, to avoid having to cope with a recent diagnosis or concurrent oncological treatment.
- Participants who chose to involve a parent could potentially gain support from being involved in the research along with a family member.
- One member of research team was the TYA service TCT Youth Support Co-ordinator (Amy Chapman). As her professional role involved support of young service users, she was ideally placed to provide additional support to research participants if needed.
- Participants could choose not to involve a parent if they were concerned about confidentiality, burdening their parent or any other reason.
- Within the prototype intervention, efforts were made to manage unrealistic expectations of benefit, given that the primary research purpose was intervention co-design.

#### **4.4.7 Research governance**

##### ***4.4.7.1 NHS and ethical approvals***

Research ethics committee approval was provided by the London-Chelsea Research Ethics Committee (REC reference: 16/LO/0575, appendix 7.4.7, page 331). The study was sponsored by the Cambridge University Hospitals NHS Trust, who provided approval following a Site Specific Assessment.

##### ***4.4.7.2 Study team and roles***

Anna Spathis was both the Chief Investigator and the Principal Investigator at the NHS site. She was involved in every step of the study conduct including: responsibility for study design, writing protocol and all study related documents, gaining research approvals, PPI, organising and conducting interviews and focus groups, chairing research group meetings, facilitating the co-design process, all data analysis and providing feedback of study outcomes to study participants.

Stephen Barclay and Sara Booth, MD supervisors, provided regular guidance and advice throughout the study. In addition, a number of colleagues made specific contributions as detailed in table 4.1.

**Table 4.1 Roles of other team members in FICS**

Laura Abbas	Former TYA cancer patient, former TCT Youth Support Co-ordinator, Cambridge University Hospitals	Provided PPI; and co-ordinated PPI from other current/former patients
Sam Barclay	Research assistant, Primary Care Unit, University of Cambridge	Initial double coding of transcripts
Julie Burkin	Occupational Therapist, Lead of Breathlessness Intervention Service, Cambridge University Hospitals	Contributed to intervention co-design process; delivered prototype intervention to participants
Amy Chapman	Current TCT Youth Support Co-ordinator, Cambridge University Hospitals	Recruitment; undertaking eight interviews and one focus group; participant support; contribution to intervention co-design process.
Faith Gibson	Professor of Children and Young People's Cancer Care, Great Ormond Street Hospital	Advice on study design
Helen Hatcher	Consultant Medical Oncologist, TYA service lead, Cambridge University Hospitals	Advice on study design; recruitment; contribution to intervention co-design process
Andre Jansen	TYA cancer service clinical nurse specialist, Cambridge University Hospitals	Recruitment; contribution to intervention co-design process
Wendy Moss	TYA service administrator, Cambridge University Hospitals	Administrative support for interviews and focus groups
Jane Robson	Lead nurse TYA cancer service, Cambridge University Hospitals	Recruitment; contribution to intervention co-design process
Paddy Stone	Professor of Palliative Medicine, University College London	Advice on study design
Ben Uttenthal	Consultant Haematologist, Cambridge University Hospitals	Recruitment; contribution to intervention co-design process

## 4.5 Results

### 4.5.1 Participants

#### 4.5.1.1 Recruitment

Thirteen TYA patients and ten parents participated. After seven weeks of recruitment, twelve patients and nine parents had agreed to take part and the study closed, as the provisional recruitment target had been met and data saturation had been achieved. However, the study was opened again to allow recruitment of one further patient-parent dyad, who had heard about the study and were particularly keen to be involved. Section 4.5.16.3 (page 197) contains discussion on the unanticipated ease of recruitment. One patient declined to take part, but gave consent for a parent to be approached [PAR13]. There thus were nine patient-parent dyads, four patients without a parent, and one parent alone.

#### 4.5.1.2 Participant characteristics

Participant characteristics are summarised in table 4.2. In line with the eligibility criteria, all participants were within one year of completion of primary cancer treatment, except for one who was within the last month of maintenance treatment for leukaemia at the time of recruitment. Most participants were female: 10/13 patients and 9/10 parents. The majority of participants (10/13) had a primary haematological malignancy; for two patients the malignancy was likely to have arisen as a consequence of immunosuppressive therapy for another medical condition. In order to protect confidentiality, individuals' details are not given and some genders have been changed.

**Table 4.2 Overview of participant characteristics**

<b>Patient characteristics (n=13)</b>	
Age at diagnosis Mean (range)	19.2 (16-23)
Age at recruitment Mean (range)	21.7 (17-24)
Screening fatigue score <sup>a</sup> Mean (range)	7.7 (6-10)
Female gender n (%)	10 (77)
Diagnosis n (%)	
Lymphoma	6 (46)
Leukaemia	4 (31)
Osteosarcoma/Ewing's sarcoma	2 (15)
Testicular cancer	1 (8)
<b>Parent characteristics (n=10)</b>	
Female gender n (%)	9 (90)

<sup>a</sup> One data item missing

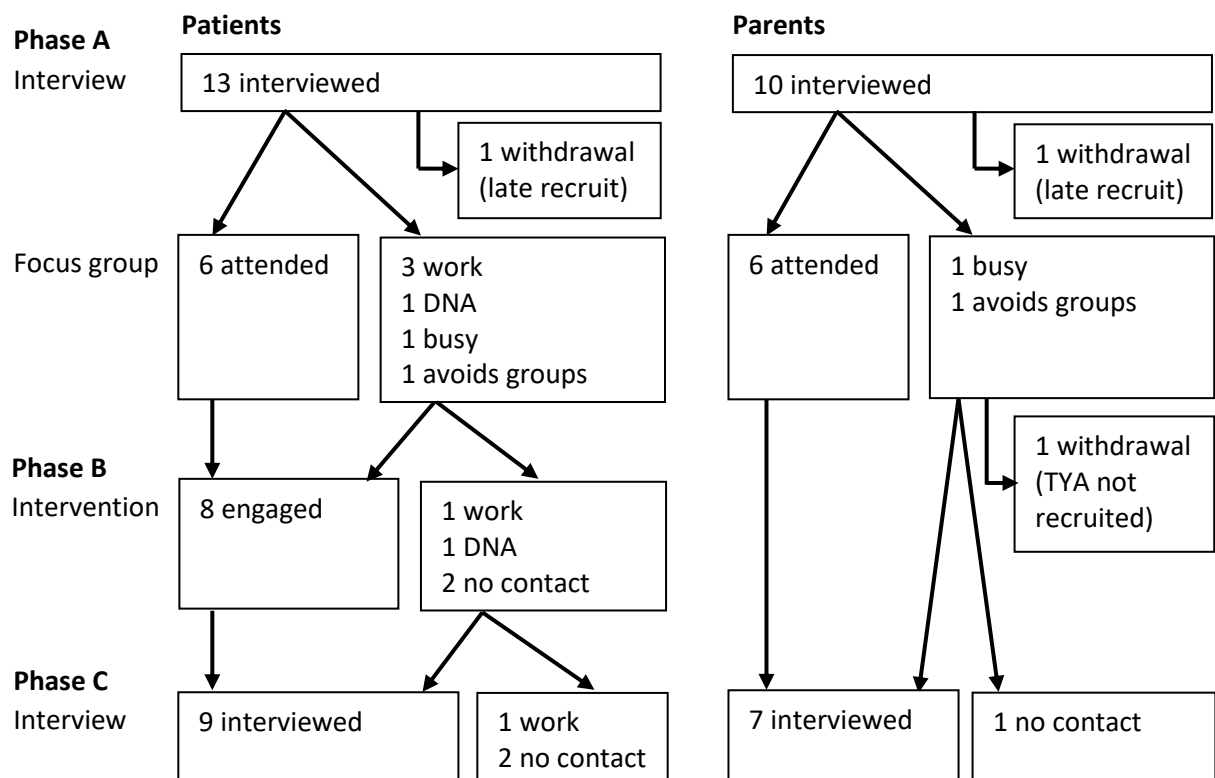
#### 4.5.2 Process measures

A total of 22 interviews were conducted during phase A: 12 patient interviews, nine parent interviews, and one joint patient/parent interview. Although the intention was to interview patients and parents individually, one dyad asked for a joint interview. Two focus groups were attended by six patients and six parents respectively.

During phase B, the interview co-design meeting was recorded, attended by researchers, healthcare professionals and a PPI representative. Prototype intervention guidance for the AHP, an occupational therapist, who delivered the intervention, is at appendix 7.4.11 (page 339). Eight patients engaged with receiving the intervention.

In phase C, 16 further interviews were conducted, involving nine patients and seven parents. The HCP who had delivered the intervention was also interviewed. Three participants could not progress to phase C, due to late recruitment after intervention delivery or due to a parent being recruited without their child. Four further participants were not involved in phase C, because they could not be contacted or were unavailable; the attrition rate was therefore 17% (4/23).

**Figure 4.1 Study flow diagram**





**Table 4.3 Overview of study participation**

	Phase A: interview	Phase A: focus group	Phase B: intervention	Phase C: interview
TYA1	✓	✓	✓	✓
-	-	-	-	-
TYA2	✓	✓	✓	✓
PAR2	✓	✓	NA	✓
TYA3	✓	✓	✓	✓
PAR3	✓	✓	NA	✓
TYA4	✓	X	X	X
PAR4	✓	✓	NA	✓
TYA5	✓	X	X	X
PAR5	✓	X	NA	X
TYA6	✓	✓	X	✓
PAR6	✓	✓	NA	✓
TYA7	✓	✓	✓	✓
PAR7	✓	✓	NA	✓
TYA8	✓	✓	✓	✓
PAR8	✓	✓	NA	✓
TYA9	✓	X	✓	✓
-	-	-	-	-
TYA10	✓	X	✓	✓
-	-	-	-	-
TYA11	✓	X	X	X
-	-	-	-	-
TYA12	✓	X	✓	✓
PAR12	✓	X	NA	✓
-	-	-	-	-
PAR13	✓	X	NA	NA
TYA14	✓	NA <sup>a</sup>	NA	NA
PAR14	✓	NA <sup>a</sup>	NA	NA

<sup>a</sup> Recruitment occurred after the focus groups had occurred

First interviews with participants were all face-to-face and occurred in the non-clinical facility for TYA cancer patients on the hospital site (n=12), on a hospital ward (n=8) and at home (n=3). All second interviews were conducted by telephone. The interview with the AHP and the research team meeting both occurred in a non-clinical area on the hospital site.

The mean study duration, defined as the time between first (phase A) and second (phase C) interviews was 24.6 weeks (range 21-34, n=16). Participants waited a mean of 10 weeks (6-14, n=8) from first interview (phase A) to the start of the intervention prototype (phase B) and the mean intervention duration (from first to last therapist contact) was 6 weeks (range 0-14, n=8).

The 42 audio files had a total running time of 22 hours and 43 minutes. The mean time of the phase A and phase C interviews were 37 minutes and 16 minutes respectively. The mean focus group duration was 83 minutes. The AHP interview was 70 minutes and recording of the co-design meeting

63 minutes. As well as transcribed audio files with a total word count of 241,000 words, there were a number of other sources of data (table 4.4). Contemporaneous field notes were written.

**Table 4.4 Summary of data sources**

Source	Description	Codes
<b>Phase A</b>		
Pre-intervention interviews	22 audiofiles involving 23 participants,	TYA#, phase A PAR#, phase A
Participant emails	2 unsolicited emails giving further information, one TYA, one PAR.	TYA#, email, phase A PAR#, email, phase A
Focus groups	2 audiofiles, one of TYA and one of PAR focus groups	TYA#, FG, phase A PAR#, FG, phase A
<b>Phase B</b>		
Co-design meeting	1 audiofile of meeting involving 2 researchers, 5HCPs and 1 PPI representative	RES, CDM, phase B HCP, CDM, phase B PPI, CDM, phase B
Audit of intervention	Audit of notes and patient letters from therapist	AUDIT
<b>Phase C</b>		
Post-intervention interviews	16 audiofiles involving 16 participants	TYA#, phase C PAR#, phase C
Therapist interview	1 audiofile from interview with the AHP who delivered the intervention	HCP, phase C

### 4.5.3 Framework development

#### 4.5.3.1 Coding process

The initial coding frame after reading four transcripts (2 TYAs, 2 parents) contained 27 codes in 5 categories. After an iterative double coding process, which included two face-to-face discussions (section 4.4.4.2, page 105) the agreed coding frame expanded to 44 codes in 5 categories.

This coding frame was applied to the remaining data. Subsequently, two pairs of categories were merged. ‘TYA experience of fatigue’ and ‘family experience of fatigue’ were combined as the experiences were closely related with many shared themes; ‘intervention principles’ and ‘intervention content’ were merged as the ‘intervention principles’ category was too small. The final coding structure contained 41 nodes in three broad categories (see appendix 7.4.10, page 338).

#### 4.5.3.2 Framework matrices

A framework matrix was developed for each of the three main categories: 1) experience of fatigue, 2) intervention principles and 3) intervention practicalities. The three frameworks each contained four sub-categories, as in table 4.5. Within each framework, the coded data were charted for each participant, the matrix cells containing case summaries as well as illustrative quotations. One of the three frameworks is provided in appendix 7.4.13 (page 340).

**Table 4.5 Overview of three framework matrices**

<b>Framework name (number of nodes incorporated)</b>	<b>1: Experience of fatigue (20)</b>	<b>2: Intervention principles (11)</b>	<b>3: Intervention practicalities (10)</b>
<b>Framework sub- categories</b>	1a. Fatigue patterns and influences	2a. Approach	3a. What?
	1b. Impact of fatigue	2b. Activity	3b. When?
	1c. Information needs	2c. Energy conservation	3c. Where?
	1d. Tensions and misunderstandings	2d. Education	3d. Who?

#### **4.5.4 Relationship between research questions, frameworks and analytical themes**

The frameworks, based on individual participants' views, were necessarily descriptive rather than interpretative. As individuals were responding to questions from a topic guide derived from the original research questions, at this predominantly deductive stage in the analysis process, there remained a close relationship between the matrix categories and the research questions (table 4.5).

However, given the unrestricted coding, unexpected and interesting themes emerged beyond those predicted at the start. Descriptive data within the frameworks exceeded those anticipated from the research questions in a number of areas. This significantly influenced analytical theme development, with only one of the six analytical themes concerned directly with the features of the 'trial ready' fatigue intervention (theme A2). An overview of the analytical themes is provided in section 4.5.5 (page 115), with extensive exploration in the subsequent sections. The longitudinal connection, from primary research questions, through to framework categories and beyond to the analytical themes, is summarised below and in table 4.6.

#### **Research question 1: To investigate the views of TYA cancer patients and their parents on factors that help and worsen fatigue and their perception of self-efficacy**

In response to open questions about their fatigue experience, participants volunteered much information relevant to the research question, particularly their perspectives on directional relationships: the causes and consequences of fatigue. The perceived impact was greatest on the key developmental needs of adolescence and young adulthood which, in turn influenced the experience of fatigue. These concepts contributed to three of the six analytical themes developed from the data, A1, C1 and C2.

**Research question 2: To understand the experiences of parents of TYA cancer patients with fatigue**

For many parents, a central part of their experience was the tension occurring between them and the young patient. However, dealing with uncertainty, misunderstandings and conflict emerged as a broad theme across participants' social experience, involving the young patient, siblings, healthcare professionals and staff at work or educational organisations, as well as parents. Exploration of these multilevel tensions led to the development of two more of the analytical themes, B1 and B2.

**Research question 3: To ascertain the views of TYA cancer patients and parents on optimal intervention design**

Participants were unrestricted and open in their views about the design of an intervention that met their needs, providing opinions that went far beyond the relatively restricted research question. They particularly expounded on age-relevant matters, such as the need to combine autonomy and individuality with specific advice. Analytical theme A2 developed from the expansion of this research question.

**Research question 4: To evaluate the experience of receiving the prototype intervention, and to amend the intervention accordingly.**

While receiving feedback on the prototype intervention enhanced intervention development, it also provided, beyond the research question, a rich opportunity to examine longitudinal participant data. Interesting patterns emerged between fatigue and symptom responses, and between participant characteristics and fatigue outcomes. These unexpected insights underpinned analytical themes C1 and C2.

**Table 4.6 Research questions, framework categories and analytical themes**

Research question	Related framework sub-categories	Related analytical themes (table 4.7)
1. To investigate the views of TYA cancer patients and their parents on factors that help and worsen fatigue and their perception of self-efficacy.	1a, 1b, 1c	A1 C1, C2
2. To understand the experiences of parents of TYA cancer patients with fatigue.	1b, 1c, 1d	B1, B2
3. To ascertain the views of TYA cancer patients and parents on optimal intervention design.	2a, 2b, 2c, 2d 3a, 3b, 3c, 3d	A2
4. To evaluate the experience of receiving the prototype intervention and to amend the intervention accordingly.	2a, 2b, 2c, 2d 3a, 3b, 3c, 3d	C1, C2

#### 4.5.5 Overview of analytical themes

The three framework matrices, containing summaries of participants' views on a case by case basis, facilitated evaluation of the data beyond a descriptive level. Patterns in the data were sought, finding associations between attitudes and behaviours, seeking explanations and formulating new ideas. This process, involving both deductive and inductive reasoning, led to the development of the six analytical themes, within three broad categories.

**Table 4.7 Overview of analytical themes**

<b>A. Young age</b>	1. TYA developmental stage compounds the impact of fatigue
	2. TYA developmental characteristics influence intervention design
<b>B. Tensions</b>	1. TYAs experience pervasive tensions and misunderstandings
	2. Fatigue-related tensions have a detrimental impact on family
<b>C. Responses</b>	1. Fatigue may perpetuate with vicious cycles
	2. Responses to fatigue relate to outcomes

Each of these themes is described in detail in the following sections. Evidence is provided in the form of quotes from participants, and each section ends with a theme discussion, contextualising and evaluating each theme. The themes are integrated, along with other study outcomes, in a final discussion in section 4.6 (page 199).

#### 4.5.6 Theme A1: TYA developmental stage compounds the impact of fatigue

Participants were universally vocal about the negative impact of fatigue on their lives. There was consistent evidence that the fatigue was particularly problematic because of its interaction and conflict with the characteristic expectations and needs of this young age. To set the scene, an overview of the links between features of the TYA age and the impact of fatigue is provided in table 4.8. There follows a detailed description of each of the adverse consequences of fatigue.

**Table 4.8 Summary of relationship between TYA developmental characteristics and the impact of fatigue**

<b>Developmental characteristics of TYA age</b>	<b>Adverse impact of fatigue</b>
Cognitive ease with good memory	Hindering cognition: The cognitive impact of fatigue on memory and concentration is worse than the physical consequences of fatigue. It makes it hard to progress in education or work, and hinders socialisation.
Emotional reactivity	Exacerbating emotional reactivity: The frustration of living with fatigue compounds the challenges of emotional regulation, with anger, irritability and low mood all considered features of living with fatigue.
Need to conform and develop peer relationships	Hampering the need to conform: It is hard to feel 'normal' when unable to keep up with peers socially. Social media paradoxically may increase the sense of isolation as it highlights what others are still able to do.
Developing independence and life direction	Dependence and demotivation: Young people are susceptible to regression when under strain. Fatigue compounds this, with increasing dependence on family support, and loss of autonomy, self-motivation and self-determination.

#### **4.5.6.1 Hindering cognition**

TYAs and parents universally described the impact of fatigue on the ability to think clearly.

...because my brain isn't functioning how I would probably say most of my friends' brains are functioning. [TYA3, phaseA]

...for instance he can't get his words out, this is a student who's done a degree, is very, very clever and he can't get his words out. [PAR2, phase A]

Fatigue had a consistently detrimental impact on concentration. This was so severe that participants described not having the concentration to read, or even watch television [supplementary data page 348].

I can't concentrate enough on anything, and I can't read, because by the time I have registered one word, and moved onto the next, I can't string them together, like I don't have the concentration to read more than one word at a time. [TYA9, phase A]

Many participants felt that cognitive fatigue adversely affected memory, as well as the ability to concentrate [supplementary data, page 348].

I have to write lists all the time. [TYA2, FG, phase A]

Then I lose my list and forget where I put them... [TYA8, FG, phase A]

There was pervasive distress about the impact of poor cognition on the ability to perform in education and work, expressed with comparable vehemence by parents. Poor memory and concentration often had a social corollary [supplementary data, page 350]

And the school expects you to work until 10:00 [pm], which is probably about four hours in their eyes. And I am too tired to do that, I can't do that. [TYA9, phase A]

Look, [TYA4] is really good, she is really on the ball. When she went back to work, and she had to go and learn this new job, she struggled massively to the point where she was coming home and crying about it at night... The stress of that learning, she just couldn't cope with it, and we had to slow it all. [PAR4, phase A]

Yeah, I find concentration quite hard especially on conversations. I zone out with my mum so much. And with my friends it's really bad, I just have to keep nodding and trying to like think of the end word they've said so I can say something about that. [TYA2, phase A]

The cognitive effect of fatigue was unexpected for some participants, fatigue being thought of as a physical tiredness. In a dominant theme, virtually every participant perceived cognitive fatigue to have a more detrimental impact than physical fatigue [supplementary data, page 348].

But it is something that I am quite shocked in myself, because I just assumed that it would be my body, because I am not used to standing up so much, and being on my feet all day at work, but it is really not. My body could get up and do another day, but mentally I just can't seem to get going that quickly. [TYA10, phase A]

Well, for me the physical isn't too bad because I've found ways of controlling it and improving it. But the mental stuff I found tricky. [TYA8, FG, phase A]

In contrast, only one TYA, the single participant with a diagnosis of CFS/ME as well as CRF, considered the physical aspects of the symptom to be more problematic than the cognitive component, with the latter remaining a significant problem.

*And is it the thinking bit or the physical bit, you know, the tiredness of your body that gets you the most? [Interviewer]*

Probably the physical gets me the most, but shortly followed by the... [TYA14, phase A]

#### **4.5.6.2 Exacerbating emotional reactivity**

The influence of fatigue on emotions was a recurrent theme, expressed by virtually every participant. A sense of emotional reactivity was often articulated.

I get really overly emotional as well, so I go one way or the other. I am either quite angry, or stressed out about something, and I lash out at them, or I find myself in tears, and it is purely because I am so tired, yes. [TYA10, phase A]

Many young patients described the predominant emotion as 'anger'. Anger was invariably described in relation to interactions with family members, rather than friends. The inevitable tensions arising from this are considered in more detail in section 4.5.9 (page 147). In contrast, parents tended to report that their son or daughter was 'frustrated', rather than 'angry'. Frustrations were invariably expressed in relation to the impact of fatigue and, of note, the cognitive impact of fatigue tended to be implicated as the source of frustration more than the physical impact [supplementary data page 349].

Mum, she always says I am a bit aggy (sic), so I am getting a bit angry all the time she reckons. She reckons my temper has gone a little bit more, so I can snap a bit more. [TYA12, phase A]

She gets frustrated a lot more with the mental side of things than she does with the physical side of things. [PAR6, FG, phase A]

As well as causing anger and frustration, the affective impact of fatigue was a strong theme, expressed particularly by parents. Low or fluctuating mood tended to be described, although one parent [PAR6] reported that fatigue provoked anxiety, due to unmet information needs in relation to fatigue, a topic that will be discussed further in section 4.5.7.2 (page 133) [supplementary data, page 349].



And it is quite hard, because I think it is like a mental thing as well, because it brings you down as well, because your body doesn't really feel up to a lot of things. [TYA7, phase A]

I mean I do attribute some of [TYA6]'s anxiety to not knowing that her body just wouldn't recover that quickly, and that she would get these bouts of fatigue. So I do feel that that kind of didn't help with her anxiety. [PAR6, phase A]

#### **4.5.6.3 *Hampering the need to conform***

A pervasive ramification of fatigue was the impact on the ability of young people to 'keep up' with their peers, and feel 'normal'. Interestingly, this emerged as an unsolicited and lively topic of conversation independently within both TYA and parent focus groups. TYAs did not tend to discuss this topic in their individual interviews, although the matter was raised by a few parents during their interviews.

The young participants were clear about wanting to 'fit in' and not appear different to their peers. Parents were also cognisant of their son or daughter struggling with perceptions of not conforming. Interestingly, several parents, but not TYAs, expressed this in terms of the inadvertently unhelpful consequences of social networking. Much of the data in this theme emerged in the focus groups, rather than individual interviews [supplementary data, page 349].

... you don't want people to look at you any differently to what they did before. [TYA3, FG, phase A]

*Does [social networking] make things worse? [Interviewer]*

It can do... it's a double edged sword... [PAR3, FG, phase A]

... they can communicate through it but then, on the other hand, you are seeing what everyone's doing and you're not doing. [PAR8, FG, phase A]

#### **4.5.6.4 *Dependence and demotivation***

Regression to a dependent state, as a consequence of fatigue, was another theme that emerged, with parents talking in terms of regression to a less autonomous and more child-like state [supplementary data, page 350].

I think it has impacted them in as much as they take me places instead of me going on my own. [TYA1, phase A]

I would say the other thing that I've noticed is he's just regressed, so sometimes I feel I'm dealing with a toddler, sometimes with a 10-year-old. The best we ever get to is an adolescent really. [PAR2, phase A]

Many participants, both TYAs and parents, described fatigue as a state of demotivation. Interest and impetus declined, with resulting loss of independence and self-direction [supplementary data, page 350].

Like first of all the first step in a way is kind of accepting it [fatigue] is a demotivated state [TYA1, phase A]

...because I have got no motivation there, which I would say is another thing that is kind of affecting [being able to do things] as well. [TYA3, phase A]

*Because of the fatigue? [Interviewer]*

Yes. I have got nothing pushing me to go... [TYA3, phase A]

#### **4.5.6.5 Theme A1 discussion**

Participants were universally vocal in their descriptions of the negative impact of fatigue on their lives. The volume of data relating to the adverse consequences of fatigue was disproportionately large, given the focus of this study on intervention co-design. A single question in the topic guide, asking about the most distressing aspect of the fatigue experience, led to a flow of largely unsolicited information.

The adverse cognitive and emotional consequences of fatigue emerged as dominant themes. The perception of impaired concentration and memory was highly detrimental to social functioning and to the ability to progress in education and work. Emotional lability was expressed mostly in terms of 'anger' by TYAs and 'frustration' by parents, with low mood also featuring strongly. Fatigue, furthermore, hindered the stereotypical adolescent need of wanting to appear to conform, while at the same time hampering the apparently opposing desire to develop autonomy, independence and self-direction.

#### Contextualising within existing literature

Irrespective of age, it has long been recognised that the experience of CRF includes both cognitive and emotional dimensions, as well as physical tiredness [1,129]. However, much of the existing literature tends to suggest that physical fatigue is the predominant experience.

Young pre-adolescent children invariably describe fatigue more in terms of its physical impact and the effect on sleep, than on the cognitive or emotional impact [178,179]. In older adults, most literature also suggests that physical fatigue predominates. In a systematic review comparing physical and cognitive fatigue in adult cancer patients, de Raaf and colleagues reported that physical fatigue was more prominent than cognitive fatigue [327]. This was particularly the case in those with advanced cancer and in those receiving cancer treatment; in survivors there was no clear signal for either physical or cognitive fatigue predominating.

Comparison of physical with emotional fatigue is hindered by the fact that most multidimensional fatigue measures do not specifically quantify an affective subscale. The exceptions are the Piper Fatigue Scale (PFS) and the Multidimensional Fatigue Symptom Inventory (MFSI). The former does not include a physical subscale, precluding comparison [328]. The latter is not widely used; the two controlled studies using this scale, both involving older adults with cancer after the end of treatment, suggested that emotional fatigue was a little worse than physical fatigue; however, there was no assessment of whether the small differences reached statistical significance [329,330]. In the TYA context, no studies have determined an emotional subscore.

As discussed in section 3.6.1.2 (page 80), only five studies evaluating TYA CRF have reported cognitive subscores, all having used the MFS measure. The four involving patients completely, or mostly, during cancer treatment revealed worse physical than cognitive fatigue subscores, whereas, Keats and colleagues, in a small uncontrolled trial, demonstrated comparable levels of cognitive and physical fatigue [218]. Across the wide range of qualitative studies in TYAs conducted in the past, none have suggested that cognitive fatigue is particularly problematic in comparison to physical fatigue in these young patients [125,131,175-177,179,185,197,220].

Overall, therefore, although cognitive and emotional fatigue experiences are an undoubted part of the fatigue experience in cancer patients of all ages, evidence suggests that physical fatigue tends to predominate. After cancer treatment, cognitive and emotional fatigue feature more prominently, but there has been no evidence to suggest that they have more of an impact than physical fatigue. Therefore, the finding from this study, that the cognitive and emotional aspects of fatigue have a worse impact, is important and original.

In terms of the other components of this theme – fatigue hindering the ability to conform, development of dependence, loss of life direction and the possible negative impact of social networking – these insights, which relate to the characteristic needs of adolescents, are unsurprisingly not present in the adult CRF literature. Equivalent consequences of fatigue in older

adults relate to the ability to work, take care of family and maintain relationships with family and friends [23].

In qualitative studies focused on the TYA experience, a few of the findings in this study have already been described. Chiang and colleagues, in a study of Taiwanese children during and after cancer treatment, describe 'lack of motivation', 'altered life plans', feeling 'distant from peers' and 'parental over-protectiveness' [179]. Adolescents attempting to return to school after cancer treatment, sometimes no longer 'fitted in', and were falling behind with their school work [185]. However, unlike in this work, no previous studies in a TYA cancer context have documented hindered conforming, development of regression, or negative aspects of social networking. It is noteworthy that this past qualitative research used either semi-structured interviews [131,179,185,197] or written data from diaries [125]. None involved focus groups or assessed the experience of parents. In the present study, the data in relation to conforming largely arose from the focus groups rather semi-structured interviews, and the insights into regression, dependence and social networking came mostly from parents. It is conceivable, therefore, that the methods of data collection used in this qualitative study have facilitated emergence of these novel findings.

The insights into the 'double-edged sword' of social networking were unanticipated; fatigued TYAs become more aware of their perceived inability to conform and 'keep up' with their peers. The topic arose in the parents' focus group discussion only. Given that a theme from the TYA participants was the need to conform, it is perhaps unsurprising that – in the context of the pervasiveness of social media – this matter was not raised by the TYAs themselves. Although this topic has not previously arisen in literature relating to TYA CRF, a body of evidence has been emerging in recent years on the detrimental and paradoxical impact of social media on psychosocial wellbeing in the young generation of 'digital natives'. Social media use has been correlated with anxiety, depression, body image concerns, poor sleep and perceived social isolation [331,332]. Although this evidence may be biased by unidentified confounders and parents, in turn, may have been influenced by the prevalent reporting of this research in the media, it remains possible that this study finding may represent another mechanism by which the impact of fatigue is compounded at a young age.

#### Integrating with Fatigue in Focus survey

Given the limited congruence between the findings in this qualitative study and existing literature, it is noteworthy that the findings are consistent with those from the preceding survey.

Unlike the evidence from the systematic review, the survey revealed comparable mean MFS general (physical) fatigue, sleep/rest fatigue and cognitive fatigue subscores. Cognitive fatigue was therefore

an important feature of the fatigue experience of those participating in the survey, although its severity was not quantitatively worse. This qualitative study, FICS, therefore builds on the survey findings by suggesting that, even when of comparable severity, as defined by the MFS, the impact of cognitive fatigue on daily life is considerably worse.

Again, there was some consistency between the survey and FICS in terms of the impact on age-related developmental needs. In the survey, over a third of participants reported a negative impact on each of the following: the ability to be independent, to have relationships with friends and to socialise. These problems were also highlighted in the limited survey qualitative data.

### Summary

The main novel outcome from this theme is that cognitive fatigue is perceived as more problematic than physical fatigue. This appears to be largely due to the impact of impaired concentration and memory on the ability to function socially, and within education or work. In turn, these social consequences hinder the ability to conform and result in dependence and loss of autonomy. In short, the consequences of cognitive fatigue directly hamper the core developmental needs of adolescence and young adulthood. Furthermore, the affective corollary of fatigue magnifies the normal emotional reactivity of this young age, compounding the symptom's negative impact. It is unsurprising, therefore, that fatigue was found to be the single most distressing symptom experienced by young cancer patients in the systematic review.

#### **4.5.7 Theme A2: TYA developmental characteristics influence intervention design**

The characteristics of this young age not only influence the experience of fatigue, as described in the preceding section but also determine, to a considerable extent, the design of the intervention. Participants were remarkably consistent in their opinions on a number of aspects of optimal intervention and their needs related closely to the characteristic features of this neurodevelopmental stage.

An overview of the relationship between age-related features and intervention design is provided in table 4.9. There follows a summary of evidence from participants that both underpinned the development of this theme and led to the generation of the prototype intervention. Data relating to this theme is presented in three subsections, relating to approach, content and practicalities. The full prototype intervention is described in section 4.5.15.1 (page 182).

**Table 4.9 Summary of TYA developmental characteristics and influence on intervention design**

Characteristic features of TYA age	Influence on intervention design [relevant subsections]
Development of identity and self-direction	<ul style="list-style-type: none"> <li>• The intervention needs to be individualised and flexible, aiming to enhance self-motivation and confidence to reach personal goals [approach, content, practicalities].</li> <li>• The focus should be on recovery and positivity rather than on fatigue or illness [approach, practicalities].</li> <li>• Support is needed explaining fatigue to prospective employers and education staff [content].</li> </ul>
Executive function maturing slowly into early adulthood	<ul style="list-style-type: none"> <li>• Plans need to be specific and clear [content].</li> <li>• The intervention needs to be age-appropriate, including allowing impulsivity, and acceptance of relatively limited attentional control [content].</li> </ul>
Increased reward and sensation-seeking behaviours	<ul style="list-style-type: none"> <li>• Wish for regular, achievable, short-term goals [content].</li> <li>• Information Technology facilitates regular feedback, particularly using Apps on a personal mobile device [content].</li> </ul>
Physical strength and reserve	<ul style="list-style-type: none"> <li>• Physical reserve contributes to periods of over-exertion; approaches such as mindfulness are more acceptable than energy conservation [content].</li> <li>• Unmet information needs centre on 'how much to push self' [content].</li> </ul>

#### **4.5.7.1 Age-related influences on intervention approach**

A strong and consistent theme, in relation to the approach of the intervention, was the importance of developing confidence in being able to achieve personal goals. Although the word 'self-efficacy' was not used by any participants, this was the concept being described. Importantly, much of this information was unsolicited, as there was no direct question about this concept in the topic guides (appendices 7.4.8, page 334; 7.4.9, page 336). Self-motivation, 'taking control' and 'taking charge' were closely related constructs that were also described [supplementary data, page 351].

If someone is more inclined towards a take charge, one can create one's own reality sort of perspective, then they are more likely to believe that their actions will affect their life. [TYA1, phase A]

I guess it does come down to your role is to give a patient confidence in themselves and their own understanding of their fatigue and what they can do and what they can't do. And your role is to give patients confidence that they will recover but that they must find their own path to recovery. [PAR14, phase A]

After receiving the prototype intervention, TYA3 spoke emphatically about the value of the intervention being a catalyst for self-motivation to achieve a meaningful personal goal.

I also spoke to her about things that I'm wanting to change... I think since speaking to [HCP] and getting myself in this like mind-set that I'm going to make myself better before Christmas has worked, because now I've found I've got a lot more energy than what I did... [TYA3, phase C]

*That's amazing, what helped you get through that hurdle, that first bit where it all feels rubbish?* [Interviewer]

Just keep telling myself that if I want to be who I want, like if I want to be able to have all the energy and enjoy my Christmas and enjoy my family and all that, I need to start being strict on myself. [TYA3, phase C]

TYA3 provided the following advice in her post-intervention interview, reinforcing the importance of the motivation and goal needing to come from an individual, rather than the person delivering the intervention.

...basically you can do that on your own because that's what I've been doing. I just think you need the motivation behind it, so kind of set a goal with them. So if you say to someone like me, so where do you want to be in three months time..? And then they'll set themselves their own goal without even thinking about it. [TYA3, phase C]

The value of a health coaching approach (section 4.5.7.4, page 142) for TYAs was explicitly endorsed by the HCP delivering the prototype intervention, emphasising the importance of facilitating self-motivation to change behaviour, rather than the HCP requesting change [supplementary data, page 351].

They did, I feel, you know, did, or could respond quite well to a coaching approach because that is very individual. And it is saying what do you want to focus on today? [HCP, phase C]

All participants, TYAs and parents, without exception, were clear that the intervention needed to be individualised, to allow young patients to determine their own goals and direction. Young people did not want an authoritarian or prescriptive approach, having to passively adhere to others' goals for them [supplementary data, page 351].

I was happy doing things I came up with. When other people told me to do stuff, it just felt like another overwhelming thing to do. [TYA1, phase A]

Because the one thing I was worried about this is that you were going to be like 'Oh you have got to have eight hours sleep a night, and do five hours of exercises a day.' I obviously am probably not like that, but I don't have time, because I would sleep more if I could. And I would exercise probably maybe if... [TYA9, phase A]

The importance of positivity, with a corresponding focus on recovery, rather than illness or fatigue, was another consistent theme from both young participants and their parents. Whereas parents talked directly about a positive approach, young participants tend to express this idea in terms of their identity, a sense of wanting to look forward, rather than to be defined by illness and associated negative connotations [supplementary data, page 352].

...so if someone says to you, 'Oh where are you going?' you don't want to say, 'look, oh, a fatigue place,' because then you're instantly like, they're judging you all in their heads. [TYA3, FG, phase A]

[TYA8] didn't want to be defined by his fatigue or his cancer. [HCP, phase C]

So you want to grab every bit of positivity you can... And if you take a positive approach you will get a better outcome, whatever that might be... I think if you focus on being tired, you will get tired. If you focus on being energised and awake and achieving something, then you are more likely to achieve that. [PAR4, phase A]

#### ***4.5.7.2 Age-related influences on intervention content***

The content of the intervention was strongly influenced by features of this young age. The three broad areas of content related to activity promotion, to conservation of energy and to information needs.

##### **Activity**

Young participants tended to speak in terms of more concrete, rather than abstract, ideas. Many participants expressed dislike for anything vague.

I don't have any in the middle, I am black and white. [TYA3, phase A]



It wasn't like any... there was no like strategies. [TYA2, FG, phase A]

They're very vague on what they want to tell you... [TYA7, FG, phase A]

Amongst those participants who were keen to be active, there was a very strong desire, with only one outlier, for activity to be supported with a specific, structured, individualised plan [supplementary data, page 352].

I would much prefer [an HCP] to say, you can do ten minutes a day of this, this and this, and then once you have done that for a week, you can do fifteen minutes a day of this, you know? ...and just very clear, especially with the exercises, very clear on how it should be done, and the way it should be done, and how long for, because I think that is very key. And if you don't know how long to do it for, and how to progress, it kind of limits the exercise as well. [TYA8, phase A]

The single outlier preferred not to be given instructions, and wanted to have freedom to make his own decisions spontaneously.

Well, I am not good at deciding on a formal exercise regime and then doing it. I prefer just waking up and deciding I am going to do some exercise now. My favourite time is the evening. [TYA1, phase A]

Parents too were in favour of specific planning, rather than vague encouragement to exercise. Planning was perceived as a way of helping young people build up activity incrementally.

I think an exercise plan would be good. Because I know he just one day said, 'Oh I am going for a run.' And I also thought he was going to die, he was so out of breath, and was going to pass out. But of course he had gone from nothing, to go for a run. [PAR12, phase A]

One parent alluded to the closely scheduled time during cancer treatment, and suggested a potential relationship with being prepared to follow an exercise plan.

Yes. I think definitely a programme would work well for [TYA6], because she is quite good at following... and obviously with the history of her illness, she has had to follow some strict guidelines over the last five or six years. So I think that is the way she works at the moment. So, yes, I think perhaps that might be the best thing. Because then again that will give her something, so she is able to plan. [PAR6, phase A]

One of the many participants who expressed a strong wish for clear planning in phase A (quote 1 below), indicated his disappointment in phase C that the prototype intervention had not been more clear (quote 2). Furthermore, concurrently but outside this study, he proactively sought support from a personal trainer at a gym, and was explicit in his praise for the more detailed individualised planning (quote 3).

1. It would be quite nice to just have like a schedule or a timetable or something. So something like practical that you can do rather than them saying why don't you try out this. Like they could give you a week by week something... like this week you've got to try out this and then you can like feed back and see if it works or not... [TYA2, phase A]

2. The main thing was it wasn't specific, and it just felt like we were having a chat, but there was no plan in place. It is just like what you are told again and again by everyone. They are like, 'Oh yes fatigue is bad, so you have to rest, eat well, exercise, take time out,' and all of that kind of thing. But there is no plan, and it doesn't really work around your life. [TYA2, phase C]

3. So they are doing like a twelve [week] exercise programme which actually has been really helpful, because the [personal trainer] has basically created a plan for me week by week to get me to be able to run/walk the marathon by [month]... [TYA2, phase C]

After having met the young participants in phase B of the study, including [TYA2], the AHP delivering the intervention was also convinced by the need for specific planning, and perceived that this was different to her experience with older adults in her usual clinical practice.

I think they want more specific advice so it's, and I guess that's true of adults as well, but they particularly wanted more. So it might be more specific advice around exercise for example and the absolute specifics of it like how much do I need to do. And it's more than the usual increase by 10% that we would suggest. So it feels like more of a prescription, if you like, that they want. [HCP, phase C]

*That's interesting, so more specific than other adults in some ways? [Interviewer]*

I would say so, yes. [HCP, phase C]

As well as wanting clear and specific planning, there was a consistent requirement for activity goals. Goals needed to be repeated and short term, rather than vague or long term [supplementary data, page 353].

That is the key to exercise I think. Because if you haven't got something to aim for, it is kind of just... especially when you say I can't be bothered. If you say I can't be bothered but you have got a target, then you might be like alright I have got something to aim for, I will feel better afterwards, rather than I can't be bothered. [TYA8, phase A]

*So do you think how we motivate everybody when we are doing this, is that quite an important thing? [Interviewer]*

Yes. But I think setting smaller goals is better than longer goals. Because if I set a goal that is really easy to achieve, or I have to push myself a little bit, but I can achieve it, and then you set another one, it feels better. You get that buzz more often, rather than having to set a long term one that takes a year to reach. It is kind of, you can lose motivation easier. [TYA8, phase A]

As suggested in this preceding quote, at least part of the value of the repeated, short-term goals was the sense of achievement or 'reward'.

Yeah, but I think setting the goals of where you want to be next time you meet is a good idea. Hitting that goal would be good. [TYA6, phase A]

It would be like a reward scheme. [TYA2, phase A]

Another value from goals was the effect of demonstrating progress. Fatigue changes slowly over time and regular, short-term goals were considered to help make progress perceptible [supplementary data, page 353].

I need to sit down with someone and maybe get a plan or a day-to-day like exercises or a sort of achievement tracker. Just something that just shows you that you are making progress... You might wake up really tired thinking, 'Oh I'm really tired again,' and slowly it gets better but as it's gone so slow you don't really notice it. [TYA6, phase A]

The importance of being able to quantify and document progress towards goals was another universal theme, amongst the many participants open to the concept of increasing activity.

*What is it you like about the gym...? [Interviewer]*

Yeah, I think it's the fact that, the more you do the more you can kind of tell you've done something. Like on the treadmill you can keep track of what you're actually doing. [TYA6, phase A]

Unsurprisingly, given the age of participants, information technology (IT), and specifically the use of mobile applications (Apps) featured repeatedly as a way of achieving this. Only one participant acknowledged his own disinterest in IT, while expressing the view that this was still likely to be a good approach for many young people.

I wouldn't necessarily want to download an App, I am not a technology person. I avoid using my phone and all sorts of other things like that if I can. But I could see loads of people finding that really useful. [TYA1, phase A]

For all other young participants, their enthusiasm for using IT was clear. Parents also raised the possibility of harnessing IT to quantify progress, mentioning its additional potential in allowing a healthcarer to access the data [supplementary data, page 353].

I think as well if you are watching what you are doing, you are more conscious about doing it. I know that recently I have been trying to make sure I walk 10,000 steps, and it has got it on my phone, and I check that every day. And I think it consciously makes you do a bit more walking, because you want to hit your target. [TYA4, phase A]

I'm quite a keen walker and I was trying to get him to come and we did the old 'Map My Walk' App. He's quite keen on goal setting and so like he'd try and walk a little bit further and things like that, we found that quite useful as a tool. [PAR8, phase A]

Yes. So the occupational therapist could link in to say [TYA12's] details, couldn't they? And say, 'Well perhaps next week you could do another half a mile?' [PAR12, phase A]

### Energy conservation

Conserving energy is an established approach to supporting adults with cancer-related and other causes of fatigue [333]. Activity pacing, prioritising tasks and planning to avoid excessive energy fluctuations are central concepts, and efforts are made to avoid so called 'boom and bust', a colloquial expression describing a period of considerable physical exertion followed by profound fatigue [334]. For the young participants in this study, these concepts were unfamiliar and not

meaningful. On a literal level, the words 'boom and bust' were difficult to understand, even with explanation.

*I'm just going to bring things back to the themes of energy conservation and [researcher] has been referring to it as like a 'boom or bust'. And what we mean by that is... you've got something on, I don't know, party, interview, event, whatever, and you're just completely ... wiped out for the next day, two days... [Interviewer]*

Do you mean you get the weak burst and then all of a sudden you're like you don't want to get out of bed? [TYA7, FG, phase A]

Importantly, the concepts were also largely irrelevant. Young participants considered it conventional behaviour to have periods of high energy usage, and then to 'crash'. To attempt to change this was not considered acceptable or feasible to many of the participants [supplementary data, page 354].

It probably... the things that were said don't really fit into my lifestyle if that makes sense. [TYA9, phase C]

...like I, when I'm at college at things I don't have a choice... [TYA9, phase C]

*Yeah, because you just have to do a lot and then you crash out? [Interviewer]*

Yeah... yeah the stuff going on in my life isn't very flexible for those kinds of things. [TYA9, phase C]

One participant felt that pacing and energy conservation were so unsuitable for young people that too much focus on these could even hinder engagement with a fatigue intervention.

...saying that one should do [pacing and energy conservation] I think that is a way of deterring people taking part in the first place. [TYA1, phase A]

There was animated conversation during the young patients' focus group about the importance of 'going out' and behaving in a perceived 'normal' impulsive adolescent way.

*...but maybe not a good idea to go to nightclub or to go to [place] or whatever. Where is the balance, how important is it to have those times where, okay, it might exhaust you for days afterwards but how important is that to still experience those things? [Interviewer]*

You have got to do it. [TYA8, FG, phase A]

Yeah. [Many voices, general agreement]

Whilst you're young I think... well, I'd do anything now. But then I've got a family where everyone's older so it's... I've seen my sister go from 18 with a baby up (sic) and it's like I don't have any of that. So I'm going out enjoying myself, I go to the pub, I go out clubbing and things like that. But then I also think like when Sunday comes that's like you sleep all day. Non stop. [TYA3, FG, phase A]

As well as energy conservation and pacing being considered irrelevant because of their inherent conflict with stereotypical adolescent behaviour of 'going out', then 'crashing', one young participant provided a further interesting insight.

Because with my body I can push myself, so I can do basically anything my friends and other people can do. In fact my friend told me that I should carry her bags and stuff. I didn't mind, because I was full of energy, but she got tired before me. But I think that is to do with me pushing myself, not realising that I am getting tired. And then when we got to her house, I would just sort of lie down on her bed and just didn't move for 30 minutes. [TYA1, phase A]

It was apparent from many participants that, consistent with their young age, they had considerable physical strength. Even when experiencing fatigue, young people had little difficulty in being physically active when they wanted to be. This led to the recurrent theme of wanting to know 'how much to push' oneself, a significant unmet information need that will be described in the following subsection (page 133).

The view that pacing was not inherently acceptable to young people was also expressed with conviction by the AHP delivering the prototype intervention.

I got very much a sense that people, particularly around the boom or bust or the activity pacing, that's a real challenge for young people, because they want to feel normal and want to do the things that other people want to do... I think it's this sense of wanting and needing to fit in... because [TYA3] was saying, 'I'd rather not do that if it means that I can't be up all night and I'd rather not do it' ...it was almost saying, 'that doesn't fit with my life,' and there was less of a willingness I think to change. [HCP, phase C]

Although physical pacing or energy conservation was largely irrelevant, in contrast, meditative and mindful approaches were highly acceptable to this young patient cohort [supplementary data, page 355].

And I found this App quite helpful, this Headspace [a mindfulness App], just because it gives you ten minutes out, and I don't know, I found it just quite helpful in terms of the fatigue and everything. So, yes, I just quite recommend that. [TYA2, phase C]

The other thing that seems to go down surprisingly actually quite well was the idea of taking, by whatever means, taking some time out during the day. So whether it be through mindfulness, relaxation ...a lot of them took on board this idea of taking that time out to focus... that idea of topping up and trying the mindfulness App, or one of the mindfulness Apps and I think that was useful as well. [HCP, phase C]

Young participants referred to the mind being too active, and appreciated any approach that could introduce a meditative focus, whether mindfulness techniques, Tai Chi or yoga [supplementary data, page 355].

...my mind doesn't shut down, so it's like that's another thing that's causing me to be tired and like not wanting to do anything because my head still constantly running. [TYA3, FG, phase A]

And [yoga therapist] constantly reminds you throughout, because obviously it is all about being mindful... being in that moment. So that is something that I have wanted to work on anyway, yes... something like yoga I think for people in my position, should really be encouraged. Because it is not just your body, it is the mind as well that it really helps with... [TYA10, phase A]

### Information needs

Participants universally expressed unmet information needs. As with other aspects of intervention content, the desired information was highly influenced by the developmental characteristics of young age. The inherent physical strength of youth meant that fatigued young participants were still able to push themselves physically. However, many TYAs, particularly those interested in undertaking formal exercise, expressed concern that they did not know 'how hard to push'. The wish to have more information about this appeared to be related to the desire to be given a specific plan with repeated short-term goals (section 4.5.7.2, page 127). Clear goals, supported by a therapist, were perceived to reduce the risk of over-exertion [supplementary data, page 355].

Because with me, I was getting very into sport, and the doctors didn't quite know. I kept getting mixed messages from one doctor and another about how hard I should push myself, how much I should do. [TYA8, phase A]

I guess when you are kind of in this situation you just learn about managing it, and pushing yourself a bit too far, and what works and what doesn't... The nice thing about [a personal trainer] was that I had this plan, and then two weeks later we went over it and said what works, what doesn't, and really adjust it. And I knew what I was going to do each day. [TYA2, phase C]

A further area of information needs, referred to either directly or implicitly by most participants, related to needing to know more about what to expect [supplementary data, page 356]. The resulting mismatch between reality and expectations led to considerable interpersonal tensions, a theme that will be explored further in section 4.5.9.1 (page 148).

I think probably if they just mentioned it, you know, if someone mentions it and you start like at least expecting it a bit. ...I don't know, it just helps with kind of thinking what actually is realistic with what you can do afterwards... because I didn't expect it to hit me that much. [TYA2, phase A]

Several parents also alluded to the importance of needing to know what to expect, in relation to normal adolescence. Fatigue, sleepiness and a desire to stay in bed in the morning can be considered stereotypical features of normal adolescent or young adult life. Parents did not know whether to attribute symptoms to this or, more seriously, to being a consequence of cancer and its treatment [supplementary data, page 356]. This was a source of internal tension for parents, as will be discussed in section 4.5.10.1 (page 154).

Yes, we have not actually been given any information about fatigue. We were told that she would be tired, but that would be normal, and that we would just have to wait until she is ready. But then also she is 17 years old. Most 17 year olds want to sleep a lot. So again it is like how much do we put down to the treatment that she has had, and how much do we put down to just her being 17? [PAR6, phase A]



A further topic raised by many participants was the need for information that would support them in talking to staff at work or higher education institutions. Being able to work or continue in education was a clear priority to participants.

*...if you had to name one priority at the moment, what would it be? If you needed to conserve all your energy for one thing, more than anything else what would be your... [Interviewer]*

College. [Unidentified voice, FG, phase A]

Work. [Unidentified voice, FG, phase A]

Several participants, whether or not they needed the help themselves, alluded to the importance of being able to explain their situation to staff in their place of education or work [supplementary data, page 356].

And kind of ways to raise it with employers rather than just be like, 'I'm really tired,' which kind of sounds like you're just being lazy... Because with my part time job that I want to go into I don't know whether I should ask for it to begin later or whether I should be like sucking it up and going in at the normal time. [TYA2, phase A]

So if other people in my situation don't have as great lecturers or teachers, then it's important to try and push for things. [TYA1, phase C]

#### **4.5.7.3 Age-related influences on intervention practicalities**

As well as providing conceptual information on the approach and content of the intervention, participants gave views on practical aspects, such as the intervention name (what), method of giving information (how), ideal timing relative to the end of cancer treatment (when), location of intervention meetings, place of activity (where) and involvement of family members (who). Preferences remained consistent with the characteristic features of this young age (table 4.9).

Identity and positivity remained an important theme, in relation to intervention practicalities, as well as approach (section 4.5.7.1, page 126). Both young participants and parents were consistent in wanting the name of the intervention to focus on positivity and recovery, rather than risking their identity becoming defined by fatigue, cancer or medicine [supplementary data, page 357].

Really something like, more of a positive outlook in the name, like... 'solving fatigue'. [TYA6, phase A]

Again, focus on the recovery not the illness. [PAR8, phase A]

I just feel like... I don't know, it's not a really big deal, but if I'm telling people, if I'm telling friends that I've gone to a fatigue workshop makes it sound I'm being... give me the sympathy sort of thing. But I'm completely against that... [TYA8, FG, phase A]

This concern led to a lack of consensus about whether or not the intervention for fatigue should directly include the word 'fatigue' within its name. There was a vehement debate about this point within the young participants' focus group, with many differing views. The TYA focus group facilitator suggested a vote, and found that the group was virtually evenly split in opinion. Interestingly, the young participants spontaneously worked to develop a consensus themselves, and suggested a name with two parts, one involving a positive word like 'recovery', and the other acknowledging the legitimising word 'fatigue'.

...do you have a name that's snappy that you can remember but then if people say, 'What's that?' then you say it, 'fatigue study' or 'group' or whatever. Instead of it being like straight in 'fatigue' because it's like... it might not attract certain people 'cause they'll think, 'Oh, it's more medical stuff'... [TYA3, FG, phase A]

Well, just have a name... and then have a subname... 'Road to Recovery: the Fatigue Workshop'. Something like that. [TYA8, FG, phase A]

Another consistent theme was the preference for information to be given in video format, rather than written information. The videos needed to be short, in the context of poor concentration. Furthermore, participants were clear about their preference for information from experienced peers rather than healthcare professionals. This was again a topic of enthusiastic debate in the TYA focus group [supplementary data, page 357].

*So what is your best way of learning [TYA 11]...? [Interviewer]*

It would probably be like a video where they tell you, and you can just sit there and listen. You don't even have to watch it. [TYA11, phase A]

*And you don't even have to read it, any of it? [Interviewer]*

Exactly. [TYA11, phase A]

Maybe something you could sort of... maybe done by other teenagers even saying 'Oh so you are feeling tired' and chatting about 'Have you thought about doing this?' Or 'What about that?' [TYA13, phase A]

But it would have to be very brief. Because I think, not like brief, but... [TYA9, phase A]

*...Succinct, to the point? [Interviewer]*

Yes. [TYA9, phase A]

In terms of the timing of the intervention, participants were universally clear about a preference for early fatigue support. Most participants, indeed, would have wanted a fatigue intervention to have started before the end of cancer treatment [supplementary data, page 358].

Yeah, I think as earlier on the better... Probably like once you've settled down into it... Yeah probably about half way through. Then you can start to work it into your life before you finish but you're already like settled into it. [TYA9, phase A]

Parents also had consistent views, advocating early input, as did the healthcare professional delivering the prototype intervention [supplementary data, page 358].

Yes. I think it probably would have been... as I say, even just even halfway through the treatment. [PAR7, phase A]

*At the end of treatment? [Interviewer]*

Earlier... I do get the sense that something earlier for everybody would have been useful. [HCP, phase C]

Only one participant explicitly stated that intervention would not have been wanted during treatment. TYA1 advocated fatigue management being at the point of ending cancer treatment, which was the latest timing suggested by any of the participants.

In my perspective, the dominant feeling I had during the treatment was feeling overwhelmed. So being asked to do other stuff would just feel overwhelming. [TYA1, phase A]

The AHP delivering the prototype intervention raised age-related practical benefits from early intervention. During the prototype intervention, it had been difficult to make contact with patients at

times. Early involvement, when patients would be attending hospital anyway, could facilitate contact with a healthcarer who could then, if preferred, follow up out of hospital. In addition, in the months after the end of cancer treatment, there was a perception that young people would be 'moving on' with their lives.

Seeing people on the ward, when they're up here, perhaps gives you more of the opportunity, if it is more part of the normal way of doing things. So if someone was popping in, much like [HCP name] would pop in, or much like the nurses would pop in, then it's more normal... [HCP, phase C]

The getting hold of people... was difficult, but maybe seeing people early. I think the other thing is the sense of, once people's hospital appointments start tailing off, it's almost like, 'That's a different part of my life.' So you've got this other situation of they're not really wanting to come back or really talk about hospitals or anything to do with that. [HCP, phase C]

The young participants further justified seeking early intervention to avoid the sudden drop in support that occurs at the time of finishing cancer treatment, with an associated sense of abandonment. This is described further in section 4.5.9.3 (page 150) [supplementary data, page 362].

A prevailing theme that emerged across many topics was the need for the intervention to retain flexibility. Diverse opinions were expressed concerning intervention location, acceptable types and location of activity, extent of family involvement, and the preferred methods of communication with an intervention therapist. Young participants tended not to be ambivalent, and had clear personal opinions.

Participants suggested a variety of venues for the intervention, including a non-clinical venue on hospital grounds, a public location such as coffee shop or park, home and a clinical hospital location. The latter two were the least acceptable locations. For some TYAs, home was a place they wanted to have a reason to leave. Two participants pointed out that leaving the house to meet a therapist would help the fatigue by enforcing activity [supplementary data, page 359].

I cannot stand sitting in my home. [TYA3, phase A]

*You just want to get out? [Interviewer]*

Yes... I think home is a bad option for me, because if you spend enough time at home, all you are doing is sitting longer at home to see someone, whereas if you have to go out... [TYA3, phase A]

I would not want to do it at home, my home. Obviously I have felt ill and stuff in my home, but nothing has ever... no-one has ever stabbed me in my home or anything... [TYA9, phase A]

*I would hope not. [Interviewer]*

*And travelling somewhere wouldn't worry you, no? [Interviewer]*

No. Because it gets you out of the house, it gets you a little bit active. [TYA11, phase A]

A minority of young participants considered home an acceptable location, for reasons of 'comfort' and 'convenience', but even this was not necessarily sufficient reason for the intervention to be home-based.

*So it wouldn't be easier to have it at home? Or do you not like the idea of..? [Interviewer]*

Well, for convenience, I suppose. But it seems kind of a waste of someone's time coming all the way out there just to do that. [TYA4, phase A]

A clinical environment in the hospital was almost universally unacceptable to young participants and their parents [supplementary data, page 361]

I guess not the hospital because it's quite medical and quite sickening... [TYA2, phase A]

In terms of types of activity, views were, again, remarkably diverse, with no common preferences. For some, a formal, structured approach to exercise in a gym environment was desirable. Others favoured walking or home-based activity. Young participants were explicit about their need for an individualised approach [supplementary data, page 359].

I think if there was a gym that understood what fatigue was, and had someone there, not necessarily specialising, but that could help people like me back on... [TYA3, phase A]

*So a sort of specialist trainer in some kind of way? [Interviewer]*

Yes. [TYA3, phase A]

Also I find it quite hard travelling 'cause I get tired so... if it was at home or just like in your garden somewhere, where you didn't have to travel to, then you wouldn't have to worry about like doing it, exhausting yourself and then having to get back. [TYA2, phase A]

Like some people might not like nature, they might not want to go for walks, they might want to go for a run. They might only like sport when it is competitive, or maybe... Yes, they might have all sorts of different perspectives. [TYA4, phase A]

*So really the core point that you are saying is it needs to be flexible, and needs to get to the essence of who somebody is. And only they can judge that, we can't. [Interviewer]*

Yes. They have to choose what to do. [TYA4, phase A]

Opinions were divided over whether to involve family members in the fatigue intervention.

My mum would [benefit] though, because she lives with me, she has watched it first hand, I think it would help her understand. [TYA3, phase A]

I think if it was my parents personally, I don't think it would make any difference to them. I think that they think they have got their opinions, and I don't think I would be able to change them. [TYA9, phase A]

Disparate views were also expounded on the preferred mode of communication with an intervention therapist: email, text, social media and telephone were all suggested. Of note, several of the younger participants made it clear that they did not like speaking by telephone, a mode of communication considered familiar and generally acceptable amongst older adults.

*But speaking on the phone, with just a voice, feels..? [Interviewer]*

No, it feels really weird. [TYA11, phase A]

*Like weird in what way? Like you can't relax? [Interviewer]*

Yes. Because you have got to sit there with the phone like that, as where with a video call you can just stick it on the table, and you can see it, so then you can hear it as well. [TYA11, phase A]

*So telephones are old-fashioned really? [Interviewer]*

Yes, pretty much. That is why they have got all these new latest Android and Apples, all touch screens and video calls. [TYA11, phase A]

There was a range of views as to the optimal discipline(s) of the healthcarer(s) providing the intervention. The prototype intervention was provided by an AHP who was an occupational therapist (OT). Some participants suggested that access to other specialists, if needed, could be helpful, specifically in relation to psychological support and support with sleep. There was no perception of stigma relating to psychological intervention [supplementary data, page 360].

There is another component and it is all to do with what you would call the mind, or the soul, or the spirit... So I don't know how you would introduce that, but I think it is crucial if you want to holistically address fatigue. [TYA1, phase A]

*So emotional support as part of the whole thing is important? [Interviewer]*

Yes. So either counselling which works for some people, and then access to information about mind/soul/spirit ideas, to people who maybe might not find counselling the best option. [TYA1, phase A]

#### **4.5.7.4 Theme A2 discussion**

These data reveal that the design of the fatigue intervention was highly influenced by the age-related needs of the young participants. It was striking that, consistent with the adolescent need to determine self-direction and identity, participants wanted an individualised and flexible intervention that promoted self-determination, control and self-confidence, and avoided being too prescriptive or authoritarian in approach. Equally, participants valued a specific, clear and concrete plan, particularly in relation to building activity, with a dislike of anything perceived as vague or abstract.

The considerable physical reserve of young age also had a major impact on the intervention design. Participants wanted to know 'how much to push' physically, when fatigued. Innate physical strength meant they could force themselves to be more active, yet they feared a detrimental impact on the fatigue. This contributed to the desire for a specific, incremental activity plan, to avoid the risk of pushing physically to the point of inadvertent harm. Electronic monitoring of progress was valued, with associated perception of reward when goals were achieved.

Physical strength, combined with the age-related need to conform, led to the unanticipated finding that energy conservation – a common approach within adult fatigue management that includes pacing, planning and task prioritisation – was often seen as irrelevant and unacceptable to TYA participants. 'Boom and bust' was considered conventional conduct at this age, and there was no

inclination to change it. In contrast, mindfulness and other meditative approaches, such as yoga and Tai Chi were much more acceptable and valued. Participants were open to psychological approaches and supportive of access to psychological input within the intervention, if required.

A further unexpected insight was that young participants had little enthusiasm for a home-based intervention, because it was physically easy to travel and also because home had become associated with dependence and illness. Hospital was even less desirable as a potential location, with its connotations of ill-health and fear. Participants wanted information to be provided in short, peer-delivered videos, rather than in written format. Being in work or education was a high priority for young participants, and they wanted support in explaining fatigue to prospective employers or education staff.

These findings lend substantial support to the premise behind this body of research. An age-appropriate intervention is indeed needed. Outcomes of research in older adults cannot, and should not, be extrapolated to young TYA patients [71]. Adolescents have unique health needs and, as exemplified by this study, health care for this population needs to be informed by, and developed with, adolescents.

#### Contextualising with existing literature

Participants confirmed, without labelling it as such, that promotion of self-efficacy, the theoretical underpinning for this work, is an approach of great relevance to them. Intervention needs were unerringly consistent with those factors known to promote self-efficacy, including goal setting, activity planning and provision of feedback on performance [335]. These findings lend support to a small body of literature involving young patients with chronic disease; research in adolescents with diabetes and juvenile rheumatoid arthritis, for example, has also shown that the concept of self-efficacy is relevant to young patients [152]. As discussed in section 1.2.4 (page 16), perceived self-efficacy mediates improved healthcare outcomes in relation to CRF, although it is not known whether its importance, in terms of either perceived relevance or health outcomes, varies according to age.

The desire for an individualised and positive approach, with personalised goals, and planning for how to achieve such goals, fits closely with the premise of health coaching. Health coaching is a positive psychological approach that empowers people to self-manage, and focuses on individuals' goals rather than on what healthcare professionals might wish for them to achieve. Interest in a coaching approach within healthcare has developed mostly over the last decade; it supports people to achieve their aspiration by helping them plan the specific and feasible steps towards the goal [336,337]. As



with the concept of self-efficacy, participants described and requested a health coaching type of approach, without labelling it as such, reinforcing its acceptability and potential applicability in this young age group. Health coaching itself is recognised to be an effective tool for increasing perceived self-efficacy for self-management [338,339]. It is not known whether there is a differential impact of a coaching approach, according to age [336,340,341].

Many of the intervention content needs of the young participants were found to differ from those of older adults, and have not previously been described. Energy conservation, for example, is an accepted and effective management approach in fatigued older adults [342]. Indeed, adult patients, with fatigue from cancer and multiple sclerosis, have chosen energy conservation as the favoured component of intervention [343,344]. For adults with CFS/ME with a mean age of 38 years, adaptive pacing therapy was as acceptable as both exercise and cognitive behavioural therapy (CBT) [345]. In contrast, this work provides the first evidence that this approach may be less acceptable in younger cancer patients. There has been no previous research evaluating energy conservation or pacing for fatigued TYAs in any context. In a qualitative study involving adults aged 24-73 with CFS/ME, as well as chronic pain conditions, there was a suggestion that older patients found pacing more acceptable than younger patients [334]. Interventional studies for CFS/ME in adolescents have, interestingly, not evaluated energy conservation or pacing as a defined outcome, the focusing tending to be on CBT and promotion of activity [346-349].

In preference to physical energy conservation, participants were very supportive of mindfulness, a form of cognitive training derived from traditional Buddhist meditative skills of awareness and self-regulation of attention [350]. Mindfulness-based cognitive therapy has been shown to be valuable in older adults with CRF [351]. In TYAs with cancer, it has been found to increase quality of life and reduce distress, but has not been evaluated in the context of fatigue management [352]. Of interest, given participants' predominantly cognitive fatigue, there is some evidence that mindfulness may particularly ameliorate cognitive, rather than, physical fatigue [353]. Out of the cancer context, young people are known to find mindfulness acceptable and effective for 'stress' and depression [354-356]. Given the relatively late maturation of the prefrontal cortex mediating attentional and emotional control (section 1.1.2.2, page 6) and the evidence that young people are inherently less mindful than older adults, mindfulness is increasingly being taught in UK schools and universities, to enhance executive functioning, and the ability to cope with 'stress' and negative emotions [357-360].

The enthusiasm for the cognitive approach of mindfulness highlights another difference between the needs of TYAs and older adults. The young participants' illness perceptions included an appreciation of psychological contributors to fatigue, and demonstrated a lack of stigma in relation to

psychological approaches. In older adults with CRF, in contrast, there is tendency towards physical causal attributions [361]. In the context of CFS/ME, there is a similar difference with age; young people are more open to the possibility of psychological explanations, unlike older adults who have a more biological focus [362-364]. A high profile UK social marketing campaign from 2009-15, aiming to reduce mental health stigma, has reported steady and significant improvements in attitudes, particularly within younger age groups [365].

The co-designed intervention needs to address the pervasive desire of young participants to find out 'how much to push' physically and their related concern that exercise may worsen fatigue, so-called activity 'fear avoidance beliefs'. Such concerns appear to be a feature of younger, rather than older patients, and therefore represents a further way that a fatigue intervention designed for young patients needs to differ from that for older adults. Fatigue-related activity fear avoidance is well-recognised to occur in patients with CFS/ME, a relatively young patient cohort; it is considered a core feature of the condition, and addressing fear avoidance beliefs has been found to be one of the key mediators of symptom improvement (section 4.6.1.3, page 203) [345]. Activity fear avoidance has also been demonstrated in a study involving patients with multiple sclerosis-related fatigue, with a mean age of 47 years [366]. In contrast, there has been no previous evidence that cancer patients experience activity fear avoidance [23,367]. The firmly established health advantages of activity for cancer patients may be dispelling fears related to activity [367]. Overall, the finding of fear avoidance beliefs in FICS suggests that younger cancer patients may experience concerns that are more comparable with those of other younger patients with long-term conditions, than with cancer patients as a whole.

Young participants' enthusiasm for peer-generated videos was interesting and innovative. In older adults, no research to date has determined preferences between electronic video-based and written information about CRF [58]. A study from over a decade ago confirmed a desire for written, in addition to oral, information [368]. Web-based education about CRF has been found to be an acceptable approach in adults, including videos of patient stories [156,369]. Some evidence suggests that video-based education may be valued in non-malignant conditions [370]. Overall, there is a lack of previous evidence on information format preferences for CRF at any age; the finding from this study contributes useful information concerning TYA preferences.

The last finding that contrasts with evidence in older adults was the preference for support to be provided away from home. Limited evidence suggests that older adult cancer patients have a preference for home-based physical activity, although no research has been done in a CRF context [371]. In non-cancer illnesses, there is good evidence that adults prefer a home setting, including for

cardiac rehabilitation [372], pulmonary rehabilitation [373] and breathlessness self-management support [374]. Home-based complex interventions have been found to be as effective as their hospital or out-patient counterparts [372,375]. Given the evidence supporting home-based intervention, this study finding is novel and important.

#### Integrating with Fatigue in Focus survey

Most survey participants did not find advice to exercise helpful, even though this was the approach they would most recommend to others. This suggested the existence of barriers to activity, most obviously the fatigue itself. This study adds the important insight that fatigue could be a barrier to activity because of activity fear avoidance beliefs, rather than by simply preventing activity on a physical level. This concept is discussed further in section 5.1.2.2 (page 220).

#### Summary

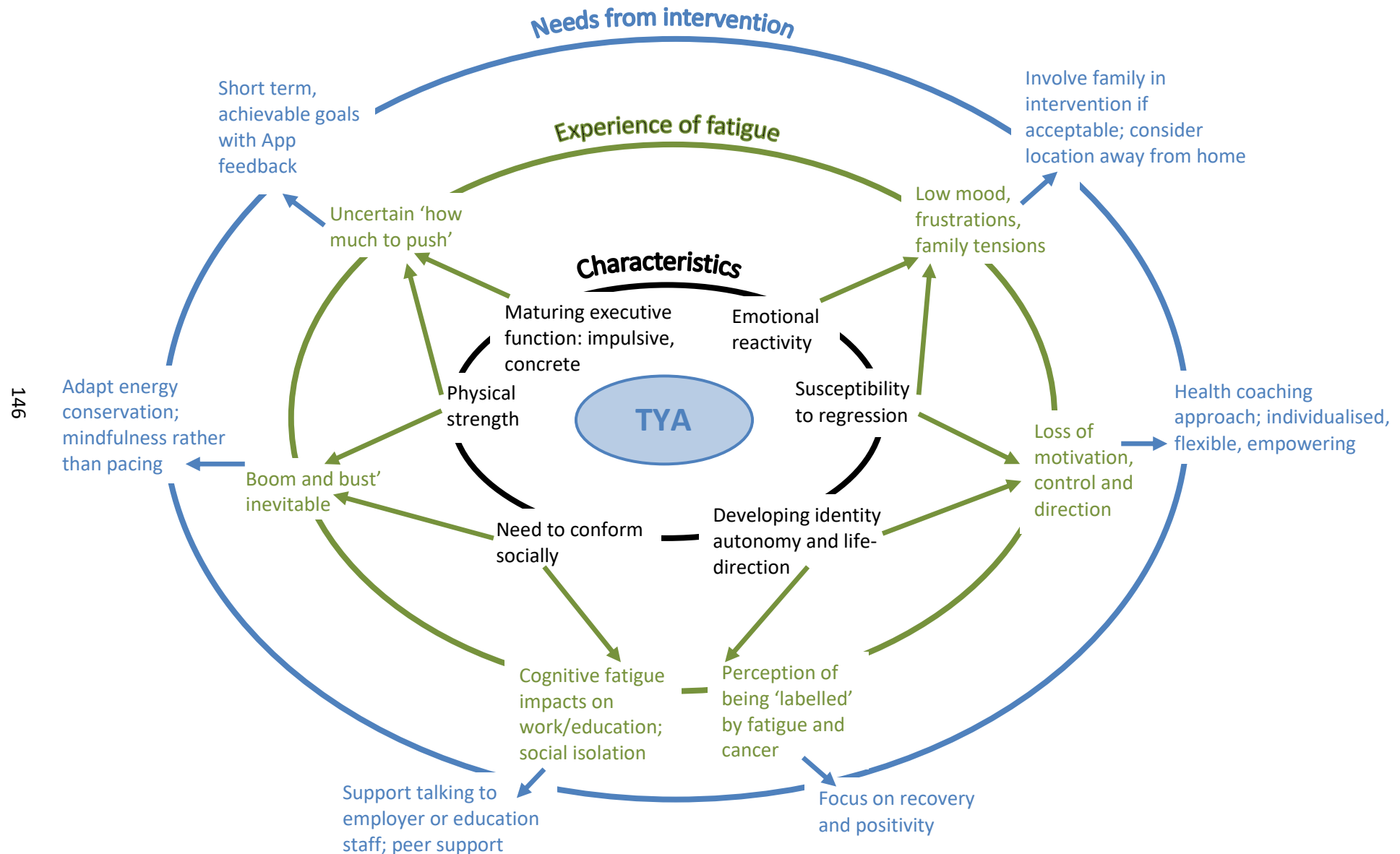
The study has revealed that young cancer patients have significant age-related intervention needs. The irrelevance of energy conservation, openness to the cognitive approach of mindfulness, concern about potential harm from activity, enthusiasm for peer-generated videos, and low interest in home as an intervention location, all differ from research findings in older patients.

#### **4.5.8 Conceptual model A: Characteristics, Experiences, Needs star model of TYA fatigue**

It has been seen in themes A1 and A2 that the developmental characteristics of young age both influence the experience of fatigue and fatigue intervention needs. This can be considered conceptually as shown in figure 4.2.

Several conceptual models of fatigue in chronic disease in young patients have been previously developed, including in juvenile arthritis and CFS/ME [376,377]. These models consistently attempt to conceptualise the complex range and interplay of factors involved in the causes and consequences of fatigue. However, no previous models have considered the impact and patient needs through the perspective of age-related characteristics. This novel approach clarifies that many of the distinct fatigue experiences of TYAs are a function of the developmental characteristics of young age. Furthermore, these experiences, in turn, directly influence the features of an age-appropriate intervention, allowing a consistent, needs-focused perspective.

Figure 4.2 Characteristics, Experiences, Needs (CEN) star model



#### **4.5.9 Theme B1: TYAs experience pervasive tensions and misunderstandings**

An unanticipated but pervasive theme was the extent of tensions arising from experiencing, or living with someone experiencing, cancer-related fatigue. The outcome of the tension was often described by TYA participants in terms of anger, as discussed in section 4.5.6.2 (page 118).

The thing that personally we have struggled with as a family is when I am tired, I am very moody and agitated, and I will lash out. And it flares up my temper, and it can cause issues at home, because I will have a falling out with my brother, or I will snap at somebody. [TYA10, phase A]

Young participants, almost without exception, described situations where conflict and misunderstandings had arisen, both on an intra-personal level (internal) and interpersonal level (with, and beyond, family).

##### **4.5.9.1 Internal tensions**

Adolescence and young adulthood is a period of rapid change and major developmental needs. As discussed previously, fatigue frustrates many key developmental needs particularly: a) the ability to socialise, b) increasing independence, and the ability to progress c) in education and d) in work. The following four quotes encapsulate the internal tensions caused by each of these points respectively.

a) I went for a couple of nights out, and I just found myself losing concentration. Like people would be talking about something, and about five minutes later I realised I had not listened to a word anyone had just said, and I think, 'Oh dear, that was rude.' [TYA12, phase A]

b) And just all the tasks, like my mum had to go and pick up some train tickets yesterday for me because I was too tired to do that. So I guess I'm quite reliant on them which I'm quite worried about because I want to move out. [TYA2, phase A]

c) So I am going to have to do most of my A-level year potentially with the same kind of memory problems, and that really worries me. [TYA9, phase A]

d) But I'm seriously worried about job interviews because I went to one before and I forgot what I was saying and so I just kind of went over it. But if it was in a different situation [and] I couldn't go over it, then I don't know what I'd do. And it just sounds like an excuse when you're like, 'Oh, sorry, I forgot the question.' [TYA2, FG, phase A]

Further tensions arose from unmet information needs. As discussed in the preceding theme, participants were often aware of the benefits of activity, while at the same time concerned about the potential harms, leading to another source of internal tension [supplementary data, page 355].

I guess also if you don't know whether to just go out and do stuff in spite of it, or whether it is better to just be lying down. [TYA2, phase A]

And then also going outside, not just staying inside, going outside and going for a walk for as long as I can. But then I have recently realised not too long, because then that is counterproductive. [TYA1, phase A]

The other area of unmet information needs, described in section 4.5.7.2 (page 126), was not knowing what to expect. This mismatch between reality and expectations was a source of tension for many participants, who felt more fatigued than expected particularly when trying to return to 'normal life' [supplementary data, page 363].

I think that brings us back to the fatigue because I think the other thing that's difficult is in his mind once he was told cancer-free then the expectation on his part and on other people's part... But of course as soon as you think, 'Right, I'm back to normality,' then you've got this whole business of, 'if life is normal then it suddenly becomes even more apparent the stuff you can't do.' [PAR2, phase A]

During my chemotherapy I was so tired... I wasn't really doing that much anyway for the first few weeks, so it wasn't too much of an issue. If I did feel tired which would be like the middle of the afternoon, then it didn't matter, I could just sit and watch TV and have a sleep if I needed it... It is more when you go and do something, like if you are going out for a family day or something, then you notice it more don't you? [TYA12, phase A]

PAR2 further alluded to the particular challenge of this level of uncertainty at a young age, and the importance for young people to feel in control.

...another effect of fatigue on [TYA2] which is that you're living with it, not knowing when it's going to end, you know? It's a lack of control, which as we all know is a horrendous place to be when you can't determine what's going to happen to you. By dint of effort, work, doing exams, you know? [PAR2, phase C]

At least I've had 50 years of living where there have been times when you're not in control and you know what it's like. I think it's very difficult when you're in your early 20s to cope with that. [PAR2, FG, phase A]

#### **4.5.9.2 *Tensions within family***

A major theme, expressed by more than half of the young participants, was the perception that their fatigue was misunderstood by parents, who appeared to attribute fatigue-related behaviour to 'laziness' or 'disorganisation' [supplementary data, page 361].

And so of course they [parents] attribute what I would call fatigue to either laziness, or lack of willpower... So they are attributing any kind of thing that could be fatigue onto my poor choices... so it is hard for me to gauge how much they understand. I would say that I have spoken to them and tried to explain that it is not laziness. Sometimes I have got through, sometimes I haven't, and they do stick to their core beliefs. [TYA1, phase A]

Parents were also perceived to underestimate fatigue, conflating it with the usual tiredness that occurs after a busy day.

So the other day I did get quite tense in that I swore at mum because she just turned round to me when I was just trying to tell her how fatigued I felt, and that when I was at work I had to say, 'No,' to some jobs because I ached, and I was tired. And she was just like, 'Well anyone would feel like that on a normal day at work.' I was like, 'You don't get it,' and then I tried to explain it more. [TYA7, phase A]

Thus, as well as the internal tensions from young participants' expectations being out of keeping with reality, TYAs perceived that parents' expectations were also unrealistic. At the end of cancer treatment, they expected life to return to 'normal' [supplementary data, page 361]

...when I finished the treatment, my parents automatically tried to get me straight back into life, as I would have done before. They were like, 'You have to get a job, you have to walk home from school.' [TYA9, phase A]

This topic led to a lively topic of conversation in the young participants' focus group, when TYAs discussed how they could enhance parental understanding.

Mine think I'm making it up. [TYA1, FG, phase A]

Yeah, feel the same. Like it kind of feels like they don't understand. [TYA7, FG, phase A]

They're like you're off treatment so now go back to normal... Can't we do this kind of thing where if a parent doesn't believe us, we like send them to the hospital and they have to watch like horrible side effects of chemo and stuff and sit there like... [TYA1, FG, phase A]

No, I don't think we should do that...! [Multiple speakers]

And then they'll understand... [TYA1, FG, phase A]

Parents were not the only family members with whom there were interpersonal tensions. Siblings were also perceived to misunderstand fatigue and its impact. While this point was particularly acknowledged by parents (section 4.5.10.2, page 155), TYAs also described this difficulty.

... my siblings are older and my sister especially, she doesn't understand how tired I do get. And it's very much like we end up arguing then because it's like, 'Why can you be this tired you don't do anything all day,' and it's a bit... I think she doesn't understand that, just because my chemo has stopped, doesn't mean that all the post [chemo] stuff does stop too. [TYA3, FG, phase A]

#### **4.5.9.3 *Tensions beyond family***

Tensions occurred with others too, beyond parents and siblings, with the source of the difficulties often attributed to misunderstandings. Friends were particularly perceived to underestimate fatigue, thinking of it merely as being 'tired' [supplementary data, page 362].

But with even things like fatigue, nobody really understands. Like just small scenarios like nights out, my friend got annoyed at me, because I didn't want... well, not annoyed, but she was a bit like, 'Why?' when I said, 'I really cannot do this night out, because I am struggling to stay awake,' and it was kind of like she didn't understand. [TYA7, phase A]

There were equivalent tensions with employers. One participant [TYA2] described fearing he would be misunderstood by his prospective employer in phase A; subsequently in phase C, he described that he had, indeed, been misunderstood in the subsequent months, requiring considerable explanation and pressure on his employer before there could be resolution.

I was meant to be starting [training in work], but I was just like I don't think I can do it. And I was asking them about making some adjustments, and they just said, 'No, we can't do that.' [TYA2, phase C]



But I have made [employer] aware, because I needed a lot of dates off, because of appointments and things, but I don't think they get it, and then that then also makes it worse for me mentally. [TYA7, phase A]

The low level of understanding extended even further, beyond family, friends and employers. The young participant below was referring to 'people in general' and included 'cancer doctors'.

I don't feel like people get it; they're just not very informed most of the time and it's hard to communicate. [TYA14, phase A]

*And what makes it hard? [Interviewer]*

Just a lack of understanding from my point of view. [TYA14, phase A]

Even within this study, one participant considered that the questioning from an interviewer, known to her as a healthcare professional, could be implying laziness or 'lack of effort'.

*Yeah, so, even though you are saying... you might just not bother doing it, there might be some bits of that intervention that you would actually give a go? Do you think it depends on how much effort it requires? [Interviewer]*

Yeah, I suppose. That makes me sound outright lazy though. [TYA5, phase A]

*Oh [TYA5], I'm sorry, I didn't mean it like that. [Interviewer]*

Most of the tension identified in this study arose from a pervasive misunderstanding of fatigue. Another source of tension was that young participants felt that staff may be aware that they were experiencing fatigue, but expected them simply to cope with it, creating a sense of abandonment [supplementary data, page 362].

Because I guess you leave the hospital, and then you kind of... I don't know, you are not really getting the same level of support that you were before. And it just seems like the fatigue is the inevitable consequence, and you just have to like deal with it. [TYA2, phase C]

#### **4.5.9.4 Theme B1 discussion**

Young participants described experiencing tensions at multiple levels: internally, within family, and beyond family. Underpinning this was the perception that fatigue was not understood, one of the most pervasive themes in the study, being expressed in some way by every TYA participant.

Not only did internal tensions arise from expectations being out of keeping with the reality of life after cancer treatment, TYAs experienced additional tension from a perception that their parents' expectations also failed to match reality. Parents expected life to return to normal after the end of treatment. Young participants felt both personally misunderstood (judged as 'lazy' or 'disorganised') and that the fatigue was misunderstood (conflated with 'being tired'). Siblings, friends, employers and healthcare professionals were all perceived to misunderstand, leading to tensions that manifested as frustration and, particularly directed towards parents, anger.

Beyond the extensive misunderstandings about fatigue, the main other source of tension resulted from frustrated social, education or work needs. This was discussed in section 4.5.6.1 (page 116) and will not be considered further here.

#### Contextualising with existing literature

The plethora of multi-level misunderstandings and tensions has not previously been described in literature relating to TYA CRF, nor indeed in relation to fatigued older adults with cancer [378,379]. These tensions may, in part, explain the review finding that fatigue is a particularly distressing symptom in young patients. Such insight is valuable, in terms of intervention development, as support to dispel misunderstandings may be effective in reducing fatigue-related distress.

It is noteworthy that, while this appears to be a novel finding in the context of CRF, tensions are well-described in CFS/ME. Extensive conflict with healthcarers has been documented, with CFS a contested diagnosis, leading to delegitimisation and stigmatisation [380]. Tensions with friends have also been described in range of qualitative studies involving both adolescents and adults with CFS/ME, including bullying from peers, negative attitudes, loss of friendships and a sense of distrust [376,381]. In relation to tensions within the family in CFS/ME, findings have been more varied. Most reports of family conflict come from studies evaluating the impact of CFS/ME in adults, rather than adolescents; non-acceptance, at least initially, appears to be common, leading to a strain on relationships, particularly with partners [380,382]. In contrast, in qualitative studies involving adolescents with CFS/ME, although some participants do describe more conflict, many others perceive an increase in the closeness and protectiveness of family relationships, with no overall negative impact in family cohesion [376,381,383].

In adolescents with CFS/ME, therefore, evidence suggests many levels of tension and misunderstandings, but greatest with healthcare professionals and least with immediate family members. Conversely, FICS participants described considerable tensions with family members, some tensions with friends, and little in relation to healthcare staff. This discrepancy between the experiences of adolescents with CFS/ME and CRF might occur due to a difference in the perceived validity – particularly from the perspective of healthcare professionals – of the underlying diagnosis. The aetiology of CRF is indisputable, unlike CFS/ME, leading to greater understanding. The tensions between TYAs and family members found in this study are particularly interesting and novel.

#### Integrating with Fatigue in Focus survey

Findings from this study are remarkably consistent with both the quantitative and qualitative data from the survey. Two-thirds of survey participants perceived friends to have poor understanding, with about a third feeling that family and friends lacked understanding. This study illuminates these findings, providing insight into the nature of the misunderstandings, for example when fatigued individuals perceive that others judge them to be 'lazy' or 'disorganised', or when there is an evident mismatch between imagined expectations and discovered reality.

This study may also provide a potential explanation for the unexpected survey outcome that fatigue prevalence appears to be worse in those more than one year after the end of cancer treatment, compared to those in the year after treatment. The qualitative evidence of a mismatch between expectations and reality could, at least in part, help explain the finding. The expectation that fatigue should be settling after the end of treatment, along with attempts to return to 'normal life', mean that ongoing fatigue is experienced as more significant than it might otherwise have been.

#### Summary

The multilevel tensions found in this theme have not previously been described in relation to CRF at any age. The fact that there is evidence for tensions occurring particularly in TYAs, rather than adults – both in the context of CRF and CFS/ME – suggests that there is an age-related component to the frictions that occur. As discussed in section 1.1.2.2 (page 6), in adolescence there is a neurodevelopmental propensity to enter into conflict with others, particularly with parents [63].

These findings have clear implications for intervention design. TYAs need to be empowered to communicate proactively and positively, explaining their fatigue experience and needs, rather than allowing misunderstandings to generate conflict. It is likely that it would also be valuable for parents to be supported within the intervention; this is discussed further in the following theme.

#### **4.5.10 Theme B2: Fatigue-related tensions have a detrimental impact on family**

This theme focuses on the perspective of parents. As with their offspring, parents also reported experiencing detrimental disharmony.

It affects [TYA5] mostly obviously but it can have a knock-on effect because she feels so tired all the time, takes it out on me, quite understandably... And sometimes she sort of gets a bit snappy if she's really tired and of course I'm the one in the firing line which I don't mind, it's very understandable after what she's been through. [PAR5, phase A]

Parents alluded to multilevel tensions, experiencing both internal tensions and interpersonal tensions across, and beyond, the family.

##### **4.5.10.1 Internal tensions**

Interviewed parents were aware that much of the frustration, and resulting anger, from young patients, was a consequence of the impact of fatigue in social, education or employment terms. After the end of cancer treatment, parents wanted to support the young person to re-engage with these activities. However, this led to parents themselves experiencing internal uncertainty and tension, particularly in relation to how much to push the young person [supplementary data, page 363].

We had our moments when we would be encouraging him, and we would have little arguments I suppose about the fact that... say week two, I am like 'Well you are a lot better this week than last week, so why don't you come here with me, or do this with me? ...and so there is a bit more conflict as time has gone by, because as his parents we feel what are you going to do with your life? [PAR13, phase A]

This was a major theme, experienced on some level by all parents except one. PAR8 did describe wanting to push her son, but stated that there were no fatigue-related tensions within the family.

...you had to just judge it. If I started pestering him to get up and I was getting nothing or a little bit of aggression I would just drop it immediately. I never pushed him like that... so we'd never get into an argument about it. [PAR8, phase A]

*So it's so interesting what you're saying, [PAR8], which is that fatigue actually didn't bring conflict into your home. [Interviewer]*

Not at all. [PAR8, phase A]

Closely related to the uncertainty about how hard to push their TYA offspring, many parents expressed frustration at not knowing what to expect in terms of fatigue severity. As described in

section 4.5.7.2 (page 134), considerable unmet information needs were reported, particularly in relation to how much of the fatigue was due to cancer and its treatment, and how much was the normal tiredness of adolescence [supplementary data, page 356].

Another significant source of internal tension for parents related to the invisibility of fatigue. Several parent participants hinted that fatigue cannot ‘be seen’, alluding also to the related scepticism this engendered.

It is quite hard, because he looked all right [PAR13, phase A]

Another parent touched on the invisibility of fatigue, along with her son’s relief that this did not prevent his fatigue being understood by her mother.

Potentially, somebody who has had a limb amputation, you would be seeing it.... he looked at me and he said, ‘Thank you so much for believing me about the fatigue.’ And I said to him, “Well why on earth would I not believe you with the fatigue?” And he said, ‘Obviously most people look at me, they don’t know, and I now have hair and all the rest of it.’ So there is that aspect. [PAR2, phase C]

*And so such a relief for him to know that he is deeply understood... needing people to know that this is invisible but massive in terms of its impact? [Interviewer]*

Yes, yes. [PAR2, phase C]

#### **4.5.10.2 Tensions within family**

Many parents, as well as young participants, described interpersonal tensions across the family. Although a few parents did not volunteer this topic, nobody denied that there was fatigue-related conflict across the family. Other than the tensions between parents and young patients described in section 4.5.9.2 (page 149), the most commonly expressed area of conflict was between siblings. The invisibility and inherent daily variability in fatigue levels led to siblings not understanding, and potentially not believing in, the fatigue [supplementary data, page 363].

[Sister] is at home now, but sometimes she just wants to go into [TYA6]’s bedroom and sort of plonk herself on the bed and chat about this and that and the other. And sometimes [TYA6] is quite happy to do that, and other times she is really tired. And I don’t think her sister can get that, so it is quite difficult, so they bicker a bit about that sometimes. [PAR6, phase A]

A further challenge for siblings, leading to tension, was the expectation that they would help with supporting the young person.

...he [brother] has been the one who's been home but he has basically, he has been relied upon and has done, well, let's call him a servant. He's been a servant to [TYA2] nonstop for a year... so we've had some terrible blow ups because of [brother], all because he's been asking him to do stuff... and of course [TYA2] just absolutely blew up and said, 'You don't know what the last year's been like' ... and just shouts... and expects him to jump. And I come in and say 'No'... [PAR2, phase A]

In one instance, the unanticipated return of a young adult into the family home led to tensions with a younger sibling. Another participant described how the caring role prevented a sibling from going to university [supplementary data, page 363].

It has taken its toll on everybody. So I think that... I haven't caused problems for them, but I was living away from home, so I have come back into the family unit... my sister didn't go to university because she was looking after me, because mum had to go to work, [TYA10, phase A]

Several parents also reported on the challenge of not being able to make, or follow through on, family plans [supplementary data, page 363].

It does mean that it is quite difficult to make plans to go... because all of our family live in [place], so it is quite a journey anyway. So, yes, it does have an impact in that way, that I can't really make plans to go and see friends and family, because I have got to basically work around [TYA6]'s fatigue. [PAR6, phase A]

Although there was extensive evidence of tensions between young participants, parents and siblings, only one parent mentioned tension between parents. PAR4 reflected on 'pushing' his son to keep active and attend work, despite his fatigue.

And I think that if you spoke to my wife, she would probably say I was quite hard in the way I pushed it, and do push it. [PAR4, phase A]

#### ***4.5.10.3 Tensions beyond family***

As with the young participants, parents perceived that extended family and peers did not understand fatigue. Two parents made an active choice not to talk to others to avoid causing, or having to receive, an emotional reaction [supplementary data, page 364].

But then I have got them [extended family] sort of 'How is he getting on, how is he getting on?' And they don't understand that some days he just wants to lie on the sofa and watch television. [PAR12, phase A]

Isolation in part comes from having to cope with the emotional reaction of others around you, friends etc. This adds the burden, so it's easier not to see them. [PAR2, FG, phase A]

Although some social isolation was by choice, parents also experienced a sense of abandonment, as discussed poignantly at the parent focus group.

...when I had a chance to kind of sit back and see who was around me there wasn't really anybody around me [PAR6, FG, phase A]

#### ***General agreement***

But I agree with you how you feel that people, you feel like one minute they were there and kind of like, where have they gone? [PAR7, FG, phase A]

Paradoxically, as will be discussed in the forthcoming conceptual model (section 4.5.11, page 160), although parents were accused by their young offspring of not understanding their fatigue predicament, parents easily perceived the misunderstandings of others and rose to the defence of their children.

In the middle of all this arguing she... and I said to her, and she's had loads of people at her, 'Are you going to go back to college? Do you want to get a part time job?' I said to her, 'If you don't want to do anything, don't do anything.' [PAR3, FG, phase A]

I think there is a little bit about not everybody, not every manager having that understanding and patience... I was able to get on the phone to the manager of the shop and say, 'She needs to get off as soon as she needs to get off.' [PAR4, phase A]

#### **4.5.10.4 Theme B2 discussion**

The parents of TYA cancer patients reported extensive areas of tension and misunderstanding, with notable concordance between their experiences and those of the TYA participants. They were similarly coping with internal tensions related to unmet information needs, and multilevel tensions beyond the family. The finding of sibling tensions was an important and relatively unexpected theme, given the focus of the study on the TYA-parent relationship. Parents provided insight into two potential sources of tension: the invisibility of fatigue and its daily fluctuation. Siblings particularly struggled with these more nebulous aspects of the symptom.

#### Contextualising with existing literature

As discussed in section 2.6.4.2 (page 43), the needs of family caregivers have been increasingly recognised over the last decade, with a plethora of research across a wide range of chronic diseases recognising the demands on caregivers. While there has been a focus on the caregivers of older adult cancer patients [384], parents of younger children with cancer [385], and parents of adolescents with paediatric multiple sclerosis [386], there has been little research concerning the experience and needs of carers of TYAs with cancer. Sawyer and colleagues recently conducted a large survey of TYA cancer patients and parent carers; the considerable unmet support needs were greatest in those receiving healthcare within adult, rather than paediatric services [99]. The financial impact on families caring for a TYA with cancer has also been estimated, with the significant economic burden being greatest when the young patient has a diagnosis of leukaemia [387].

In relation to care giving for patients with CRF, one small exploratory study has been conducted, evaluating the impact of CRF on spousal carers of older adults. Up to a half of the participants experienced high levels of strain and depression, with higher levels in those caring for patients with more severe fatigue; almost a third reported a reduction in their ability to work [277]. No previous research has investigated the impact on caregivers of TYAs with CRF. This qualitative study therefore provides the first evidence from the perspective of TYA parent caregivers, revealing a negative impact with multilevel sources of tension.

Considerably more research has been conducted into the experiences of caregivers of people with CFS/ME. A recent systematic review, evaluating levels of psychological distress in 'significant others' of patients of all ages with CFS/ME, revealed consistently high levels of distress in the parents of fatigued children and adolescents [388]; the TYA age group was not investigated separately. Furthermore, amongst studies evaluating the impact of care giving to adolescents with CFS/ME, there are notable parallels with the findings of the current study. Crawley and colleagues revealed that parents struggled with a similar sense of uncertainty and with having to cope with an 'invisible



illness', with those around them appearing to discredit their experience [389]. As with CRF, the adverse impact on siblings includes 'conflict' and 'resentment'. A study focused on siblings revealed frustration with changing roles within the family, resentment that the fatigued sibling may have unfair advantages, and difficulty coping with symptom variability and the related inability to plan ahead; many siblings did not believe that the CFS/ME was genuine and attributed it to laziness [390]. In contrast to the experiences of TYA care givers, evidence regarding older CFS/ME patients is more mixed with one qualitative study revealing a resigned acceptance of the CFS/ME diagnosis over time and relatively little adverse impact on carers [391].

The novel findings from this study therefore appear to align remarkably closely with the experiences of young people with CFS/ME. Although there is only limited evidence available in older adults with CFS/ME or with CRF, it appears that the experiences of parents of TYAs with CRF are more a feature of the young age of their offspring, than of the specific underlying cause of the fatigue. This will be discussed further in section 4.6.1.1 (page 199).

#### Integrating with Fatigue in Focus survey

The survey provided only proxy reports on parental perspectives. Almost half the TYA survey participants felt that their fatigue had an impact on their caregiver by causing 'upset', 'frustration' or 'limiting rest time', with the impact tending to be worse for those caring for a TYA with more severe fatigue. The findings in this theme are consistent with the survey, building on them by revealing, despite the perception of misunderstandings, the similar perspectives of TYAs and their parents.

#### Summary

This theme provides, for the first time, direct evidence from parents of fatigued TYAs of considerable burden. A conspicuous degree of congruence was found between the multilevel tensions experienced by TYAs and by their parents, supporting the conceptual model in the following section.

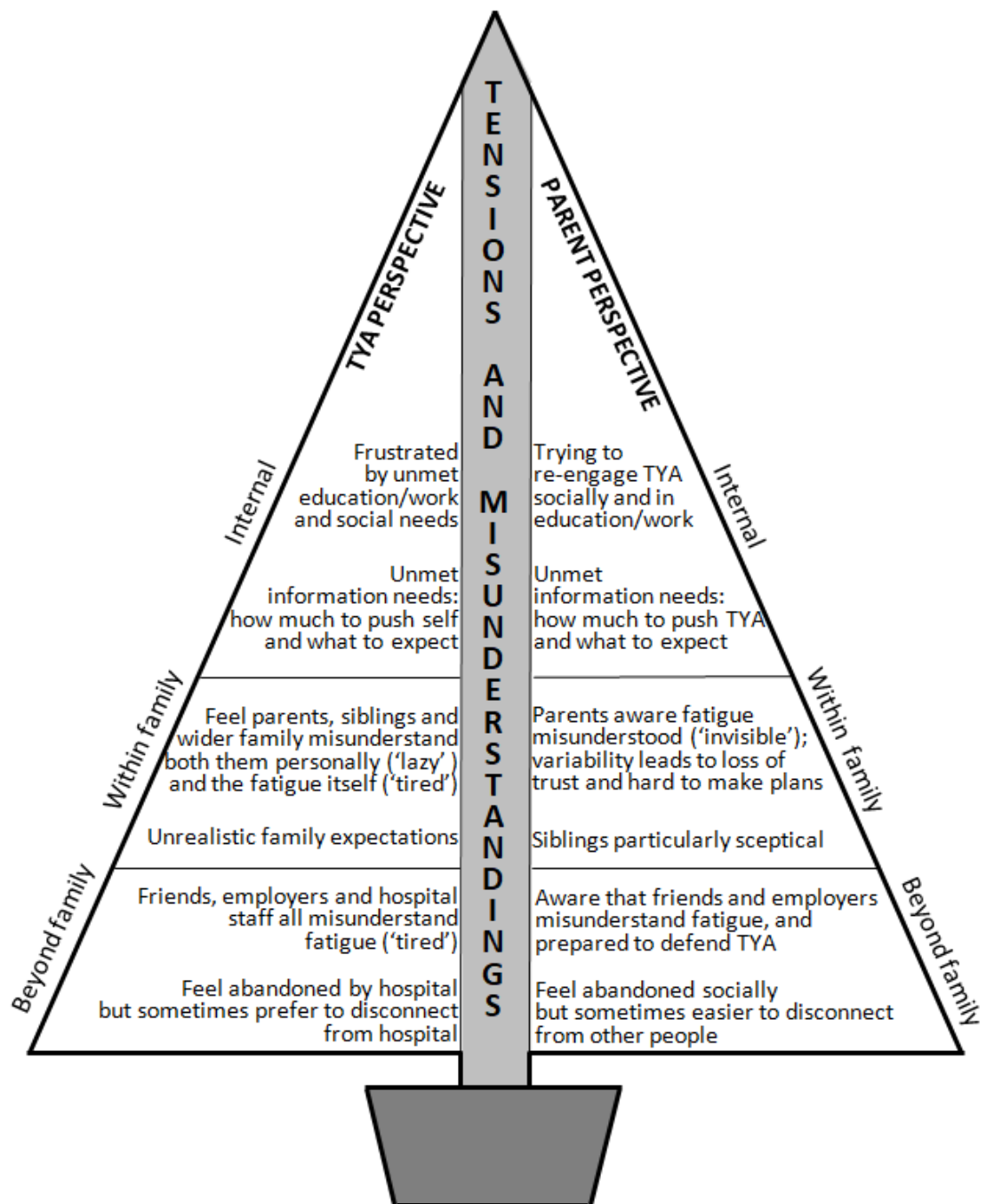
There is compelling evidence that the experiences of both parents and siblings of fatigued TYA cancer patients are similar to those of CFS/ME care givers. Data from this theme have highlighted the hitherto unevaluated topic of the experiences of siblings of young cancer patients, finding evidence of loss of trust, frustration and conflict, in the context of fatigue variability and invisibility.

There is clearly a strong argument for including parents and siblings in an age-appropriate fatigue intervention. As described in section 4.5.7.3 (page 140), there was a range of views amongst young participants as to whether they would want parents to be involved. For those finding such involvement acceptable, it is likely that both TYAs and parents would benefit from such support.

#### 4.5.11 Conceptual model B: the Concordant Tension Tree

The concordance between tensions experienced by TYAs and their parents have been conceptualised in the model below. It attempts to encapsulate the oxymoron of concordant discord. Although tensions between adolescents and parents are well described out of the CRF context, as discussed in the preceding section, there has been no previous work suggesting analogous tensions. The potential value of this conceptualisation is that it is conceivable that simply supporting communication between TYAs and their parents, within a fatigue intervention, could be therapeutic in itself, leading to a sharing of similar perspectives and de-escalation of tension.

Figure 4.3 Concordant Tension Tree



#### **4.5.12 Theme C1: Fatigue may perpetuate with vicious cycles**

This theme can be encapsulated by a short phrase, stated almost identically by both members of a TYA-parent dyad:

The only thing I got told at the beginning was the 'fatigue breeds fatigue', which is true.

[TYA8, phase A]

'Fatigue breeds fatigue' in my head. [PAR8, phase A]

The pivotal concept raised within this theme was that the fatigue had the potential to worsen simply because of its presence. In a variety of ways, fatigue was described as leading to consequences which, in turn, could intensify the fatigue itself. This led to vicious cycles developing that could perpetuate the symptom. The unhelpful consequences of fatigue included physical inactivity, negative thoughts and poor sleep habits, and are described in detail below.

Not only were vicious cycles described, but the converse – virtuous cycles, or cycles of improvement – were also reported. PAR6 described this concept in terms of use of energy generating more energy, the antithesis of 'fatigue breeds fatigue'.

...she finds that when she actually gets up and does something it gives her more energy, as opposed to when she's feeling fatigued... before, what she was doing was just spending the day in bed, and it was just making her feel worse... [PAR6, phase C]

*Where did [TYA6] and you get this idea that energy breeds energy, the thing that we were talking about before? How did that come about?*

I think it's just something my mum always used to say to me, that if I said, 'Oh mum, I'm really not feeling too well today, can I just like lay on the sofa?' she'd say, 'the best thing you can do is get up and do something. Whatever it may, just go for a walk,' she said, 'because you always feel much better doing something.' When you feel ill and you act ill... you feel worse. [PAR6, phase C]

##### **4.5.12.1 Activity**

One of the most pervasive themes that emerged was the perception that fatigue led to people being less active and that, in turn, inactivity had the capacity to make the fatigue worse. Fatigue leading to enforced inactivity was described by many young participants.

...it's just like a ton of brick pressing on you. It's just like me needing to sit down all the time, or needing... you know, when you're so tired that you can't sleep, almost too tired, it's like that and everything slows down and all I want to do is just get onto the sofa and lie down. [TYA2, phase A]

I am just sat, and I won't move. It is like trying to lift a house up off the sofa, it is hard. [TYA3, phase A]

Parents also described this intuitive corollary of fatigue but also alluded to the inactivity as a habit, compounded by family members undertaking the activities the young person would previously have done.

There's then this habituation which I'm sure you're going to see with fatigue, where the habitual behaviour is... so basically [TYA2] sits on the sofa and just, he's called [sibling name]. And just shouts, '[sibling name]!' and expects him to jump. [PAR2, phase A]

You see I would love to say that I do a lot for her because of her fatigue, but I think it is just force of habit now. Because she has been ill for so long, I have got into the habit of doing everything for her. I think that she is capable of doing a lot more for herself, but I have just got into that bad habit of doing it all for her... before she became ill, her and her sister both had their set chores... But she doesn't do any of that now. [PAR6, phase A]

This relative lack of activity, caused both by the fatigue and others' help with the activities of daily living, was frequently described by both young participants and their parents as worsening the fatigue itself [supplementary data, page 365].

...if I just sit around and do nothing I feel even tired-er sometimes. [TYA2, phase A]

Because obviously the more you sit still, whoever you are and whatever you have done, the more you feel tired. [PAR7, phase A]

Further weight was given to this concept by the many participants who described the negative impact of rest and the positive impact of activity on the fatigue within the same phrase [supplementary data, page 365].

Like if I spent a week doing nothing, and staying in bed, my fatigue would get worse. Whereas if I get up and walked, or even something small like just a five minute bike ride or something, if I did that every day I would feel much better than before, if I didn't do it, if that makes sense? [TYA8, phase A]

This quote also provides an example of an important concept that emerged in all three facets of theme C1, and will be highlighted within each section. A small change, 'a five minute bike ride every day', was considered to have the capacity to lead to a sizeable benefit.

Although no participants used the term 'vicious cycle', it was often implicit.

But it's a long haul because... and I think if you're tired and exhausted through no fault of your own, if you then do nothing you get even more tired and exhausted. [PAR3, FG, phase A]

Furthermore, the concept of a vicious cycle was invariably understood by participants when it was raised in discussion by the interviewer.

*... that classic vicious circle where if you are fatigued, you are less active, and if you are less active you get unfit, and if you are unfit, you get more fatigue, which I guess is what is behind how you know that you wanted to be more active with walking. [Interviewer]*

Yes, yes. [TYA10, phase A]

*So you knew that already? [Interviewer]*

Definitely, yes. [TYA10, phase A]

The description of the benefits from activity included the concept of breaking a vicious cycle, to turn the situation into a cycle of improvement.

You just push through the initial thing, and you feel much better afterwards, and then even the next day you will feel more motivated to do it than the day before. [TYA8, phase A]

Participants' narratives often included their views on the mechanisms for the benefit of activity. Although at times the mechanism was described in physical terms, such as 'getting fitter', more participants perceived the mechanism as having a psychological component. Activity was considered to help the mind by relieving tension, avoiding self-pity and providing a distraction from focusing on fatigue [supplementary data, page 365].

I did find that being active helped not only my tiredness but my mental wellbeing, because it kind of like was something positive... I found it kind of like helped my mind as well, but it helped the tiredness. Because I felt that the days where I was just at home in bed feeling sorry for myself, it didn't really help much, and you actually made yourself feel worse. It is like when I am feeling anxious at home, if I am low, going on a run does help that... [TYA7, phase A]

I need to be up and doing something, and then I forget about feeling tired, because I'm busy. [TYA10, phase C]

But it is like it is psychological isn't it...? And if it is helping in your head, then it helps the rest of your body. [PAR7, phase A]

#### **4.5.12.2 Thoughts**

All participants were cognisant of the importance of the mind in the experience of fatigue; no-one viewed fatigue as a purely physical symptom. As described above, not only was it recognised that inactivity had a negative psychological impact that worsened the perception of fatigue, but it was also recognised that the fatigue itself had an impact on thoughts and emotions that could worsen the symptom, in a vicious cycle.

The first part of the vicious cycle, the psychological impact of fatigue, has already been described in detail in several of the preceding themes. Participants reported tensions resulting from the mismatch between expectations and reality, along with pervasive misunderstandings (section 4.5.9, page 147); the age-related propensity for emotional reactivity compounded the experience of frustration, anger and low mood (section 4.5.6.2, page 118). Furthermore, thinking about the potential meaning of fatigue, whether it may be representing a return to ill-health, also exacerbated the emotional impact of fatigue.

I think the thing with cancer is, is that there isn't an end to it... So for us at the minute it is every three months. So you are always waiting for the next 'okay'. So if [TYA4] gets tired, then you are thinking, 'Oh is there a reason why she is getting tired, is it just because she is working, or is she okay...?' [PAR4, phase A]

*So it is the meaning of the fatigue, rather than the fatigue itself, is the impact on you?*

*[Interviewer]*

Yes. [PAR4, phase A]

Importantly, participants also recognised the converse, that psychological factors could, in turn, influence the feeling of fatigue. This insight was particularly evident in the views of parents, rather than TYAs, and most often talked about in terms of the impact of mood on fatigue [supplementary data, page 365].

I think your mood will make you more tired. So if you do sit in a room, it is going to make you more tired, and you are going to feel more fatigued. [PAR7, phase A]

We realised that sometimes being happy and having fun can actually give you a boost of energy. [PAR14, email, phase A]

Only one young participant expressed a similar insight; her views were expressed in the third person, in relation to her friends rather than herself.

I think, like I tried to mention earlier, there is another component and it is all to do with what you would call the mind, or the soul, or the spirit... I was talking to people at Uni... and I was working out that what they were feeling was fatigue was actually they were just psychologically unhappy with where they were. The moment they changed that, they no longer felt fatigue. [TYA1, phase A]

As described in relation to activity in the previous section, the quote above again demonstrates the emerging theme of small changes having the potential to lead to significant benefit. Although TYA1 did not explicitly state that dealing with being 'unhappy with where they were' would be a small change, it could be considered to be implied by the word 'moment'.

The term 'vicious cycle' was clearly well recognised as a concept when described by the researcher to participants, although it was not volunteered by participants, who tended to use the term 'spiral' instead. On two occasions a 'spiral' of low mood impacting on fatigue was described, both times mediated by low mood influencing activity levels.

...it spirals, because then if my mood is low I want to go out even less, then I don't get the exercise. [TYA1, phase A]

Because I think they can start falling into this spiral of, 'I can't do it, I don't want,' you know, 'I can't do anything,' and all this negativity... I've suffered with a lot of depression in my life and I know that no matter how I was feeling, no matter how bad I was feeling, if I could get up and walk around or just do something, anything, you don't even need to have a purpose, just walk, I would be better. And then I was able to do something more... But you have to take that first bit, literally your first step. [PAR8, phase A]

The focus of thoughts was mentioned by a number of participants; thinking about fatigue could make it worse, leading to a 'self-fulfilling prophecy'.

I think if you focus on being tired, you will get tired. If you focus on being energised and awake and achieving something, then you are more likely to achieve that. [PAR4, phase A]

Conversely, moving one's focus away from the myriad of thoughts, toward a mindful focus on the present, was perceived by several young participants as helpful for the fatigue, consistent with the findings discussed in section 4.5.7.2 (page 132).

#### ***4.5.12.3 Sleep***

Despite the fact that topic of sleep was not explicitly included in the interview and focus group topic guides, virtually every young participant provided unsolicited descriptions of sleep changes, reports that were invariably corroborated by their parents. Poor sleep was, unsurprisingly, considered to cause fatigue.

Although some participants described needing to sleep more than usual, the main concern was the converse, with difficulty getting enough sleep [supplementary data, page 366].

I can't go to sleep before 2:00am... I am up at like 7:00am... I am not sleeping. I have got sleepers and they are just not... well they do work, but it takes like an hour and a half for them to kick in. And then it is only there for a couple of hours, and then I am awake again. [TYA11, phase A]

I'm not getting much sleep at all but I don't think there's anything that you guys could have done about that... I've sort of got into a routine at the minute where I know that I'm not going to get much sleep so I just deal with it. Like I've sort of got into the habit now not getting much sleep and feeling tired in the mornings, so that's sort of my routine at the minute. [TYA12, phase C]



[TYA6] hasn't actually slept now for about three weeks, it went from her just like sleeping sporadically but now she's just not sleeping at all. [PAR6, phase A, FG]

A number of participants volunteered unhelpful sleep habits they had identified themselves, most commonly going to bed too late, or sleeping too late in the morning [supplementary data, page 366].

There is an aspect of my habits that could help the fatigue, which... I don't go to bed at good times... I have never had a good bedtime routine. So they are attributing any kind of thing that could be fatigue onto my poor choices... [TYA1, phase A]

Where she had the exams, there was a reason for her to have to get up in the morning. But now I do find that she is sleeping later in the day, and then she is finding it really difficult to sleep at night. [PAR6, phase A]

When the subject was raised by the interviewer, many participants did report use of electronic, light-emitting devices in the bedroom, acknowledging the potential negative impact on sleep [supplementary data, page 366].

He hasn't been sleeping well... [PAR12, phase A]

*So there is light in the bedroom. [Interviewer]*

Normally have light from the phone. [PAR12, phase A]

As well as sleep-related habits that impacted on the amount of sleep gained, a few participants described a state of arousal that hindered sleep. Anxiety related to the cancer diagnosis was sometimes implicated [supplementary data, page 366].

And I think that thinking back on it, one of the biggest issues was that [TYA4] couldn't sleep. And so she didn't share what was going on in her head with us, but you can guess that the fear of the whole thing was meaning that she was having a lot of broken sleep, so she wasn't sleeping solidly through the night. [PAR4, phase A]

Several young participants expressed anxiety or frustration about the difficulty sleeping [supplementary data, page 368].

I'm not getting anywhere near as much as I probably should. I'm not sure why... That's been my main thing that I've been worried [about]... [TYA12, phase C]

One parent described the fatigue directly making it hard to sleep.

You can get too tired to sleep too, don't you? So you didn't sleep last night. [PAR14, phase A]

As with 'activity' and 'thoughts' above, the same interesting theme emerged, of small changes being able to lead to a significant or sizeable benefit. Several TYA and parent participants provided insight into how feasible it was to break unhelpful sleep habits, to improve both sleep and fatigue. TYA6 described the vicious cycle of being too tired to function effectively during the day, with the resulting daytime inactivity hindering sleep at night. She broke this cycle by taking medication to help her sleep for just two nights [supplementary data, page 367, for full quote].

...but I really didn't want to take it at first, but I took it for, like, two nights, and then I was really well rested. And then I just woke up that day and was, like, I need to do something.

[TYA6, phase C]

*That's really interesting. So it was actually taking that medication that got rid of the, sort of, vicious circle you were in of being too tired to do other things. [Interviewer]*

Yeah. [TYA6, phase C]

Another participant, TYA3, described a dramatic transformation after receiving the prototype intervention, by fixing her sleeping and waking times, and by stopping use of energy drinks to keep awake during the day. After receiving the prototype intervention, she said:

I've managed to build my energy back up and I'm now doing things that I thought I wouldn't be able to do... [TYA3, phase C]

*...what's made the difference? [Interviewer]*

I started recording my sleep pattern... So instead of drinking like numerous amount of energy drinks to keep yourself awake, I started drinking just water... My sleep pattern, because I was like waking up in the night, I just decided I needed to put it on like a time thing, so I set an alarm for when I need to go up to bed, and then set an alarm for when I need to get up.

[TYA3, phase C]

TYA3 followed these comments with an implicit acknowledgement of the 'hurdle', referring to the hardest part when the change was made. This was then followed by increasing improvement, a vicious cycle having been broken and turned into the converse, a virtuous cycle.

I mean starting off I thought no, I can't do this, it's going to wear me out even more, and once you get over that kind of bit of a hurdle... your body is like, 'I'm not used to this, this isn't right,' it starts kind of getting better each week, and then it starts getting better each day. Like you get to where I am now and I can wake up at like 9 o'clock, and I can be awake until gone 11, and I'm fine. [TYA3, phase C]

TYA10 described the benefits of keeping busy during the day. This avoided the unhelpful sleep habit of sleeping during the day, and her phrase, 'it just gets better from there,' again implied transition into a virtuous cycle of improvement.

I think you need something to take your mind off the fact that you feel tired, because once you're sucked into something else you forget that you were tired, and then the whole day has gone past and you realise that you haven't actually had to have a sleep in the afternoon, say. It just gets better from there. [TYA10, phase C]

#### **4.5.12.4 Theme C1 discussion**

This theme has described three areas where the emotional and behavioural responses to fatigue contributed to the symptom. This provides potential for a vicious cycle, which can perpetuate fatigue beyond the underlying trigger, such as cancer treatment, so that it becomes a self-sustaining phenomenon.

First, participants noticed that fatigue led to inactivity, both by its direct effect on energy levels and because of well-meaning family members trying to help by undertaking the activities themselves. However, resting was described by many participants as unhelpful for the fatigue, for both physical and psychological reasons. Second, fatigue led to thoughts and emotions, including symptom focus, tensions and low mood, with the 'state of mind' then appearing to worsen the perception of fatigue. Third, unhelpful sleep habits, including use of electronic devices in the bedroom, sleeping during the day, and worrying about the impact of lack of sleep, all had the capacity to worsen sleep and therefore fatigue.

Participants recognised the development of ‘vicious cycles’, either by concurring with the interviewer when the term was used, or by volunteering the term ‘spiral’. Furthermore, several participants revealed insight into how making small changes, particularly in relation to keeping active during the day and developing good sleep habits, could make a big difference to fatigue. In other words, small changes were breaking a vicious cycle and allowing the converse, a virtuous cycle of improvement, to develop.

#### Contextualising with existing literature

The relationships between emotional and behavioural factors and fatigue are well-established, as discussed in section 1.1.1.3 (page 3). In a large prospective study of breast cancer survivors, Schmidt and colleagues found that chemotherapy use was not associated with long-term fatigue, whereas a range of psychological and lifestyle factors did correlate with the symptom [42]. Building on this, in another longitudinal cohort study involving breast cancer survivors, Andrykowski and colleagues revealed slight worsening of fatigue in the years after the end of cancer treatment; fatigue severity was predicted by the emotional and behavioural factors of poor coping, such as preoccupation with symptoms, but only in those patients with persistent late fatigue 42 months after the end of treatment, and not in those with early fatigue. This suggests that the emotional and behavioural factors may have a role in perpetuating fatigue.

Relationships have been found between a number of symptoms – including breathlessness and pain – and emotional and behavioural factors; these connections are thought to be mediated through activation of the cortico-limbic area of the brain [392,393]. This region subserves awareness of threats to survival, and generates avoidance behaviours motivated by emotion, which confer a survival advantage in an acute threat to homeostasis [394]. Chronic perceived threats – symptoms being defined as a ‘perceived threat to health’ [145] – appear, however, to lead to maladaptive emotional and behavioural responses that can inadvertently worsen the symptom [394]. Of note, adolescent neurodevelopment has evolved to have a low threshold for picking up perceived threats, given the stereotypical context of moving from a safe parental, to a novel, environment (section 1.1.2, page 7)[66]; it is conceivable that the young brain may have a particular propensity for generating such responses to the perceived threat of symptoms.

Previous research supports each of the bidirectional relationships described in this theme, and is summarised in the following paragraphs. This evidence does not specifically relate to the TYA CRF context; it comes mostly from research evaluating CRF in older adults and CFS/ME.

Regarding the connections between fatigue and activity, it is intuitively clear that CRF is a barrier to activity, supported by evidence, not least from the survey. The reciprocal, that inactivity contributes to fatigue, is consistent with the evidence that exercise ameliorates CRF [56,164,243]. FICS participants considered that exercise improved fatigue through physical and, particularly, psychological mechanisms, views that are also well evidence-based. Exercise in adults with CRF and CFS/ME increases fitness [164,345,395], with reconditioning mediating some of the beneficial effects of activity on fatigue [396]. Activity is also known to be psychologically beneficial, improving mood and anxiety which, in turn, ameliorates fatigue, as discussed below [345,397,398]. Other factors known to mediate the beneficial effects of activity on CRF include improving self-efficacy [399], reducing systemic inflammation [400], improving sleep [400], and in CFS/ME rather than CRF, reducing activity fear avoidance beliefs [395]. Through a range of mechanisms, therefore, fatigue and activity are linked by bidirectional relationships.

The link between fatigue and low mood is well-established in adult CRF and in CFS/ME [401,402]. Although the two symptoms often co-occur, as part of an established symptom cluster [403], association of the symptoms as a consequence of a shared mechanism has not been proven. Indeed, fatigue and depression, although related, appear to be biologically distinct. Fatigue, for example, is associated with a hypoactive HPA axis, and depression with the converse, a hyperactive axis [404,405]; furthermore, depression responds to paroxetine in patients with cancer, whereas fatigue does not [406]. It appears that fatigue and low mood have a causal relationship, rather than sharing a common mechanism. However, there is no clear evidence to date as to the predominant direction of causality, with conflicting longitudinal studies in adults with breast cancer suggesting that depression predicts the onset of fatigue [40], that fatigue precedes depression [407] and that neither symptom predicts the onset of the other [408]. A large longitudinal study involving patients with unexplained fatigue, including CFS/ME, suggested that each symptom could act as an independent risk factor for each other [402]. It seems likely, therefore, that the relationship is bidirectional.

Anxiety also appears to cause, and be caused by, fatigue. As established in the systematic review, fatigue is a distressing symptom for TYA cancer patients. Although the evidence for anxiety and tension being able to cause fatigue is less strong than it is for depression [401], anxiety has been shown to be an independent predictor of CRF in adults [272], and longitudinal follow-up of patients with breast cancer suggests that anxiety can predict future fatigue development [40]. It is relevant that in the context of the closely related symptom of breathlessness, fMRI evaluation has suggested that anxiety may influence the gain of sensory information processing in the paralimbic system, therefore changing the perception of symptom intensity [409].

Sleep and fatigue are particularly closely associated, which again appears to be due to the two symptoms causing each other, rather than the presence of a shared underlying mechanism. Bower and colleagues have demonstrated that, in patients after breast cancer treatment, systemic inflammation contributes to fatigue, but not to sleep disturbance [410]. While impaired sleep unsurprisingly results in fatigue [41,411], there is ample evidence for the converse. Evidence-based models of insomnia involve maladaptive emotional and behavioural responses to daytime fatigue that inadvertently worsen the insomnia, further perpetuating the problem [412-415]. Such responses include spending more time in bed, napping during the day, irregular sleep-wake schedule, catastrophising about the impact of insomnia and nocturnal use of light-emitting electronic devices [118,414]. Much of the evidence for perpetuating psycho-behavioural factors comes from studies evaluating non-cancer patients with primary insomnia, in which daytime sleepiness and fatigue are not always assessed [413,416,417]. There is a smaller volume of evidence for the same processes occurring in CRF; Rumble and colleagues' longitudinal study in adults with breast cancer, found that dysfunctional thoughts and behaviours were antecedents of insomnia [411].

Overall, for each of the vicious cycles relating to activity, thoughts and sleep, there is some evidence in the literature for bidirectional relationships with CRF in adults, albeit not in TYAs. The potential for reciprocal causality to lead to vicious cycle development has long been conceptualised, particularly within the clinical practice of Allied Health Professionals, such as physiotherapists and psychologists [418,419]. Vicious cycles of thoughts, emotions and behaviours are believed, for example, to maintain affective disorders such as anxiety, depression and insomnia [415,420,421]. Elucidating and breaking these cycles is fundamental to the practice of cognitive behavioural therapy (CBT) [422,423]. In CFS/ME, psychologists have recently developed a Cognitive and Behavioural Responses Questionnaire to measure those responses that are recognised to perpetuate fatigue [424]. However, these findings from FICS appear to be the first research report of vicious cycles contributing to the perpetuation of cancer-related fatigue.

Furthermore, no research has been found that explicitly acknowledges and examines the possibility that making a small cognitive or behavioural change has the potential to lead to a sizeable benefit, by breaking the perpetuating vicious cycle and generating the converse, a virtuous cycle of improvement. This suggests that this finding may also be a novel insight.

### Integrating with Fatigue in Focus survey

These qualitative findings were consistent with a number of survey results: that fatigue is a barrier to exercise, that exercise is considered the most helpful approach for fatigue, and that fatigue clusters most closely with low mood and anxiety. In addition, these data provide potential explanations for survey findings. While the cross-sectional survey could only indicate associations, FICS could assess causality because of its qualitative and longitudinal design, revealing bidirectional relationships. The unanticipated survey finding that fatigue severity was worse more than one year after the end of cancer treatment could, at least in part, be explained by vicious cycles perpetuating the symptoms, beyond the initial triggers of cancer diagnosis and treatment. The finding that fatigue treatment was considered less successful in those survey participants further from the end of cancer treatment may also be explained by the entrenchment of the symptom with vicious cycles. Equally, as discussed in section 3.6.1.3 (page 82), these findings could be explained by selection bias or by an increasing mismatch between expectations and reality.

### Summary

The existence of bidirectional relationships between fatigue and the domains of activity, thoughts and sleep is already established in the literature. However, this study has taken this a step further with the insights that vicious cycles may contribute to the persistence of CRF, and that these cycles can be broken with relatively small interventions.

This theme not only explains fatigue perpetuation beyond the initial trigger but also contributes to the design of the fatigue intervention itself. Insight into vicious cycles may help patients understand why a symptom is persisting. Self-efficacy may be enhanced by providing a rationale for how a small and feasible change, that breaks a vicious cycle, can make a meaningful difference. These points are discussed further in section 4.5.14 (page 180).

#### 4.5.13 Theme C2: Responses to fatigue relate to outcomes

During the course of analysis, a set of associations emerged between responses to fatigue and fatigue-related outcomes. Examples of identified responses and outcomes are detailed below.

**Table 4.10 Examples of responses and outcomes**

	<b>Positive</b>	<b>Negative</b>
<b>Responses</b>	Proactive approach to activity Positive, confident thoughts Active self-management of sleep Engagement with intervention	Fearful avoidance of activity Negative, overwhelmed thoughts Acceptance of poor sleep habits Lack of engagement with intervention
<b>Outcomes</b>	Confidence in fatigue management Improvement in fatigue severity Ability to return to education / work	Lack of confidence in fatigue self-management Unchanging fatigue severity Limited return to education / work

In the initial exploratory analysis, participants were divided into four broad categories in relation to the extent of positive or active approach, the degree of intervention engagement, and the level of improvement in fatigue between the end of cancer treatment and the end of study involvement (represented in table 4.11 by + + / + / - / - -). Judgement was based on participants' own reports of their outcomes and the prototype intervention audit (section 4.5.15.1, page 184). The following data patterns were found. TYA participants with a positive and proactive approach, in terms of affect or activity, achieved better fatigue outcomes than those with negative, fearful or passive attitudes. Further, there was a relationship between the extent to which an individual participant took a positive or active approach, and the degree of intervention engagement.

**Table 4.11 Exploratory tabulation of participant approaches, engagement and fatigue outcomes**

<b>TYA</b>	<b>Positive or active approach</b>	<b>Intervention engagement</b>	<b>Improvement in fatigue</b>
1	+	+	+
2	+	++	+
3	+	+	+
4*	++	-	++
5	--	--	--
6	+	-	+
7	++	+	++
8	++	++	++
9	-	+	-
10*	++	-	++
11	--	--	--
12	++	++	++
14	--	NA	--

+ + most; - - least; \* pattern outliers



The qualitative and longitudinal nature of the data provided insight into the perceived mechanisms driving the positive or negative outcomes. Participants were regrouped according to the predominant approach, within the ‘categories of ‘activity’, ‘thoughts and ‘sleep’ (table 4.12), that they reported most strongly influenced their outcome. This led to the emergence of the pattern shown below.

**Table 4.12 Predominant mediating approach for positive outcomes**

Most positive outcomes ←		Mixed outcomes		Least positive outcomes →	
TYA	Approach	TYA	Approach	TYA	Approach
4	Activity	1	Thoughts	5	NA
7	Activity	2	Thoughts	9	NA
8	Activity	3	Sleep	11	NA
10	Activity	6	Sleep	14	NA
12	Activity				

Activity: regular exercising, ranging from walks to formal gym-based activity

Thoughts: insight into the influence of thoughts and mood on fatigue; seeking ways to calm the mind

Sleep: making efforts to improve sleep habits

NA: not applicable

#### **4.5.13.1 Positive outcomes**

The five participants who described most improvement in their fatigue, and reported the easiest reintegration into work and education were the five young people who were most active, undertaking regular physical activity each week. Of note, these participants were all active *before* the point of recruitment and needed little encouragement to continue this during the study itself, raising questions about the relative importance of innate attitudes and external intervention, as discussed below. Two participants, TYA4 and TYA10, while evidently engaged in the research, did not feel it necessary to engage with the prototype intervention, as fatigue had already improved and their lives were busy with education or work. They are the two outlying points in table 4.11, marked with \* [supplementary data, page 368].

So long walks has always been a part of family life. So I try to involve myself more in that, to up my energy levels, and I did find that was really helping. [TYA10, phase A]

...but I was at school for the whole time while I was on chemo so my brain was active, it was still... but maybe that's why it's not as bad as some of... [TYA8, FG, phase A]

Yeah... some other people... [Multiple voices, FG, phase A]

Those participants with positive outcomes were often described by others as having a positive psychological approach, indeed, although not explicitly named as such by participants, as having self-efficacy for self-management. For example, the therapist providing the prototype intervention made the following comment in relation to TYA7:

She felt very grateful for the diagnosis... because she felt like it had directed her life, and now she is studying...which is something she had always wanted to do but never really organised herself to do it...she was exercising probably about five times a week and feeling the best she had ever felt. [HCP, phase C]

Two of the most active and positive TYA participants were exposed to particularly positive and proactive attitudes from their parents [supplementary data, page 368].

I think if you focus on being tired, you will get tired. If you focus on being energised and awake and achieving something, then you are more likely to achieve that... And if you take a positive approach you will get a better outcome, whatever that might be. [PAR4, phase A]

We really need to get people to understand that they are responsible for their own health. [PAR8, phase A]

While physical activity and a positive approach were most strongly associated with good outcomes, active attempts to influence one's emotions and sleeping were also helpful. Several of the young participants with reasonably positive outcomes reported benefit from mindfulness and equivalent approaches. As described in section 4.5.12.3 (page 168), for participants TYA3 and TYA6, the positive impact of small changes on fatigue was particularly striking: fixing bed and waking times, and two doses of sleeping tablets respectively led to definite improvement in fatigue. Others reported that keeping busy during the day led to better night-time sleep and improved fatigue.

... she found that actually when she got up and made herself do something, then she slept better than she did if she didn't. So actually there was some motivation in terms of going to work, which was helping her to then sleep better at night afterwards. [PAR4, phase A]

#### **4.5.13.2 Negative outcomes**

Participants reporting less good outcomes shared some characteristics in their responses to experiencing fatigue: negativity, passivity and limited engagement with the intervention.

Avoidance of activity, because of a perceived negative impact on fatigue severity, was pervasive amongst this group of participants [supplementary data, page 368].

...at the moment exercise just seems to make it worse. I just end up drained rather than like bouncing. [TYA2, phase A]

*What do you think made it [fatigue] a little bit better than the summer? [Interviewer]*

Maybe the rest and time I guess. [TYA9, phase C]

Although concerned about possible detrimental consequences of activity, many of these less active participants did express some awareness that activity or exercise could be helpful.

*So, do you go for walks, or out on a bike? [Interviewer]*

I know that it is something that probably would help. [TYA5, phase A]

Only the dyad TYA14 and PAR14 did not talk about any potential benefits at all, reporting only the adverse consequences. TYA14 was the only participant with concurrent CFS/ME and CRF. This is discussed further in section 4.5.16.2 (page 193).

*“But actually to you, you knew what was going to keep you safe. [PAR14, phase A]*

*Safe from...? [Interviewer]*

Being deathly ill from doing too much. [TYA14, phase A]

The participants with most negative outcomes, along with some of those with mixed outcomes, tended to articulate negative or overwhelmed thoughts, and express lack of self-efficacy for self-management [supplementary data, page 368]. They were more likely to feel misunderstood and to experience tensions, or to express loss of hope or motivation.

*And what, can you kind of identify what’s stopping you from acting on that advice [about being active]?*

I don’t know really, lack of motivation then that all stems from other things I guess. I have always been like that to some extent. [TYA5, phase A]

This same group of participants tended to describe poor sleep patterns and unhelpful sleep habits.

I am not sleeping. I have got sleepers [sleeping tablets] and they are just not... well they do work, but it takes like an hour and a half for them to kick in. And then it is only there for a couple of hours, and then I am awake again. ...It makes me really tired in the day, but then when I try and close my eyes it just... as soon as I close my eyes I am back awake again... Like the other night I didn't go to sleep until 6:00am, and I was awake again at 8:00am. [TYA11, phase A]

Participants with the most negative outcomes were those who engaged least with the prototype intervention. Only one engaged; TYA9 met the intervention therapist on one occasion only and did not respond to follow up.

#### **4.5.13.3 Theme C2 discussion**

The core finding of this theme was the association between participant responses to fatigue and fatigue outcomes. Responses, in terms of three domains described in the previous theme – activity, thoughts and sleep – had a relationship with the outcomes of confidence in managing fatigue, the degree of improvement in fatigue and the ability to return to education and work. Specifically, positive, active, engaged approaches related to better outcomes, whereas negative, passive or disengaged approaches were associated with worse outcomes. Other than two participants, who wanted to support the research but did not feel they required the prototype intervention as their fatigue was already much improved, there was a marked relationship between engagement with the prototype fatigue intervention and fatigue outcomes.

There was a suggestion that baseline activity was an important mediator of outcomes. Participants achieving the best fatigue outcomes attributed the benefit to activity, and were invariably active before the point of recruitment. Conversely, those with the worst outcomes tended to describe activity fear avoidance beliefs.

As with the prior theme, the longitudinal and qualitative nature of data allowed causal inferences to be drawn, beyond simple descriptions of associations. As well as participants providing insights into the mediators of fatigue outcomes, data collection occurring over several months revealed temporal patterns in relevant parameters. Two participants, for example, changed sleep behaviours and described subsequent benefits in terms of fatigue, suggesting a causal relationship.

The pattern of participants with the better fatigue outcomes already being active at the time of recruitment raises important questions. To what extent are fatigue responses inherent? Is

intervention needed in those proactive people with high baseline activity? These points will be considered in relation to existing literature, below, and also in section 4.6.1.2 (page 202).

#### Contextualising with existing literature

It has long been recognised that some characteristics of people living with chronic health conditions can influence health outcomes. Two key constructs described in the literature are a) patient activation and b) perceived self-efficacy.

Patient activation is a concept developed by Hibbard and colleagues, defined as ‘an individual’s knowledge, skill and confidence for managing their health and health care’ [425]. There is robust evidence that high activation levels are associated with a wide range of positive health outcomes, including parameters of good control of chronic disease, engagement with healthcare services, positive experience of healthcare, reduced utilisation of hospital and lower healthcare costs [426]. It is a largely inherent characteristic, involving patients’ general approaches and behaviours relating to health; there is limited evidence that it can be changed by intervention [427].

As discussed in section 1.2.4 (page 16), perceived self-efficacy is a closely-related concept that refers to confidence in achieving specific goals [141]. Unlike patient activation, it is not a trait and thus is more amenable to change with intervention [154,155,428]. Perceived self-efficacy has been widely used in the context of cancer symptom self-management, and mediates improved outcomes [145-147,149,150].

Those FICS participants with confidence in their ability to manage fatigue were manifesting high self-efficacy for fatigue management. The proactive approach to activity, engagement with intervention and ability to return to education or work are broader features suggestive of higher patient activation. Both constructs and associated features were associated with better patient outcomes in this study, consistent with the literature [429].

The good outcomes in those TYAs with highly activated parents is again congruent with existing literature. Parents’ support for activity has been shown to be an independent predictor of activity in adolescent cancer survivors, although no research has evaluated such relationships in CRF [430]. Open and supportive family relationships predict treatment engagement and adherence in adolescent and young adult cancer patients [90].

#### Integrating with Fatigue in Focus Survey

Although the survey did evaluate potential fatigue responses to a limited extent, such as participants' views on the best treatments for fatigue, it could only indicate associations, not causal relationships; there was no way of differentiating whether these were responses to, or causes of, the symptom. There was a suggestion from the survey, a trend that was not statistically significant, that participants considering active treatments for fatigue to be better than passive treatments had lower fatigue scores. The FICS findings support the suggestion that an active approach in response to fatigue may indeed have a causal influence on improved fatigue outcomes.

#### Summary

Overall, this theme suggests that active, positive and engaged responses to the experience of fatigue were not only associated with, but actually caused, improved fatigue outcomes. These types of responses are consistent with high activation or self-efficacy, constructs well-explored in the literature, and known to influence health outcomes.

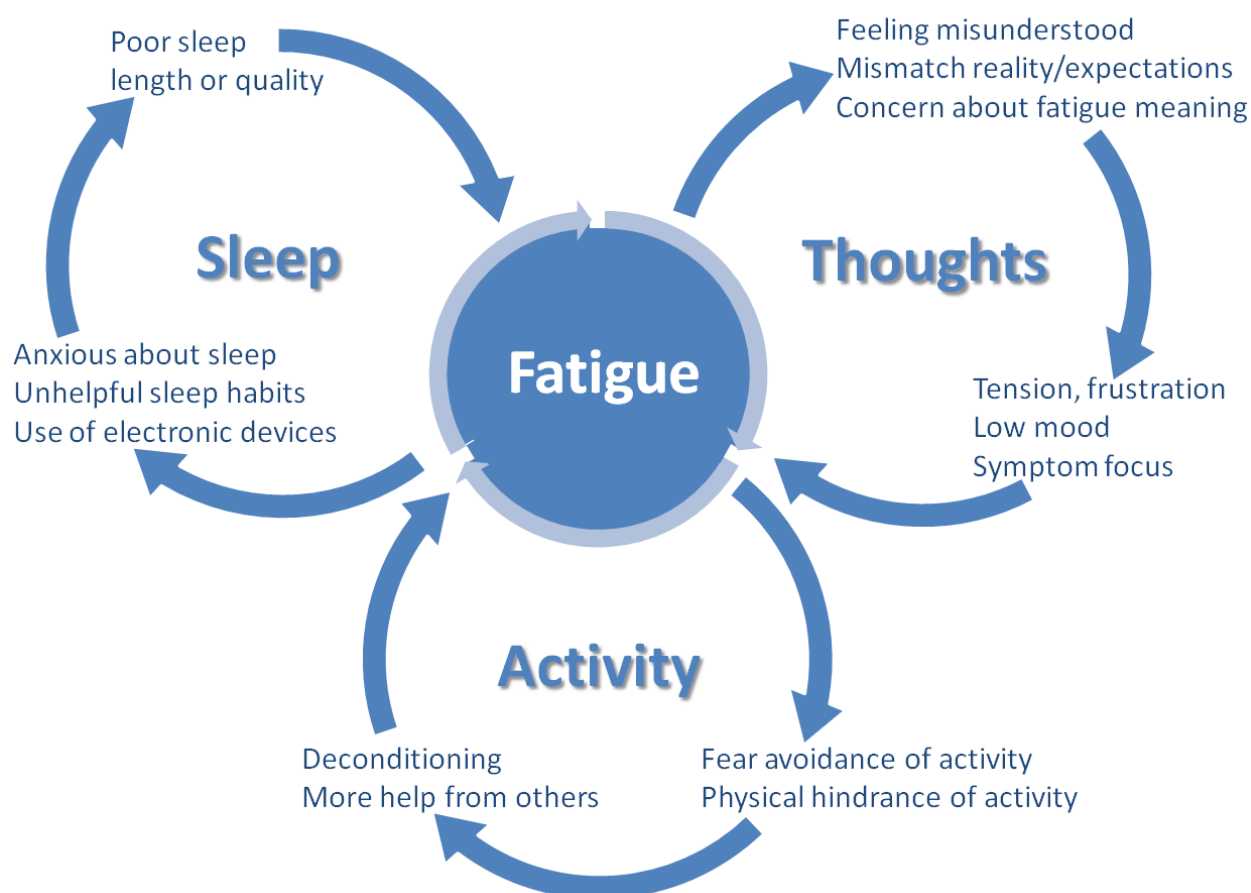
This theme reinforces the theoretical underpinning of this work, that self-efficacy is an important predictor of outcomes in TYA cancer-related fatigue. Given that self-efficacy is goal-specific and amenable to change with intervention, improving perceived self-efficacy for fatigue self-management is a suitable objective for the definitive intervention. Participants with an active approach, even before receiving the prototype intervention, had improved outcomes that did not appear to be related to intervention. The relevance of this to intervention personalisation will be considered in section 4.6.1.2 (page 202).

#### **4.5.14 Conceptual model C: Sleep, Thoughts, Activity (STA) model of TYA fatigue**

The vicious cycles caused by bidirectional relationships between fatigue and the domains of sleep, thoughts and activity has led to the development of the following conceptual model (figure 4.4). The data underpinning this model are predominantly from theme C1, and also from themes B1 and C2.

This type of model is termed a 'vicious flower' maintenance formulation, and is widely used within psychology. First conceptualised by Salkovskis and colleagues in relation to treating obsessive compulsive disorder, it has since been used in a number of psychological conditions, including depression [431,432]. This type of formulation has been previously proposed by Spathis and colleagues, in relation to vicious cycles maintaining the symptom of breathlessness in the context of advanced cardio-respiratory disease (discussed from a reflexivity perspective in section 4.5.16.3, page 196), but has not otherwise been used outside of a psychology context [433].

**Figure 4.4 Sleep, Thoughts, Activity (STA) conceptual model of TYA CRF**



Each vicious cycle in the conceptual model serves to feed back and worsen the fatigue. The central circular arrow demonstrates the suggestion from theme C1 that there is a degree of interaction between the three ‘petals’. For example, participants described how activity relieved tension (page 163); others commented on the relationship between improved sleep and being able to be more active (page 176, page 367). The literature supports such interaction between sleep, thoughts and activity; tension or distress can lead to sleep disturbance that impacts on CRF [434], and improved sleep quality partially mediates the benefit of exercise on CRF [400].

Cognitive behavioural conceptual models of fatigue have previously been developed in the context of several chronic conditions: CFS/ME, rheumatoid arthritis, multiple sclerosis and stroke [435-438]. However, this is the first such model generated in the context of CRF for patients at any age. Induction of a cognitive behavioural model is consistent with the increasing evidence for psychological therapies, including cognitive behavioural therapy (CBT), being effective for CRF in older adults [48,56]. Given the adverse impact of cognitive fatigue in TYAs, it is noteworthy that CBT

appears to be of particular value for the treatment of cognitive fatigue in adult cancer patients after cancer treatment [439].

This conceptual model has potential to support perceived self-efficacy for fatigue self-management. The presence of vicious cycles can make sense of the symptom by explaining how fatigue can persist beyond the initial trigger of cancer and its treatment. Given the prevalent therapeutic scepticism (section 3.5.5.2, page 73), it may be empowering for patients to understand that benefit can be achieved by breaking a vicious cycle. Further motivation may come from understanding that a small change, sufficient to interrupt a vicious cycle, may result in a sizeable impact through generation of a virtuous cycle of improvement.

From a healthcarer perspective, the proposed model reinforces the value of early intervention, before entrenchment of vicious cycles. It could also be professionally motivating, countering any professional scepticism, a point explored further in relation to an outlying case (section 4.5.16.2, page 192). Use of the model may allow focus on the predominant vicious cycle – the ‘active ingredient’ for an individual – increasing intervention efficiency and potentially improving adherence, given the impact of fatigue on concentration and memory (section 4.5.6.1 page 116) [440]. Simply addressing the misconception driving the predominant vicious cycle for an individual has the potential to form a brief and effective intervention, for example: ‘many people get on their phones if they’re up at night, but the light from the phone keeps them awake’ (sleep); ‘feeling more fatigued one day doesn’t mean you’re getting ill again’ (thoughts); or ‘building up activity slowly over time won’t make the fatigue worse’ (activity).

#### **4.5.15 Co-designed intervention**

The aim of this study was to co-design a non-pharmacological fatigue intervention, by ascertaining views on optimal intervention design (study objective 3) and evaluating the experience of having received the prototype intervention (study objective 4). During phases A and B of this three phase study, the intervention prototype was developed and delivered. In phase C, participants provided feedback on the prototype, to refine it further into the ‘trial ready’ co-designed intervention.

##### ***4.5.15.1 Intervention prototype***

The intervention prototype design was informed by the following:

- 1) Patient and parent participants views on optimal design, gathered in 21 individual semi-structured interviews.
- 2) Two focus groups, one of patients and one of parents, providing further design advice.
- 3) A co-design meeting discussion involving the research team, a former patient (and PPI lead) and the AHP delivering the prototype intervention.



Those attending the co-design meeting were provided with a summary of views gathered in phase A. The prototype was fundamentally based on the synthesised opinions of TYA and parent participants. The research team influenced the prototype in two ways. First, a brief overview of research evidence for helpful approaches for CRF was provided to participants during the interviews in phase A; second, a small number of pragmatic decisions were made by considering what would be feasible to deliver within the practical constraints of the research study:

1. Participants' aspiration was for the HCP to be available for weekly contact; however, resource constraints meant that it was agreed that the intervention prototype would involve a minimum of one face-to-face contact with each participant, with subsequent contact by a mutually convenient method, such as telephone, email or Skype. If further face-to-face contact was clinically indicated, it would be offered only if the AHP had capacity.
2. Although participants suggested that short peer-produced videos would be the optimal way to provide information, these had not yet been produced at the time of prototype delivery. Information was therefore given with a standardised 'Tips for managing fatigue' sheet created by the AHP, and by sharing a link to an online Evans Health Lab video on CRF freely available on Youtube [441].

Full guidance on the intended features of the prototype intervention was created for the AHP delivering the prototype (appendix 7.4.11, page 339). An overview of the intended prototype is provided in the first column of table 4.13. After the intervention delivery phase, a retrospective audit of the clinical case notes was undertaken to find out what, in practice, the delivered prototype intervention had been documented to involve. Details are provided in the second column of table 4.13.

The main difference between the intended and delivered intervention was the limited involvement of parents. The AHP involved parents if they were present when she met the young patient or there was apparent interest in this, but did not proactively try to involve parents; only two parents were involved in phase B of the study [PAR3, PAR12].

**Table 4.13 Overview comparison of intended and delivered features of prototype intervention**

Intended prototype intervention	Delivered prototype intervention
<b>Intervention name</b> Road to Recovery: Fatigue Support (R2R)	
Available to all participants.	8/12 participants engaged with intervention (1/12 no response to contact, 3/12 no response after first telephone or text initial contact).
<b>Principles</b>	
Flexible and individualised.	Evidence in all 8 participants, with every aspect of intervention content individualised.
Involving parents where wanted by YP.	Only 2/8 participants involved a parent; the others did not proactively request parental inclusion (although not asked their views on this).
<b>Content</b>	
<b>1. Education/guidance</b>	
Electronic, preferably video format.	7/8 participants given link to Dr Evans Health Lab video.
May include: information about fatigue, managing expectations, information about improving sleep pattern.	Individualised information in all 8 participants.
<b>2. Exercise/activity</b>	
Promotion of activity of YP's choice.	7/8 participants.
May include: structured incremental activity with clear goals, monitoring using health Apps.	2/7 given general information and 5/7 given specific individualised advice. 3/7 documented advice to monitor with specific health Apps.
<b>3. Energy conservation</b>	
May include: analysing priorities, support with pacing, short relaxation techniques.	Evidence in 8/8 participants. In 7/8 participants given information about 'boom and bust' avoidance, and in 7/8 encouraged to use mindfulness App (Headspace).
<b>Process</b>	
Mutually convenient location, and mode of communication.	Location: home (n=2), ward (n=2), non-clinical hospital location (n=2), coffee shop (n=1).
At least one face-to-face meeting, with subsequent contact flexible according to needs.	7/8 had one face-to face meeting (none had more than one meeting). Main mode of contact other than face to face: telephone (n=4), text (n=3), email (n=1). Total number of clinical contacts: mean 1.4 (range 1-3).
Give individualised Tips list as PDF to download on phone.	7/8 participants.
One letter to YP, with copy to specialist healthcare team.	Letter to YP in 7/8 participants, with copies to consultant in 5/8.
Maximum intervention length three months.	Maximum intervention length 14 weeks (range 1-14 weeks, mean 5.8 weeks).

#### ***4.5.15.2 'Trial ready' co-designed intervention***

The interviews undertaken with patient and parent participants in phase C, after having received the prototype intervention, provided valuable information that allowed further optimisation of the intervention. The AHP, who had delivered the intervention, was also interviewed.

##### Overview of feedback on prototype intervention

The majority of the feedback was complimentary; much of this has already been extensively described in preceding sections.

There were three areas of particularly positive feedback (section 4.5.7). First, many participants spoke about appreciating specific advice on how to build up exercise, given their unmet information need relating to 'how much to push' (page 133). Second, participants attached much importance to people being able to set meaningful personal goals (page 129), to enhance motivation; without labelling it as such, participants were supporting a health coaching approach (page 125). Third, several participants gave positive feedback on their experience of using App-based short mindfulness techniques (page 133).

All these points indicated the single most valued aspect of intervention: the provision of information. Even in those parts of the intervention that could be construed as involving behaviour change, participants appeared to attach most value to gaining knowledge and to being given information and advice. Participants appreciated knowing what to expect, knowing how to build up activity and 'how much to push', advice on how to speak to a prospective employer, and information about helpful sleep habits. As the AHP who delivered the prototype summarised:

So it's actually the information sharing is a much more important part of this than I think I've given credit before. And therefore it can be a brief and early intervention. [HCP, phase C]

As well as intervention prototype validation, there was also constructive and valuable negative feedback. The main point was the wish to have more regular contact with the AHP than was provided. This level of contact was considered necessary to support an individualised, specific and structured plan (section 4.5.7, page 128).

Yes, so if there was kind of more contact with someone, maybe? Even if it was like via choice, like email or like phone call? [TYA7, phase C]

But as I say I think that goes along with the fact that he is very disappointed to have just one meeting to, as he sees it, to help his fatigue. [PAR2, phase C]

Two other areas of suggestions for change were made. There was much feedback on the irrelevance of talking about pacing (section 4.5.7.2, page 131). There was also little interest in the written information 'Tips for managing fatigue' sheet, which received no positive comments. This is consistent with the requests in phase A for individualised information in electronic format, with advice from peers rather than healthcareers (section 4.5.7.2, page 136). One participant provided negative feedback:

To be honest I saw the sheet and then just looked at it and it wasn't relevant at that time. I put it away and just didn't look at it again. It may have had something on, but I just didn't... [TYA2, phase C]

#### 'Trial ready' co-designed intervention

The features of the 'trial ready' co-designed intervention are summarised in table 4.14. The evidence underpinning each of the components of the intervention has already been provided throughout the discussion of the six major themes, particularly in relation to theme A2: 'TYA developmental characteristics influence intervention design.' The intervention content falls within three categories, 'activity', 'information' and 'mindfulness', with the acronym 'AIM.'

An inherent tension in the design of this 'trial ready' intervention was the need to balance the flexibility and individualisation required by young patients, with the necessity for a well-defined, prescriptive intervention that can be reliably and consistently delivered. Intervention fidelity is recognised to be particularly challenging in the field of complex interventions; there is some evidence that restricting flexibility in intervention delivery can impact negatively on outcomes [442,443]. A balance has therefore been struck, seeking to define the 'trial ready' intervention as well as possible, whilst supporting flexibility by providing principles along with a range of options in each category. At this stage, the STA conceptual model has not been included in the intervention because it requires further evaluation, as discussed in section 4.6.5.2 (page 210). In the future, its incorporation could add value to an intervention by promoting self-efficacy, explaining the mechanism for change and providing insight into the 'active ingredient' for an individual (section 4.5.14, page 182).

**Table 4.14 Features of the ‘trial ready’ fatigue intervention**

<b>‘Trial ready’ fatigue intervention</b> Road to Recovery: Fatigue Support (R2R)	<b>Comments</b>
<b>Principles</b>	
<ul style="list-style-type: none"> <li>• Promotes self-efficacy for fatigue self-management.</li> <li>• Flexible and individualised.</li> <li>• Health coaching approach.</li> <li>• Involving parents at young person’s discretion.</li> <li>• Provide as early as possible, during cancer treatment or at the point of it finishing.</li> </ul>	<p>Proactively ask if want parents to be involved, as no evidence from prototype experience that patient will raise this.</p> <p>No need to continue with constraint of prototype intervention timing (during year after end of cancer treatment).</p>
<b>Content (AIM)</b>	
<b>1. Activity</b> <ul style="list-style-type: none"> <li>• Specific support with activity of young person’s choice.</li> <li>• Structured incremental activity towards young person’s own goal.</li> <li>• Monitoring using a health App (individualised choice).</li> </ul>	<p>Call ‘activity’ rather than ‘exercise’ as more inclusive for people who do not want to formally exercise.</p> <p>Feedback emphasised need for regular contact and support with ‘how much to push’ oneself.</p> <p>Include addressing fear avoidance beliefs as data analysis revealed importance of this concept.</p> <p>Promotes self-efficacy through activity planning, goal setting and feedback.</p>
<b>2. Information</b> <ul style="list-style-type: none"> <li>• Individualised content may include: information about fatigue, managing expectations, sleep hygiene, speaking to employer.</li> <li>• Range of formats: short videos available on social media made by young cancer patients, written information for parents.</li> </ul>	<p>Call ‘information’ rather than ‘education’, as this is the term TYAs consistently used.</p> <p>Minimise leaflets and written information for young people.</p> <p>Promotes self-efficacy through vicarious experience, social comparison and modelling.</p>
<b>3. Mindfulness</b> <ul style="list-style-type: none"> <li>• Regular periods of ‘time out’ and ‘relaxation’.</li> <li>• Mindfulness techniques can be accessed with an App such as ‘Headspace’.</li> <li>• Yoga and Tai Chi are alternative options.</li> </ul>	<p>‘Time out’ and ‘relaxation’ are more relevant than ‘energy conservation’ or ‘avoiding boom and bust’.</p> <p>Feedback suggested App-based mindfulness techniques are particularly acceptable.</p>
<b>Process</b>	
<ul style="list-style-type: none"> <li>• Mutually convenient location, mostly out of hospital.</li> <li>• At least one face-to-face meeting, with subsequent individualised contact often by email or text.</li> <li>• Minimum of one personal letter to TYA, with copy to specialist healthcare team.</li> <li>• Provision by an AHP, with access to other AHPs including a psychologist if needed.</li> </ul>	<p>Individualised, paper ‘tips’ list was unhelpful.</p> <p>Avoid constraints of prototype intervention (the maximum intervention length was 3 months, and delivered by an OT only).</p> <p>More regular contact wanted; this could be provided by some mode of electronic communication.</p>

**Table 4.15 Techniques to establish the trustworthiness of the research findings [444,445]**

Techniques	Comments	Quality
<b>Credibility</b>		
Prolonged engagement and persistent observation	Every member of the research team, involved directly in the research process, was either a member of the TYA cancer service or had collaborated clinically with it over several years. This lead to a deep familiarity and understanding of the research context, as well as trust between researchers and clinicians, sufficient to allow individuals to express potentially eccentric or uncomfortable perspectives.	High
Triangulation	There was extensive triangulation on many levels: between sources (TYAs, parents, HCP), between individuals at different time points, between researchers (two people involved in interviewing), and between methods of qualitative data collection (interviews and focus groups). Triangulation is described in detail in section 4.5.16.1 (page 191).	High
Deviant case analysis	Although consistency was high in the triangulation process, two cases provided data that appeared, to some extent, to be inconsistent with the prevailing data patterns. Slightly refining the data analysis, so that these deviant views could be fully integrated within the whole, was valuable in this study, as described in section 4.5.16.2 (page 192).	High
Member-checking	Extensive opportunities arose to check the interpretations and conclusions with members of the groups from whom the data was obtained. Examples include the sharing of findings from the interviews at the focus groups, the summarising of preliminary findings at the co-design meeting and phase C interviews, provision of a formal outcome summary to all participants after the study with encouragement to feedback, and many post-study discussions of the findings with patientgroups (section 5.2, page 225).	High
Support of participant honesty	Efforts were made to avoid coercing potential participants to get involved, participants were encouraged to be frank with explicit assurance of confidentiality, and participants could withdraw at any time without their care being affected. Some participants did, indeed, feel safe to express negative views about healthcare provision, as well as the prototype intervention. However, participants were aware that the researchers were clinicians, so it was not possible to mitigate the potential impact of this on truth-telling fully.	Medium
Peer debriefing and scrutiny	Anna Spathis (AS) had monthly supervisions when aspects of this project could be discussed, and the work was presented to peer academics, both locally and nationally, and to the local TYA service healthcare team on several occasions throughout the project. The feedback and fresh perspectives challenged assumptions and helped refine insights. AS was, however, the only researcher who scrutinised all the data, and undertook the analysis.	Medium

Researcher reflective commentary	AS kept an electronic iterative record of observations, reflections and insights throughout the conduct of the study. This informal commentary has been valuable in the process of noticing patterns and connections within the data and, therefore, supporting data analysis. Researcher reflexivity is discussed further in section 4.5.16.3 (page 195).	Medium
Referential adequacy	This involves archiving a section of the data before analysis, and returning to it subsequently to test the validity of the preliminary findings; it was not undertaken in this project.	Low
<b>Transferability</b>		
Thick description	An in depth discussion of each of the key themes of this work has been undertaken, which includes an attempt to contextualise the experiences with findings in other patient groups, in different settings and at different times relative to medical treatment. For example, it has been particularly valuable to consider the external validity of these findings in relation to CFS/ME in adolescents and young adults (section 4.6.1.1, page 199)	Medium
<b>Dependability</b>		
External audit	No external audit was undertaken to check the research process, and to evaluate independently whether or not the findings and their interpretations are supported by the raw data. However, sufficient raw data are provided in sections 4.5.6-4.5.13 and in appendices 7.4.14-7.4.15, to facilitate the reader in developing his or her own impressions.	Medium
<b>Confirmability</b>		
Triangulation	This is described above and in section 4.5.16.1 (page 191).	High
Audit trail	Electronic records have been kept of every stage of the research process, including the raw data itself, anonymised data, steps within data synthesis, process and reflective notes. These are sufficient to provide a clear description of the research process, and the choices and decisions made within it.	Medium
Reflexivity	This is described above and in section 4.5.16.2 (page 192).	Medium

#### 4.5.16 Trustworthiness of research

In the preceding sections of this chapter, many findings of potential interest and importance have been described. However, before conclusions can be drawn, it is vital to evaluate the trustworthiness of this work [446]. How valid and reliable are these research findings?

The value of qualitative research has long been questioned, particularly by those schooled in the positivist paradigm of a single reality, found through objective and unbiased measurement [447]. Naturalistic inquiry is underpinned by different ontological and epistemological beliefs to scientific positivism. It reflects a 'real world' complex reality, with emphasis on experiences, perspectives and meaning [448].

In a seminal and widely accepted approach, Lincoln and Guba have developed four constructs to evaluate the trustworthiness of qualitative research that correspond closely to the criteria of validity, generalisability, reliability and objectivity used by a positivist investigator [445].

1) **Credibility.** This refers to confidence in the 'truth' of the findings. It is one of the most important factors in establishing trustworthiness, equivalent to the concept of internal validity in quantitative research.

2) **Transferability.** The applicability of the findings to other contexts corresponds to the positivist concepts of external validity and generalisability.

3) **Dependability.** Analogous to 'reliability', this construct considers whether the findings are consistent and could be repeated.

4) **Confirmability.** This considers the objectivity of the research. Confirmability is influenced by the neutrality of researchers, and the extent to which the findings are shaped by researcher and respondent bias.

Each of these evaluative criteria can be assessed by a series of techniques [444,445]. These approaches are summarised in table 4.15, along with a researcher assessment of the relative strength of the study in relation to each technique. Without attempting to weight the relative importance of the techniques, the overall quality and trustworthiness of this research appears to be moderate to high. Three of the techniques, triangulation, deviant case analysis and researcher reflexivity are described in detail in the following sections.



#### **4.5.16.1 Triangulation**

The design of this study facilitated extensive data triangulation. Data was multi-perspective, multiphase and collected with multiple methods (interviews and focus groups). Integration of qualitative and quantitative research findings between this study and the survey also provided further potential for triangulation; this is considered within the multimethod analysis section in chapter 5, as it relates to findings from more than one study.

During data analysis, contemporaneous notes were made of concordance and discordance between data sources, between data time points and between methods of data collection. The key finding from the triangulation process was the remarkable level of concordance. The overall level of consistency is highly supportive of the credibility of the data. An example of the level of congruence between a TYA and parent is given below. Further examples of each type of concordance, including between data time points and across different methods of data collection, are provided in appendix 7.4.15 (page 370).

And they [parents] get quite upset seeing that if I've got plans and I have to cancel them, they can get upset about it. I think that makes them quite upset. [TYA6, phase A]

It is quite upsetting sometimes to see her sort of separating herself from her friends, because she doesn't feel that she can keep up with them. [PAR6, phase A]

While the congruence between one individual at different time points and in different data collection contexts (individual interviews versus focus groups) was not unexpected, the virtually universal congruence between young people and their parents was notable. This important finding has already been described in relation to the tensions experienced by young patients and their families, described in theme B2 and modelled in the 'Concordant Tension Tree' (section 4.5.11, page 160).

There was only one example of clearly inconsistent triangulation. This was between a young participant's perspective and that of AHP providing the prototype intervention, and is discussed as one of the two deviant cases in the following section. There were a number of additional minor and unsurprising differences in perspective between TYAs and their parents, which have already been described in the theme narratives. Examples of this include: young people considering that fatigue makes them feel 'angry' whereas parents were more likely to say it caused their child to feel 'frustrated'; TYAs talking in terms of having to 'rely' on others but parents describing it as 'regression'; and young people being more likely to engage with electronic and visual communication than their parents, who prefer paper written information.

#### **4.5.16.2 Deviant case analysis**

Two outlying cases became apparent during the thematic analysis, each of which allowed the analysis to be further refined [449]. Case 1, by revealing a small inconsistency in data triangulation, provided insight into the potential role of the ‘small change leading to large benefit’ theme in dispelling therapeutic scepticism. Case 2, considering a participant with concurrent CFS/ME, provided insights into study generalisability.

##### Case 1: TYA3

The perspectives of TYA3 and the AHP providing the intervention were entirely, indeed diametrically, different. The AHP identified TYA3 as the single person she was concerned would do least well from the intervention, and might not progress well in the future. In contrast, TYA3’s fatigue improved enormously, and she gave amongst the most positive feedback on the intervention of any of the participants. This conflict in view was the single significant example of incongruence during the triangulation process, and is encapsulated in the two quotes below.

I don’t think you’re missing anything, I think how you helped me was just perfect for me, I think it kind of depends on everyone and how they take things. [TYA3, phase C]

...with the exception of one person, [TYA3] was probably less engaged in things, and I think that was probably a pattern of behaviour. It’s quite difficult to tap into something that might be helpful for her really. [HCP, phase C]

As previously described, TYA3 provided details of the factors that had facilitated her recovery from fatigue (section 4.5.12.3, page 168). She volunteered the importance of the intervention in ‘motivating’ people to reach their ‘own goal’, describing a health coaching approach (section 4.5.7.1, page 125). This being a patient-led process, the AHP was not easily able to anticipate how TYA3 would proceed after their consultation. It was evident, in retrospect, that finding out about the patient’s personal goal – feeling healthier by Christmas – and ‘planting a few ideas’ was sufficient for considerable behaviour change after the intervention.

*So in a way, am I right in understanding that [HCP] kind of planted a few ideas in your mind, but you’ve sort of decided which bits make sense to you. And then it sounds like you’ve more than done them, and really done them very ... in a very determined way. [Interviewer]*

Yes. [TYA3, phase C]

TYA3 simply fixed her sleep time and cut down on energy drinks. The improved sleep led to her feeling more energetic during the day; she therefore needed less energy drinks and was able to be become more active, leading to a series of interlinked virtuous cycles and a highly positive outcome.

[TYA3] looks the picture of health, she can do things, she puts her mind to it, she'll go, "Right, I'm going to do so and so." ...I mean, yesterday we were at the hospital and then she went ice skating last night. [PAR3, phase C]

This triangulation incongruence deepens insight into the potential interventional value of the 'small change, significant benefit' concept within theme C1 (section 4.5.12, page 161). The AHP scepticism, 'difficult to tap into something that might be helpful for her,' was at odds with the considerable subsequent benefit. Understanding the potential benefits from small changes is likely to be motivating for healthcare professionals as well as for patients; HCPs would then be better placed to enhance the confidence of patients in their capacity to improve their fatigue.

#### Case 2: TYA14 and PAR14

This TYA-parent dyad was an outlier in several ways. TYA14 and PAR14 were recruited after the study had closed for recruitment and after prototype intervention delivery, because of their desire to increase healthcare professionals' understanding of fatigue; they did not wish to receive the fatigue intervention themselves.

In several instances, their views were at one end of the spectrum of opinion across the research cohort. They were the only participants who explicitly stated that healthcare professionals did not understand their fatigue-related experiences and needs (page 151). Whereas all other participants considered cognitive fatigue to be more problematic than physical fatigue, TYA14 described physical fatigue as the worst, 'shortly followed by' cognitive fatigue (page 118). A final difference was that TYA14 was the only participant who did not consider activity to have any potential benefits, reporting only the adverse consequences of activity and endorsing rest; the other participants expressing activity fear avoidance beliefs still perceived, at some level, the inherent benefits of activity (page 177).

TYA14 was the only participant with a CFS/ME diagnosis as well as CRF. Qualitative research strives to attain maximum variety patient samples, in order to be as 'information-rich' as possible [450]. It is worth considering whether the diversity provided by this dyad was such that their views risked reducing the credibility of the findings, or whether their inclusion did, conversely, enhance the research insights.

Several arguments support the latter view. TYA14's views remained within the spectrum of perspectives across all participants, albeit at one end. For example, TYA14 still considered cognitive fatigue to be highly problematic, along with the other participants. Although, TYA14 and PAR14 were the only people to challenge healthcare providers' understanding of fatigue explicitly, this perspective could have been in the mind of participants who spoke in general terms about misunderstandings.

I think as far as the fatigue thing goes, everybody goes, 'Oh, the cancer's gone, you're fine now.' [TYA3, phase C]

This study was carried out in a single centre, with core members of the healthcare team also part of the wider research team. It is, therefore, unlikely that participants would have felt safe to challenge healthcare provider perceptions so openly, even in the context of assurances of confidentiality. TYA14, in contrast, was speaking with the experience of a CFS/ME diagnosis that predated the cancer, and many years of interacting with professionals beyond those in the TYA cancer service.

It is well recognised that people with CFS/ME perceive poor healthcare provider understanding, in the context of a contested diagnosis (section 4.5.9.4 page 152). Furthermore, the other difference in the perspective of TYA14 and PAR14 – activity fear avoidance beliefs – is also highly consistent with research findings in CFS/ME, as described in the forthcoming discussion (section 4.6.1.1, page 199).

It can therefore be argued that the subtlety of the differences in perspectives between this dyad and the cohort as a whole, along with the consistency of their views with that documented in the CFS/ME literature, has not threatened the credibility of the findings. Unlike in a quantitative study where outlying data can fundamentally alter results, the 'thick description' (page 190) in the thematic analysis allows the findings to be appropriately contextualised. Indeed, the relatively small and evidence-supported differences in perspective gained from the single participant with concurrent CFS/ME reinforces the argument for fatigue being a trans-diagnostic symptom (section 4.6.1.1, page 200); it is conceivable that the research findings can, at least in part, be generalised to other groups of young fatigued people.

#### **4.5.16.3 Reflexivity**

Reflexivity refers to the consideration of the influence of researchers' perspectives on the research process itself. As stated by Malterud, 'preconceptions are not the same as bias, unless the researcher fails to mention them' [451]. Rosaldo described the impact of personal position on depth of understanding in his poignant account of the death of his wife, which influenced significantly his insights in his own research into the experience of rage in bereavement [452].

Lincoln and Guba describe three steps that foster reflexivity in research [445]. The first is to report researcher values, beliefs and perspectives within any research manuscript of publication. The second is to design research that includes multiple investigators. The third is for the researcher to record personal reflections on the research process in a reflexive journal. These points are considered below. *Due to the personal nature of this short account, this section is – uniquely – written in the first person.*

### **Multiple investigators**

This research necessarily involved the perspectives of many others. Although I (Anna Spathis) undertook every step of the data analysis, during the research conduct phase and both through and after the data analysis stage, I undertook extensive and critical dialogue about this study with a broad range of individuals. This includes the following:

#### Psychologist in TYA CFS/ME

During qualitative data analysis, I corresponded and spoke regularly with a psychologist from another centre in the UK working with adolescents with CFS/ME. This was a particularly fruitful collaboration that broadened my insights considerably. It led at times to consensus, for example that fatigue is a trans-diagnostic symptom, the experience being age-dependent. At other times it led to unresolved debate; for example, this research suggested that pacing was of limited relevance to TYAs, whereas it remained an important component of the psychologist's practice.

#### Assistant with fatigue insight

Early transcripts were double-coded with a research assistant who had suffered from chronic fatigue in a non-cancer context. As well as striving to achieve consensus on the initial coding, the process lead to valuable debate and reflection on early findings.

#### Wider research team

Throughout this work, most aspects of the research process and findings have been discussed with my MD supervisors and with the wider research team (section 4.4.7.2, page 107). The co-design process itself involved discussion with research colleagues and other healthcare professionals, contributing significantly to the depth of insights and providing scope to redress inherent perspective biases.

### Dialogue after presentations

This work has been presented at a wide range of meetings, with clinicians and academics, both at the host organisations and at other centres nationally. The discussion after such presentations has also been highly valuable and reflexive, further fostering the reliability of the study findings.

### **Reflexive diary**

Although I did not write a formal paper 'diary', I made continual additions to an electronic 'notes' document throughout the entire research process, in order to capture ideas and insights for incorporation in the data analyses and discussions throughout this thesis, and to reflect on my own position within the research process. Apart from reflections on the practical experience of undertaking the research and my considerable personal learning from the process, there were three topics of particular importance. All three related to my primary professional role as a clinician working with symptomatic patients.

### Rapid recruitment

The ease of recruitment is worthy of reflection given the pervasive challenge of recruiting to clinical research, particularly when involving potentially vulnerable participants [326]. I have reflected on whether there might have been hope that the intervention would be helpful, despite the primary aim of the research being intervention co-design rather than successful fatigue treatment. Participants may have volunteered, or the usual healthcare team may have encouraged recruitment, due to such hope. Many participants did indeed express benefit from the research, TYAs in terms of fatigue support and parents from the experience of the focus group:

I think this has been amazing, knowing that there are other people in this black hole with me is great. I thought I was going mad, my child's disappeared into the demon, you know...

[PAR3, FG, phase A]

I think it was quite therapeutic though... I think that group where we turned up was really helpful. I found it really helpful. [PAR8, phase C]

Although participants explicitly knew that the purpose of the research was to help future symptomatic patients rather than themselves, research involvement often leads to participant benefit, from a sense of altruism and from the research process itself [453]. Young patients are particularly known to be keen to take part in research and to influence future healthcare [136,137]. Whilst not possible to exclude the possibility of undue influence, several factors suggest that altruism was the predominant driver for recruitment. No evidence emerged that participants misunderstood

the research premise. The two participants for whom the study re-opened to recruitment were explicit in their desire for others to learn from their experiences, and did not want to receive the intervention themselves. Another potential contributor to the ease of recruitment may have been that most patients were initially approached by the TYA service Youth Support Co-ordinator; evidence suggests that TYA cancer patients in the UK feel that non-clinical Youth Support Co-ordinators are particularly well-suited to a recruitment role [454].

#### Previous model development

As described in the personal statement in the preface (page iv), I work as a palliative care consultant in a clinical service providing an intervention for patients with intractable breathlessness, the Cambridge Breathlessness Intervention Service. With the benefit of previous (basic level) cognitive behavioural therapy training, over recent years I had noticed that vicious cycles were inadvertently worsening breathlessness. This led to proposal of the Breathing, Thinking, Functioning (BTF) clinical framework, describing three key vicious cycles [433]. The model has been recognised as a valuable educational tool in clinical practice [455,456]. However, although the model describes the content of an evidence-based, cost-effective complex intervention [457], the BTF framework itself is empirical, being based on clinical observation and experience.

The Sleep, Thoughts, Activity (STA) model described in section 4.5.14 (page 181) has undoubtedly been influenced by my experience of developing the BTF clinical framework. I was already cognisant of the concept of vicious cycles worsening and perpetuating symptoms, such as breathlessness and fatigue, and was therefore in a position to notice the occurrence of these with TYA participants. My appraisal of the model's potential utility in clinical practice (page 182) has also been influenced by my clinical experiences of using the BTF framework to support breathlessness management.

I consider that my clinical experience has allowed me to extend the analysis of the relevant data about vicious cycles more rapidly and to a greater depth than might otherwise have occurred, particularly in relation to the clinical implications of the vicious cycles. On careful reflection, I do not believe it has impacted on the credibility of the findings. Although I had the empirical impression from clinical experience that perpetuating vicious cycles were occurring in chronic fatigue, I certainly did not intend or expect this study, focused on intervention co-design, to generate a model based on the emotional and behavioural responses to fatigue. It was the strength of the research data, including unsolicited insights such as 'fatigue breeds fatigue' [TYA8, PAR8], that led to the unanticipated development of theme C1 and resulting STA conceptual model.

### Prediction of participant outcomes

As with theme C1, theme C2 – responses to fatigue predict outcomes – was unexpected and strong. I became self-aware during the months that the study was running that, as a clinician, I was instinctively appraising the likely forward health trajectory of participants. Indeed, during phase C, these appraisals were mostly found to be accurate; the theme emerged out of the insight that it was those participants with the most positive, proactive, confident and physically active approach who achieved the best fatigue and broader health outcomes.

Although, on reflection, I do not believe it would have been possible for me to ignore professional experience and clinical acumen, two points still lead me to consider this theme credible. First, I did not anticipate the emergence of the theme prior to the research. It was the consistent and strong evidence that led to theme development, rather than preconceptions. Second, as described in section 4.5.16.2 (page 192), one participant's outcomes were far from congruent with those anticipated. Preconceptions, by definition, played no part in this outlying case where analysis indeed led to extension of research insights.



## 4.6 Discussion

This multiphase, multi-perspective, qualitative study has attained its primary aim of working with TYAs and their parents to develop a ‘trial ready’ fatigue intervention. The prototype intervention – the outcome of the first phase of individual interviews, focus groups and a co-design meeting – was delivered to participants, with subsequent feedback and further amendment resulting in the ‘trial ready’ intervention described in section 4.5.15.2 (page 187). The key finding has been the clarification that TYAs have unique age-related intervention needs. Consistent with WHO guidance [79], research findings relating to older adults cannot be extrapolated to younger patients. This fully justifies having carried out this work to design a TYA-focused intervention.

Of particular interest is the extent to which unanticipated insights have emerged from this study, beyond description of the ‘trial ready’ intervention. The longitudinal and qualitative design facilitated elucidation of causality, with evidence emerging for fatigue leading to emotional and behavioural responses that can inadvertently feed back to worsen the symptom. The resulting vicious cycles can explain the perpetuation of fatigue beyond the initial trigger of a cancer diagnosis and treatment and, importantly, may support effective intervention; small changes, sufficient to break a vicious cycle, can lead to relatively large gains, so promoting self-efficacy for fatigue self-management.

Each of the themes has been discussed and contextualised individually in the preceding sections of this chapter. This overall discussion seeks to integrate the six themes together into three overarching concepts. The integrated findings will be considered both in the context of existing literature and relative to the underpinning theoretical framework, before consideration of the strengths and limitations of this work, and its implications.

### 4.6.1 Integration of themes

Three overarching concepts have emerged from this study. These can be encapsulated as TYA cancer-related fatigue being ‘more about young age than cancer’, ‘more about responses to fatigue than the symptom itself’ and ‘more about cognitions than behaviours’.

#### 4.6.1.1 *More about young age than cancer*

As discussed in relation to themes A1, A2 and B1, the experiences and needs of young participants were strongly related to the developmental characteristics of their age. Further, they appeared similar to those of young people with CFS/ME. Table 4.16 considers features of CRF and CFS/ME within the broad categories of ‘younger’ and ‘older’ patients, contextualising FICS findings with other relevant literature, much of which has been previously discussed. Although limited by lack of evidence in some areas, the table can be seen to demonstrate a general pattern of age appearing to have more influence on the fatigue experience than the underlying cause of the symptom.

**Table 4.16 Features of CRF and CFS/ME in young patients relative to older adults**

	Younger patients [evidence source]		Older patients [evidence source]	
	CRF	CFS/ME	CRF	CFS/ME
Illness perceptions, causal attributions	Psychological and physical [FICS]	Psychological and physical [362,364]	Mostly physical [361]	Mostly physical [458]
Adverse impact on family from care-giving	Higher [FICS]	Higher [388,389]	Limited evidence	Lower [391]
Activity fear avoidance beliefs	Higher [FICS]	Higher [345]	Lower [367]	Limited evidence
Acceptance of energy conservation, pacing	Lower [FICS]	High but relatively lower than older CFS/ME [334]	Higher [342,343]	Higher [459]

The relative concordance between young people with different chronic diseases suggests that fatigue is a trans-diagnostic symptom, influenced by factors beyond the underlying pathology. Although fatigue is highly prevalent in many chronic diseases, it has to date tended to be evaluated using a disease-specific approach [460,461]. In a highly relevant recent study, a Dutch team analysed fatigue severity data from 15 studies involving 1696 patients with a range of non-malignant chronic diseases [461]. The type of chronic disease predicted only 11% of the variance in fatigue severity, whereas a range of trans-diagnostic cognitive and behavioural factors increased the predicted variance to 61%. Of note, young age was a significant predictor of increased fatigue across the entire patient cohort.

Why might it be that young age has such an influence on the experience of fatigue, irrespective of diagnosis? Many of the features of adolescent cognition and behaviour can be explained with a neurobiological model of brain development (section 1.1.2.2, page 6), including a focus on self-identity, seeking independence from parents, getting into conflict, conforming with peers, impulsivity and emotional reactivity [66,461]. As outlined in theme A1, fatigue directly hinders many of these age-related developmental needs, contributing to the negative and distressing experience of fatigue. Importantly, such needs, being age-related, are likely to occur irrespective of the underlying diagnosis that triggered the fatigue. Furthermore, as described in theme C2, cognitive and behavioural responses to the fatigue in turn influenced the symptom itself. Not only does this mean that the fatigue is modified by factors beyond the underlying diagnosis, the cognitive and behavioural responses themselves will be influenced by young age, such as development of interpersonal tensions or poor sleep due to nocturnal use of electronic devices.

There are considerable implications from this integrated theme. It justifies the need to develop an age-appropriate intervention, rather than attempt to extrapolate findings from older adults. Importantly, it also gives potential for the findings of this research to be generalisable, at least in part, beyond the TYA cancer population to other young people experiencing fatigue.

Other than in relation to cancer and CFS/ME, little literature has considered fatigue in the context of chronic illness in young patients. A small qualitative study has evaluated the experiences of adolescents with paediatric multiple sclerosis, and found that cognitive fatigue had a highly negative impact, as in the current study [386]. There have been sporadic reports in paediatric inflammatory bowel disease [462], juvenile arthritis [463] and chronic neurological conditions [464]. Type 1 diabetes is a relatively common, serious chronic illness in children and young people [465]; in a cohort of type 1 diabetics with a mean age of 48 years, fatigue was the most troublesome symptom of the 34 symptoms assessed and, interestingly, young age was a predictor of fatigue severity [466].

These studies suggest that fatigue is a significant and under-investigated problem in young people with a range of chronic conditions, beyond cancer and CFS/ME. Given the apparent trans-diagnostic nature of fatigue, there is potential that the findings of this research may be relevant to these other young patient groups. The research implications will be discussed in section 4.6.5.2 (page 209).

#### ***4.6.1.2 More about the responses to fatigue than the symptom itself***

With its design allowing inferences of causality, this study has confirmed bidirectional relationships between fatigue and a number of cognitive and behavioural factors. Although it is increasingly well established that such factors can predict fatigue [461], are associated with fatigue continuing long term [42], and can be amended to improve fatigue [56], there has not as yet been any attempt to model exactly *how* such factors interact with the symptom. The novel finding of reciprocal relationships, encapsulated in the STA conceptual model (section 4.5.14, page 180), provides a mechanism for how fatigue can perpetuate beyond the initial trigger of cancer and its treatment, as well as a rationale for how small changes can lead to sizeable outcomes.

The longitudinal study design has also provided a valuable opportunity to examine temporal patterns and ‘turning’ or ‘tipping points’ (section 4.2.2.2, page 101). It has generated insights into the relationship between fatigue responses and subsequent healthcare outcomes, described in theme C2. Those participants with positive fatigue responses tended to avoid the vicious cycles in the STA model and had more favourable outcomes. Theme C2 therefore reinforces and validates the premise of theme C1.

System dynamics is a mathematical methodology developed in the 1950, initially from an engineering perspective, to understand complex systems. ‘Tipping points’ are well-recognised, with reinforcing feedback loops leading to a new equilibrium, and small changes effecting substantial outcomes. Within health, ‘systems thinking’ has been used to understand complex healthcare systems as a whole [467]. In recent years, a number of psychopathological states have begun to be characterised as complex dynamic systems, with the resulting statistical modelling and simulation studies starting to generate clinically relevant insights [468]. For example, in a recent study of the first systems model of major depression, the strengths of the links (‘connectivity’) between depression and associated symptoms were mathematically shown to impact on system stability [469]. The authors identified ‘tipping points’ where small influences led to rapid and significant change, and argued that their findings could help elucidate mechanisms for CBT. The findings from FICS appear to fit with a system dynamics approach; this is novel in the context of fatigue, and potentially worthy of future research evaluation (section 4.6.5.2, page 210).

This overarching concept of the importance of fatigue responses is supported not only by themes C1 and C2, but also by insights from the co-design process, in relation both to intervention timing and personalisation. FICS participants revealed a clear preference for early intervention (section 4.5.7.3, page 137). In a qualitative process evaluation of RESTORE, a web-based intervention to enhance self-efficacy to manage CRF, Foster and colleagues also found that cancer patients expressed the same preference, and highlighted the value of identifying a ‘teachable moment’ when recipients of the intervention would be most receptive [300]. There is growing evidence for the benefits of early supportive care in cancer, in parallel with disease-modifying treatment, with potential to increase survival, as well as quality of life [470-472]. This has led to the NHS driving nationwide development of Enhanced Supportive Care Services. Furthermore, early CBT has been found to be more helpful than later CBT in a number of circumstances, including after surgery and in PTSD [473], and this may, at least in part, be due to the prevention of cognitive and behavioural changes becoming ‘entrenched and habitual’ [474]. In this context, early fatigue intervention may be more effective than later input by preventing the responses that inadvertently perpetuate fatigue from fully establishing.

Fatigue responses are also relevant when considering treatment personalisation. Personalised medicine is a key concept in modern healthcare. Rather than a ‘one size fits all’ approach, it uses certain health-related characteristics to provide an optimal, individualised approach with maximum cost-effectiveness [475]. As described in theme C2, participants with high activation and positive responses to fatigue achieved better outcomes. Recognition of these individuals may allow determination of those requiring less intensive intervention, for example simply reinforcing and supporting their inherent approach. Those FICS patients with lowest activation and engagement

were less likely to engage with the prototype intervention. For those individuals, full intervention to improve self-efficacy for fatigue self-management may still be valuable, given that self-efficacy is goal-focused, less inherent and more amenable to change. However, it may be challenging to motivate these patients to engage. Promotion of self-efficacy is likely to be crucial; the potential role of the STA model in enhancing self-efficacy will be discussed further in section 4.6.2 (page 205).

#### **4.6.1.3 *More about cognitions than behaviours***

Findings from this study, contextualised within existing literature, generate an argument for the relative importance of managing cognitions, rather than behaviours, in the field of TYA CRF management. Much of the prototype intervention was cognitive in focus, using mindfulness to provide periods of calm awareness, and providing information about many aspects of fatigue, such as how to speak with an employer. Further, intervention can involve simply addressing misconceptions driving vicious cycles; challenging activity fear avoidance beliefs and misconceptions about sleep were important parts of the prototype intervention (section 4.5.14, page 182)

Although many of these approaches may lead to subsequent behaviour change, such as increasing activity or speaking with an employer, the benefits reported by participants in phase C were a consequence of the initial cognitive step, with participants particularly valuing information giving (section 4.5.15.2, page 185). This is consistent with Self-Efficacy Theory as will be discussed below; self-efficacy is a cognitive concept that, in turn, mediates behaviour change. The main behavioural consequences from the intervention were changing sleep habits, in a small number of participants.

It is increasingly recognised that, in order to intervene successfully, a focus on the brain and cognitions is needed. Acknowledgement of the therapeutic value of the placebo effect and the need to ‘make mind-set matter’ has grown rapidly with recent years, along with acceptance of the high degree to which expectations and beliefs can influence objective healthcare outcomes [476,477].

The value of addressing activity fear avoidance beliefs, rather than the behaviour change of increased activity, is increasingly recognised. In 2011, the PACE trial established that, for people with CFS/ME across a wide age spectrum, graded exercise therapy (GET) and CBT were effective treatment approaches, unlike adaptive pacing therapy [345]. A secondary analysis of the data found conclusively that reduction in activity fear avoidance beliefs was the greatest mediator of benefit from the intervention, whereas increasing fitness did not mediate treatment effects [395]. An earlier study evaluating GET for CFS/ME had also found that those who subjectively improved with intervention were not fitter than the rest of the cohort [478]. FICS provides evidence consistent with this, suggesting, for the first time, that activity fear avoidance may mediate outcomes in TYA CRF (section 4.5.13.2, page 177).

Participants favoured mindfulness over the behavioural construct of energy conservation and pacing. Mindfulness, a cognitive psychological approach, has been found to be helpful for a range of symptoms including breathlessness [479,480], chronic pain [481] and persistent fatigue in older adult cancer survivors [482]. Participants in this study, not only divulged their views on the role of the 'mind' in fatigue management, but also valued support to practise mindfulness during the intervention prototype. Such evidence, both from existing literature and from FICS, further supports the argument that influencing the brain and cognition is of particular importance.

This perspective is increasingly accepted across a range of symptoms. Considering symptoms as a 'perceived threat to health' [145], it is that perception that can be cognitively modulated, without necessarily having to follow through to the subsequent step of behaviour change. Breathlessness severity, for example, correlates poorly with the severity of underlying respiratory pathology, and there is increasing acceptance that successful breathlessness management requires a focus on the brain (cognitions) rather than the lungs [483]. In an article entitled 'Treating breathlessness via the brain', Herigstad and colleagues undertook fMRI imaging of patients throughout pulmonary rehabilitation; they revealed that changes in breathlessness correlated with changes in activity in the brain's stimulus valuation network, highlighting the importance of cognitive expectations and interpretations of respiratory sensations [409].

Focusing on cognitive, rather than behavioural, change has a number of positive implications. It may increase the effectiveness of intervention; changing health-related behaviour can be difficult and often fails [484]. Determinants of behaviour change are mostly cognitive in nature: knowledge, social/professional identity, beliefs about capabilities, beliefs about consequences, motivation, goals, memory and attention [485]; successful intervention therefore requires cognitive mediation. Another important implication is that a cognitive focus gives potential for brief intervention, for example giving information or reframing beliefs, rather than waiting for behaviour change.

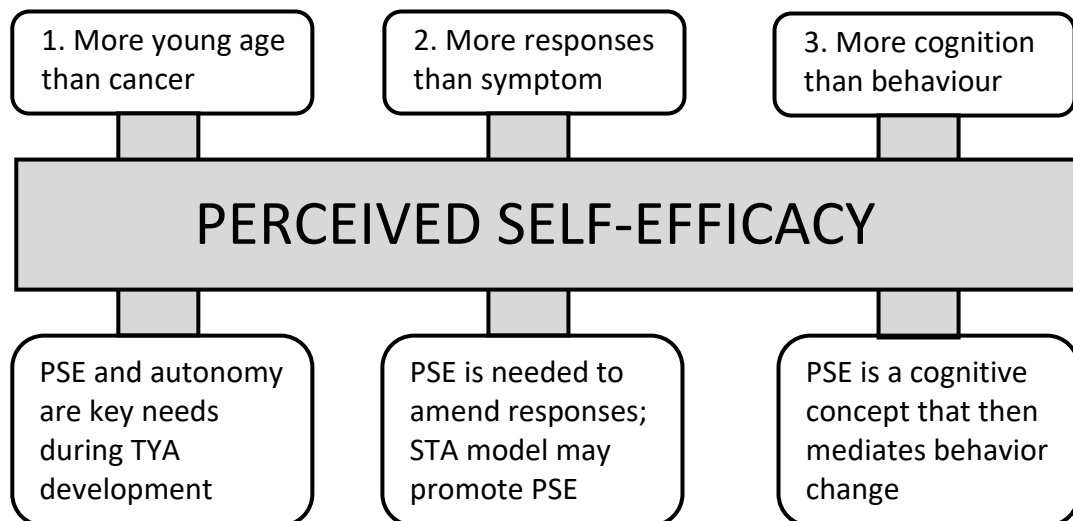
#### **4.6.2 Theoretical underpinning**

A number of factors led to the choice to underpin this programme of research with Self-Efficacy Theory (section 1.2.4, page 16). This choice has been validated by the study outcomes, both in relation to individual themes, and the overarching concepts described in the previous section.

In theme A2, participants described, without labelling it as such, the importance of perceived self-efficacy (page 124). Their intervention needs were consistent with those known to promote self-efficacy, including goal setting, activity planning and provision of feedback on performance [335]. In his Theory of Self-Efficacy, Bandura posits that two key sources for increasing self-efficacy are

‘vicarious experience’ and ‘social persuasion’. The short videos requested by participants would help achieve this, with experienced peers demonstrating successful fatigue management [141]. In addition, within theme C2, longitudinal analysis revealed a connection between descriptors of self-efficacy and fatigue outcomes, both in terms of the presence of self-efficacy and good outcomes, and the converse (pages 176, 177). A further validation of the relevance of Self-Efficacy Theory to this work is that each of the overarching concepts link with self-efficacy, as shown in figure 4.5 below.

**Figure 4.5 Interaction between overarching concepts and perceived self-efficacy (PSE)**



1. Autonomy and competence are key adolescent developmental needs; these constructs are closely related to PSE, the confidence in one’s ability to carry out a task. Autonomy refers to a sense of control, and competence to the perception of capability. Research efforts to conceptually separate competence and PSE suggest that the main difference is that the latter includes the confidence to carry out behaviours, even in challenging circumstances [486]. It is recognised that self-efficacy is a particularly important concept during adolescence [487,488].
2. The STA conceptual model is a cognitive-behavioural formulation describing responses to fatigue. Promotion of self-efficacy is one of the mechanisms of change within CBT, and it is intuitively reasonable that higher self-efficacy could facilitate response shift [487]. As the model provides a rationale for why fatigue persists beyond its trigger, and because it gives the potential for small changes leading to larger outcomes, it is conceivable that the model may promote PSE.
3. The Theory of Self-Efficacy sits within Social Cognitive Theory [141]. PSE is a cognitive mediator and key determinant of behaviour change and is amenable to change itself. The finding that participants needed a primarily cognitive approach to intervention, with subsequent behaviour change of secondary importance, sits well with the theory underpinning the intervention.

### **4.6.3 Methodological discussion**

Although co-design is often used in service improvement [489], it is less often used in the design of complex interventions. It is therefore worth appraising the methodological aspects of this study.

Whereas use of innovative methods tends to reveal unanticipated process challenges, as with the electronic survey, this co-design process has been notably positive. EBCD appeals to young and vulnerable patient groups, ‘whose voices are not often considered’; young cancer patients want an active part in research, particularly that focusing on quality of life (section 1.1.3, page 10) [107,490].

Consistent with this, FICS led to an unanticipated level of mutual benefit, both for participants and researchers. Not only did the process allow design of an acceptable intervention, but the qualitative design led to valuable unforeseen research findings. Participants also appeared to benefit (section 4.5.16.3, page 189). Recruitment was rapid, with clear enthusiasm for involvement; indeed the study re-opened to recruitment because two further people actively wished to engage. During final interviews, participants often described personal benefit from study involvement, both in altruistic and practical terms. There was considerable engagement with the co-design process, with a few participants continuing the dialogue with unsolicited telephone and email contact.

Inclusion of both interviews and focus groups was valuable, as they produced different types of data. The individual interviews allowed views to emerge without participants influencing, or being inhibited by, each other; eliciting tensions between TYAs and parents, for example, may not have been captured in shared interviews. The focus groups led to animated discussions on a number of topics, such as young people’s desire to ‘fit in’ and a debate about the intervention name, producing data less likely to have been generated in an interview context. Overall, therefore, the use of multiple methods of data collection was valuable and increased the breadth of research insights.

### **4.6.4 Strength and limitations**

#### **4.6.4.1 Strengths**

As discussed in section 4.5.16 (page 188), the multiphase, multi-perspective and multimethod approach led to the study findings being of high quality and trustworthiness, particularly due to the ability to triangulate data. Specifically, the study scored ‘high’ or ‘medium’ quality for all but one of the techniques to assess credibility, transferability, dependability and confirmability.

#### **4.6.4.2 Limitations**

The main limitations have already been described. Although multiple investigators provided invaluable perspectives including initial double-coding, one researcher (Anna Spathis) undertook every aspect of the data analysis. While this allowed a single person to have oversight sufficient to



integrate all aspects of the considerable dataset, this approach equally risked excessive influence from a single perspective, a point reflected upon in section 4.5.16.3 (page 195).

Defining the 'trial ready' intervention necessarily involved attempting to balance the need for clearly standardised content, to support future intervention fidelity, with participants' need for it to be flexible and individualised (section 4.5.15.2, page 186). The process was made considerably easier by the strength of many of the themes. However, there is an inherent tension between standardisation and individualisation, and it is possible that the optimal balance was not found.

A number of other limitations need to be considered. Although there was high apparent congruence between patients and parents, four TYAs chose not to involve their parents; it is possible that these parents may have held different views to their offspring, and that the high concordance was biased by this. There was only one formal phase of feedback within the study; the credibility of the findings would have been increased further with further cycles of feedback and prototype amendment.

#### **4.6.5 Implications**

##### ***4.6.5.1 Clinical practice and policy***

The primary aim of this work was to co-design an intervention that could then undergo formal research evaluation of its effectiveness. However, a number of clinical implications have still arisen.

It would be reasonable to incorporate some aspects of TYA intervention needs into clinical practice, without waiting for the results of the definitive trial. Young cancer patients need help explaining fatigue, particularly cognitive fatigue, to staff at education or work; exercise advice is most helpful when it includes an individualised structured plan; information about mindfulness is likely to be more acceptable than energy conservation. An output of this research has been the professional production by Macmillan of a series of short peer videos (appendix 7.1.1, page 269); these are available on the internet and can be used by clinicians. The evident age-related needs suggest it would be optimal for CRF support to be provided by an HCP experienced in providing care to TYAs.

While the review and survey both suggest that proactive patient discussion about fatigue may be valuable, FICS builds on this in a number of ways. Early discussion – no later than the end of cancer treatment – has now been justified, and it may be valuable to involve parents, if acceptable to their TYA family member. Given the largely congruent tensions between TYAs and parents, it is likely that a skilled HCP could resolve tensions, building a shared understanding based on mutual concerns. This study suggests it would be worthwhile clinicians evaluating potential fatigue responses relating to activity, thoughts, emotions and sleep. Although the STA conceptual model requires further research

evaluation before it can be used clinically, simply explaining the role these responses and the value of small changes could empower and promote self-efficacy. The evidence for bidirectional relationships between fatigue and other symptoms lends support to careful concurrent symptom management in TYAs, an approach for fatigue management that is already evidence-based in older adults [44].

The finding that fatigue can be considered a trans-diagnostic symptom, with age-related needs potentially being more important than the underlying diagnosis, suggests that symptom- rather than diagnosis-based services may be of value, for example involving adolescents with CRF and CFS/ME. Indeed, a concept mapping study has been published for the first generic fatigue clinic in the UK, albeit attended by patients with a mean age of 62 years. Such an approach would need to be carefully evaluated to determine the benefits and any inadvertent harms.

#### **4.6.5.2 Future research**

There are extensive implications for future research. These predominantly relate to future interventional trial design and to evaluating the STA conceptual model.

##### Future trial design

An age-appropriate 'trial ready' intervention is now ready for evaluation of effectiveness and cost-effectiveness in a definitive controlled trial that randomises patients between fatigue intervention and 'usual care'. Many aspects of design for the future trial are now clear. The content has been established, Activity, Information, Mindfulness (AIM), and is known to be acceptable to young patients. The Perceived Self-Efficacy for Fatigue Self-Management (PSEFSM) measure is an appropriate primary outcome; it has been validated in cancer patients and this programme of research has confirmed the relevance and importance of this concept to fatigued TYAs [148]. As well as mediating fatigue outcomes and being amenable to change, the evidence for day-to-day fatigue fluctuations (page 155) further suggests that change of PSEFSM would be a more reliable primary outcome, than fatigue severity. Optimal timings have been established, with intervention needing to be early at, or before the end, of cancer treatment. There needs to be capacity to involve parents.

However, a number of other important matters are still not known. It is therefore, as originally planned, necessary to undertake a preliminary feasibility study (section 1.2.1 page 14). Most crucially, although recruitment to FICS was rapid, it is not known whether the possibility of randomisation to 'usual care' is acceptable to young patients. A 'deferred entry' trial design, with the 'usual care' group offered the intervention after the primary end point, is an approach previously used in palliative care trials to increase acceptability by allowing all participants to receive the intervention [457,491]. However, the duration of the FICS intervention (mean 6 weeks, range 1-14

weeks, table 4.13, page 184) suggests the need for intervention deferral of at least 2-3 months in the 'usual care' group, which may still hinder recruitment.

A considerable number of secondary measures would be needed. Assessment of fatigue responses would be required, potentially including the Cognitive and Behavioural Responses to Symptoms questionnaire [424]. Collecting data on the predictors for good outcomes suggested in FICS would be valuable, including activation levels, baseline activity and activity fear avoidance beliefs; this would not only meet current national research priorities [25], but would support treatment personalisation. The usefulness of the study would increase if powered to evaluate outcomes in subgroups with high and low baseline activation levels, but knowledge of the standard deviation of each measure in the TYA cancer population is unknown. Assessment of biomarkers for systemic inflammation would also be valuable (section 5.1.3.2, page 223). It is vital that the acceptability of these many measures is tested before embarking on the definitive study, not least with cognitive fatigue potentially hindering completion of lengthy questionnaires.

An alternative to a feasibility study could be to move straight to a definitive trial that includes an internal pilot phase. Progression from the pilot phase to the main trial would need to be carefully planned, with clear progression and modification criteria [492]. An ongoing international drive is attempting to promote research efficiency and it is increasingly accepted that an internal pilot phase can enhance efficiency, prevent the resource waste and avoid recruitment to a trial that does not have the capacity to deliver the definitive outcomes [492]. An internal pilot would still allow testing of the acceptability of randomisation to 'usual care', and of the many secondary outcome measures. However, it would provide less potential to fundamentally amend the study design if significant problems become apparent. It is possible that a prospective study funder would consider the risks of funding a definitive study, albeit with internal pilot, as too high given the extent of the uncertainties.

Overall, it is clear that the choice of approach would need to be made by an experienced trial steering group, with a range of expertise, particularly relating to trials design and health psychology. Health economics support to evaluate cost-effectiveness would be important, given the potential to impact on a long-term symptom that affects the ability to work and be in education, in a young cohort with the possibility of years of health service utilisation and societal contribution ahead.

#### STA conceptual model evaluation

As previously discussed, the model may have clinical utility, with its potential to promote self-efficacy for fatigue self-management and underpin a brief cognitive intervention.

A qualitative study is required to test model acceptability and gain feedback, both from patients and healthcareers. The model may have utility beyond TYAs, and it would be valuable to recruit participants of all ages. The non-pharmacological approaches needed to break the vicious cycles, including sleep hygiene measures, promotion of activity and stress or tension management, are all facets of the emerging 'Lifestyle Medicine' approach. While increasingly popular, it is recognised that there is a risk of patients perceiving they are being blamed for their health [493]. It is vital to ensure that no harm results from use of the model, and a qualitative study would provide further insight.

A separate evaluation of the model from a system dynamics perspective could be a novel collaborative approach, leading to valuable insights. Research partnership with experts in complex systems modelling and mathematics, along with health psychologists, would allow quantification of the suggestion that a small change can lead to considerable benefit by interrupting a single feedback loop, using statistical modelling and simulation techniques.

#### Other implications

It would be important to assess the generalisability of the study findings, beyond the TYA cancer population. Although this may be particularly relevant to TYAs with CFS/ME, there are other smaller groups of young patients where fatigue appears to be a neglected symptom, including those with juvenile inflammatory conditions and type 1 diabetes. A mixed-methods study involving a diagnostically mixed cohort of young patients could be valuable, and could determine the validity of considering fatigue as a trans-diagnostic symptom.

Given the emphasis on cognitions in the study outcomes, it would be interesting to conduct a neuroimaging study, involving serial fMRI scans of fatigued patients. As previously discussed, this type of research has already been undertaken in other symptoms including chronic pain and breathlessness [409,494,495]. It could allow elucidation of the exact brain regions involved in fatigue perception, and help determine the importance of so called 'priors', the sensation predictions based on previous experiences [483]. This could provide an objective, although indirect, measure of fatigue perception, could examine the paralimbic brain regions subserving emotional and behavioural fatigue responses, and may provide valuable insight into intervention mechanisms of action.

The IT literacy of young patients, combined with the clear demand for technology-based approaches, has a range of research implications. A TYA CRF self-management App could be developed, with concurrent research evaluation, potentially based around the STA conceptual model. Generic mindfulness Apps are widely used, but there have been no previous attempts to provide mindfulness techniques that specifically support the experience of fatigue in chronic disease.

## **4.7 Key points**


This Fatigue Intervention Co-design Study has been novel in a range of ways. This has been the first attempt to co-design a symptom control complex intervention in TYA cancer patients. The process has not only been mutually beneficial, it has determined the unique needs of this young cohort and the inadvisability of attempting to extrapolate research findings from older adults to TYAs. The multiphase and multi-perspective qualitative study design has also led to findings of interest and potential importance. The presence of fatigue-related tensions between TYAs and their parents has been established; the tensions are paradoxically concordant and therefore more likely to be amenable to brief intervention. Furthermore, the unanticipated insights into the importance of responses to fatigue in perpetuating the symptom, determining outcomes and promoting self-efficacy to self-manage are worthy of further research evaluation.

The key study findings are summarised in table 4.17. The table includes findings from the systematic review and survey, to demonstrate the sequential building and synthesis of research findings across this thesis. Formal integration of all three studies to generate meta-themes in a multi-method synthesis will be undertaken in the following, final chapter.

**Table 4.17 Fatigue Intervention Co-design Study key points in context**

<b>TYA CRF topic</b>	<b>Study 1: Systematic review</b>	<b>Study 2: Fatigue in Focus survey</b>	<b>Study 3: Fatigue Intervention Co-design Study</b>
<b>Prevalence</b>	The prevalence range was 9-67% after cancer treatment; fatigue was the first and second most prevalent symptom in 11 and 6 of 20 studies respectively.	Fatigue was the most prevalent symptom experienced by 85% of participants after the end of cancer treatment. Cognitive fatigue was particularly prevalent, compared to previous studies evaluating patients during cancer treatment.	High prevalence was indirectly supported by rapid recruitment of participants within seven weeks. Cognitive fatigue was particularly problematic in this cohort.
<b>Temporal pattern</b>	Only one longitudinal study has evaluated fatigue beyond the end of cancer treatment.	Fatigue severity was higher more than one year after the last cancer treatment, compared to during the year after treatment ends. Further research is needed to gain insight into the cause(s) of fatigue persistence.	Insights were generated into the factors that may perpetuate fatigue due to vicious cycle formation. The mismatch between reality and expectations may also worsen fatigue perception.
<b>Symptom correlates</b>	Physical and psychological symptoms most commonly associated with fatigue were poor sleep and low mood respectively.	Significant correlation was found between fatigue and other symptoms, fatigue forming a symptom cluster with low mood and anxiety. It could not be determined whether this represents association or causal relationships.	Bidirectional causal relationships were found between fatigue and low mood, tension and anxiety (particularly in relation to fear avoidance of activity), and difficulty sleeping.
<b>Impact</b>	The most commonly reported impact was 'distress', followed by fatigue being a barrier to physical and to social activities.	Fatigue was the symptom with the worst impact on daily life, and an independent predictor of poor quality of life. The greatest impact was on exercise, school/work attendance and socialising, potentially suggesting some sources of fatigue-related distress.	Further insights were generated into the contributors to the negative impact of fatigue, including multi-level tensions, and cognitive fatigue impacting on socialising and the ability to work or be in education.

<b>Parents' perspectives</b>	No past research has evaluated the perspectives of parents or other carers.	Parents were the main carers. Only 13% of participants perceived no negative impact on carers, with 'upset' and 'frustration' occurring commonly. A third of parents were perceived to misunderstand the symptom, although the causes and impact of this have not been established. Direct parent views are needed in future research.	Direct parent data built on the proxy data from the survey. The negative impact on parents was confirmed, with insights into causes including extensive tensions and misunderstandings. The paradoxically congruent data between individual TYAs and their parents suggests amenability to brief intervention.
<b>Management</b>	No studies have evaluated an intervention with a fatigue related primary outcome; current clinical practice, in terms of symptom management, is also unknown.	Most participants, almost 3 out of 5, had been recommended a fatigue treatment, most commonly advice to exercise. Participants themselves recommended active treatments more than rest-focused ones. However, therapeutic scepticism prevails with no treatments apart from blood transfusion perceived to be successful. Interventional research is needed, with a design that promotes adherence.	There were multiple age-related fatigue intervention needs. Participants valued support explaining cognitive fatigue to staff at education or work. Advice to exercise was most helpful when it included an individualised, structured plan, given physical reserve and activity fear avoidance beliefs. Energy conservation was irrelevant, with a preference for App-based mindfulness techniques. Information was most acceptable in short, peer-produced video format.







## **5 Research synthesis**

This final chapter seeks to synthesise this work into a connected whole. Three methodologically diverse studies have been described, each part of one overall aim: to increase understanding of CRF in teenagers and young adults in order to be able to develop an effective fatigue intervention. The work has examined the spectrum of the past, present and future, by respectively undertaking a systematic literature review, evaluating current clinical practice and co-designing a potential complex intervention.

Within each preceding chapter, there has already been detailed discussion of the research findings from each study, contextualising with existing literature and with each other. This chapter considers overarching findings, with multimethod integration across all three studies. Research outputs are described, and the chapter concludes with overall clinical and research recommendations.

### **5.1 Multimethod integration**

#### **5.1.1 Integration method**

Multimethod research is characterized by the co-existence of different methodologies [496]. All methods have strengths and weaknesses, and their combination can allow the strengths of one method to compensate for the weaknesses of another [497]. Although ‘multimethod’ and ‘mixed-methods’ research are two terms that are often used interchangeably, the two methods differ [496,498]. Multimethod research combines any different methods, whereas mixed-methods research specifically combines qualitative and quantitative data and can therefore be thought of as a subset of the former [496]. In addition, the more the methods influence each other along the trajectory of the research process, the more the research can be called ‘mixed-methods’ rather than ‘multimethod’ [499].

There are at least forty mixed-methods designs reported in the literature [500]. Of the six most commonly used, sequential explanatory design is particularly popular; it involves collecting quantitative data first, followed by a qualitative phase that generates further insight into the quantitative finding [449]. This approach would appear to suit the quantitative survey and subsequent qualitative Fatigue Intervention Co-design Study.

Two factors, however, led to the choice to take a multimethod approach in preference to an explanatory sequential mixed-methods design. First, although the intermediate phase, where the quantitative data influence the collection of the subsequent qualitative data, did occur, it was only to

a partial extent [501]. For example, although FICS was focusing on intervention co-design, participants were questioned on how fatigue affects their lives and causes distress, following the survey's finding that fatigue predicts a poor quality of life. However, such integration was not a formal, prospectively planned part of the design of the qualitative study. In addition, there were no efforts to purposively recruit participants to FICS who might best have been able to provide insight into survey findings. It might, for example, have been interesting to gain insight from those survey participants who had found exercise advice unhelpful but, paradoxically, would still recommend exercise to others.

The second reason for choosing a multimethod approach was that it would allow integration of all three studies in this thesis, including the systematic review. Multimethod synthesis allows integration of any data type: diverse methodological approaches in the review, quantitative with some qualitative data in the survey, and qualitative data in FICS.

Mixed-methods designs have been increasingly defined in the literature, in an effort to standardise this rapidly growing, complex and diverse approach [500]. Multimethod integration is much less well described, generally only when multimethod and mixed-methods approaches have been conflated or not explicitly differentiated [502,503]. It is recognised that the integration of data is frequently flawed and rarely described [504]. It was therefore decided that a structured and explicit approach to multimethod data integration would be undertaken.

Three main data integration techniques have been described: 'following a thread', mixed-methods matrix, and triangulation [505]. A mixed-methods matrix requires availability of both data types on the same cases; this technique was discounted as the co-design study and survey did not knowingly recruit any of the same patients. 'Following a thread' involves identifying a question or theme from one type of data and then following it across other components. Although the 'key points' tables at the end of each chapter (pages 44, 96 and 212) appear to have 'followed a thread' across the three studies, strictly this was not the case. The technique applies earlier, in the data analysis phase, with a thread followed from one dataset to another and then back again [506]. This was not possible in this work, as the survey analysis was completed before FICS started.

The third and most suitable method is triangulation, a technique used in the data interpretation phase in which researchers list findings from each part of the research, and consider whether the data within each 'meta-theme' agree, are complementary or are dissonant [505,507]. Inter-method discrepancies are considered valuable, as exploration can increase the depth of insight; benefits

emerge ‘only through the struggle to reconcile discrepant results and may provide a sum that is great than the individual qualitative and quantitative parts’ [508].

### **5.1.2 Triangulation of research outcomes**

The outcomes of data triangulation are summarised in the integration matrix in table 5.1. This table differs from the cumulative ‘key points’ tables at the end of each chapter in three ways. First, rather than selecting points of importance and interest from within each study, findings were selected entirely from the perspective of their connection across the studies. Second, the selected findings were organised into three broad meta-themes relating to fatigue causes, consequences and management [507]. Third, the degree of congruence between studies was categorised according to whether findings agreed, were complementary or were dissonant.

The triangulation process revealed a number of interesting findings. None of the integrated findings simply ‘agreed’, and most were complementary. The prominence of ‘complementary’ integration outcomes are consistent with the diverse methodologies leading to findings that built upon each other, rather than being the same. The findings from FICS consistently explained those from the quantitative study, the latter describing ‘what’, and the former explaining ‘how’. The qualitative approach could determine relationship directionality and delve iteratively into findings of interest, helping make sense of the numerical findings. For example, whereas the survey established the presence of associations between symptoms, the qualitative data could deepen insight by revealing bidirectional causal relationships and their potential therapeutic role.

The dissonant findings were of particular interest and value. Moffatt and colleagues have described six ways to explore discrepant findings, albeit in a mixed-methods interventional study context. Five of these have potential relevance to this work: treating the methods as fundamentally different, exploring the methodological rigour of each component, exploring study population comparability, exploring comparability of outcomes for each component, and collecting additional data to make further comparisons [509]. The three areas of dissonance in table 5.1 are each explored in the following sections, using these approaches. Given the pervasive theme of the importance of cognition across this programme of work – the impact of cognitive fatigue experience and co-design of a predominantly cognitive intervention – it is perhaps unsurprising that all three areas of dissonance relate to aspects of cognition.

**Table 5.1 Multimethod integration matrix**

Meta-theme	Study 1: Systematic review	Study 2: Fatigue in Focus survey	Study 3: Fatigue Intervention Co-design Study	Integration
<b>Causes</b> Fatigue is not simply related to cancer and its treatment.	Fatigue was associated with a few other symptoms, particularly low mood and poor sleep.	Fatigue associated with most symptoms tested, and formed a cluster with low mood and anxiety (sleep not assessed).	Fatigue formed bidirectional relationships with other symptoms including low mood, anxiety, poor sleep.	Comp.
	There has been no evaluation of perceived fatigue causes.	84% of participants perceived fatigue was caused by cancer or its treatment.	Fatigue perpetuation beyond the trigger of cancer or its treatment may be caused by vicious cycles of emotional and behavioural responses to fatigue, and by a mismatch between reality and expectations.	Comp.
	Only one study evaluated fatigue beyond cancer treatment.	Fatigue persisted beyond the end of cancer treatment, and may even worsen.		Comp.
<b>Consequences</b> Fatigue has broad impact far beyond the physical effect on the patient.	Cognitive fatigue was less severe than other fatigue dimensions.	Cognitive fatigue was as severe as other fatigue dimensions.	Cognitive fatigue had the worst impact, and influenced the ability to study and work.	Diss.
	The impact most commonly described was distress, followed by impact on the ability to exercise.	The main impact of fatigue was on the ability to exercise, followed by the ability to attend school/work and socialise.	The impact on the ability to exercise was more due to fear that exercise may cause harm than physical inability.	Comp/ diss.
	Impact on parents has not been described in the literature.	Only 13% of young patients felt fatigue did not impact negatively on parents.	Parents described considerable personal negative impact from their child's fatigue.	Comp.
	Impact on relationships with others has not been described.	Young patients felt misunderstood by others, including parents.	Although multilevel tensions existed, patient and parental perspectives were congruent.	Comp/ diss.
<b>Management</b> Age - appropriate support may address therapeutic scepticism.	No research has evaluated current fatigue management. There has been little interventional research and no controlled trial evidence of benefit from exercise, despite it being the most strongly evidence-based intervention for fatigue in older cancer patients.	2 in 5 young people had not received fatigue support, and less than 1 in 5 believed fatigue could be treated.	Young patients and parents described unmet fatigue management needs; they require age-appropriate support, promoting self-efficacy.	Comp.
		Exercise was the management advice most commonly given and most recommended by TYAs to others; however TYAs did not find it helpful.	Young patients require individualised structured activity support and regular short term goals, to avoid concerns about 'pushing too much' worsening fatigue.	Comp.

Comp, complementary; diss, dissonant.

### **5.1.2.1 *Relative importance of cognitive fatigue***

The systematic review suggested that cognitive fatigue was less severe than physical fatigue, the survey revealed comparable cognitive and physical fatigue, while the co-design study found cognitive fatigue consistently had the worse impact. Exploration of these apparent discrepancies reveals several potential explanations.

First, the studies providing data on cognitive fatigue in the review mostly recruited patients receiving cancer treatment, whereas the survey and co-design study involved patients post-treatment (section 3.6.1.2, page 80). The different study populations restrict comparability of findings; for example, it may be that cognitive fatigue is less apparent to individuals during cancer treatment, in comparison to later cognitive demands, such as at school or work [168].

Second, cognitive fatigue quantified in the review and survey cannot be directly compared with the qualitative evidence from FICS. The question asked in the topic guide that elicited extensive views on cognitive fatigue was, 'What do you find most distressing about your fatigue?' Participants were describing an undefined but closely-related series of concepts including 'fatigue severity', 'fatigue-related impact' and 'fatigue-related distress.'

Third, qualitative research has particular utility, compared to quantitative work, for developing new ideas and seeking explanations. The open nature of the questioning in FICS allowed participants to give their own views, rather than simply being asked to rank pre-defined options in a survey. Whereas the survey could only establish that fatigue had a negative impact on the ability to be in work or education, the qualitative study was able to question 'why' and 'how' this occurred, unexpectedly eliciting the particular importance of cognitive fatigue. The qualitative data increased the depth of understanding.

Resolution of the data incongruity may have been possible with further data collection, if the survey and co-design study had been integrated more closely in design and time, in line with a mixed-methods, rather than, multimethod approach. In retrospect, it could have been valuable to have asked survey participants which dimension of fatigue was leading to the negative impacts described. In a larger survey, potentially using electronic tablets to encourage responses from those on cancer treatment, it may have been possible to compare cognitive fatigue severity between those during and after cancer treatment. It would have been illuminating to explore the meanings that FICS participants ascribed to the terms 'severity' and 'impact', and the degree to which these related concepts were conflated.

### **5.1.2.2 Redefining exercise 'ability'**

Survey participants considered that the aspect of daily life that fatigue most affected was the 'ability to exercise'. The co-design study revealed a subtle, but important, difference; young people described physical ability to exercise, but the barrier to activity was the fear that it may worsen the fatigue, by 'pushing' too hard: activity fear avoidance beliefs. In table 5.1, the integration outcome is described as 'complementary/ dissonant'. 'Complementary' reflects a broad interpretation of the word 'ability' that means that the co-design study findings complement the survey by defining the relevant aspect of this meaning; in contrast, use of a narrower definition of 'ability', as physical capacity, would lead to the findings being interpreted as dissonant.

The literature review findings were apparently consistent with the survey, but too limited to draw meaningful conclusions. Six studies described an impact on the ability to exercise. The two quantitative studies simply elicited that fatigue was one of a list of barriers to exercise, without attempting to establish the mechanism [219,223]. The remaining four were qualitative or mixed methods studies that did not report evaluation of the way fatigue impacted on exercise ability, other than one study describing 'parental over-protectiveness' hindering sport; it is conceivable that this reflected parental activity fear avoidance [179].

The difference between physical capacity and activity fear avoidance may appear subtle but, in clinical terms, reflects the difference between a behavioural intervention that increases physical activity and a cognitive intervention that reframes a perception. As discussed in section 4.6.1.3 (page 204), behaviour change interventions require considerable engagement, take time and are often unsuccessful, whereas a cognitive intervention has potential to work more rapidly and effectively. Again, qualitative data has increased the depth of understanding of the quantitative findings. It was not anticipated that fatigued participants would describe activity fear avoidance, rather than physical incapacity. The exploratory nature of qualitative research, open to emergent themes, led to this important insight.

Additional data collection could have been valuable. For example, if it had been possible to undertake further survey questioning after these insights from the qualitative study, it would have been interesting to ask survey participants to rank or quantify the extent to which exercise was limited physically or hindered by fear avoidance. Equally, further exploration within the co-design study could have enhanced understanding even further, for example probing to discover the respective contexts within which physical incapacity or fear avoidance prevail.

### **5.1.2.3 *Less misunderstanding than perceived***

The final incongruent topic relates to misunderstandings between young people and others. The FICS findings could be considered dissonant to those of the survey, in that direct discussion with parents revealed less misunderstanding than that apparently perceived by TYAs in the survey, and indeed with the co-design study itself. Parents' perceptions were remarkably analogous to their offspring, leading to the 'Concordant Tension Tree' model (section 4.5.11, page 160). Parents had insight into how fatigue is misunderstood with its inherent invisibility, they understood the impact on their child, and they were prepared to defend their child against the misunderstandings of others.

The integration outcome in table 5.1 was both complementary and dissonant. The relevant survey question was 'Do you think the effect of fatigue on your life is understood by the people around you?' Considered in the broader meaning of seeking the young person's perception, the co-design findings are congruent with the survey as, in both contexts, the young person perceived misunderstanding. Using a more literal sense of whether there were true misunderstandings, rather than simply perceptions of misunderstandings, the co-design study generated dissonant findings that can be entirely explained by the use of a different study population: parents as well as TYAs.

If there had been an opportunity to undertake a further phase of interviews, it would have been interesting to reflect the findings of congruent tensions back to the young participants. How, for example, would young participants themselves explain this apparent dissonance? However, generation of the 'Concordant Tension Tree' model occurred after data collection had ceased, precluding this further iterative step.

### **5.1.3 Discussion**

Multimethod integration has revealed a complementary relationship between the studies, each consistently building on those preceding. All but one outcome in the integration matrix was judged to be at least partially 'complementary'.

There are a number of possible reasons for the high degree of complementarity. First, the three studies represent the three timescales of past, present and future: the systematic review described research knowledge generated in the past, the survey evaluated current experiences and management, and the qualitative study designed a future fatigue treatment. Second, the studies involved three diverse methods: narrative synthesis of varied study designs, quantitative multicentre survey, and qualitative study involving individual interviews and focus groups. Third, the studies incorporated different temporal profiles: the survey provided a cross-sectional perspective, while the qualitative study was multiphase and longitudinal in design.

While such diversity enriched the insights gained from this programme of work, study heterogeneity did lead to a degree of non-comparability of study populations and measures, causing the few examples of integration dissonance. The systematic review appraised literature relating to TYAs both during and after cancer treatment, the survey attempted the same but only those after the end of treatment participated, and FICS recruited only young people within the first year after the end of cancer treatment.

The integration matrix reveals that the quantitative survey findings tend to be explained and illuminated by the qualitative co-design study. Furthermore, it can be argued that the insights from the qualitative study may be most useful, both for future clinical practice and research (section 5.4, page 229). While the survey provided evidence for the persistence of fatigue long after the end of cancer treatment, the explanation for why this occurs, with generation of vicious cycles, adds further insight and creates potential for an effective intervention through targeting the perpetuating mechanism. Knowing that fatigue is a barrier to exercise is helpful; however, understanding that the mechanism may be activity fear avoidance beliefs rather than physical incapacity increases insight into intervention needs. The significance and utility of the qualitative findings is consistent with Brannen's statement: qualitative research is no longer regarded as the 'poor relation to quantitative research that it has been in the past' [510].

The strengths and limitations of each study have already been considered within each chapter. As part of this final stage, appraising the three studies as an integrated whole, it is worth considering overall strengths and limitations in relation to the starting position detailed in chapter 1: the original research plan, fatigue pathophysiology, TYA health and underlying theory.

#### **5.1.3.1 *Link back to original research plan***

The overall aim of this programme of research was to increase understanding of the problem of TYA CRF in order to be able to develop an effective non-pharmacological fatigue intervention. It is submitted that this work has amply realised this core aim.

The integration process has revealed limitations in the approach taken, beyond those of the individual studies. In retrospect, it would have been preferable to have made an *a priori* decision to set up the survey and co-design study for a mixed-methods, rather than multimethod analysis [501]. Formal integration phases between the studies during their conduct, instead of only after completion, could have increased research productivity.

An integration phase between the literature review and survey could have led to survey participants being questioned on sleep, an oversight given that poor sleep has been associated with fatigue in



past research (section 2.5.6, page 34). Such a phase between the survey and co-design study may usefully have influenced the topic guides; for example, given that only one in five survey participants believed that fatigue could be treated, it would have been valuable to try to gain qualitative insight into this.

#### ***5.1.3.2 Link back to fatigue pathophysiology***

As described in section 1.1.1.3 (page 2), although fatigue is thought to be a consequence of systemic inflammation, it is also recognised that this cannot be the only explanation; a number of psychological and behavioural factors predict fatigue severity, and treatment of concurrent symptoms can improve fatigue. The finding that these factors can be both causes and consequences of fatigue, with the resulting potential for symptom perpetuation, contributes considerably to understanding their importance.

Having argued beyond the role of systemic inflammation, it must be remembered that the responses to fatigue, in themselves, also induce systemic inflammation. Inactivity, low mood, anxiety and poor sleep are examples of psycho-behavioural factors associated with higher levels of systemic inflammation and neuroinflammation [511-513]. Such inflammation may therefore still have a mechanistic role in CRF, but through the psycho-behavioural responses and contributors to fatigue, as well as the direct effect of cancer and its treatment. Efforts to reduce systematic inflammation, with its adverse consequences on wellbeing and health, could therefore helpfully focus on increasing activity, promoting sleep hygiene and reducing tension, rather than simply considering underlying chronic disease management.

The design of this research programme precluded further investigation of fatigue pathophysiology. If the survey and FICS could have been undertaken concurrently, survey data on cancer stage and participant activity would have been helpful to allow comparison of the influence of fatigue triggers (cancer stage and treatment) and fatigue responses (including activity, sleep and thoughts). There was no capacity to assess measures of systemic inflammation, such as CRP in this work; this would however be valuable in future research (section 5.4.2, page 230).

#### ***5.1.3.3 Link back to TYA health***

A key strength of this programme of work has been the focus on the specific needs of this young age, with close collaboration between young patients, parents and the research team realising significant mutual benefit. Breadth of contact in the multicentre survey and depth of contact in the multiphase qualitative study were gained by using novel methodology: electronic patient research survey and intervention co-design respectively.

Despite the efforts to engage this patient group, there were limitations to access. The youngest patients recruited were aged 17, a minimum age of 16 years having been set in both studies because of the ethical and practical challenges of recruiting children. Despite the survey being open to patients both on, and after, treatment, only those after the end of cancer treatment responded. Further research is needed in 13-16 year olds, and in patients during cancer treatment.

#### ***5.1.3.4 Link back to Self-Efficacy Theory***

The co-design study findings have already been theoretically contextualised in section 4.6.2 (page 205). This theory appears to have been an appropriate choice to underpin this work, not least as it underpins the intervention mechanism. In retrospect, considering all three studies as an integrated whole, opportunities were missed to maximise insights into perceived self-efficacy for fatigue self-management.

Self-efficacy was not used as a search term within the systematic review. This had no eventual implications, as the broad eligibility of studies meant that no relevant studies were missed; there is no existing research evaluating the concept of self-efficacy in TYA CRF. It would however have been valuable for the survey to have included questions on participants' confidence that they could improve their fatigue, and to have allowed participants to choose amongst potential factors known to promote perceived self-efficacy. Furthermore, the co-design study involved no direct questioning about self-efficacy and how to improve it. The fact that unsolicited evidence for the importance of building confidence and motivation emerged from the FICS data increases the credibility of the findings in relation to self-efficacy (section 4.5.7.1). However, it is possible that further valuable data could have been gained by explicit questioning.

## **5.2 Programme research outputs**

This section summarises the key outputs from the three studies described in this thesis. Further details are available at appendix 7.1 (page 269).

### **5.2.1 Public dialogue**

#### ***5.2.1.1 Teenage Cancer Trust Way Forward Programme***

This charitable programme runs two-day residential courses across the UK to help young people addressing the issues being faced with a cancer diagnosis. Anna Spathis and Julie Burkin delivered a one-hour interactive workshop at four events (East Anglia: March 2017 and March 2018; London and South East: Sept 2017 and Sept 2018). Discussion with TYA patients was stimulated by a quiz based on research findings.

#### ***5.2.1.2 Shine Cancer Support National Conference***

In May 2018, Anna Spathis delivered the keynote lecture at this conference in London, for over one hundred young adults with cancer. This involved discussing fatigue and sharing research findings, followed by a 'chat show style' dialogue with attendees to promote mutual learning. It was live-streamed on Facebook, for those unable to attend in person.

### **5.2.2 Educational materials**

A series of short peer videos, involving TYAs talking about cancer-fatigue, were a key research output. They were requested as the optimal form of information-giving by participants in FICS, and subsequently professionally produced by Macmillan Cancer Support.

The trailer and three videos were launched on Facebook in October 2017, with over one million cumulative hits since. The following quotes encapsulate the tone of the dialogue: 'I am really keen to see this. Sitting here having a little cry, as I thought it was just me and telling myself to get a grip'; 'Thank you for this inspirational video'; 'I struggle with unpredictable fatigue. This awareness campaign is greatly appreciated. I hope that it creates awareness that we are not lazy, we are genuine.'

### **5.2.3 University of Cambridge research award**

This work resulted in Anna Spathis and Stephen Barclay receiving a University of Cambridge Vice-Chancellor's Public Engagement with Research Award in July 2018 (see appendix 7.1.2, page 269, for hyperlink to related blog).

#### **5.2.4 Dissemination of findings**

By March 2019, Anna Spathis will have delivered three oral presentations, relating to each of the three studies, at national conferences, and two further poster presentations (appendix 7.1.3, page 269). Two peer-reviewed publications have been published at the time of thesis submission, relating to the literature review and survey [514,515]. The former was one of the 'top ten most cited publications' in 2017 for the *Journal of Adolescent and Young Adult Oncology*, and the latter one of the 'top ten most read publications' in both 2017 and 2018. This relates to publications since the journal's inception in 2011.

The following papers are planned, based on material in this thesis, to be submitted for publication during 2019.

1. Methodological paper on the multicentre survey innovative electronic survey methods.
2. Paper describing the Fatigue Intervention Co-design Study and unique needs of TYAs and their parents.
3. Multimethod paper evaluating the impact of cancer-related fatigue on the parents of young patients.
4. Brief report describing the Sleep, Thoughts, Activity conceptual model and its potential clinical implications.

### **5.3 Ten key novel findings from integrated research programme**

1. Fatigue is the most common and most distressing symptom experienced by teenagers and young adults with cancer. It is the symptom with the worst impact on daily life, and is an independent predictor of poor quality of life.
2. Fatigue can persist long after the end of cancer treatment. This may be due to the development of emotional and behavioural responses to fatigue that worsen the symptom, forming vicious cycles that perpetuate it beyond the original trigger.
3. Cognitive fatigue, with its effect on concentration and memory, has a more negative impact than physical fatigue. It influences the ability to work, be in education or socialise, hindering key age-related developmental needs of conforming and autonomy.
4. Parents contend with considerable adverse consequences, experiencing conflict and unmet information needs. Both young patients and their parents describe multilevel interpersonal tensions and perceptions of misunderstandings, although these are paradoxically congruent.
5. Despite the enormity of the problem, cancer-related fatigue has been neglected in teenagers and young adults with no previous interventional trials focused on this symptom. Fatigue is currently inadequately managed in the UK, with many patients not receiving support; most find fatigue treatment ineffective and believe the symptom cannot be improved.
6. Teenagers and young adults have demonstrated extensive and unique age-related needs from the fatigue intervention. For example, short videos are more acceptable than written information. Findings from fatigue management research in older adults cannot be extrapolated to younger patients.
7. The co-designed intervention is largely cognitive in approach, for example using mindfulness techniques rather than energy conservation. It aims to promote self-efficacy for fatigue self-management, empowering patients to make small changes to fatigue responses.
8. Although advice to exercise is the commonest approach and most recommended by young patients, the main impact of fatigue is on the ability to exercise, and exercise advice tends to be unhelpful. Structured support with regular short-term goals is needed, given the physical reserve of youth and fear that activity may worsen fatigue.

9. Young patients asked for, and helped drive, this programme of work. Recruitment was relatively easy, engagement with the research process was high and participants embraced the two innovative research methods: electronic survey and intervention co-design.
10. Information has been generated that will optimise the design of the future definitive trial testing intervention effectiveness. Early, individualised, predominantly cognitive intervention will be provided for patients and parents, with measures including perceived self-efficacy for fatigue self-management, return to education or work, healthcare utilisation and biomarkers for systemic inflammation.

## **5.4 Ten key recommendations**

The clinical and research implications of each of the three studies have already been described in the relevant study chapters. This section gives a synthesised list of overall recommendations in point form, for clarity.

### **5.4.1 Recommendations for clinical practice and policy**

Although definitive study of the effectiveness of the co-designed intervention has not yet been undertaken, it would be reasonable to incorporate aspects of TYA intervention needs into clinical practice at this stage. The following principles are therefore recommended:

1. Clinicians should proactively enquire about the presence of fatigue in TYA cancer patients at an early stage, before the end of cancer treatment. Many patients do not raise this topic and subsequently do not gain support. Simple acknowledgement of this 'invisible' symptom, along with addressing information needs, may be of therapeutic value in itself.
2. Given the close relationship of fatigue with other symptoms, optimal concurrent symptom control is important, particularly focusing on insomnia, anxiety, depression and pain. Evaluation of emotional and behavioural responses to fatigue, such as poor sleep hygiene or activity fear avoidance beliefs, may allow insights to be gained into any perpetuating vicious cycles.
3. When agreed by young patients, involvement of parents and siblings could be valuable, given the considerable unmet information needs and perceptions of misunderstandings. Facilitated family discussions may reduce tensions and promote mutual understanding.
4. Clinical education could be provided to train healthcare professionals to understand the unique needs of fatigued TYAs, including recognising cognitive fatigue, supporting discussion with senior staff at patients' education or work, providing individualised and structured exercise plans, and encouraging App-based mindfulness techniques. AHPs and psychologists, with experience of the distinct needs of TYAs, may have a particular role in supporting fatigue management.
5. The videos produced as a research output are available on-line, and are likely to be valuable for patients and healthcare staff. Access needs to be made easier for those not using social media.

### **5.4.2 Recommendations for future research**

Many implications for research have already been described in relation to the three individual studies. The following recommendations form a synthesis of the most important points:

1. A prospective, longitudinal cohort study is needed to ascertain the temporal pattern of fatigue during, and after, cancer treatment. International collaboration would facilitate a study large enough to have the power to test predictors of fatigue severity and of fatigue perpetuation, including cancer stage, fatigue-related expectations and a range of emotional and behavioural fatigue responses.
2. The features of the 'trial ready' TYA fatigue intervention are now known, including that it will be an early, individualised, predominantly cognitive intervention provided for patients and parents. Activity support, Information and Mindfulness (A.I.M) will form the key content, and the aim will be to promote perceived self-efficacy for fatigue self-management.
3. The definitive randomised controlled trial will require UK-wide senior collaboration, including experts in clinical trials and health psychology. A prior feasibility trial or an internal pilot phase is needed to confirm that the proposed measures are not excessively burdensome in the context of cognitive fatigue, and to determine if randomisation to 'usual care' is acceptable.
4. The Sleep, Thoughts, Activity (STA) conceptual model requires evaluation initially with a qualitative study, in order to refine it, test its acceptability as a clinical and educational tool, and evaluate its role in promoting perceived self-efficacy. Collaboration is needed with health psychologists and, potentially, with experts in systems dynamics.
5. Subsequent research could include evaluation of the generalisability of these research findings to TYAs with CFS/ME and other chronic conditions, neuroimaging studies, and development of a mobile App to support fatigue self-management. Further research is needed in fatigued TYAs during cancer treatment and in younger adolescents.



## 5.5 Concluding comments

In the middle of difficulty lies opportunity.

*Einstein*

She was quite incredible... she said that it was a blessing that this had happened to her.

She felt very grateful for the diagnosis... because she felt like it had directed her life,  
and now she is studying... and feeling the best she had ever felt.

*HCP reflection on meeting a young research participant*

The challenges faced by young cancer patients and their families, already coping with a devastating illness, are compounded by fatigue. This thesis describes an effort to counter the prevailing neglect of this debilitating and distressing symptom. The programme of research has been inspired, and driven by, young cancer patients since its inception. It has been a privilege to work in partnership with young patients and their parents, to witness their resilience during adversity, and to promote mutual learning from their expertise.

Fatigue can persist, perpetuating beyond the trigger of cancer and its treatment, with potential for long term adverse impact at this formative age. This research has started the process of developing an intervention, enhancing young patients' confidence to respond to fatigue with thoughts and emotions that propel vicious cycles into virtuous cycles, and empowering them to live life, even if limited in length, to the full.

Between stimulus and response there is a space. In that space is our power  
to choose our response. In our response lies our growth and our freedom.

*Viktor Frankl*

Fatigue breeds fatigue... Energy breeds energy

*Young research participants*



## 6 References

1. National Comprehensive Cancer Network (NCCN), *NCCN Clinical Practice Guidelines in Oncology: Version 2*. 2018. Available from: [https://www.nccn.org/professionals/physician\\_gls/default.aspx#fatigue](https://www.nccn.org/professionals/physician_gls/default.aspx#fatigue) [Accessed 30th December 2018].
2. Glaus A, Crow R, Hammond S. A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals. *Supportive Care in Cancer*. 1996;4(2):82-96.
3. Jacobsen P, Hann D, Azzarello L, Horton J, Balducci L, et al. Fatigue in women receiving adjuvant chemotherapy for breast cancer: characteristics, course, and correlates. *Journal of Pain and Symptom Management*. 1999;18(4):233-242.
4. Poulson M. Not just tired. *Journal of Clinical Oncology*. 2001;19(21):4180-4181.
5. Butt Z, Wagner L, Beaumont J, Paice J, Peterman A, et al. Use of a single-item screening tool to detect clinically significant fatigue, pain, distress and anorexia in ambulatory cancer practice. *Journal of Pain and Symptom Management*. 2008;35(1):20-30.
6. Bower J, Bak K, Berger A, Breitbart W, Escalante C, et al. Screening, assessment and management of fatigue in adult survivors of cancer: an American Society of Clinical Oncology Clinical Practice Guideline adaptation. *Journal of Clinical Oncology*. 2014;32(17):1840–1850.
7. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, et al. Development of a fatigue scale. *Journal of Psychosomatic Research*. 1993;37(2):147-153.
8. Piper B, Dibble S, Dodd M, Weiss M, Slaughter R, et al. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. *Oncology Nursing Forum*. 1998;25(4):677-684.
9. Mendoza T, Wang X, Cleeland C, Morrissey M, Johnson B, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer*. 1999;85(5):1186-1196.
10. Yellen S, Cella D, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of Pain and Symptom Management*. 1997;13(2):63-74.
11. Vogelzang N, Breitbart W, Cella D, Curt G, Groopman J, et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition. *Seminars in Hematology*. 1997;34(Suppl 1):4-12.
12. Curt G, Breitbart W, Cella D, Groopman J, Horning S, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist*. 2000;5(5):353-360.
13. Teunissen S, Wesker W, Kruitwagen C, de Haes H, Voest E, et al. Symptom prevalence in patients with incurable cancer: a systematic review. *Journal of Pain and Symptom Management*. 2007;34(1):94-104.
14. Bower J. Cancer-related fatigue-mechanisms, risk factors, and treatments. *Nature Reviews Clinical Oncology*. 2014;11(10):597-609.

15. Henry D, Viswanathan H, Elkin E, Traina S, Wade S, et al. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. *Supportive Care in Cancer*. 2016;24(7):791-801.
16. Kuhnt S, Ernst J, Singer S, Ruffer JU, Kortmann R, et al. Fatigue in cancer survivors-prevalence and correlates. *Onkologie*. 2009;32(6):312-317.
17. Bower J, Ganz P, Desmond K, Bernards C, Rowland J, et al. Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. *Cancer*. 2006;106(4):751-758.
18. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients: a cross-sectional study. *Annals of Oncology*. 2002;13(4):589-598.
19. Groenvold M, Petersen M, Idler E, Bjorner J, Fayers PM, et al. Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. *Breast Cancer Research and Treatment*. 2007;105(2):209-219.
20. Quinten C, Maringwa J, Gotay C, Martinelli F, Coens C, et al. Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival. *Journal of the National Cancer Institute*. 2011;103(24):1851-1858.
21. Cox B. *Health and Lifestyle Survey, 1984-1985*. UK Data Service. 1988. Available from: <http://doi.org/10.5255/UKDA-SN-2218-1> [Accessed 30th December 2018].
22. Passik S, Kirsh K, Donaghy K, Holtsclaw E, Theobald D, et al. Patient-related barriers to fatigue communication: initial validation of the fatigue management barriers questionnaire. *Journal of Pain and Symptom Management*. 2002;24(5):481-493.
23. Stone P, Richardson A, Ream E, Smith A, Kerr D, et al. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. Cancer Fatigue Forum. *Annals of Oncology*. 2000;11(8):971-975.
24. National Cancer Institute, *Strategic Priorities: Symptom Management and Quality of Life Steering Committee*. 2015. Available from: <https://www.cancer.gov/about-nci/organization/ccct/steering-committees/2015-SxQoLSC-StrategicPriorities>. [Accessed 30th December 2018].
25. National Cancer Research Institute, *James Lind Alliance Priority Setting Partnership: The UK Top Ten Living With and Beyond Cancer Research Priorities*. 2018. Available from: [https://www.ncri.org.uk/lwbc/#lwbc\\_questions](https://www.ncri.org.uk/lwbc/#lwbc_questions) [Accessed 30th December 2018].
26. Wang X, Williams AR, Krishnan S, Liao Z, Liu C, et al. Serum sTNFR1, IL6, and the development of fatigue in patients with gastrointestinal cancer undergoing chemoradiation therapy. *Brain, Behavior, and Immunity*. 2012;26(5):699-705.
27. Wang Z, Shi Q, Williams L, Mao L, Cleeland C, et al. Inflammatory cytokines are associated with the development of symptom burden in patients with NSCLC undergoing concurrent chemoradiation therapy. *Brain, Behavior, and Immunity*. 2010;24(6):968-974.
28. Schrepf A, Clevenger L, Christensen D, DeGeest K, Bender D, et al. Cortisol and inflammatory processes in ovarian cancer patients following primary treatment: relationships with depression, fatigue, and disability. *Brain, Behavior, and Immunity*. 2013;30:S126-134.

29. Cleeland C, Bennett G, Dantzer R, Dougherty P, Dunn A, et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. *Cancer*. 2003;97(11):2919-2925.
30. Bower J, Ganz P, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. *Psychosomatic Medicine*. 2005;67(2):277-280.
31. Bower J, Ganz P, Dickerson S, Petersen L, Aziz N, et al. Diurnal cortisol rhythm and fatigue in breast cancer survivors. *Psychoneuroendocrinology*. 2005;30(1):92-100.
32. Weinrib A, Sephton S, Degeest K, Penedo F, Bender D, et al. Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer. *Cancer*. 2010;116(18):4410-4419.
33. Fagundes C, Murray D, Hwang B, Gouin J, Thayer J, et al. Sympathetic and parasympathetic activity in cancer-related fatigue: more evidence for a physiological substrate in cancer survivors. *Psychoneuroendocrinology*. 2011;36(8):1137-1147.
34. McEwen B, Biron C, Brunson K, Bulloch K, Chambers W, et al. The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. *Brain Research Reviews*. 1997;23(1-2):79-133.
35. Irwin M, Cole S. Reciprocal regulation of the neural and innate immune systems. *Nature Reviews Immunology*. 2011;11(9):625-632.
36. Collado-Hidalgo A, Bower J, Ganz P, Cole S, Irwin M. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. *Clinical Cancer Research*. 2006;12(9):2759-2766.
37. Dhruva A, Dodd M, Paul S, Cooper BA, Lee K, et al. Trajectories of fatigue in patients with breast cancer before, during, and after radiation therapy. *Cancer Nursing*. 2010;33(3):201-212.
38. Goldstein D, Bennett B, Webber K, Boyle F, de Souza P, et al. Cancer-related fatigue in women with breast cancer: outcomes of a 5-year prospective cohort study. *Journal of Clinical Oncology*. 2012;30(15):1805-1812.
39. Miaskowski C, Paul S, Cooper BA, Lee K, Dodd M, et al. Trajectories of fatigue in men with prostate cancer before, during, and after radiation therapy. *Journal of Pain and Symptom Management*. 2008;35(6):632-643.
40. Fabi A, Falcicchio F, Giannarelli D, Maggi G, Cognetti F, et al. The course of cancer-related fatigue up to ten years in early breast cancer patients: what impact in clinical practice? *Breast*. 2017;34:44-52.
41. Jim H, Jacobsen P, Phillips K, Wenham R, Roberts W, et al. Lagged relationships among sleep disturbance, fatigue and depressed mood during chemotherapy. *Health Psychology*. 2013;32(7):768-774.
42. Schmidt M, Chang-Claude J, Seibold P, Vrieling A, Heinz J, et al. Determinants of long-term fatigue in breast cancer survivors: results of a prospective patient cohort study. *Psycho-Oncology*. 2015;24(1):40-46.
43. De Raaf P, van der Rijt C. Can you help me feel less exhausted all the time? *Journal of Clinical Oncology*. 2013;31(25):3056-3060.

44. De Raaf P, de Klerk C, Timman R, Busschbach J, Oldenmenger W, et al. Systematic monitoring and treatment of physical symptoms to alleviate fatigue in patients with advanced cancer: a randomised controlled trial. *Journal of Clinical Oncology*. 2013;31(6):716-723.
45. Oh H, Seo W. Systematic review and meta-analysis of the correlates of cancer-related fatigue. *Worldviews on Evidence-Based Nursing*. 2011;8(4):191-201.
46. Thornton L, Andersen B, Blakely W. The pain, depression, and fatigue symptom cluster in advanced breast cancer: covariation with the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. *Health Psychology*. 2010;29(3):333-337.
47. Thomas B, Waller A, Malhi R, Fung T, Carlson L, et al. A longitudinal analysis of symptom clusters in cancer patients and their sociodemographic predictors. *Journal of Pain and Symptom Management*. 2014;47(3):566-578.
48. Mustian KM, Alfano CM, Heckler C, Kleckner AS, Kleckner IR, et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. *JAMA Oncology*. 2017;3(7):961-968.
49. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. Psychostimulants for the management of cancer-related fatigue: a systematic review and meta-analysis. *Journal of Pain and Symptom Management*. 2011;41(4):761-767.
50. Minton O, Stone P, Richardson A, Sharpe M, Hotopf M. Drug therapy for the management of cancer related fatigue. *Cochrane Database of Systematic Reviews*. 2008;23(1):CD006704.
51. Cella D, Eton D, Lai JS, Peterman A, Merkel D. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *Journal of Pain and Symptom Management*. 2002;24(6):547-561.
52. Bruera E, Yennurajalingam S, Palmer J, Perez C, P., Frisbee-Hume S, et al. Methylphenidate and/or a nursing telephone intervention for fatigue in patients with advanced cancer: a randomized, placebo-controlled, phase II trial. *Journal of Clinical Oncology*. 2013;31(19):2421-2427.
53. Stockler M, O'Connell R, Nowak A, Goldstein D, Turner J, et al. Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-blind randomised trial. *Lancet Oncology*. 2007;8(7):603-612.
54. Spathis A, Fife K, Blackhall F, Dutton S, Bahadori R, et al. Modafinil for the treatment of fatigue in lung cancer: results of a placebo-controlled, double-blind, randomized trial. *Journal of Clinical Oncology*. 2014;32(18):1882-1888.
55. Yennurajalingam S, Frisbee-Hume S, Palmer J, Delgado-Guay M, Bull J, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *Journal of Clinical Oncology*. 2013;31(25):3076-3082.
56. Hilfiker R, Meichtry A, Eicher M, Nilsson Balfe L, Knols R, et al. Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis. *British Journal of Sports Medicine*. 2017;52(10):651-658.
57. Kelley GA, Kelley KS. Exercise and cancer-related fatigue in adults: a systematic review of previous systematic reviews with meta-analyses. *BMC Cancer*. 2017;17(1):693-693.

58. Bennett S, Pigott A, Beller EM, Haines T, Meredith P, et al. Educational interventions for the management of cancer-related fatigue in adults. *Cochrane Database of Systematic Reviews*. 2016;11:CD008144.
59. [Editors]. What should the age range be for AYA oncology? *Journal of Adolescent and Young Adult Oncology*. 2011;1(1):3-10.
60. Teenage Cancer Trust (TCT). *A blueprint of care for teenagers and young adults with cancer*. Second edition. 2016. Available from: [https://www.teenagecancertrust.org/sites/default/files/BlueprintOfCare\\_2ndEdition.pdf](https://www.teenagecancertrust.org/sites/default/files/BlueprintOfCare_2ndEdition.pdf) [Accessed 31st December 2018].
61. Ernst M, Pine D, Hardin M. Triadic model of the neurobiology of motivated behavior in adolescence. *Psychological Medicine*. 2006;36(3):299-312.
62. Thomas F, Renaud F, Benefice E, de Meeus T. International variability of ages at menarche and menopause: patterns and main determinants. *Human Biology*. 2001;73:271–290.
63. Sawyer S, Azzopardi P, Wickremarathne D, Patton G. The age of adolescence. *Lancet Child and Adolescent Health*. 2018;2(3):223-228.
64. Hagell A, Shah R, Coleman J. *Key data on young people: latest information and statistics*. Association for Young People's Health. 2017. Available from: <http://www.ayph.org.uk/keydata2017/FullVersion2017> [Accessed 31st December 2018].
65. World Health Organisation (WHO), *Health for the World's Adolescents: a Second Chance in the Second Decade*. Available from: [https://www.who.int/maternal\\_child\\_adolescent/documents/second-decade/en/](https://www.who.int/maternal_child_adolescent/documents/second-decade/en/) [Accessed 31st December 2018].
66. Casey B, Jones R, Hare T. The Adolescent Brain. *Annals of the New York Academy of Sciences*. 2008;1124:111-126.
67. Sawyer S, Afifi R, Bearinger L, Blakemore S, Dick B, et al. Adolescence: a foundation for future health. *Lancet*. 2012;379(6736):1630-1640.
68. Whitaker K, Vertes P, Romero-Garcia R, Vasa F, Moutoussis M, et al. Adolescence is associated with genomically patterned consolidation of the hubs of the human brain connectome. *Proceedings of the National Academy of Sciences*. 2016;113(32):9105-9110.
69. Ellis B, Dishion T, Gray P, Hawley P, Volk A, et al. The evolutionary basis of risky adolescent behaviour: implications for science, policy and practice. *Developmental Psychology*. 2012;48(3):598-623.
70. Steinberg L. Cognitive and affective development in adolescence. *Trends in Cognitive Science*. 2005;9(2):69-74.
71. World Health Organisation (WHO), *Global Accelerated Action for the Health of Adolescents (AA-HA!)* 2017. Available from: [https://www.who.int/maternal\\_child\\_adolescent/topics/adolescence/framework-accelerated-action/en/](https://www.who.int/maternal_child_adolescent/topics/adolescence/framework-accelerated-action/en/) [Accessed 31st December 2018].
72. Barry C, Sidoti C, Briggs S, Reiter S, Lindsey R. Adolescent social media use and mental health from adolescent and parent perspectives. *Journal of Adolescence*. 2017;1:1-11.

73. Viner R, Coffey C, Mathers C, Bloem P, Costello A, et al. 50-year mortality trends in children and young people: a study of 50 low-income, middle-income, and high-income countries. *Lancet*. 2011;377(9772):1162–1174.
74. Patton G, Coffey C, Sawyer S, Viner R, Haller D, et al. Global patterns of mortality in young people: a systematic analysis of population health data. *Lancet*. 2009;374(9693):881-892.
75. Viner R, Hargreaves D, Coffey C, Patton G, Wolfe I. Death in young people aged 0–24 years in the UK compared with the EU15+ countries: analysis of WHO Mortality Database. *Lancet*. 2014;384:880–892.
76. Hargreaves D, Viner R. Adolescent inpatient activity 1999–2010: analysis of English Hospital Episode Statistics data. *Archives of Disease in Childhood*. 2014;99(9):830-833.
77. McGrady M, Hommel K. Medication adherence and health care utilization in pediatric chronic illness: a systematic review. *Pediatrics*. 2013;132:730-740.
78. Beaglehole R, Bonita R, Horton R, Adams C, Alleyne G, et al. Priority actions for the non-communicable disease crisis. *Lancet*. 2011;377(9775):1438-1447.
79. World Health Organisation (WHO), *Global standards for quality health-care services for adolescents*. 2015. Available from: [https://www.who.int/maternal\\_child\\_adolescent/documents/global-standards-adolescent-care/en/](https://www.who.int/maternal_child_adolescent/documents/global-standards-adolescent-care/en/) [Accessed 31st December 2018].
80. Hargreaves D, Djafari Marbini A, Viner R. Inequality trends in health and future health risk among English children and young people, 1999–2009. *Archives of Disease in Childhood*. 2013;98:850-855.
81. Albon L, Vaughan L. Adolescents and young adults on the acute medical unit: how might we do better? *Clinical Medicine*. 2014;14(6):618-622.
82. Rhee H, Pesis-Katz I, Xing J. Cost benefits of a peer-led asthma self-management program for adolescents. *Journal of Asthma*. 2012;49(6):606-613.
83. Thurston I, Bogart L, Wachman M, Closson E, Skeer M, et al. Adaptation of an HIV medication adherence intervention for adolescents and young adults. *Cognitive and Behavioural Practice*. 2014;21:191-205.
84. Hargreaves D, McDonagh J, Viner R. Validation of You're Welcome quality criteria for adolescent health services using data from national inpatient surveys in England. *Journal of Adolescent Health*. 2013;52:50-57.
85. DiNapoli P, Murphy D. The marginalization of chronically ill adolescents. *Nursing Clinics of North America*. 2002;37(3):565-572.
86. Rahdar A, Galvan A. The cognitive and neurobiological effects of daily stress in adolescents. *Neuroimage*. 2014;92:267-273.
87. Steinberg L, Morris A. Adolescent development. *Annual Reviews in Psychology*. 2001;52:83-110.
88. Sawyer S, Drew S, Yeo M, Britto M. Adolescents with a chronic condition: challenges living, challenges treating. *Lancet*. 2007;269(9571):1481-1489.
89. Sawyer S, Aroni R. Sticky issue of adherence. *Journal of Pediatric Child Health*. 2003;39(1):2-5.



90. Butow P, Palmer S, Pai A, Goodenough B, Lockett T, et al. Review of adherence-related issues in adolescents and young adults with cancer. *Journal of Clinical Oncology*. 2010;28(32):4800-4809.
91. Cancer Research UK (CRUK), *Teenage and Young Adult Cancer Statistics*. 2018. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/young-peoples-cancers> [Accessed 31st December 2018].
92. National Cancer Registration and Analysis Service (NCRAS). The Macmillan-NCRAS work plan: the UK Cancer Prevalence Project. 2015. Available from: [http://www.ncin.org.uk/about\\_ncin/segmentation](http://www.ncin.org.uk/about_ncin/segmentation) [Accessed 31st December 2018].
93. Macmillan Cancer Support. *The Rich Picture: Teenagers and Young Adults with Cancer*. 2014. Available from: [https://www.macmillan.org.uk/\\_images/Teenagers-Young-Adults-Living-with-Cancer\\_tcm9-282795.pdf](https://www.macmillan.org.uk/_images/Teenagers-Young-Adults-Living-with-Cancer_tcm9-282795.pdf) [Accessed 31st December 2018].
94. Mulrooney D, Yeazel M, Kawashima T, Mertens AC, Mitby P, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *British Medical Journal*. 2009;339:b4606.
95. Robson L, Hudson M. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nature Reviews of Cancer*. 2014;14(1):61-70.
96. Sender L, Zabokrtsky K. Adolescent and young adult patients with cancer: a milieu of unique features. *Nature Reviews Clinical Oncology* 2015;12:465-480.
97. Birch M, Alston RD, Kelsey A, Quinn M, Babb P, et al. Classification and incidence of cancers in adolescents and young adults in England 1979-1997. *British Journal of Cancer*. 2002;87(11):1267-1274.
98. Taylor R, Pearce S, Gibson F, Fern L, Whelan J. Developing a conceptual model of teenage and young adult experiences of cancer through meta-synthesis. *International Journal of Nursing Studies*. 2013;50(6):832-846.
99. Sawyer S, McNeil R, McCarthy M, Orme L, Thompson K, et al. Unmet need for healthcare services in adolescents and young adults with cancer and their parent carers. *Supportive Care in Cancer*. 2017;25:2229-2239.
100. Stark D, Bielack S, Brugieres L, Dirksen U, Duarte X, et al. Teenagers and young adults with cancer in Europe: from national programmes to a European integrated coordinated project. *European Journal of Cancer Care*. 2016;25(3):419-427.
101. Vindrola-Padros C, Taylor R, Lea S, Hooker L, Pearce S, et al. Mapping adolescent cancer services: how do young people, their families, and staff describe specialised cancer care in England? *Cancer Nursing*. 2016;39(5):358-366.
102. Haward R. The Calman-Hine report: A personal retrospective on the UK's first comprehensive policy on cancer services. *Lancet Oncology*. 2006;7:336-346.
103. Taylor R, Fern L, Whelan J, Pearce S, Grew T, et al. "Your place or mine?" Priorities for a specialist teenage and young adult (TYA) cancer unit: disparity between TYA and professional perceptions. *Journal of Adolescent and Young Adult Oncology*. 2011;1(3):145-151.
104. National Institute for Health and Care Excellence (NICE), *Guidance on Cancer Services: Improving Outcomes in Children and Young People with Cancer*. 2005. Available from:

<https://www.nice.org.uk/guidance/csg7/resources/improving-outcomes-in-children-and-young-people-withcancer-update-773378893> [Accessed 31st December 2018].

105. Teenage Cancer Trust (TCT). *Young people with cancer need specialised nursing care and support*. 2018. Available from: <https://www.teenagecancertrust.org/> [Accessed 31st December 2018].
106. Fern L, Whelan J. National Cancer Research Institute Teenage and Young Adult Clinical Studies Group: the United Kingdom approach to research. International perspectives on AYAO, Part 4. *Journal of Adolescent and Young Adult Oncology*. 2013;2(4):161-166.
107. Aldiss S, Fern L, Phillips B, Gibson F, on behalf of the Teenage and Young Adult Cancer Priority Setting Partnership Steering Group. *Teenage and Young Adult Cancer: Research Priorities. Final Report of the James Lind Alliance Priority Setting Partnership*. 2018. Available from: <http://www.jla.nihr.ac.uk/priority-setting-partnerships/teenage-and-young-adult-cancer/> [Accessed 31st December 2018].
108. Ghandour R, Overpeck M, Huang Z, Kogan M, Scheidt P. Headache, stomachache, backache, and morning fatigue among adolescent girls in the United States: associations with behavioral, sociodemographic, and environmental factors. *Archives of Pediatric Adolescent Medicine*. 2004;158(8):797-803.
109. Rhee H. Relationships between physical symptoms and pubertal development. *Journal of Pediatric Health Care*. 2005;19(2):95-103.
110. Ter Wolbeek M, Van Doornen L, Kavelaars A, Heijnen C. Predictors of persistent and new onset fatigue. *Pediatrics*. 2008;121:449-457.
111. Ter Wolbeek M, van Doornen L, Kavelaars A, Tersteeg-Kamperman M, Heijnen C. Fatigue, depressive symptoms, and anxiety from adolescence up to young adulthood: a longitudinal study. *Brain Behaviour Immunity*. 2011;25(6):1249-1255.
112. Fukuda K, Straus S, Hickie I, Sharpe M, Dobbins J, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Internal Medicine*. 1994;121:953-959.
113. Rimes K, Goodman R, Hotopf M, Wessely S, Meltzer H, et al. Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: a prospective community study. *Pediatrics*. 2007;119(3):e603–e609.
114. Norris T, Collin S, Tilling K, Nuevo R, Stansfeld S, et al. Natural course of chronic fatigue syndrome/myalgic encephalomyelitis in adolescents. *Archives of Disease in Childhood*. 2017;102:522-528.
115. Bakken IJ, Tveito K, Gunnes N, Ghaderi S, Stoltenberg C, et al. Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: a population-based registry study from Norway 2008-2012. *BMC Medicine*. 2014;12(1):167.
116. Crowley S, Acebo C, Carskadon M. Sleep, circadian rhythms, and delayed phase in adolescence. *Sleep Medicine*. 2007;8:602-612.
117. Dahl R, Lewin D. Pathways to adolescent health sleep regulation and behavior. *Journal of Adolescent Health*. 2002;31(Suppl 6):175-184.

118. Chang A, Aeschbach D, Duffy J, Czeisler C. Evening use of light-emitting eReaders negatively affects sleep, circadian timing and next-morning alertness. *Proceedings of the National Academy of Sciences*. 2015;112(4):1232-1237.
119. Hysing M, Pallesen S, Stormark K, Jakobsen R, Jundervold A, et al. Sleep and use of electronic devices in adolescence: results from a large population-based study. *British Medical Journal Open*. 2015;5:e006748.
120. Enskär K, von Essen L. Prevalence of aspects of distress, coping, support and care among adolescents and young adults undergoing and being off cancer treatment. *European Journal of Oncology Nursing*. 2007;11(5):400-408.
121. Baggott C, Cooper B, Marina N, Matthay K, Miaskowski C. Symptom cluster analyses based on symptom occurrence and severity ratings among pediatric oncology patients during myelosuppressive chemotherapy. *Cancer Nursing*. 2012;35(1):19-28.
122. Nowe E, Stobel-Richter Y, Sender A, Leuteritz K, Friedrich M, et al. Cancer-related fatigue in adolescents and young adults: a systematic review of the literature. *Critical Reviews in Oncology-Hematology*. 2017;118:63-69.
123. Perdikaris P, Merkouris A, Patiraki E, Tsoumakas K, Vasilatou-Kosmidis E, et al. Evaluating cancer related fatigue during treatment according to children's, adolescents' and parents' perspectives in a sample of Greek young patients. *European Journal of Oncology Nursing*. 2009;13(5):399-408.
124. Winters-Stone K, Bennett JM, Nail L, Schwartz A. Strength, physical activity and age predict fatigue in older breast cancer survivors. *Oncology Nursing Forum*. 2008;35(5):815-821.
125. Erickson JM, Beck SL, Christian B, Dudley WN, Hollen PJ, et al. Patterns of fatigue in adolescents receiving chemotherapy. *Oncology Nursing Forum*. 2010;37(4):444-455.
126. Langeveld N, Ubbink M, Smets E. 'I don't have any energy': the experience of fatigue in young adult survivors of childhood cancer. *European Journal of Oncology Nursing*. 2000;4(1):20-28.
127. Hinds P, Hockenberry M. Developing a research program on fatigue in children and adolescents diagnosed with cancer. *Journal of Pediatric Oncology Nursing*. 2001;18(2(supp 1)):3-12.
128. Hinds PS, Hockenberry M, Rai SN, Zhang L, Razzouk BI, et al. Nocturnal awakenings, sleep environment interruptions, and fatigue in hospitalized children with cancer. *Oncology Nursing Forum*. 2007;34(2):393-402.
129. Hinds PS, Hockenberry M, Tong X, Gattuso JS, McCarthy K, et al. Validity and reliability of a new instrument to measure cancer-related fatigue in adolescents. *Journal of Pain and Symptom Management*. 2007;34(6):607-618.
130. Hinds PS, Hockenberry-Eaton M, Gilger E, Kline N, Burleson C, et al. Comparing patient, parent, and staff descriptions of fatigue in pediatric oncology patients. *Cancer Nursing*. 1999;22(4):277-289.
131. Gibson F, Mulhall AB, Richardson A, Edwards JL, Ream E, et al. A phenomenologic study of fatigue in adolescents receiving treatment for cancer. *Oncology Nursing Forum*. 2005;32(3):651-660.

132. Hamre H, Zeller B, Kanellopoulos A, Kiserud CE, Aakhus S, et al. High prevalence of chronic fatigue in adult long-term survivors of acute lymphoblastic leukemia and lymphoma during childhood and adolescence. *Journal of Adolescent and Young Adult Oncology* 2013;2(1):2-9.
133. Hooke M, Garwick A, Gross C. Fatigue and physical performance in children and adolescents receiving chemotherapy. *Oncology Nursing Forum*. 2011;38(6):649-657.
134. Hockenberry MJ, Hooke MC, Gregurich M, McCarthy K. Carnitine plasma levels and fatigue in children/adolescents receiving cisplatin, ifosfamide, or doxorubicin. *Journal of Pediatric Hematology/Oncology*. 2009;31:664-669.
135. Craig P, Dieppe P, Macintyre S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *British Medical Journal*. 2008;337:a1655.
136. Furness C, Smith L, Morris E, Brocklehurst C, Daly S, et al. Cancer patient experience in the teenage and young adult population - key issues and trends over time: an analysis of the United Kingdom National Cancer Patient Experience Surveys. *Journal of Adolescent and Young Adult Oncology*. 2017;3:450-458.
137. Brady L, Templeton L, Toner P, Watson J, Evans D, et al. Involving young people in drug and alcohol research. *Drugs and Alcohol Today*. 2018;18(1):28-38.
138. Lowes L, Robling M, Bennert K, Crawley C, Hambly H, et al. Involving lay and professional stakeholders in the development of a research intervention for the DEPICTED Study. *Health Expectations*. 2011;14(3):250-260.
139. Bandura A. Self-efficacy: towards a unifying theory of behavioral change. *Psychology Reviews*. 1977;84(2):191-215.
140. Bandura A. Self-efficacy. In Ramachaudran V (Ed.) *Encyclopedia of human behavior*. New York: Academic Press; 1994. p.71-81.
141. Bandura A. *Social Foundations of Thought and Action: A Social Cognitive Theory*. Prentice Hall: Englewood Cliffs, NJ; 1986.
142. Náfrádi L, Nakamoto K, Schulz P. Is patient empowerment the key to promote adherence? A systematic review of the relationship between self-efficacy, health locus of control and medication adherence. *PLoS One*. 2017;12(10):e0186458.
143. Jones F, Riazi A. Self-efficacy and self-management after stroke: a systematic review. *Disability and Rehabilitation*. 2011;33(10):797-810.
144. Bertholet N, Gaume J, Faouzi M, Gmel G, Daepfen J. Predictive value of readiness, importance, and confidence in ability to change drinking and smoking. *BMC Public Health*. 2012;12:708.
145. Hoffman A. Enhancing self-efficacy for optimized patient outcomes through the Theory of Symptom Self-Management. *Cancer Nursing*. 2013;36(1):E16-E26.
146. Hoffman A, von Eye A, Gift A, Given B, Given C, et al. Testing a theoretical model of perceived self-efficacy for cancer-related fatigue self-management and optimal physical functional status. *Nursing Research*. 2009;58(1):32-41.

147. Porter L, Keefe F, Garst J, McBride C, Baucom D. Self-efficacy for management pain, symptoms and function in patients with lung cancer and their informal caregivers. *Pain*. 2008;137(2):306-315.
148. Hoffman A, von Eye A, Gift A, Given B, Given C, et al. The development and testing of an instrument for perceived self-efficacy for fatigue self-management. *Cancer Nursing*. 2011;34(3):167-175.
149. Foster C, Fenlon D. Recovery and self-management support following primary cancer treatment. *British Journal of Cancer*. 2011;105:S21-S28.
150. Foster C, Breckons M, Cotterell P, Barbosa D, Calman L, et al. Cancer survivors' self-efficacy to self-manage in the year following primary treatment. *Journal of Cancer Survivorship*. 2015;9:11-19.
151. Richardson G, Bojke C, Kennedy A, Reeves D, Bower P, et al. What outcomes are important to patients with long term conditions. *Value in Health*. 2009;12(2):331-339.
152. Cramm J, Strating, Nieboer A. The importance of general self-efficacy for the quality of life of adolescents with diabetes or juvenile rheumatoid arthritis over time: a longitudinal study among adolescents and parents. *Frontiers in Pediatrics*. 2013;1:40.
153. Lorig K, Ritter P, Stewart A, Sobel D, Brown B, et al. Chronic disease self-management program: 2-year health status and health care utilization outcomes. *Medical Care*. 2001;39(11):1217-1223.
154. Gallagher M, Payne L, White K, Shear K, Woods S, et al. Mechanisms of change in cognitive behavioural therapy for panic disorder: the unique effects of self-efficacy and anxiety sensitivity. *Behavioural Research and Therapies*. 2013;51(11):767-777.
155. Brown L, Wiley J, Wolitzky-Taylor K, Roy-Byrne P, Sherbourne C, et al. Changes in self-efficacy and outcomes-expectancy as predictors of anxiety outcomes from the CALM study. *Depression and Anxiety*. 2014;31(8):678-689.
156. Foster C, Grimmer C, May CM, Ewings S, Myall M, et al. A web-based intervention (RESTORE) to support self-management of cancer-related fatigue following primary cancer treatment: a multi-centre proof of concept randomised controlled trial. *Supportive Care in Cancer*. 2016;24(6):2445-2453.
157. Hoffman A, Brintnall R, Given B, von Eye A, Jones L, et al. Using perceived self-efficacy to improve fatigue and fatigability in post-surgical lung cancer patients: a pilot randomized controlled trial. *Cancer Nursing*. 2017;40(1):1-12.
158. Maddison R, Prapavessis H, Armstrong G, Hill C. A modeling intervention in heart failure. *Annals of Behavioural Medicine*. 2008;36(1):64-69.
159. De Silva M, Breuer E, Lee L, Asher L, Chowdhary N, et al. Theory of Change: a theory-driven approach to enhance the Medical Research Council's framework for complex interventions. *Trials*. 2014;15:267.
160. Erickson JM. Fatigue in adolescents with cancer: a review of the literature. *Clinical Journal of Oncology Nursing*. 2004;8(2):139-145.
161. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer*. 2002;94:2090-2106.

162. Daniëls L, Oerlemans S, Krol A, van de Poll-Franse L, Creutzberg C. Persisting fatigue in Hodgkin lymphoma survivors: a systematic review. *Annals of Hematology*. 2013;92(8):1023-1032.
163. Erickson J, Macpherson C, Ameringer S, Baggott C, Linder L, et al. Symptoms and symptom clusters in adolescents receiving cancer treatment: a review of the literature. *International Journal of Nursing Studies*. 2013;50(6):847-869.
164. McMillan E, Newhouse I. Exercise is an effective treatment modality for reducing cancer-related fatigue and improving physical capacity in cancer patients and survivors: a meta-analysis. *Applied Physiology, Nutrition and Metabolism*. 2011;36(6):892-903.
165. Chang C, Mu P, Jou S, Wong T, Chen Y. Systematic review and meta-analysis of nonpharmacological interventions for fatigue in children and adolescents with cancer. *Worldviews Evidence Based Nursing*. 2013;10(4):208-217.
166. Gough D. Weight of Evidence: a framework for the appraisal of the quality and relevance of evidence. *Research Papers in Education*. 2007;22(2):213-228.
167. Wesley K, Zelikovsky N, Schwartz LA. Physical symptoms, perceived social support, and affect in adolescents with cancer. *Journal of Psychosocial Oncology*. 2013;31(4):451-467.
168. Daniel LC, Brumley LD, Schwartz LA. Fatigue in adolescents with cancer compared to healthy adolescents. *Pediatric Blood and Cancer*. 2013;60:1902-1907.
169. Hamre H, Zeller B, Kanellopoulos A, Ruud E, Fossa SD, et al. Serum cytokines and chronic fatigue in adults surviving after childhood leukemia and lymphoma. *Brain, Behavior, and Immunity*. 2013;30:80-87.
170. Yeh C, Chiang Y, Chien L, Lin L, Yang C, et al. Symptom clustering in older Taiwanese children with cancer. *Oncology Nursing Forum*. 2008;35(2):273-281.
171. Yeh C, Wang C, Chiang Y, Lin L, Chien L. Assessment of symptoms reported by 10- to 18-year-old cancer patients in Taiwan. *Journal of Pain and Symptom Management*. 2009;38(5):738-746.
172. Erickson JM, Beck SL, Christian BR, Dudley W, Hollen PJ, et al. Fatigue, sleep-wake disturbances, and quality of life in adolescents receiving chemotherapy. *Journal of Pediatric Hematology/Oncology*. 2011;33:e17-e25.
173. Hockenberry MJ, Hooke MC, Gregurich M, McCarthy K, Sambuco G, et al. Symptom clusters in children and adolescents receiving cisplatin, doxorubicin, or ifosfamide. *Oncology Nursing Forum*. 2010;37(1):E16-27.
174. Hockenberry M, Hooke M, McCarthy K, Gregurich M. Sickness behavior clustering in children with cancer. *Journal of Pediatric Oncology Nursing*. 2011;28(5):263-272.
175. Hedström M, Haglund K, Skolin I, von Essen L. Distressing events for children and adolescents with cancer: child, parent, and nurse perceptions. *Journal of Pediatric Oncology Nursing*. 2003;20(3):120-132.
176. Hedström M, Ljungman G, Von Essen L. Perceptions of distress among adolescents recently diagnosed with cancer. *Journal of Pediatric Hematology/Oncology*. 2005;27:15-22.
177. Hedström M, Skolin I, von Essen L. Distressing and positive experiences and important aspects of care for adolescents treated for cancer. Adolescent and nurse perceptions. *European Journal of Oncology Nursing*. 2004;8:6-17.

178. Collins JJ, Byrnes ME, Dunkel IJ, Lapin J, Nadel T, et al. The measurement of symptoms in children with cancer. *Journal of Pain and Symptom Management*. 2000;19:363-377.
179. Chiang Y, Yeh C, Wang K, Yang C. The experience of cancer-related fatigue in Taiwanese children. *European Journal of Cancer Care* 2009;18(1):43-49.
180. Hinds P, Quargnenti A, Bush A, Pratt C, Fairclough D, et al. An evaluation of the impact of a self-care coping intervention on psychological and clinical outcomes in adolescents with newly diagnosed cancer. *European Journal of Oncology Nursing*. 2000;4:6-17.
181. Hinds P, Nuss S, Ruccione K, Withycombe J, Jacobs S, et al. PROMIS pediatric measures in pediatric oncology: valid and clinically feasible indicators of patient-reported outcomes. *Pediatric Blood and Cancer*. 2013;60:402-408.
182. Hinds P, Hockenberry M, Gattuso J, Srivastava D, Tong X, et al. Dexamethasone alters sleep and fatigue in pediatric patients with acute lymphoblastic leukemia. *Cancer*. 2007;110:2321-2330.
183. Lai J, Cella D, Kupst M, Holm S, Kelly M, et al. Measuring fatigue for children with cancer: development and validation of the pediatric functional assessment of chronic illness therapy-fatigue (pedsFACIT-F). *Journal of Pediatric Hematology/Oncology*. 2007;29:471-479.
184. Mandrell B, Yang J, Hooke M, Wang C, Gattuso J, et al. Psychometric and clinical assessment of the 13-Item reduced version of the Fatigue Scale-Adolescent instrument. *Journal of Pediatric Oncology Nursing*. 2011;28(5):287-294.
185. McLoone J, Wakefield C, Butow P, Fleming C, Cohn RJ. Returning to school after adolescent cancer: a qualitative examination of Australian survivors' and their families' perspectives. *Journal of Adolescent and Young Adult Oncology*. 2011;1:87-94.
186. Meeske K, Katz ER, Palmer SN, Burwinkle T, Varni JW. Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. *Cancer*. 2004;101:2116-2125.
187. Mulrooney DA, Ness KK, Neglia JP, Whitton JA, Green DM, et al. Fatigue and sleep disturbance in adult survivors of childhood cancer: a report from the childhood cancer survivor study (CCSS). *Sleep*. 2008;31:271-281.
188. Smith AW, Bellizzi KM, Zebrack B, Chen VW, Neale AV, et al. Health-related quality of life of adolescent and young adult patients with cancer in the United States: the adolescent and young adult health outcomes and patient experience study. *Journal of Clinical Oncology*. 2013;31(17):2136-2145.
189. Ameringer S, Erickson J, Macpherson C, Stegenga K, Linder LA. Symptoms and symptom clusters identified by adolescents and young adults with cancer using a symptom heuristics App. *Research in Nursing and Health*. 2015;38(6):436-448.
190. Macpherson C, Hooke M, Friedman D, Campbell K, Withycombe J, et al. Exercise and fatigue in adolescent and young adult survivors of Hodgkin Lymphoma: a report from the Children's Oncology Group. *Journal of Adolescent and Young Adult Oncology*. 2015;4(3):137-140.
191. Calaminus G, Dorffel W, Baust K, Teske C, Riepenhausen M, et al. Quality of life in long-term survivors following treatment for Hodgkin's disease during childhood and adolescence in the German multicentre studies between 1978 and 2002. *Supportive Care in Cancer*. 2014;22(6):1519-1529.

192. Adams MJ, Lipsitz SR, Colan SD, Tarbell NJ, Treves ST, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *Journal of Clinical Oncology*. 2004;22:3139-3148.
193. Zupanec S, Jones H, Stremmler R. Sleep habits and fatigue of children receiving maintenance chemotherapy for ALL and their parents. *Journal of Pediatric Oncology Nursing*. 2010;27(4):217-228.
194. Aksnes LH, Hall KS, Jebsen N, Fossa SD, Dahl AA. Young survivors of malignant bone tumours in the extremities: a comparative study of quality of life, fatigue and mental distress. *Supportive Care in Cancer*. 2007;15:1087-1096.
195. Azizi N, Mansour L, Tahmassian K, Mosavi F. Determining, ranking and comparing treatment stressors in children and adolescents with cancer in Tehran. *Iranian Journal of Cancer Prevention*. 2012;5:138-143.
196. Ameringer S, Shockey DP, Dillon R. A pilot exploration of symptom trajectories in adolescents with cancer during chemotherapy. *Cancer Nursing*. 2013;36(1):60-71.
197. Ream E, Gibson F, Edwards J, Seption B, Mulhall A, et al. Experience of fatigue in adolescents living with cancer. *Cancer Nursing*. 2006;29(4):317-326.
198. Gibson F, Edwards J, Seption B, Richardson A. Cancer-related fatigue in children and young people: survey of healthcare professionals' knowledge and attitudes. *European Journal of Oncology Nursing*. 2006;10(4):311-316.
199. Whitsett SF, Gudmundsdottir M, Davies B, McCarthy P, Friedman D. Chemotherapy-related fatigue in childhood cancer: correlates, consequences, and coping strategies. *Journal of Pediatric Oncology Nursing*. 2008;25(2):86-96.
200. Nunes M, Jacob E, Adlard K, Secola R, Nascimento L. Fatigue and sleep experiences at home in children and adolescents with cancer. *Oncology Nursing Forum*. 2015;42(5):498-506.
201. Hooke MC, McCarthy K, Taylor O, Hockenberry MJ. Fatigue and carnitine levels over multiple cycles of chemotherapy in children and adolescents. *European Journal of Oncology Nursing*. 2015;19(1):7-12.
202. Portenoy RK, Thaler HT, Kornblith AB, Lepore JM, Friedlander-Klar H. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *European Journal of Cancer*. 1994;30A(9):1326-1336.
203. Chang V, Hwang S, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. *Cancer*. 2000;88(9):2164-2171.
204. Aaronson N, Ahmedzai S, Berman B, Bullinger M, Cull A, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute*. 1993;85(5):365-376.
205. McCorkle R. The measurement of symptom distress. *Seminars in Oncology Nursing*. 1987;3:248-256.
206. Hughes R, Holland L, Zanino D, Link E, Michael N, et al. Prevalence and intensity of pain and other physical and psychological symptoms in adolescents and young adults diagnosed with cancer on referral to a palliative care service. *Journal of Adolescent and Young Adult Oncology*. 2015;4(2):70-75.



207. Baggott C, Gibson F, Coll B, Kletter R, Zeltzer P, et al. Initial evaluation of an electronic symptom diary for adolescents with cancer. *JMIR Research Protocols* 2012;1(2):e23.
208. Corey AL, Haase JE, Azzouz F, Monahan PO. Social support and symptom distress in adolescents/young adults with cancer. *Journal of Pediatric Oncology Nursing*. 2008;25:275-284.
209. Enskar K CM, Golsater M, Hamrin E. Symptom distress and life situation in adolescents with cancer. *Cancer Nursing*. 1997;20(1):23-33.
210. Walker A, Gedaly-Duff V, Miaskowski C, Nail L. Differences in symptom occurrence, frequency, intensity, and distress in adolescents prior to and one week after the administration of chemotherapy. *Journal of Pediatric Oncology Nursing*. 2010;27:259-265.
211. Williams PD, Williams AR, Kelly KP, Dobos C, Gieseck A, et al. A symptom checklist for children with cancer: the Therapy-Related Symptom Checklist-Children. *Cancer Nursing*. 2012;35:89-98.
212. Baggott C, Dodd M, Kennedy C, Marina N, Matthay KK, et al. Changes in children's reports of symptom occurrence and severity during a course of myelosuppressive chemotherapy. *Journal of Pediatric Oncology Nursing*. 2010;27:307-315.
213. Miller E, Jacob E, Hockenberry MJ. Nausea, pain, fatigue, and multiple symptoms in hospitalized children with cancer. *Oncology Nursing Forum*. 2011;38(5):E382-393.
214. Atay S, Conk Z, Bahar Z. Identifying symptom clusters in paediatric cancer patients using the Memorial Symptom Assessment Scale. *European Journal of Cancer Care* 2012;21(4):460-468.
215. Hinds P, Hockenberry M, Rai S, Zhang L, Razzouk B, et al. Clinical field testing of an enhanced-activity intervention in hospitalized children with cancer. *Journal of Pain and Symptom Management*. 2007;33:686-697.
216. Orsey AD, Wakefield DB, Cloutier MM. Physical activity (PA) and sleep among children and adolescents with cancer. *Pediatric Blood and Cancer*. 2013;60:1908-1913.
217. Hockenberry M, Hinds P, Barrera P, Bryant R, Adams-McNeill J, et al. Three instruments to assess fatigue in children with cancer: the child, parent and staff perspectives. *Journal of Pain and Symptom Management*. 2003;25(4):319-328.
218. Keats MR, Culos-Reed SN. A community-based physical activity program for adolescents with cancer (project TREK): program feasibility and preliminary findings. *Journal of Pediatric Hematology/Oncology*. 2008;30:272-280.
219. Arroyave WD, Clipp EC, Miller PE, Jones LW, Ward DS, et al. Childhood cancer survivors' perceived barriers to improving exercise and dietary behaviors. *Oncology Nursing Forum*. 2008;35(1):121-130.
220. Cassano J, Nagel K, O'Mara L. Talking with others who 'just know': perceptions of adolescents with cancer who participate in a teen group. *Journal of Paediatric Oncology Nursing*. 2008;25(4):193-199.
221. Griffith KC, Hart LK. Characteristics of adolescent cancer survivors who pursue postsecondary education. *Cancer Nursing*. 2000;23(6):468-476.
222. Hinds P, Quargnenti A, Wentz T. Measuring symptom distress in adolescents with cancer. *Journal of Pediatric Oncology Nursing*. 1992;9:84-86.

223. Lockwood R, Smith C. Physical activity during and after treatment for cancer: what do teenagers and young adults want from a service? Presented at: *Teenage Cancer Trust 7th International Conference on Teenage and Young Adult Cancer Medicine*. 2012. London, UK.
224. Diorio C, Schechter T, Lee M, O'Sullivan C, Hesser T, et al. A pilot study to evaluate the feasibility of individualized yoga for inpatient children receiving intensive chemotherapy. *BMC Complementary and Alternative Medicine*. 2015;15:2.
225. Ruccione K, Lu Y, Meeske K. Adolescents' psychosocial health-related quality of life within 6 months after cancer treatment completion. *Cancer Nursing*. 2013;36:E61-E72.
226. Pan H, Wu L, Wen S. Quality of life and its predictors among children and adolescents with cancer. *Cancer Nursing*. 2017;40(5):343-351.
227. Rosenhagen A, Bernhorster M, Vogt L, Weiss B, Senn A, et al. Implementation of structured physical activity in the pediatric stem cell transplantation. *Klinische Padiatrie*. 2011;223:147-151.
228. Atkinson M, Osborn M. A structured ten-week exercise intervention is associated with improvements in quality of life, fatigue, and functional status in adolescents and young adults with cancer. *Asia-Pacific Journal of Clinical Oncology*. 2012;8:213.
229. Jacobs S, Mowbray C, Cates LM, Baylor A, Gable C, et al. Pilot study of massage to improve sleep and fatigue in hospitalized adolescents with cancer. *Pediatric Blood & Cancer*. 2016;63(5):880-886.
230. Singer S, Kuhnt S, Zwerenz R, Eckert K, Hofmeister D, et al. Age- and sex-standardised prevalence rates of fatigue in a large hospital-based sample of cancer patients. *British Journal of Cancer*. 2011;105(3):445-451.
231. Bifulco G, De Rosa N, Tornesello ML, Piccoli R, Bertrando A, et al. Quality of life, lifestyle behavior and employment experience: a comparison between young and midlife survivors of gynecology early stage cancers. *Gynecologic Oncology*. 2012;124(3):444-451.
232. Sanford SD, Zhao F, Salsman J, Chang V, Wager L, et al. Symptom burden among young adults with breast or colorectal cancer. *Cancer*. 2014 120(15):2255-2263.
233. Kreissl S, Mueller H, Goergen H, Mayer A, Brillant C, et al. Cancer-related fatigue in patients with and survivors of Hodgkin's lymphoma: a longitudinal study of the German Hodgkin Study Group. *Lancet Oncology*. 2016;17(10):1453-1462.
234. Behringer K, Goergen H, Muller H, Thielen I, Brillant C, et al. Cancer-related fatigue in patients with and survivors of Hodgkin Lymphoma: the impact on treatment outcome and social reintegration. *Journal of Clinical Oncology*. 2016;34(36):4329-4337.
235. Geue K, Sender A, Schmidt R, Richter D, Hinz A, et al. Gender-specific quality of life after cancer in young adulthood: a comparison with the general population. *Quality of Life Research*. 2014;23(4):1377-1386.
236. de la Cruz M, Hui D, Parsons H, Bruera E. Placebo and nocebo effects in randomized double-blind clinical trials of agents for the therapy for fatigue in patients with advanced cancer. *Cancer*. 2010;116(3):766-774.
237. Gibson F, Garnett M, Richardson A, Edwards J, Sepion B. Heavy to carry: a survey of parents' and healthcare professionals' perceptions of cancer-related fatigue in children and young people. *Cancer Nursing*. 2005;28(1):27-35.

238. Grieser H, Vu M, Bedimo-Rung A, Neumark-Sztainer D, Moody J, et al. Physical activity attitudes, preferences and practices in African American, Hispanic and Caucasian girls. *Health Education and Behavior*. 2006;33(1):40-51.
239. Tomlinson D, Zupanec S, Jones H, O'Sullivan C, Hesser T, et al. The lived experience of fatigue in children and adolescents with cancer: a systematic review. *Supportive Care in Cancer*. 2016;24(8):3623-3631.
240. Lopes-Junior LC, Bomfim EO, Nascimento LC, Nunes MD, Pereira-da-Silva G, et al. Non-pharmacological interventions to manage fatigue and psychological stress in children and adolescents with cancer: an integrative review. *European Journal of Cancer Care*. 2016;25(6):921-935.
241. Curt G, Johnston P. Cancer fatigue: the way forward. *Oncologist*. 2003;8(Suppl 1):27-30.
242. Hoenemeyer T, Kaptchuk T, Mehta T, Fontaine K. Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. *Scientific Reports*. 2018;8(1):2784.
243. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database of Systematic Reviews*. 2012;11:CD006145.
244. Ibrahim E, Al-Homaidh A. Physical activity and survival after breast cancer diagnosis: meta-analysis of published studies. *Medical Oncology*. 2010;28(3):753-765.
245. Meyerhardt J, Giovannucci E, Holmes M, Chan A, Chan J, et al. Physical activity and survival after colorectal cancer diagnosis. *Journal of Clinical Oncology*. 2006;24:3527-3534.
246. Segal R, Reid R, Courneya K, Malone S, Parliament M, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *Journal of Clinical Oncology*. 2003;21:1653-1659.
247. Speck R, Courneya K, Masse L, Duval S, Schmitz K. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Journal of Cancer Survivorship*. 2010;4:87-100.
248. Holmes M, Chen W, Feskanich D, Kroenke C, Colditz G. Physical activity and survival after breast cancer diagnosis. *Journal of the American Medical Association*. 2005;293(20):2479-2486.
249. Park S, Kim Y, Kim S, Choi J, Lim H, et al. Impact of caregivers' unmet needs for supportive care on quality of terminal cancer care delivered and caregiver's workforce performance. *Supportive Care in Cancer*. 2010;18(6):699-706.
250. National Institute for Health and Care Excellence (NICE), *Guidance on cancer services improving supportive and palliative care for adults with cancer [CSG 4]*. 2004. Available from: <https://www.nice.org.uk/guidance/csg4> [Accessed 31st December 2018].
251. Grande G, Austin L, Ewing G, Leary N, Roberts C. Assessing the impact of a Carer Support Needs Assessment Tool (CSNAT) intervention in palliative home care: a stepped wedge cluster trial *British Medical Journal Supportive & Palliative Care*. 2017;7:326-334.
252. Kelley K, Clark BJ, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. *International Journal for Quality in Health Care*. 2003;15(3):261-266.
253. McPeake J, Bateson J, O'Neill A. Electronic surveys: how to maximise success. *Nurse Researcher*. 2013;21(3):24-26.

254. Scott A, Jeon S, Joyce C, Humphrey J, Kalb G, et al. A randomised trial and economic evaluation of the effect of response mode on response rate, response bias, and item non-response in a survey of doctors. *BMC Medical Research Methodology*. 2011;11:126.
255. Braithwaite D, Emery J, de Lusignan S, Sutton S. Using the internet to conduct surveys of health professions: a valid alternative? *Family Practice*. 2003;20(5):545-551.
256. Remillard M, Mazor K, Cutrona S, Gurwitz J, Tjia J. Systematic review of the use of online questionnaires among the geriatric population. *Journal of the American Geriatric Society*. 2014;62(4):696-705.
257. Horevoorts N, Vissers P, Mols F, Thongs M, van de Poll-Franse L. Response rates for patient-reported outcomes using web-based versus paper questionnaires: comparison of two invitation methods in older colorectal cancer patients. *Journal of Medical Internet Research*. 2015;17(5):e111.
258. Harlan L, Lynch C, Keegan T, Ikuko K, West M, et al. Recruitment and follow-up of adolescent and young adult cancer survivors: the AYA HOPE Study. *Journal of Cancer Survivorship*. 2011;5:305-314.
259. Pit S, Vo T, Pyakurel S. The effectiveness of recruitment strategies on general practitioner's survey response rates - a systematic review. *BMC Medical Research Methodology*. 2014;14:76.
260. Martins Y, Lederman R, Lowenstein C, Joffe S, Neville B, et al. Increasing response rates from physicians in oncology research: a structured literature review and data from a recent physician survey. *British Journal of Cancer*. 2012;106:1021-1026.
261. Edwards P, Roberts I, Clarke M, DiGuseppi C, Wentz R, et al. Methods to increase response to postal and electronic questionnaires. *Cochrane Database of Systematic Reviews*. 2009;3:MR000008.
262. Office of National Statistics (ONS), *Internet access - households and individuals*. 2018. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/householdcharacteristics/homeinternetandsocialmediausage/datasets/internetaccesshouseholdsandindividualsreferencetables> [Accessed 31st December 2018].
263. Office of National Statistics (ONS), *Internet users, UK: 2018*. 2018. Available from: <https://www.ons.gov.uk/businessindustryandtrade/itandinternetindustry/bulletins/internetusers/2018> [Accessed 31st December 2018].
264. de Boer A, van Lanschot J, Stalmeier P, van Sandick J, Hulscher J, et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? *Quality of Life Research*. 2004;13(2):311-320.
265. Huschka M, Mandrekar S, Schaefer P, Jett J, J. S. A pooled analysis of quality of life measures and adverse events data in North Central Cancer Treatment Group lung cancer clinical trials. *Cancer*. 2002;109(4):787-795.
266. National Institute of Healthcare Research (NIHR), *Good Clinical Practice (GCP) reference guide*. 2016. Available from: <https://www.nihr.ac.uk/our-research-community/documents/GCP%20Reference%20Guide.pdf> [Accessed 31st December 2018].
267. Kim H. Statistical notes for clinical researchers: assessing normal distribution using skewness and kurtosis. *Restorative Dentistry and Endodontics*. 2013;38(1):52-54.

268. Ward J. Hierarchical grouping to optimize an objective function. *Journal of the American Statistical Association*. 1963;58:236–244.
269. Austin P, Steyerberg E. The number of subjects per variable required in linear regression analyses. *Journal of Clinical Epidemiology*. 2015;68(6):627-6336.
270. Andrykowski M, Donovan K, Laronga C, Jacobsen P. Prevalence, predictors and characteristics of off treatment fatigue in breast cancer survivors. *Cancer*. 2010;116:5740-5748.
271. Courneya KS, Sellar CM, Stevinson C, McNeely ML, Peddle CJ, et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *Journal of Clinical Oncology*. 2009;27(27):4605-4612.
272. Day J, Berntzen B, Harden S, Williams S, Peoples S, et al. Physical disability and anxiety are independent predictors of fatigue in stable primary brain tumour patients. *Neurological Oncology*. 2015;17(Suppl 5):v176.
273. Hwang S, Chang V, Rue M, Kasimis B. Multidimensional independent predictors of cancer-related fatigue. *Journal of Pain and Symptom Management*. 2003;26(1):604-614.
274. Tranmer J, Heyland D, Dudgeon D, Groll D, Squires-Graham M, et al. Measuring the symptom experience of seriously ill cancer and noncancer hospitalized patients near the end of life with the Memorial Symptom Assessment Scale. *Journal of Pain and Symptom Management*. 2003;25(5):420-429.
275. Department of Health and Social Care, *Recognised, valued and supported: next steps for the Carers Strategy*. 2010. Available from: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/213804/dh\\_122393.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/213804/dh_122393.pdf) [Accessed 31st December 2018].
276. Kent E, Rowlands J, Northouse L, Litzelman K, Wen-Ying S, et al. Caring for caregivers and patients: research and clinical priorities for informal cancer caregiving. *Cancer*. 2016;122(13):1987–1995.
277. Passik S, Kirsh K. A pilot examination of the impact of cancer patients' fatigue on their spousal caregivers. *Palliative and Supportive Care*. 2005;3:273-279.
278. Parás-Bravo P, Paz-Zulueta M, Alonso-Blanco M, Salvadores-Fuentes P, Alconero-Camarero A, et al. Association among presence of cancer pain, inadequate pain control, and psychotropic drug use. *PLoS One*. 2017;12(6):e0178742.
279. Laugsand E, Jakobsen G, Kaasa S, Klepstad P. Inadequate symptom control in advanced cancer patients across Europe. *Supportive Care in Cancer*. 2011;19(12):2005-2014.
280. Fielding S, Maclennan G, Cook J, Ramsay C. A review of RCTs in four medical journals to assess the use of imputation to overcome missing data in quality of life outcomes. *Trials*. 2008;9(51):doi: 10.1186/1745-6215-1189-1151.
281. Décieux J, Mergener A, Marliese Neufang K, Sischka P. Implementation of the forced answering option within online surveys: do higher item response rates come at the expense of participation and answer quality? 2015;48:311-326.
282. Coulter A, Locock L, Ziebland S, Calabrese J. Collecting data on patient experience is not enough. *British Medical Journal*. 2014;348:15-17.

283. Nulty D. The adequacy of response rates to online and paper surveys: what can be done? *Assessment and Evaluation in Higher Education*. 2008;33(3):301-314.
284. Saunders C, Elliott M, Lyratzopoulos G, Abel G. Do differential response rates to patient surveys between organizations lead to unfair performance comparisons? Evidence from the English Cancer Patient Experience Survey. *Medical Care*. 2016;54(1):45-54.
285. Cook J, Dickinson H, Eccles M. Response rates in postal surveys of healthcare professionals between 1996 and 2005: An observational study. *BMC Health Services Research*. 2009;9:160.
286. Dunlop S, Freeman B, Jones S. Marketing to youth in the digital age: the promotion of unhealthy products and health promoting behaviours on social media. *Media and Communication*. 2016;4(3):35-49.
287. Carr R, Whiteson M, Edwards M, Morgan S. Young adult cancer services in the UK: the journey to a national network. *Clinical Medicine*. 2013;13:258-262.
288. Van Mol C. Improving web survey efficiency: the impact of an extra reminder and reminder content on web survey response. *International Journal of Social Research Methodology*. 2017;20(4):317-327,.
289. Christensen A, Elkholt O, Kristensen P, Larsen F, Vinding A, et al. The effect of multiple reminders on response patterns in a Danish health survey *European Journal of Public Health*. 2015;25(1):156–161.
290. Morton S, Bandara D, Robinson E, Atatoa-Carr P. In the 21st Century, what is an acceptable response rate? *Australian and New Zealand Journal of Public Health*. 2012;36(2):106-108.
291. Mealing N, Banks E, Jorm L, Steel D, Clements M, et al. Investigation of relative risk estimates from studies of the same population with contrasting response rates and designs. *BMC Medical Research Methodology*. 2010;10:26.
292. Sullivan G, Artino Jr. A. Analyzing and interpreting data from Likert-type scales. *Journal of Graduate Medical Education*. 2013;5(4):541-542.
293. Groves R, Presser S, Dipko S. The role of topic interest in survey participation decisions *Public Opinion Quarterly*. 2004;68(1):2-31.
294. Sedgewick P. Multiple hypothesis testing and Bonferroni's correction. *British Medical Journal*. 2014;349:a6284.
295. Haverman L, Limperg P, van Oers H, van Rossum M, Maurice-Stam H, et al. Psychometric properties and Dutch norm data of the PedsQL Multidimensional Fatigue Scale for Young Adults. *Quality of Life Research*. 2014;23:2841-2847.
296. Taddeo D, Egedy M, Frappier J-Y. Adherence to treatment in adolescents. *Paediatric Child Health*. 2008;13(1):19-24.
297. Bond C, Aiken L, Somerville S. The health belief model and adolescents with insulin-dependent diabetes mellitus. *Health Psychology*. 1992;11(3):190-198.
298. Becker WC, Dorflinger L, Edmond SN, Islam L, Heapy AA, et al. Barriers and facilitators to use of non-pharmacological treatments in chronic pain. *BMC Family Practice*. 2017;18(1):41-41.

299. Goedendorp M, Gielissen M, Verhagen C, Bleijenberg G. Psychosocial interventions for reducing fatigue during cancer treatment in adults. *Cochrane Database of Systematic Reviews*. 2009;1:CD006953.
300. Myall M, May CR, Grimmett C, May CM, Calman L, et al. RESTORE: an exploratory trial of a web-based intervention to enhance self-management of cancer-related fatigue: findings from a qualitative process evaluation. *BMC Medical Informatics and Decision Making*. 2015;15:94.
301. Michie S, Brown J, Geraghty A, Miller SM, Yardley L, et al. Development of StopAdvisor: a theory-based interactive internet-based smoking cessation intervention. *Translational and Behavioural Medicine*. 2012;2(3):263-267.
302. Foster C, Calman L, Grimmett C, Breckons M, Cotterell P, et al. Managing fatigue after cancer treatment: development of RESTORE, a web-based resource to support self-management. *Psycho-Oncology*. 2015;24(8):940-949.
303. Dumith S, Gigante D, Domingues M, Kohl H, Samuel C. Physical activity change during adolescence: a systematic review and a pooled analysis *International Journal of Epidemiology*. 2011;40(3):685-698.
304. Badr H, Chandra J, Paxton R, Ater J, Urbauer D, et al. Health-related quality of life, lifestyle behaviors, and intervention preferences of survivors of childhood cancer. *Journal of Cancer Survivorship*. 2013;7(4):523-534.
305. Keats MR, Culos-Reed S, Courneya K, McBride C. An examination of physical activity behaviors in a sample of adolescent cancer survivors. *Journal of Pediatric Oncology Nursing*. 2006;23(3):135-142.
306. Peters D, Adam T, Alonge O, Agyepong I, Tran N. Implementation research: what it is and how to do it. *British Medical Journal*. 2013;347(f6753).
307. Mallonee S, Fowler C, Istre G. Bridging the gap between research and practice: a continuing challenge. *Injury Prevention*. 2006;12(6):357-359.
308. Mulley A, Richards T, Abbasi K. Delivering health with integrity of purpose. *British Medical Journal*. 2015;351:h4448.
309. Janamian T, Crossland L, Wells L. On the road to value co-creation in health care: the role of consumers in defining the destination, planning the journey and sharing the drive. *Medical Journal of Australia*. 2016;204(Suppl 7):S12-14.
310. Bate P, Robert G. Experience-based design: from redesigning the system around the patient to co-designing services with the patient. *Quality and Safety in Health Care*. 2006;15(5):307-310.
311. Robert G. Participatory action research: using experience-based co-design to improve the quality of healthcare services. In: Ziebland S, Coulter A, Calabrese J, Locock L (eds.) *Understanding and Using Experiences: Improving Patient Care*. Oxford University Press, Oxford; 2013. p.138-149.
312. Donetto S, Tsianakas V, Robert G. King's College London, *Using Experience-Based Co-Design to improve the quality of healthcare: mapping where we are now and establishing future direction*. 2014. Available from: <https://www.kcl.ac.uk/nursing/research/nnru/publications/Reports/EBCD-Where-are-we-now-Report.pdf> [Accessed 31st December 2018].
313. Springham N, Robert G. Experience based co-design reduces formal complaints on an acute mental health ward. *British Medical Journal Open Quality*. 2015;4:u209153.w203970.

314. Robert G, Cornwell J, Locock L, Purushotha A, Sturmey G, et al. Patients and staff as codesigners of healthcare services. *British Medical Journal*. 2015;350:g7714.
315. Ream E, Tsianakas V, Verity R, Oakley C, Murrells T, et al. King's College London, *Enhancing the role of carers in the outpatients chemotherapy setting: a participatory action research project: final report*. 2013. Available from: <http://www.dimblebycancercare.org/wp-content/uploads/2017/04/Emma-Ream-Final-Report-28-08-2013.pdf> [Accessed 4th September 2018].
316. Tsianakas V, Robert G, Richardson A, Verity R, Oakley C, et al. Enhancing the experience of carers in the chemotherapy outpatient setting: an exploratory randomised controlled trial to test impact, acceptability and feasibility of a complex intervention co-designed by carers and staff. *Supportive Care in Cancer*. 2015;23(10):3069-3080.
317. Greenhalgh T, Annandale E, Ashcroft R, Barlow J, Black N, et al. An open letter to The BMJ editors on qualitative research. *British Medical Journal*. 2016;352:i563.
318. Noyes J. Never mind the qualitative feel the depth! The evolving role of qualitative research in Cochrane intervention reviews. *Journal of Research in Nursing*. 2010;15(6):525-534.
319. Farquhar M, Ewing G, Booth S. Using mixed methods to develop and evaluate complex interventions in palliative care research. *Palliative Medicine*. 2011;25(8):748-757.
320. Guest G, Namey E, Taylor J, Eley N, McKenna K. Comparing focus groups and individual interviews: findings from a randomized study. *International Journal of Social Research Methodology*. 2017;20(6):693-708.
321. Lambert S, Loiselle C. Combining individual interviews and focus groups to enhance data richness. *Journal of Advanced Nursing*. 2008;62(2):228-237.
322. Kendall M, Murray S, Carduff E, Worth A, Harris F, et al. Use of multiperspective qualitative interviews to understand patients' and carers' beliefs, experiences, and needs. *British Medical Journal*. 2009;339:b4122.
323. Hermanowicz J. Longitudinal Qualitative Research. In: Shanahan M, Mortimer J, Kirkpatrick Johnson M. (eds.) *Handbook of the Life Course*. Handbooks of Sociology and Social Research. Springer International Publishing. 2016. p.419-513.
324. Ritchie J, Lewis J. *Qualitative research practice: a guide for social science students and researchers*. 2nd edition. London: Sage; 2014.
325. Gale N, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology*. 2013;13 (117); DOI: 10.1186/1471-2288-13-117.
326. Kenten C, Martins A, Fern LA, Gibson F, Lea S, et al. Qualitative study to understand the barriers to recruiting young people with cancer to BRIGHTLIGHT: a national cohort study in England. *British Medical Journal Open*. 2017;7(11):e018291.
327. De Raaf P, de Klerk C, van der Rijt C. Elucidating the behaviour of physical fatigue and mental fatigue in cancer patients: a review of the literature. *Psycho-Oncology*. 2013;22:1919-1929.
328. Stein KJ, Jacobsen P, Blanchard C, Thors C. Further validation of the multidimensional fatigue symptom inventory-short form. *Journal of Pain and Symptom Management*. 2004;27:14-23.



329. Broekel J, Jacobsen P, Horton J, Balducci L, Lyman G. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology*. 1998;16:1689-1696.
330. Ritterband L, Bailey E, Thorndike F, Lord H, Farrell L, et al. Initial evaluation of an internet intervention to improve the sleep of cancer survivors with insomnia. *Psycho-Oncology*. 2012;21:695-705.
331. Lin L, Sidani J, Shensa A, Radovic A, Miller E, et al. Association between social media use and depression among U.S. young adults. *Depression and Anxiety*. 2016;33:323-331.
332. Primack B, Shensa A, Sidani J, Whaite E, Lin L, et al. Social media use and perceived social isolation among young adults in the U.S. *American Journal of Preventative Medicine*. 2017;53(1):1-8.
333. Sadeghi E, Gozali N, Tabrizi F. Effects of energy conservation strategies on cancer related fatigue and health promotion lifestyle in breast cancer survivors: a randomized control trial. *Asia-Pacific Journal of Cancer Prevention*. 2016;17(10):4783-4790.
334. Antcliff D, Keeley P, Campbell M, Woby S, McGowan L. Exploring patients' opinions of activity pacing and a new activity pacing questionnaire for chronic pain and/or fatigue: a qualitative study. *Physiotherapy*. 2016;102(3):300-307.
335. Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. *Health Psychology*. 2008;27(3):379-387.
336. Wolever R, Simmons L, Sforzo G, Dill D, Kaye M, et al. A systematic review of the literature on health and wellness coaching: defining a key behavioural intervention in health care. *Global Advances in Health and Medicine*. 2013;4(2):1-19.
337. Health Education East of England, *Health Coaching for Behaviour Change: Interim Progress Report*. 2014. Available from: [https://eoeleadership.hee.nhs.uk/sites/default/files/1404813191\\_LmkH\\_health\\_coaching\\_interim\\_progress\\_report.pdf](https://eoeleadership.hee.nhs.uk/sites/default/files/1404813191_LmkH_health_coaching_interim_progress_report.pdf) [Accessed 31st December 2018].
338. Linden A, Butterworth S, Prochaska J. Motivational interviewing-based health coaching as a chronic care intervention. *Journal of Evaluation of Clinical Practice*. 2010;16(1):166-174.
339. Cinar A, Schou L. The role of self-efficacy in health coaching and health education for patients with type 2 diabetes. *International Dental Journal*. 2014;64(3):155-163.
340. Long D. Wellness program satisfaction, sustained health coaching participation, and achievement of health goals. *Occupational and Environmental Medicine*. 2012;54(5):592-597.
341. Rabius V, McAlister A, Geiger A, Huang P, Todd R. Telephone counselling increases cessation rates among young adults smokers. *Health Psychology*. 2012;23(5):539-541.
342. Barsevick A, Dudley W, Beck SL, Sweeney C, Whitmer K, et al. A randomised clinical trial of energy conservation for patients with cancer-related fatigue. *Cancer*. 2004;100:1302-1310.
343. Chan R, Yates P, McCarthy A. Fatigue self-management behaviours in patients with advanced cancer: a prospective longitudinal survey. *Oncology Nursing Forum*. 2016;43(6):762-771.
344. Thomas S, Kersten P, Thomas P, Slingsby V, Nock A, et al. Exploring strategies used following a group-based fatigue management programme for people with multiple sclerosis (FACETS) via

the Fatigue Management Strategies Questionnaire (FMSQ). *British Medical Journal Open*. 2015;5:e008274.

345. White P, Goldsmith K, Johnson A, Potts L, Walwyn R, et al. Comparison of adaptive pacing therapy, cognitive heabior therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet*. 2011;377:823-836.
346. Crawley E, Gaunt D, Garfield K, Hollingworth W, Sterne J, et al. Clinical and cost-effectiveness of the Lightning Process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial. *Archives of Disease in Childhood*. 2018;103:155–164.
347. Stulemeijer M, de Jong L, Fiselier T. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. *British Medical Journal*. 2005;330:14.
348. Al-Naggar Z, Al-Haggar M, Abdel-Salam M. Biofeedback and cognitive behavioral therapy for Egyptian adolescents suffering from chronic fatigue syndrome. *Journal of Paediatric Neurology*. 2006;4:161–169.
349. Nijhof S, Bleijenberg G, Uiterwaal C. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. *Lancet*. 2012;379:1412–1418.
350. Bishop S, Lau M, Shapiro S, Carlson L, Anderson N, et al. Mindfulness: a proposed operational definition. *Clinical Psychology: Science and Practice*. 2004;11:230–241.
351. van der Lee M, Garssen B. Mindfulness-based cognitive therapy reduces chronic cancer-related fatigue: a treatment study. *Psycho-Oncology*. 2012;21(3):264-272.
352. Van der Gucht K, Takano K, Labarque V, Vandenabeele K, Nolf N, et al. A mindfulness-based intervention for adolescents and young adults after cancer treatment: effects on quality of life, emotional distress, and cognitive vulnerability. *Journal of Adolescent and Young Adult Oncology*. 2017;6(2):307-317.
353. Ulrichsen KM, Kaufmann T, Dørum ES, Kolskår KK, Richard G, et al. Clinical utility of mindfulness training in the treatment of fatigue after stroke, traumatic brain injury and multiple sclerosis: a systematic literature review and meta-analysis. *Frontiers in Psychology*. 2016;7:912-912.
354. Ellis DA, Carcone A, Slatcher R, Sibinga E. Feasibility of Mindfulness-Based Stress Reduction for older adolescents and young adults with poorly controlled type 1 diabetes. *Health Psychology and Behavioral Medicine*. 2018;6(1):1-14.
355. Sibinga E, Kerrigan D, Stewart M, Johnson K, Magyari T, et al. Mindfulness-based stress reduction for urban youth. *Journal of Alternative and Complementary Medicine*. 2011;17(3):213-218.
356. Racey D, Fox J, Berry V, Blockley K, Longridge R, et al. Mindfulness-based cognitive therapy for young people and their carers: a mixed-method feasibility study. *Mindfulness*. 2017. Available from: [http://oxfordmindfulness.org/wp-content/uploads/2017/08/Racey\\_et\\_al-2017-Mindfulness.pdf](http://oxfordmindfulness.org/wp-content/uploads/2017/08/Racey_et_al-2017-Mindfulness.pdf) [Accessed 31st December 2018].
357. Sanger K, Dorjee D. Mindfulness training for adolescents: a neurodevelopmental perspective on investigating modifications in attention and emotion regulation using event-related brain potentials. *Cognitive, Affective and Behavioural Neuroscience*. 2015;15(3):696-711.

358. Wilde S, Sonley A, Crane C, Ford T, Raja A, et al. Mindfulness Training in UK Secondary Schools: a Multiple Case Study Approach to Identification of Cornerstones of Implementation. *Mindfulness*. 2018. Available from <https://doi.org/10.1007/s12671-018-0982-4> [Accessed 31st December 2018].
359. Shook N, Ford C, Strough J, Delaney R, Barker D. In the moment and feeling good: age differences in mindfulness and positive affect. *Translational Issues in Psychological Science*. 2017;3(4):338-347.
360. Galante J, Dufour G, Vainre M, Wagner AP, Stochl J, et al. A mindfulness-based intervention to increase resilience to stress in university students (the Mindful Student Study): a pragmatic randomised controlled trial. *The Lancet Public Health*. 2018;3(2):e72-e81.
361. Siegel K, Lekas H-M, Maheshwari D. Causal attributions for fatigue by older adults with advanced cancer. *Journal of Pain and Symptom Management*. 2012;44(1):52-63.
362. Loades M, Rimes K, Lievesley K, Chalder T. Illness beliefs of adolescents with CFS and their parents: the perceived causes of illness and beliefs about recovery. *International Journal of Adolescent Medicine and Health*. 2018. Available from: <https://doi.org/10.1515/ijamh-2017-0197> [Accessed 31st December 2018].
363. Moss-Morris R. Symptom perception, illness beliefs and coping chronic fatigue syndrome. *Journal of Mental Health*. 2005;14(3):223-235.
364. Gray S, Rutter D. Illness representations in young people with Chronic Fatigue Syndrome. *Psychology and Health*. 2006;22(2):159-174.
365. Henderson C, Robinson E, Evans-Lacko S, Corker E, Rebollo-Mesa I, et al. Public knowledge, attitudes, social distance and reported contact regarding people with mental illness 2009–2015. *Acta Psychiatrica Scandinavica*. 2016;134(S446):23-33.
366. Bol Y, Duits A, Lousberg R, Hupperts R, Lacroix M, et al. Fatigue and physical disability in patients with multiple sclerosis: a structural equation modeling approach. *Journal of Behavioral Medicine*. 2010;33:355-363.
367. Blaney J, Lowe-Strong A, Rankin-Watt J, Campbell A, Gracey J. Cancer survivors' exercise barriers, facilitators and preferences in the context of fatigue, quality of life and physical activity participation: a questionnaire survey. *Psycho-Oncology*. 2013;22(1):186-194.
368. Piredda M, De Marinis M, Rocci L, Gualandi R, Tartaglini D, et al. Meeting information needs on cancer-related fatigue: an exploration of views held by Italian patients and nurses. *Supportive Care in Cancer*. 2007;15(11):1231-1241.
369. Yun Y, Lee K, Kim Y, Park S, Lee E, et al. Web-based tailored education program for disease-free cancer survivors with cancer-related fatigue: a randomized controlled trial. *Journal of Clinical Oncology*. 2012;30(12):1296-1303.
370. Kamat N, Rajan Mallayasamy S, Sharma PSVN, Kamath A, Pai CG. Video assisted patient education improves compliance with follow up and depression scores in Inflammatory Bowel Diseases. *Postgraduate Medicine*. 2018;130(3):355-360.
371. Hardcastle S, Maxwell-Smith C, Kamarova S, Lamb S, Millar L, et al. Factors influencing non-participation in an exercise program and attitudes towards physical activity in cancer survivors. *Supportive Care in Cancer*. 2018;26(4):1289-1295.

372. Dalal H, Evans P, Campbell J, Taylor R, Watt A, et al. Home-based versus hospital-based rehabilitation after myocardial infarction: a randomized trial with preference arms — Cornwall Heart Attack Rehabilitation Management Study (CHARMS). *International Journal of Cardiology*. 2007;19(2):202-211.
373. Keating A, Lee A, Holland A. What prevents people with chronic obstructive pulmonary disease from attending pulmonary rehabilitation? A systematic review. *Chronic Respiratory Disease*. 2011;8:89-99.
374. Booth S, Farquhar M, Gysels M, Bausewein C, I. H. The impact of a breathlessness intervention service (BIS) on the lives of patients with intractable dyspnoea: a qualitative phase I study. *Journal of Palliative and Supportive Care*. 2006;4:287-293.
375. Holland A, Mahal A, Hill C, Lee A, Burge A, et al. Home-based rehabilitation for COPD using minimal resources: a randomised, controlled equivalence trial. *Thorax*. 2016;72:57–65.
376. Parslow R, Patel A, Beasant L, Haywood K, Johnson D, et al. What matters to children with CFS/ME? A conceptual model as the first stage in developing a PROM. *Archives of Disease in Childhood*. 2015;100(12):1141-1147.
377. Armbrust W, Siers NE, Lelieveld OTHM, Mouton LJ, Tuinstra J, et al. Fatigue in patients with juvenile idiopathic arthritis: a systematic review of the literature. *Seminars in Arthritis and Rheumatism*. 2016;45(5):587-595.
378. James S, Wright P, Scarlett C, Young T, Jamal H, et al. Cancer-related fatigue: results from patient experience surveys undertaken in a UK regional cancer centre. *Supportive Care in Cancer*. 2015;23(7):2089-2095.
379. Bennett B, Goldstein D, Friedlander M, Hickie I, Lloyd A. The experience of cancer-related fatigue and chronic fatigue syndrome: a qualitative and comparative study. *Journal of Pain and Symptom Management*. 2006;34(2):126-135.
380. Dickson A, Knussen C, Flowers P. Stigma and the delegitimation experience: an interpretative phenomenological analysis of people living with chronic fatigue syndrome. *Psychology and Health*. 2007;22(7):851-867.
381. Fisher H, Crawley E. Why do young people with CFS/ME feel anxious? A qualitative study. *Clinical Child Psychology and Psychiatry*. 2012;18:556-573.
382. Schweitzer R, Kelly B, Foran A, Terry D, Whiting J. Quality of life in chronic fatigue syndrome. *Social Science and Medicine*. 1995;41(10):1367-1372.
383. Kennedy G, Underwood C, Belch J. Physical and functional impact of chronic fatigue syndrome/myalgic encephalomyelitis in childhood. *Pediatrics*. 2010;125(6):e1324-1330.
384. Stenberg U, Ruland C, Miaskowski C. Review of the literature on the effects of caring for a patient with cancer. *Psycho-Oncology*. 2010;19(10):1013-1025.
385. Rosenberg A, Dussel V, Kang T, Russel Geyer J, Gerhardt CA, et al. Psychological distress in parents of children with advanced cancer. *JAMA Pediatrics*. 2013;167(6):537-543.
386. Carroll S, Chalder T, Hemingway C, Heyman I, Moss-Morris R. "It feels like wearing a giant sandbag." Adolescent and parent perceptions of fatigue in paediatric multiple sclerosis. *European Journal of Paediatric Neurology*. 2016;20(6):938-945.

387. Pagano E, Baldi I, Mosso M, di Montezemolo L, Fagioli F, et al. The economic burden of caregiving on families of children and adolescents with cancer: a population-based assessment. *Pediatric Blood & Cancer*. 2014;61(6):1088-1093.
388. Harris K, Band R, Cooper H, Macintyre V, Mejia A, et al. Distress in significant others of patients with chronic fatigue syndrome: a systematic review of the literature. *British Journal of Health Psychology*. 2016;21(4):881-893.
389. Haig-Ferguson A, Potgienter R, Beasant L, Crawley E. The impact of managing a child's Chronic Fatigue Syndrome / Myalgic Encephalopathy (CFS/ME) on family relationships. *SM Journal of Family Medicine*. 2017;1(1):1010.
390. Velleman S, Collin S, Beasant L, Crawley E. Psychological wellbeing and quality of life among siblings of paediatric CFS/ME patients: a mixed-methods study. *Clinical Child Psychology and Psychiatry*. 2016;21(4):618-633.
391. Ax S, Gregg V, Jones D. Caring for a relative with chronic fatigue syndrome: difficulties, cognition and acceptance over time. *Journal of Royal Society of Promotion of Health*. 2002;122(1):35-42.
392. Evans K, Banzett R, Adams L, McKay L, Frackowiak R, et al. Bold fMRI identifies limbic, paralimbic, and cerebellar activation during air hunger. *Journal of Neurophysiology*. 2002;88:1500-1511.
393. Banzett R, Mulnier H, Murphy K, Rosen S, Wise R, et al. Breathlessness in humans activates insular cortex. *Neuroreport*. 2000;11:2117-2120.
394. Parshall M, Schwartzstein L, Banzett R, Manning H, Bourbeau J, et al. An official American Thoracic Society Statement: update on the mechanisms, assessment and management of dyspnea. *American Journal of Respiratory and Critical Care Medicine*. 2012;185(4):435-452.
395. Chalder T, Goldsmith K, White P, Sharpe M, Pickles A. Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial. *Lancet Psychiatry*. 2015;2(2):141-152.
396. Rabin C, Pint B, Frierson G. Mediators of a randomised controlled physical activity intervention for breast cancer survivors. *Journal of Sport and Exercise Physiology*. 2006;28(3):269-284.
397. Chen H, Tsai C, Wu Y, Lin K, Lin C. Randomised controlled trial on the effectiveness of home-based walking exercise on anxiety, depression and cancer-related symptoms in patients with lung cancer. *British Journal of Cancer*. 2015;112:438-445.
398. Carayol M, Bernard P, Boiche J, Riou F, Mercier B, et al. Psychological effect of exercise in woman with breast cancer receiving adjuvant therapy: what is the optimal dose needed? *Annals of Oncology*. 2013;24:291-300.
399. Buffart LM, Ros W, Chinapaw MJ, Brug J, Knol D, et al. Mediators of physical exercise for improvement in cancer survivors' quality of life. *Psycho-Oncology*. 2014;23(3):330-338.
400. Rogers L, Vicari S, Trammell R, Hopkins-Price P, Fogleman A, et al. Biobehavioural factors mediate exercise effects on fatigue in breast cancer survivors. *Medical Science Sports Exercise*. 2014;46(6):1077-1088.
401. Brown L, Kroenke K. Cancer-related fatigue and its associations with depression and anxiety: a systematic review. *Psychosomatics*. 2009;50(5):440-447.

402. Skapinakis P, Lewis G, Baveas V. Temporal relations between unexplained fatigue and depression: longitudinal data from an international study in primary care. *Psychosomatic Medicine*. 2004;66(3):330-335.
403. Laird B, Scott A, Colvin L, McKeon A, Murray G, et al. Pain, depression, and fatigue as a symptom cluster in advanced cancer. *Journal of Pain and Symptom Management*. 2011;42(1):1-11.
404. Duval F, Mokrani M, Monreal-Ortiz J, Fattah S, Champeval C, et al. Cortisol hypersecretion in unipolar major depression with melancholic and psychotic features: dopaminergic, noradrenergic and thyroid correlates. *Psychoneuroendocrinology*. 2006;31(7):876-888.
405. Cleare A. The neuroendocrinology of chronic fatigue syndrome. *Endocrinology Reviews*. 2003;24(2):236-252.
406. Morrow G, Hickok J, Roscoe J, Raubertas R, Andrews P, et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. *Journal of Clinical Oncology*. 2003;21(24):4635-4641.
407. Ho S, Rohan K, Parent J, Tager F, McKinley P. A longitudinal study of depression, fatigue and sleep disturbance as a symptom cluster in women with breast cancer. *Journal of Pain and Symptom Management*. 2015;49(4):707-715.
408. Brown LF, Rand K, Bigatti S, Stewart J, Theobald D, et al. Longitudinal relationships between fatigue and depression in cancer patients with depression and/or pain. *Health Psychology*. 2013;32(12):1199-1208.
409. Herigstad M, Faull O, Yaen A, Evans E, Hardinge FM, et al. Treating breathlessness via the brain: changes in brain activity over a course of pulmonary rehabilitation. *European Respiratory Journal*. 2017;50(3):1701029.
410. Bower J, Ganz P, Irwin M, Kwan L, Breen E, et al. Inflammation and behavioural symptoms after breast cancer treatment: do fatigue, depression and sleep disturbance share a common underlying mechanism? *Journal of Clinical Oncology*. 2011;29(26):3517-3521.
411. Rumble M, Keefe F, Edinger J, Affleck G, Marcom P, et al. Contribution of cancer symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors to the insomnia process in breast cancer survivors: a daily process analysis. *Sleep*. 2010;33(11):1501-1509.
412. Morin C. *Insomnia: psychological assessment and management*. New York: The Guilford Press; 1993.
413. Morin C, Stone J, Trinkle D, mercer J, Remsberg S. Dysfunctional beliefs and attitudes about sleep among older adults with and without insomnia complaints. *Psychology of Aging*. 1993;8(3):463-467.
414. Spielman A, Caruso L, Glovinsky P. A behavioral perspective on insomnia treatment. *Psychiatric Clinics in North America*. 1987;10(4):541-553.
415. Savard J, Morin C. Insomnia in the context of cancer: a review of a neglected problem. *Journal of Clinical Oncology*. 2001;19(3):895-908.
416. Edinger J, Fins A, Glenn D, Sullivan R, Bastian L, et al. Insomnia and the eye of the beholder: are there clinical markers of objective sleep disturbances among adults with and without insomnia complaints? *Journal of Consulting and Clinical Psychology*. 2000;68(4):586-593.

417. Ong J, Ulmer C, Manber R. Improving sleep with mindfulness and acceptance: a metacognitive model of insomnia. *Behavioral Research and Therapy*. 2012;50(11):651-660.
418. Whitehead B. Investigating the function spiral in later life: aging attitudes, physical activity and gait. *Journal of Health Psychology*. 2017. Available from: <https://journals.sagepub.com/doi/10.1177/1359105317710814> [Accessed 31st December 2018].
419. Sanghvi S. Chapter 8: Cardiac rehabilitation. In: Porter S (ed.) *Tidy's Physiotherapy*, 15th Edition. Churchill Livingstone. 2013. p.147-168.
420. Teasdale J. Negative thinking in depression: cause, effect or reciprocal relationship? *Advances in Behaviour Research and Therapy*. 1983;5(1):3-25.
421. Stallard P. *Think Good - Feel Good: A Cognitive Behaviour Therapy Workbook for Children and Young People*. Wiley; 2002. Available from: [https://blogs.sch.gr/fmarvel/files/2014/04/Paul\\_Stallard\\_Think\\_Good\\_-\\_Feel\\_Good\\_.pdf](https://blogs.sch.gr/fmarvel/files/2014/04/Paul_Stallard_Think_Good_-_Feel_Good_.pdf) [Accessed 31st December 2018].
422. Greenberger D, Padesky C. *Mind Over Mood: A Cognitive Therapy Treatment Manual for Clients*. New York: Guilford Press; 1995.
423. Finning K, Richards D, Moore L, Ekers D, McMillan D, et al. Cost and outcome of behavioural activation versus cognitive behavioural therapy for depression (COBRA): as qualitative process evaluation. *British Medical Journal Open*. 2017;7:e014161.
424. Ryan E, Vitoratou S, Goldsmith K, Chalder T. Psychometric properties and factor structure of a long and shortened version of the Cognitive and Behavioural Responses Questionnaire. *Psychosomatic Medicine*. 2018;80(2):230-237.
425. Hibbard J, Stockard J, Mahoney E, Tusler M. Development of the patient activation measure (PAM): conceptualizing and measuring activation in patients and consumers. *Health Services Research*. 2004;39:1005–1026.
426. Hibbard J, Gilbert H. *Supporting people to manage their health. An introduction to patient activation*. The King's Fund. 2014. Available from: [https://www.kingsfund.org.uk/sites/default/files/field/field\\_publication\\_file/supporting-people-manage-health-patient-activation-may14.pdf](https://www.kingsfund.org.uk/sites/default/files/field/field_publication_file/supporting-people-manage-health-patient-activation-may14.pdf) [Accessed 31st December 2018].
427. Hibbard J, Mahoney E, Stock R, Tusler M. Do increases in patient activation result in improved self-management behaviors? *Health Services Research*. 2007;42(4):1443–1463.
428. Dohnke B, Knauper B, Muller-Fahrnow W. Perceived self-efficacy gained from, and health effects of, a rehabilitation program after hip joint replacement. *Arthritis Care and Research*. 2005;53(4):585-592.
429. Gerber L, Stout N, McGarvey C, Soballe P, Shieh C, et al. Factors predicting clinically significant fatigue in women following treatment for primary breast cancer. *Supportive Care in Cancer*. 2011;19:1581-1591.
430. Gilliam M, Madan-Swain A, Whelan K, Tucker D, Demark-Wahnefried W, et al. Social, demographic, and medical Influences on physical activity in child and adolescent cancer survivors. *Journal of Pediatric Psychology*. 2012;37(2):198-208.

431. Salkovskis P. The devil is in the detail: conceptualising and treating obsessional problems. In: Tarrier N, Wells A, Haddock G (eds.) *Treating Complex Cases: The Cognitive Behaviour Therapy Approach*. Chichester: Wiley; 1998. p.46-80.
432. Moorey S. The six cycles maintenance model: growing a 'vicious flower' for depression. *Behavioural and Cognitive Psychotherapy*. 2010;38(2):173-184.
433. Spathis A, Booth S, Moffat C, Hurst R, Ryan R, et al. The Breathing, Thinking, Functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease. *Primary Care Respiratory Medicine*. 2017;27(1):27.
434. Akechi T, Okuyama T, Akizuki N, Shimizu K, Inagaki M, et al. Associated and predictive factors of sleep disturbance in advanced cancer patients. *Psycho-Oncology*. 2007;16(10):888-894.
435. Wessely S, Hotopf M, Sharpe M. *Chronic fatigue and its syndromes*. New York: Oxford University Press; 1998.
436. Hewlett S, Chalder T, Choy E, Cramp F, Davis B, et al. Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology*. 2011;50:1004-1006.
437. Ingles J, Eskes G, Phillips S. Fatigue after stroke. *Archives of Physical Medicine and Rehabilitation*. 1999;80:173-178.
438. van Kessel K, Moss-Morris R. Understanding multiple sclerosis fatigue: a synthesis of biological and psychological factors. *Journal of Psychosomatic Research*. 2006;61:583-585.
439. Goedendorp MM, Knoop H, Gielissen MF, Verhagen CA, Bleijenberg G. The effects of cognitive behavioral therapy for postcancer fatigue on perceived cognitive disabilities and neuropsychological test performance. *Journal of Pain and Symptom Management*. 2014;47(1):35-44.
440. Moore G, Audrey S, Barker M, Bond L, Bonell C, et al. Process evaluation of complex interventions: Medical Research Council guidance. *British Medical Journal*. 2015;350:h1258.
441. DocMikeEvans. *Cancer-related fatigue*. Available from: <https://www.youtube.com/watch?v=YTFPMYGe86s> [Accessed 31st December 2018].
442. Castonguay LG, Goldfried MR, Wiser S, Raue PJ, Hayes AM. Predicting the effect of cognitive therapy for depression: a study of unique and common factors. *Journal of Consulting and Clinical Psychology*. 1996;64(3):497-504.
443. Mars T, Ellard D, Carnes D, Homer K, Underwood M, et al. Fidelity in complex behaviour change interventions: a standardised approach to evaluate intervention integrity. *British Medical Journal Open*. 2013;3(11):e003555.
444. Shenton A. Strategies for ensuring trustworthiness in qualitative research projects. *Education for Information*. 2004;22:63-75.
445. Lincoln Y, Guba E. *Naturalistic inquiry*. Newbury Park, CA: Sage Publications; 1985.
446. Silverman D. *Interpreting qualitative data*. SAGE, London; 2014.
447. Tavakol M, Zeinaloo A. Medical research paradigms: positivistic inquiry paradigm versus naturalist inquiry paradigm. *Journal of Medical Education*. 2004;5(2):75-80.



448. Pope C, Mays N. Qualitative research: research the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *British Medical Journal*. 1995;311(6996):42-45.
449. Creswell J, Plano Clark V. *Designing and conducting mixed methods research*. Third edition. Thousand Oaks, CA: Sage; 2018.
450. Patton M. *Qualitative research and evaluation methods*. Fourth edition. Thousand Oaks, CA: Sage; 2015.
451. Malterud K. Qualitative research: standards, challenges and guidelines. *Lancet*. 2001;358:483-488.
452. Rosaldo R. Grief and a Headhunter's Rage: On the Cultural Force of Emotions. In: Bruner E (ed.) *Text, Play, and Story: The Construction and Reconstruction of Self and Society*. Washington, DC: American Ethnological Society; 1984.178-195.
453. McCann SK, Campbell MK, Entwistle VA. Reasons for participating in randomised controlled trials: conditional altruism and considerations for self. *Trials*. 2010;11:31-31.
454. Taylor R, Solanki A, Aslam N, Whelan J, Fern L. A participatory study of teenagers and young adults views on access and participation in cancer research. *European Journal of Oncology Nursing*. 2016;20:156-164.
455. Maddocks M, Lovell N, Booth S, Man W, Higginson I. Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. *Lancet*. 2017;390:988-1002.
456. Bausewein C, Schunk M, Schumacher P, Dittmer J, Bolzani A, et al. Breathlessness services as a new model of support for patients with respiratory disease. *Chronic Respiratory Disease*. 2018;15(1):48-59.
457. Farquhar M, Prevost A, McCrone P, Brafman-Price B, Bentley A, et al. Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? Findings of a mixed-method randomised controlled trial. *BMC Medicine*. 2014;12(1):194.
458. Moss-Morris R. Symptom perceptions, illness beliefs and coping chronic fatigue syndrome. *Journal of Mental Health*. 2005;14(3):223-235.
459. Whiteson M. The Teenage Cancer Trust - advocating a model for teenage cancer services. *European Journal of Cancer*. 2003;39:2688-2693.
460. Swain M. Fatigue in chronic disease. *Clinical Science*. 2000;99(1):1-8.
461. Menting J, Tack C, Bleijenberg G, Donders R, Droogleever Fortuyn H, et al. Is fatigue a disease-specific or generic symptom in chronic medical conditions? *Health Psychology*. 2018;37(6):530-543.
462. Marcus S, Strople J, Neighbors K, Weissberg-Benchell J, Nelson S, et al. Fatigue and health-related quality of life in pediatric inflammatory bowel disease. *Clinical Gastroenterology and Hepatology*. 2009;7(5):554-561.

463. Butbul A, Stremler R, Benseler S, Cameron B, Laxer R, et al. Sleep and fatigue and the relationship to pain, disease activity and quality of life in juvenile idiopathic arthritis and juvenile dermatomyositis. *Rheumatology (Oxford, England)*. 2011;50(11):2051-2260.
464. Nutini M, Karczewski M, Capoor J. Fatigue in children with neurologic impairments. *Physical Medicine and Rehabilitation Clinics*. 2009;20(2):339-346.
465. Miller G, Coffield E, Leroy Z, Wallin R. Prevalence and costs of five chronic conditions in children. *Journal of the School of Nursing*. 2016;32(5):357-364.
466. Goedendorp M, Tack C, Steggink E, Bloot L, Bazelmans E, et al. Chronic fatigue in type 1 diabetes: highly prevalent but not explained by hyperglycemia or glucose variability. *Diabetes Care*. 2014;37(1):73-80.
467. Rwashana A, Nakbulwa S, Makkeeto-Kijjambu M, Adam T. Advancing the application of systems thinking in health: understanding the dynamics of neonatal mortality in Uganda. *Health Research Policy and Systems*. 2014;12(36). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4134459/pdf/1478-4505-12-36.pdf> [Accessed 31st December 2018].
468. Patterson T. A cognitive behavioral systems approach to family therapy. *Journal of Family Psychotherapy*. 2014;25(2):132-144.
469. Cramer A, van Borkulo C, Giltay E, van der Maas H, Kendler K, et al. Major depression as a complex dynamic system. *PloS One*. 2016;11(12):e0167490.
470. Temel J, Greer J, Muzikansky A, Gallagher E, Admane S, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *New England Journal of Medicine*. 2010;363(8):733-742.
471. Bakitas M, Tosteson T, Li Z, Lyons K, Hull J, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. *Journal of Clinical Oncology*. 2015;33(13):1438-1445.
472. Monery D, Benson S, Griffiths A, Cadwallader C, Hampton-Matthews J, et al. Multi-professional-delivered enhanced supportive care improves quality of life for patients with incurable cancer. *International Journal of Palliative Nursing*. 2018;24(10):510-514.
473. Doering, Chen B, Cross R, Magsarili M, Nyamathi A, et al. Early cognitive behavioural therapy for depression after cardiac surgery. *Journal of Cardiovascular Nursing*. 2013;28(4):370-379.
474. Patten S. A major depression prognosis calculator based on episode duration. *Clinical Practice and Epidemiology in Mental Health*. 2006;2:13.
475. Redekop W, Mladi D. The faces of personalized medicine: a framework for understanding its meaning and scope. *Value in Health*. 2-13;16:S4-S9.
476. Kaptchuk T, Miller F. Placebo effects in medicine. *New England Journal of Medicine*. 2015;373(1):8-9.
477. Crum A, Leibowitz K, Verghese A. Making mindset matter. *British Medical Journal*. 2017;356:j674.
478. Fulcher K, White P. Randomised controlled trial of graded exercise in patients iwth the chronic fatigue syndrome. *British Medical Journal*. 1997;314:1647-1652.

479. Chan R, Giardino N, Larson J. A pilot study: mindfulness meditation intervention in COPD. *International Journal of COPD*. 2015;10:445-454.
480. Malpass A, Feder G, Dodd J. Understanding changes in dyspnoea perception in obstructive lung disease after mindfulness training. *British Medical Journal Open Respiratory Research*. 2018;5:e000309.
481. Hilton L, Hempel S, Ewing B, Apaydin E, Xenakis L, et al. Mindfulness meditation for chronic pain: systematic review and meta-analysis. *Annals of Behavioural Medicine*. 2017;51:199-213.
482. Johns S, Brown L, Beck-Coon K, O'Monahan P, Tong Y, et al. Randomised controlled pilot study of mindfulness-based stress reduction for persistently fatigued cancer survivors. *Psycho-Oncology*. 2015;24(8):885-893.
483. Booth S, Chin C, Spathis A. The brain and breathlessness: understanding and disseminating a palliative care approach. *Palliative Medicine*. 2015;29(5):396-398.
484. Kelly M, Barker M. Why is changing health-related behaviour so difficult? *Public Health*. 2016;136:109-116.
485. Atkins L, Francis J, Islam R, O'Connor D, Patey A, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. *Implementation Science*. 2017;12(1):77.
486. Rodgers W, Markland D, Selzler A, Murray T, Wilson P. Distinguishing perceived competence and self-efficacy: an example from exercise. *Research Quarterly for Exercise and Sport*. 2014;85:527-539.
487. Armum P, Chellappan K. Social and emotional self-efficacy of adolescents: measured and analysed interdependencies within and across academic achievement level. *International Journal of Adolescence and Youth*. 2016;21(3):279-288.
488. Tsang S, Hui E, Law B. Self-efficacy as a positive youth development construct: a conceptual review. *The Scientific World Journal*. 2012;2012:452372.
489. Stevens M, Beynon P, Cameron A, Cargill J, Cheshire J, et al. Understanding and utilizing the unmet needs of teenagers and young adults with cancer to determine priorities for service development: the Macmillan On Target Programme. *Journal of Adolescent and Young Adult Oncology*. 2018. Available from: <https://www.liebertpub.com/doi/pdf/10.1089/jayao.2018.0044>. [Accessed 31st December 2018].
490. Mulvale A, Mitello A, Hackett C, Mulvale G. Applying experience-based co-design with vulnerable populations: lessons from a systematic review of methods to involve patients, families and service providers in child and youth mental health service improvement. *Patient Experience Journal*. 2016;3(1):117-129.
491. Higginson I, Booth S. The randomized fast-track trial in palliative care: role, utility and ethics in the evaluation of interventions in palliative care? *Palliative Medicine*. 2011;25(8):741-747.
492. Avery K, Williamson P, Gamble C, O'Connell Franchischetto E, Metcalfe C, et al. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. *British Medical Journal Open*. 2017;7(2):e013537.
493. Sayburn A. Lifestyle medicine: a new medical specialty? *British Medical Journal*. 2018;363:k4442.

494. Faull O, Hayen A, Pattinson K. Breathlessness and the body: neuroimaging clues for the inferential leap. *Cortex*. 2017;95:211-221.
495. Bantick S, Wise R, Ploghaus A, Clare S, Smith S, et al. Imaging how attention modulates pain in humans using functional MRI. *Brain*. 2002;125:310-319.
496. Anguera M, Blanco-Villaseñor A, Losada J. Revisiting the difference between mixed methods and multimethods: is it all in the name? *Quality & Quantity: International Journal of Methodology*. 2018;52(6):2757-2770.
497. Hunter A, Brewer J. Designing Multimethod Research. In: Hesse-Biber S, Burke Johnson R. (eds.) *The Oxford Handbook of Multimethod and Mixed Methods Research Inquiry*. Oxford University Press, Oxford; 2015. p.185-205.
498. Stange K, Crabtree B, Miller W. Publishing multimethod research. *Annals of Family Medicine*. 2006;4:292-294.
499. Yin R. Mixed methods research: are the methods genuinely integrated or merely parallel? *Research in the Schools*. 2006;13(1):41-47.
500. Tashakkori A, C. T. *Mixed methodology; combining qualitative and quantitative approaches*. Applied Social Research Methods Series. Thousand Oaks, CA: Sage; 1998.
501. Ivankova N, Creswell J, Stick S. Using mixed-methods sequential explanatory design: from theory to practice. *Field Methods*. 2006;18(1):3-20.
502. Stange K, Miller W, Crabtree B, O'Connor P, Zyzanski S. Multimethod research: approaches for integrating qualitative and quantitative methods. *Journal of General Internal Medicine*. 1994;9(5):278-282.
503. Maxwell J, Chmiel M, Rogers S. Designing integration in multimethod and mixed methods research. In: Hesse-Biber S, Burke Johnson R. (eds.) *The Oxford Handbook of Multimethod and Mixed Methods Research Inquiry*. Oxford University Press, Oxford; 2015. p.223-240.
504. Lewin S, Glenton C, Oxman A. Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study. *British Medical Journal*. 2009;339:b3498.
505. O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. *British Medical Journal*. 2010;341:c4587.
506. Adamson J, Ben-Shlomo Y, Chaturvedi N, Donavan J. Exploring the impact of patient views on 'appropriate' use of services and help seeking: a mixed method study. *British Journal of General Practice*. 2009;59:496-502.
507. Farmer T, Robinson K, Elliott S, Eyles J. Developing and implementing a triangulation protocol for qualitative health research. *Qualitative Health Research*. 2006;16(3):377-394.
508. Wagner K, Davidson P, Pollini R, Strathdee S, Washburn R, et al. Reconciling incongruous qualitative and quantitative findings in mixed methods research: exemplars from research with drug using populations. *International Journal of Drug Policy*. 2012;23(1):54-61.
509. Moffatt S, White M, Mackintosh J, Howel D. Using quantitative and qualitative data in health services research - what happens when mixed method findings conflict? *BMC Health Services Research*. 2006;6:28.

510. Brannen J. Mixing methods: the entry of qualitative and quantitative approaches into the research process. *International Journal of Social Research Methodology*. 2005;8:173-184.
511. Roxburgh C, McMillan D. Cancer and systemic inflammation: treat the tumour and treat the host. *British Journal of Cancer*. 2014;110(6):1409-1412.
512. Laird B, McMillan D, Fayers P, Fearon K, Kaasa S, et al. The systemic inflammatory response and its relationship to pain and other symptoms in advanced cancer. *The Oncologist*. 2013;18(9):1050-1055.
513. Jeon SW, Kim YK. Neuroinflammation and cytokine abnormality in major depression: cause or consequence in that illness? *World Journal of Psychiatry*. 2016;6(3):283-293.
514. Spathis A, Booth S, Grove S, Hatcher H, Kuhn I, et al. Teenage and young adult cancer-related fatigue is prevalent, distressing and neglected: it is time to intervene. A systematic literature review and narrative synthesis. *Journal of Adolescent and Young Adult Oncology*. 2015;4(1):3-17.
515. Spathis A, Hatcher H, Booth S, Gibson F, Stone P, et al. Cancer-related fatigue in adolescents and young adults after cancer treatment: persistent and poorly managed. *Journal of Adolescent and Young Adult Oncology*. 2017;6(3):489-493.



## 7 Appendices

### 7.1 Research outputs

#### 7.1.1 Educational materials

These have been described in section 5.2.2, page 225. Further details, including hyperlinks and hits, are as follows:

Video trailer: 24,766 views, 99 shares, 268 likes

<https://www.facebook.com/macmillancancer/videos/10155290388552199/>

Ruth video: 45,974 views, 137 shares, 415 likes

<https://www.facebook.com/macmillancancer/videos/10155326007497199/>

or <https://youtu.be/aCrEXJZKyHI>

Ellis video: 44,522 views, 199 shares, 485 likes

<https://www.facebook.com/macmillancancer/videos/10155319941992199/>

or <https://youtu.be/6XpX5RANLdQ>

Faye video: 26,661 views, 108 shares, 299 likes

<https://www.facebook.com/macmillancancer/videos/10155329396727199/>

or <https://youtu.be/OHELcqBc6yg>

Blog shared on Macmillan social media channels:

[https://community.macmillan.org.uk/blogs/b/community\\_news/archive/2017/10/10/guest-post-39-we-need-help-to-live-too-39](https://community.macmillan.org.uk/blogs/b/community_news/archive/2017/10/10/guest-post-39-we-need-help-to-live-too-39)

A short version of Ellis' video: over 1,000,000 views

<https://www.facebook.com/StudentProblems/videos/this-is-great-/1533592736767454/>

#### 7.1.2 University of Cambridge research award

The University of Cambridge Vice-Chancellor's Public Engagement with Research Award (July 2018) led to the following publicity and related blog:

<https://www.cam.ac.uk/news/vice-chancellors-awards-showcase-cambridge-researchers-public-engagement-and-societal-impact>

<https://www.phpc.cam.ac.uk/pcu/i-thought-it-was-just-me-mutual-benefit-from-public-involvement-in-research/>

#### 7.1.3 National presentations

##### 7.1.3.1 Oral presentations

Spathis A, Booth S, Grove S, Hatcher H, Kuhn I, Barclay S. Teenage and young adult CRF: a systematic review and narrative synthesis. Oral presentation at Society of Academic Primary Care London and South East Regional Meeting, Cambridge, January 2015.

Spathis A, Hatcher H, Booth S, Brimicombe J, Moss W, Barclay S. Conducting healthcare research in young adult cancer patients by email alone: feasible, acceptable and efficient. Oral presentation at Public Health England Conference: Cancer Data and Outcomes, Manchester, June 2016.

Spathis A, Chapman A, Burkin J, Hatcher H, Uttenthal B, Robson J, Abbas L, Gibson F, Stone P, Booth S, Barclay S. Fatigue Intervention Co-design Study: unique needs of teenagers and young adults with CRF. Oral presentation Association of Palliative Medicine Supportive and Palliative Care Conference, Harrogate, March 2019.

#### **7.1.3.2 Poster presentations**

Spathis A, Hatcher H, Booth S, Gibson F, Stone P, Abbas L, Brimicombe J, Thiemann P, McCabe M, Campsey R, Hooker L, Moss W, Robson R, Barclay S. A multicentre survey of teenage and young adult cancer patients: fatigue is prevalent, poorly managed and perpetuates long-term. Poster presentation at NCRI conference, Liverpool, November 2016.

Spathis A, Hatcher H, Booth S, Gibson F, Stone P, Abbas L, Brimicombe J, Thiemann P, McCabe M, Campsey R, Hooker L, Moss W, Robson R, Barclay S. A multicentre survey of teenage and young adult cancer patients: fatigue is prevalent, poorly managed and perpetuates long-term. Poster presentation at Teenage Cancer Trust conference, Edinburgh, December 2016.

#### **7.1.4 Publications**

##### **7.1.4.1 Published**

Spathis A, Booth S, Grove S, Hatcher H, Kuhn I, Barclay S. Teenage and young adult cancer-related fatigue is prevalent, distressing and neglected: it is time to intervene. A systematic literature review and narrative synthesis. *Journal of Adolescent and Young Adult Oncology*. 2015;4(1):3-17.

Spathis A, Hatcher H, Booth S, Gibson F, Stone P, Abbas L, Barclay M, Brimicombe J, Thiemann P, McCabe M, Campsey R, Hooker L, Moss W, Robson J, Barclay S. Cancer-related fatigue in adolescents and young adults after cancer treatment: persistent and poorly managed. *Journal of Adolescent and Young Adult Oncology*. 2017;6(3):489-493.

The former was one of the 'top ten most cited publications' in 2017 for the *Journal of Adolescent and Young Adult Oncology*, and the latter one of the 'top ten most read publications' in both 2017 and 2018. This relates to publications since the journal's inception in 2011.

These two publications are provided in full in the following pages of this appendix.

##### **7.1.4.2 In press**

Spathis A, Chapman A, Burkin J, Hatcher H, Uttenthal B, Robson J, Abbas L, Gibson F, Stone P, Booth S, Barclay S. Fatigue Intervention Co-design Study: unique needs of teenagers and young adults with cancer-related fatigue. For abstract publication in *BMJ Supportive and Palliative Care*.



# Teenage and Young Adult Cancer-Related Fatigue Is Prevalent, Distressing, and Neglected: It Is Time to Intervene. A Systematic Literature Review and Narrative Synthesis

Anna Spathis, MSc,<sup>1,2</sup> Sara Booth, MD,<sup>1,3</sup> Sarah Grove, MB BChir,<sup>1</sup> Helen Hatcher, PhD,<sup>4</sup> Isla Kuhn, MSc,<sup>5</sup> and Stephen Barclay, MD<sup>2</sup>

**Purpose:** Cancer-related fatigue in adults has been the subject of considerable recent research, confirming its importance as a common and debilitating symptom, and establishing a number of evidence-based interventions. There has, however, been limited focus on the fatigue suffered by teenagers and young adults with cancer, a group recognized as having unique experiences and developmental needs. We have undertaken a systematic review of the literature to provide a comprehensive overview of studies evaluating fatigue in this younger patient group in order to guide clinical practice and future research.

**Method:** We searched MEDLINE, EMBASE, PsycINFO, and CINAHL databases for literature containing data relating to any aspect of fatigue in patients aged 13–24 at cancer diagnosis or treatment.

**Results:** Sixty articles were identified, of which five described interventional clinical trials. Cancer-related fatigue was consistently one of the most prevalent, severe, and distressing symptoms, and it persisted long-term in survivors. It was associated with a number of factors, including poor sleep, depression, and chemotherapy. There was little evidence for the effectiveness of any intervention, although exercise appears to be the most promising. Importantly, fatigue was itself a significant barrier to physical and social activities.

**Conclusion:** Cancer-related fatigue is a major and disabling problem in young cancer patients. Effective management strategies are needed to avoid compounding the dependence and social isolation of this vulnerable patient group. Future research should focus on providing evidence for the effectiveness of interventions, of which activity promotion and management of concurrent symptoms are the most promising.

**Keywords:** fatigue, prevalence, impact, intervention

CANCER IS THE LEADING CAUSE of disease-related death in teenagers and young adults (TYAs) in the United States and Europe.<sup>1,2</sup> Each year, more than 11,000 TYA patients in the United States and over 2000 in the United Kingdom are diagnosed with cancer, and incidence rates are rising.<sup>2,3</sup> It is increasingly recognized that such patients have experiences and needs that differ significantly from those of children and adults.<sup>4</sup> As well as having to negotiate the physical, cognitive, emotional, and behavioral changes that occur in adolescence, young people can suffer from a different cancer profile, longer periods of cancer treatment, a worse prognosis, and a particularly devastating sense of despair and iso-

lation.<sup>3,5,6</sup> There has been an international drive to develop age-appropriate specialist care and to generate an evidence base addressing the specific needs of this patient group.<sup>4,7</sup>

Cancer-related fatigue is a “persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning.”<sup>8</sup> It is a multidimensional symptom with physical, affective, and cognitive components. The range of perceptions may include a feeling of weakness and inability to perform tasks, decreased motivation and low mood, and difficulty in thinking clearly.<sup>9</sup> It differs from fatigue felt by healthy individuals in that it is of greater magnitude, disproportionate to the level of exertion, and incompletely relieved by rest.

<sup>1</sup>Department of Palliative Care, Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust Foundation, Cambridge, United Kingdom.

<sup>2</sup>Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom.

<sup>3</sup>University of Cambridge, Cambridge, United Kingdom.

<sup>4</sup>TYA Cancer Service, Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust Foundation, Cambridge, United Kingdom.

<sup>5</sup>University of Cambridge Medical Library, Cambridge, United Kingdom.

Fatigue appears to be both the most common and the most distressing symptom experienced by adult patients with cancer.<sup>10,11</sup> Many surveys suggest a prevalence of over 75%, with rates increasing in conjunction with oncological treatment.<sup>12,13</sup> Adult patients report that fatigue is the symptom which has the greatest negative impact on their quality of life.<sup>11</sup>

Despite the size of the problem, cancer-related fatigue has traditionally been neglected both in clinical and research terms, with healthcare staff and patients tending to consider it an unavoidable consequence of cancer and its treatment.<sup>10,14</sup> However, over the last two decades, a substantial evidence base has been developing in the adult literature. Systematic reviews of research in older adults has shown that—apart from treating reversible underlying causes—the most promising approaches are exercise<sup>15</sup> and psychosocial interventions such as education.<sup>16</sup>

Recognition of the particular importance of cancer-related fatigue in younger cancer patients has only emerged over the last 5–10 years. Lack of energy has been shown to be the most common symptom in children with cancer, with children placing emphasis on a sense of physical weakness, associating fatigue with disruption of sleep.<sup>17</sup> TYA cancer patients also appear to suffer from significant fatigue,<sup>18–20</sup> unsurprising given that even healthy teenagers and young adults have a propensity to experience fatigue. The developmental need for longer sleep during this important phase of brain maturation is hindered by circadian rhythm shifts and a tendency to develop unhelpful sleep habits.<sup>21,22</sup> TYAs perceive fatigue in both cognitive and physical terms.<sup>5</sup> Fatigue is believed to have a particularly negative impact on quality of life in this group, as it hinders many of the key developmental needs of this age, such as autonomy and the formation of close peer relationships.<sup>23</sup> Many TYA cancer patients remain or return to being dependent on their parents at a time when they would have been expecting to achieve independence. It is well recognized clinically that the parents of fatigued TYAs bear a considerable burden.

In one previous review of fatigue in teenagers in cancer published a decade ago,<sup>20</sup> Erikson found there was minimal research focusing on fatigue in this age range. Given the number of articles published since that review, it was decided to systematically appraise the current evidence base with a focus on the TYA age group. The review was designed to be broad to provide a comprehensive overview of studies investigating any aspect of cancer-related fatigue in patients diagnosed or treated for cancer while aged 13–24 years old. The research questions were:

1. What is the prevalence and severity of cancer-related fatigue in TYA patients during and after treatment?
2. What is the impact of fatigue on TYA cancer patients?
3. What is the experience of parents of fatigued TYA cancer patients?
4. What are the correlates of cancer-related fatigue in this patient group?
5. How effective are interventions to manage fatigue in TYA patients?

## Methods

### Literature search strategy

The literature was searched within MEDLINE, EMBASE, PsycINFO, and CINAHL databases for January 1981 through

TABLE 1. SEARCH TERMS

#1	exp fatigue/
#2	fatigue* or tire* or exhaust* or lethargy* (title or abstract)
#3	exp neoplasm/
#4	neoplasm* or cancer* or carcinoma* or lymphoma* or leukaemia* or leukemia* (title or abstract)
#5	1 or 2
#6	3 or 4
#7	5 and 6
#8 <sup>a</sup>	limit 7 to “adolescent” or “young adult”
#9	tya* or teenage* or “young adult”* (title or abstract)
#10	7 and 9
#11	8 or 10

<sup>a</sup>Both “adolescent” and “young adult” limiting terms were available in the MEDLINE and CINAHL database searches, but only “adolescent” was available for the EMBASE and PsycINFO searches.

October 2013. Preliminary searches had suggested that there was no literature of relevance published prior to 1981. The search strategy is detailed in Table 1. Reference and citation searches were also undertaken, with manual searching of all issues of a key journal—the *Journal of Adolescent and Young Adult Oncology* (issues 1–4 of both volume 1 and volume 2)—as well as the proceedings of the 2012 Teenage Cancer Trust International Conference. Related systematic reviews were searched, including reviews evaluating symptoms experienced by teenagers with cancer,<sup>24</sup> fatigue in lymphoma patients,<sup>25</sup> and interventions for fatigue in children and adults.<sup>26,27</sup> Experts in teenage and young adult cancer-related fatigue were also contacted.

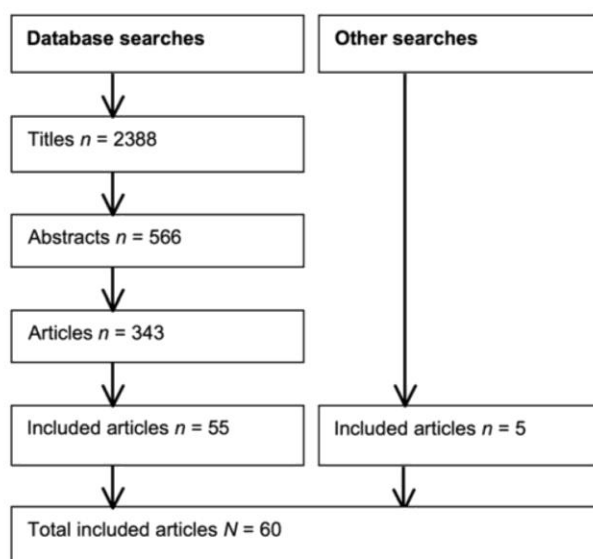
### Selection criteria

The key inclusion criteria were that all study participants had malignant disease, and that either the majority were aged 13–24 years old at the time of cancer diagnosis or treatment or the results for this age subgroup were presented separately. Included studies could investigate any aspect of cancer-related fatigue, use any outcome measure, and employ quantitative or qualitative methods. Exclusion criteria included non-English language publication, absence of original empirical data, phase I/II clinical trials, trials involving fewer than 10 patients, case reports, and retrospective case note reviews. Studies of TYA-aged survivors of pediatric cancer were not included.

### Quality assessment and data analysis

Gough’s Weight of Evidence Framework<sup>28</sup> was employed to assess article quality, relevance, and bias, and to generate an overall judgment about contribution. This framework includes analysis of “fitness for purpose” and relevance to the research question, providing a more applied synthesis of evidence than simply assessing the generic quality of each article. Four scores of “low,” “medium,” or “high” are given for each of the following:

- Weight of Evidence A: The integrity of the evidence in its own terms
- Weight of Evidence B: The appropriateness of method for answering the review questions



**FIG. 1.** PRISMA flowchart of included articles. *Note.* Although four pairs of articles and two groups of three articles were publications describing different aspects of the same study's data set, because of the distinct areas of focus, the 60 articles have been viewed as 60 separate studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

- Weight of Evidence C: The appropriateness of the focus or relevance for answering the review questions
- Weight of Evidence D: The overall rating generated by combining the Weight of Evidence A, B, and C scores

All articles, irrespective of relevance and quality, were included, but those rated "medium" and "high" were given greater weight in the analysis.

The searches produced 2388 unique titles that were initially screened by one researcher (AS). After 566 abstracts were reviewed by two researchers (AS and SG), 343 full articles were read by one researcher (AS), who excluded most of them on the basis of the participants' ages. Two researchers (AS and SB) read the remaining articles, with disagreements resolved by discussion. The final number of included articles was 60 (Fig. 1). A narrative synthesis was undertaken in relation to each of the research questions.

## Results

### Description of articles

Thirty-seven of the 60 included articles were from the United States or Canada, eight were from Norway or Sweden, and three were from the United Kingdom. All were published between 1992 and 2013. The 60 articles encompassed a total of 52 separate studies, as four pairs of articles<sup>23,29–35</sup> and two groups of three articles<sup>36–41</sup> were publications describing different aspects of the same study's data set. It was decided to handle these as different studies, because of their distinct areas of focus. Therefore, for the purposes of this review, the 60 articles were viewed as 60 separate studies.

Thirty-six studies were cross-sectional and observational. Of the 24 prospective longitudinal studies, five were inter-

ventional clinical trials. Most studies involved only quantitative methods, though seven were qualitative and eight employed a mixed-methods design. Most were rated as medium or poor on Gough's Weight of Evidence Framework. Although 13 were of high quality on Weight of Evidence A (integrity of the evidence in its own terms),<sup>17,30,40,42–51</sup> only three were judged to be of overall high quality by Weight of Evidence D.<sup>17,30,47</sup>

All participants (aside from those in some of the control groups) had a cancer diagnosis. Five studies only recruited patients with lymphoma and/or leukemia,<sup>31,32,45,52,53</sup> and one had only patients with extremity bone tumors.<sup>54</sup> All of the remaining studies investigated more than one cancer type. The majority of participants were in the 13–24 years old age range in 46 studies; subgroup data for this age range was presented separately in the remaining 14 papers. The number of patients within each study ranged from 8<sup>55</sup> to 199,<sup>56</sup> and the median or mean time since diagnosis ranged from 2 months<sup>57</sup> to 20 years.<sup>32</sup>

Fatigue was the study's focus and the first outcome measure described in the results for only 18 studies;<sup>5,18,19,23,30–32,35,36,42,46,47,50,54,58–61</sup> two of these involved validating symptom measures<sup>46,59</sup> and none were interventional. Across the 60 included studies, the most commonly used fatigue outcome measures were the Fatigue Scale-Adolescent (FS-A),<sup>59</sup> the Multidimensional Fatigue Scale (MFS),<sup>62</sup> and the Memorial Symptom Assessment Scale (MSAS 10–18),<sup>63</sup> used in 14, 12, and 8 studies, respectively. Eleven studies used a range of other validated fatigue measures, including the Chalder Fatigue Questionnaire, Piper Fatigue Scale, and the Functional Assessment in Chronic Illness Therapy fatigue scale. Eight studies used unvalidated measures, and the remaining seven studies were entirely qualitative in design. Table 2 provides further detail on the more commonly used measures.

### Fatigue prevalence

Twenty-four studies investigated the prevalence of TYA cancer-related fatigue (Table 3). Fatigue was measured during treatment in 14 studies, after treatment in five studies, and in a mixed population of patients both during and after treatment in five studies. A "fatigue case" was most commonly defined as fatigue being scored as "present" using the MSAS, a score of anything other than "no fatigue" on a 5-point Likert scale, or a dichotomized score of  $\geq 4$  on the Chalder Fatigue Scale.<sup>64</sup>

The heterogeneity of study populations, outcome measures, and definitions of "fatigue case" hindered comparison of prevalence data between studies and prevented meta-analysis. Fatigue prevalence ranged from 7%<sup>47</sup> to 100%<sup>65</sup> during treatment, 9%<sup>50</sup> to 67%<sup>66</sup> after treatment, and between 31%<sup>56</sup> and 100%<sup>67</sup> in the mixed populations. As detailed in Table 3, the prevalence of fatigue and other symptoms were compared on 20 occasions in 10 studies; it was the most prevalent symptom on 11 occasions<sup>17,33,34,65,68–71</sup> and the second-most prevalent on six occasions.<sup>17,71–73</sup>

Two studies—both with survivor populations—included a control group; both used non-contemporaneous controls. Aksnes et al. found a fatigue prevalence of 14% in extremity bone tumor survivors, which was not significantly different from that of age- and gender-matched cases from healthy

TABLE 2. SUMMARY OF KEY FATIGUE OUTCOME MEASURES

<i>Name of measure</i>	<i>Description</i>
Chalder Fatigue Questionnaire <sup>64</sup>	11-item multidimensional fatigue scale developed for use in adult epidemiological studies of patients with chronic disease, and to find fatigue “cases.” It is scored using a 4-point verbal rating scale, with a case is defined as a score of $\geq 4$ dichotomized bimodal scoring.
Fatigue Scale-Adolescent <sup>59</sup>	14-item multidimensional scale developed specifically to assess cancer-related fatigue in adolescents 13–18 years old. It is scored using a 5-point verbal rating scale, and parent and staff proxy versions have been developed.
Functional Assessment in Chronic Illness Therapy fatigue scale <sup>100</sup>	Initially developed as a multidimensional measure of fatigue in adult oncology patients with anemia, its use has been widened to include fatigue assessment in chronic illness. It is a standalone scale within the wider FACIT measurement system. It has 13 items, scored using a 5-point verbal rating scale.
Memorial Symptom Assessment Scale <sup>17</sup>	32-item scale developed to assess the frequency, severity, and associated distress of 32 common symptoms, (including fatigue) in adult cancer patients. Each symptom is measured with 4-point (frequency and severity) or 5-point (distress) numerical rating scales. It has been modified for use for patients 10–18 (30-item) and 7–12 (8-item) years old; a number of other revised versions also exist.
Multidimensional Fatigue Scale <sup>62</sup>	18-item scale developed to measure fatigue in pediatric cancer patients and now used as a generic multidimensional measure in all pediatric patient populations. It is a module of the PedsQL measurement model, which assesses pediatric quality of life. Versions are available for patients 5–7, 8–12, 13–18, and 18–24 years old, with associated parent proxy versions.
Piper Fatigue Scale <sup>101</sup>	Multidimensional fatigue scale developed for use in adult cancer patients. A number of versions exist, including the original 40-item scale and a revised 22-item scale. Each item is scored with a 0–10 numerical rating scale. It assesses four domains of fatigue—behavioral/severity, affective meaning, sensory, and cognitive/mood—and generates a score for each domain as well as a total score.
Symptom Distress Scale <sup>102</sup>	11-item scale that measures distress related to symptoms (including fatigue) scored using a 5-point verbal rating scale. It was developed specifically to identify the concerns of adult patients receiving cancer treatment.

population surveys ( $p=0.30$ ).<sup>54</sup> In contrast, Hamre et al. reported a fatigue prevalence of 34% in survivors of Hodgkin lymphoma, compared to 8% in an unmatched healthy control population ( $p<0.001$ ).<sup>32</sup>

#### *Fatigue severity*

The severity of fatigue was measured in 32 instances: 20 studies during treatment, five studies after treatment, six studies with a mixed cohort of patients both during and after treatment, and one study that provided data on two separate patient cohorts during and after treatment, respectively. Seven studies reported relative severity of fatigue in comparison to other symptoms: fatigue was most severe in four studies,<sup>34,52,68,69</sup> second-<sup>70</sup> and third-most<sup>72</sup> severe in one study each, and fourth-most severe in two studies.<sup>40,67</sup> Fourteen different outcome measures were used across these 30 studies. The most commonly used outcome measures were the FS-A, MFS, and MSAS, in nine, eight, and four studies each, respectively. Comparison and synthesis of severity scores was again not possible due to heterogeneity of study populations, methods of reporting the data (for example, absolute score or percentage with score above a defined value), or measures used.

Three studies incorporated a control group, all of which compared fatigue severity in patients during treatment to that in survivors (Table 4). Controls ranged from contemporaneous recruits to unmatched reference data. All three studies showed significantly greater fatigue severity in the cancer groups compared to the controls.

Eight studies compared fatigue severity between younger children and teenagers treated for cancer, of which five measured fatigue with both the Fatigue Scale-Adolescent (FS-A) and the Fatigue Scale-Child (FS-C).<sup>37,53,60,74,75</sup> The FS-A and FS-C<sup>76</sup> each use 14 age-appropriate questions and are validated for 13–18 and 7–12 year olds, respectively. Fatigue was reported as being more severe in adolescents than in younger children in all but one of the eight studies.<sup>53</sup>

Many of the studies that used the FS-A outcome also measured parent reports of fatigue,<sup>37,38,47,49,59,60,74,75,77</sup> but patient and parent scores are not directly comparable. One study did directly compare the fatigue scores of TYA patients with proxy scores from their caregivers, and found that their caregivers tended to overestimate their fatigue severity.<sup>30</sup>

Fatigue severity was assessed over time in 11 longitudinal studies; all involved participants currently receiving chemotherapy.<sup>23,35,37,57,60,68,71,75,77–79</sup> In general, fatigue scores

TABLE 3. STUDIES EVALUATING FATIGUE PREVALENCE, GROUPED BY RELATIONSHIP TO CANCER TREATMENT

Study	Aim(s)	Participants (mixed tumors unless stated)	Study design and fatigue assessments	Definition of fatigue "case"	Fatigue prevalence (rank compared to other symptoms)	Weight of Evidence D score
<b>DURING TREATMENT</b>						
Ameringer et al. 2013 <sup>57</sup>	Examine the trajectory of symptoms across a chemotherapy cycle	<ul style="list-style-type: none"> <li>N=9</li> <li>Mean age: 15.3 years</li> <li>Mean since diagnosis: 2.6 months</li> </ul>	<ul style="list-style-type: none"> <li>Longitudinal observational pilot</li> <li>FS-A</li> </ul>	Not described	<ul style="list-style-type: none"> <li>All participants experienced some fatigue at every time point</li> </ul>	Low
Atay et al. 2012 <sup>3</sup>	Determine symptom prevalence 1, 2, and 3 months after diagnosis	<ul style="list-style-type: none"> <li>N=54</li> <li>61% 13–18 years</li> </ul>	<ul style="list-style-type: none"> <li>Longitudinal observational</li> <li>MSAS 10–18</li> </ul>	Presence of "lack of energy" in last week on MSAS	<ul style="list-style-type: none"> <li>Month 1: 66.7% (5 of 30)</li> <li>Month 2: 75.9% (2 of 30)</li> <li>Month 3: 63% (joint 2 of 30)</li> </ul>	Medium
Baggott et al. 2010 <sup>1</sup>	Describe changes in symptoms at weekly intervals from D1	<ul style="list-style-type: none"> <li>N=66</li> <li>Mean age: 14.8 years</li> <li>Mean since diagnosis: 16.3 months</li> </ul>	<ul style="list-style-type: none"> <li>Longitudinal observational</li> <li>Revised MSAS 10–18</li> </ul>	Presence of "lack of energy" in last week on MSAS	<ul style="list-style-type: none"> <li>Week 0: 75.8% (1 of 31)</li> <li>Week 1: 70.5% (2 of 31)</li> <li>Week 2: 57.4% (2 of 31)</li> <li>Significant linear decrease over time</li> </ul>	Medium
Baggott et al. 2012 <sup>65</sup>	Describe the usefulness of eDiary to record symptoms over a 3-week trial	<ul style="list-style-type: none"> <li>N=10</li> <li>Mean age: 18.2 years</li> <li>Mean since diagnosis: 12.2 months</li> </ul>	<ul style="list-style-type: none"> <li>Longitudinal observational</li> <li>2 questions from FS-A in a VAS format</li> </ul>	VAS >30 on 0–100 scale on at least 1 day	<ul style="list-style-type: none"> <li>Reported fatigue-physical and fatigue-mental: 100% (1 of 11)</li> <li>% days that VAS &gt;30 on 0–100 scale, 64% and 62%, respectively (1 of 11)</li> <li>75.6% (1 of 31)</li> </ul>	Low
Baggott et al. 2012 <sup>70</sup>	Evaluate symptom clusters	<ul style="list-style-type: none"> <li>N=131</li> <li>Mean age: 14.8 years</li> <li>Median since diagnosis: 3.3 months</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional on D0 of ≥ cycle 2 of chemotherapy</li> <li>Revised MSAS 10–18</li> </ul>	Presence of "lack of energy" in last week on MSAS	<ul style="list-style-type: none"> <li>ARM 2 (recent diagnosis): 42.5%</li> </ul>	Medium
Corey et al. 2008 <sup>56</sup>	Describe the relationship between support and symptom distress	<ul style="list-style-type: none"> <li>N=72 (ARM 2)</li> <li>Mean age: 14.8 years (ARM 2)</li> <li>Mean since diagnosis: 3.75 years (ARM 1 and 2)</li> </ul>	<ul style="list-style-type: none"> <li>Secondary analysis of data from 2 studies</li> <li>Symptom Distress Scale</li> </ul>	3–5 on 1–5 Likert scale	<ul style="list-style-type: none"> <li>ARM 2 (recent diagnosis): 42.5%</li> </ul>	Medium
Enskar et al. 2007 <sup>66</sup>	Evaluate distress, coping support, and care	<ul style="list-style-type: none"> <li>N=54</li> <li>Mean age: 16.0 years</li> <li>32 were &lt;3 months of diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional</li> <li>LSS-A</li> </ul>	Anything other than "not at all"/"do not agree at all" on 1–5 VRS	<ul style="list-style-type: none"> <li>For 15 patients on treatment: 93%; significantly more than patients off treatment (<math>p &lt; 0.05</math>)</li> </ul>	Medium
Erickson et al. 2010 <sup>23</sup>	Describe fatigue patterns during month of chemotherapy	<ul style="list-style-type: none"> <li>N=20</li> <li>Mean age: 16.1 years</li> <li>Mean since starting chemotherapy: 8.71 weeks</li> </ul>	<ul style="list-style-type: none"> <li>Longitudinal mixed methods</li> <li>Daily fatigue NRS, MFS</li> </ul>	>0 on 0–10 NRS	<ul style="list-style-type: none"> <li>Experienced fatigue at some point, including during "days immediately following chemotherapy"; 100%</li> </ul>	Medium
Erickson et al. 2011 <sup>35</sup>	Describe relationship between fatigue and sleep-wake disturbances	<ul style="list-style-type: none"> <li>N=20</li> <li>Mean age: 16.1 years</li> <li>Mean since starting chemotherapy: 8.71 weeks</li> </ul>	<ul style="list-style-type: none"> <li>Longitudinal observational</li> <li>Weekly MFS from D1 for 5 weeks</li> </ul>	"Feeling tired" "sometimes," "often," or "almost always"	<ul style="list-style-type: none"> <li>At some point over study period: 75%</li> </ul>	Medium
Hedstrom et al. 2005 <sup>40</sup>	Investigate perceptions of distress amongst recently diagnosed adolescents	<ul style="list-style-type: none"> <li>N=56</li> <li>Age (years): 13–15; <math>n = 35</math>; 16–19; <math>n = 21</math></li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional, mixed methods</li> <li>Fatigue assessed as an aspect of distress using Likert scale</li> </ul>	3–5 on 0–5 Likert scale	<ul style="list-style-type: none"> <li>62% (4 of 20)</li> </ul>	Medium



TABLE 3. (CONTINUED)

Study	Aim(s)	Participants (mixed tumors unless stated)	Study design and fatigue assessments	Definition of fatigue "case"	Fatigue prevalence (rank compared to other symptoms)	Weight of Evidence D score
Mandrell et al. 2011 <sup>47</sup>	Calculate the revised FS-A score that defines a fatigue "case" meriting clinical intervention	<ul style="list-style-type: none"> <li>N=138</li> <li>Mean age: 14.83–16.27 years across all studies</li> </ul>	<ul style="list-style-type: none"> <li>Analysis of data from 9 studies</li> <li>FS-A and FS-P</li> </ul>	>31 on scale of 13–65	<ul style="list-style-type: none"> <li>ALL: 15%; 7–14%/26–33% (ALL off/on DXM)</li> <li>Solid tumor or AML: 10% (D1), 28% (D2), 50% (D3–4)</li> <li>Mixed diagnoses: 36% (D1); 56% (final day); 54% (1 week after end)</li> <li>49.6% (2 of 31)</li> </ul>	High
Miller et al. 2011 <sup>72</sup>	Describe prevalence, frequency, severity, and distress of multiple symptoms	<ul style="list-style-type: none"> <li>N=39</li> <li>Mean age: 13.5 years</li> </ul>	<ul style="list-style-type: none"> <li>Longitudinal observational</li> <li>MSAS 10–18 daily for 5 days evaluating symptoms from "past day"</li> </ul>	Presence of "lack of energy" in last week on MSAS		Medium
Walker et al. 2010 <sup>68</sup>	Describe symptoms before (T1) and 1 week after (T2) chemotherapy	<ul style="list-style-type: none"> <li>N=51</li> <li>Mean age: 14.2 years</li> <li>Mean since diagnosis: 6 months</li> </ul>	<ul style="list-style-type: none"> <li>Longitudinal observational in 2 centers</li> <li>MSAS 7–12</li> </ul>	Presence of "tiredness" in last week on MSAS 7–12	<ul style="list-style-type: none"> <li>T1: 54.3% (1 of 9)</li> <li>T2: 67.4% (1 of 9)</li> </ul>	Medium
Williams et al. 2012 <sup>69</sup>	Calibrate the Therapy-Related Symptom Checklist-Children	<ul style="list-style-type: none"> <li>N=163</li> <li>Subgroup of 385 participants in age range 12–17 years</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional</li> <li>TRSC-C</li> </ul>	Severity of "feeling sluggish" of more than 0 on 0–4 Likert	<ul style="list-style-type: none"> <li>81% (1 of 31)</li> </ul>	Medium
<b>AFTER TREATMENT</b>						
Adams et al. 2004 <sup>52</sup>	Evaluate cardiovascular function after mediastinal RT	<ul style="list-style-type: none"> <li>N=48 HD survivors</li> <li>Median age at diagnosis: 14.2 years</li> <li>Median since diagnosis: 14.3 years</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional</li> <li>General Health Survey (unvalidated tool)</li> </ul>	≥1 on 0–4 Likert scale of fatigue severity	<ul style="list-style-type: none"> <li>67%</li> </ul>	Medium
Aksnes et al. 2007 <sup>54</sup>	Examine fatigue, mental distress, and QOL in EBT survivors compared to matched controls	<ul style="list-style-type: none"> <li>N=57 EBT survivors</li> <li>Mean age at diagnosis across subgroups: 16–25 years</li> <li>Mean since diagnosis: 9–14 years</li> </ul>	<ul style="list-style-type: none"> <li>Case-control (non-contemporaneous controls HD, TC, NORMS)</li> <li>CFQ</li> </ul>	Sum of ≥4 using dichotomized (0, 0, 1, 1) 4-point Likert scale	<ul style="list-style-type: none"> <li>EBT survivors: 14%</li> <li>HD survivors: 21%</li> <li>TC survivors: 16%</li> <li>NORMS: 10%; <math>p=0.3</math></li> <li>EBT vs. NORMS</li> </ul>	Medium
Enskar et al. 2007 <sup>66</sup>	Evaluate distress, coping support, and care	<ul style="list-style-type: none"> <li>N=54</li> <li>Mean age: 16.0 years</li> <li>32 were &lt;3 months of diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional</li> <li>LSS-A</li> </ul>	Anything other than "not at all" on 1–5 VRS	<ul style="list-style-type: none"> <li>For 39 patients after treatment: 67%, less than on treatment (<math>p&lt;0.05</math>)</li> </ul>	Medium
Hamre et al. 2013 <sup>32</sup>	Determine prevalence of chronic fatigue in leukemia/lymphoma survivors	<ul style="list-style-type: none"> <li>N=92 (subgroup of 290); all HD</li> <li>Mean age diagnosis: 14.6 years</li> <li>Mean age at survey: 35.0 years</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional</li> <li>CFQ</li> </ul>	Sum of ≥4 using dichotomized (0, 0, 1, 1) 4-point Likert scale	<ul style="list-style-type: none"> <li>35% vs. 8% in control group (note control group age = 19–50 years)</li> <li>Adjusted odds ratio of fatigue in HD vs. control: 5.9</li> </ul>	Low
Mulrooney et al. 2008 <sup>50</sup>	Describe prevalence and risk factors for fatigue and sleep disturbance	<ul style="list-style-type: none"> <li>N=631 (subgroup of 1897)</li> <li>Diagnosed age: 15–21 years</li> <li>&gt;5 years from diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>26-center cohort study</li> <li>FACIT-fatigue</li> </ul>	Score below 10th percentile for sibling cohort	<ul style="list-style-type: none"> <li>8.6%</li> </ul>	Medium

(continued)

TABLE 3. (CONTINUED)

Study	Aim(s)	Participants (mixed tumors unless stated)	Study design and fatigue assessments	Definition of fatigue “case,”	Fatigue prevalence (rank compared to other symptoms)	Weight of Evidence D score
<b>MIXED DURING AND AFTER TREATMENT</b> Collins et al. 2000 <sup>17</sup>	Determine symptom prevalence, characteristics, and distress	<ul style="list-style-type: none"> <li>• N = 160</li> <li>• 70 had chemotherapy within last 2–4 weeks, 58 &gt; 4 months ago</li> <li>• Mean age: 14.0 years</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional</li> <li>• MSAS 10–18</li> </ul>	Presence of “lack of energy” in last week on MSAS	<ul style="list-style-type: none"> <li>• Overall: 49.7% (1 of 30)</li> <li>• CNS tumor: 66.7% (1 of 30)</li> <li>• Lymphoma: 50% (1 of 30)</li> <li>• Leukemia: 43.8% (2 of 30)</li> <li>• Solid tumor: 53.7% (3 of 30)</li> </ul>	Medium
Corey et al. 2008 <sup>56</sup>	Describe relationship between distress and three sources of support	<ul style="list-style-type: none"> <li>• N = 127 (ARM 1)</li> <li>• Mean age: 16.4 years (ARM 1)</li> <li>• Mean since diagnosis: 3.75 years (ARM 1 and 2)</li> </ul>	<ul style="list-style-type: none"> <li>• Secondary analysis of data from 2 studies</li> <li>• Symptom Distress Scale</li> </ul>	3–5 on 1–5 Likert scale	<ul style="list-style-type: none"> <li>• ARM 1 (mixed population): 31.4%</li> <li>• 1-year increase in age increased odds of fatigue by 1.23–1.25</li> </ul>	High
Enskar et al. 1997 <sup>67</sup>	Evaluate adolescents’ experience of areas of life affected by the disease	<ul style="list-style-type: none"> <li>• N = 10</li> <li>• Age 13–16 years at diagnosis n = 8</li> <li>• Age at interview: 15–20 years</li> <li>• N = 22</li> <li>• Age: 13–20 years</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional</li> <li>• observational</li> <li>• 5-point NRS (non-validated questionnaire)</li> <li>• Longitudinal, mixed methods</li> <li>• Daily diary entry and completion of fatigue NRS</li> </ul>	≥ 2 on 1–5 NRS	<ul style="list-style-type: none"> <li>• 100%</li> </ul>	Medium
Ream et al. 2006 <sup>18</sup>	Investigate impact of fatigue on adolescents	<ul style="list-style-type: none"> <li>• N = 22</li> <li>• Age: 13–20 years</li> </ul>	<ul style="list-style-type: none"> <li>• Longitudinal, mixed methods</li> <li>• Daily diary entry and completion of fatigue NRS</li> </ul>	Mention of fatigue in diary entries	<ul style="list-style-type: none"> <li>• Mentioned fatigue during treatment: 32; 30% in early remission (1–2 years after treatment), 10% in late remission (&gt; 5 years)</li> </ul>	Medium
Yeh et al. 2008, <sup>33</sup> 2009 <sup>34</sup>	Assess symptoms in older Taiwanese children	<ul style="list-style-type: none"> <li>• N = 144</li> <li>• Mean age: 14.2 years</li> <li>• For 108 on treatment, mean since diagnosis: 21.2 months</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional</li> <li>• observational</li> <li>• MSAS 10–18</li> </ul>	Presence of “lack of energy” in last week on MSAS	<ul style="list-style-type: none"> <li>• 52% (1 of 30)</li> <li>• On/off treatment: 52.8%, 50.0%</li> <li>• Leukemia: 57.3%</li> <li>• Lymphoma: 46.2%</li> <li>• Solid tumor: 46.5%</li> </ul>	Medium

ALL, acute lymphatic leukemia; AML, acute myeloid leukemia; ARM 1, Adolescent Resilience Model study 1; ARM 2, Adolescent Resilience Model study 2; CFQ, Chalder Fatigue Questionnaire; CNS, central nervous system; D1, D2, etc., day 1, day 2, etc.; DXM, dexamethasone; EBT, extremity bone tumor; FACIT-fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; FS-A, Fatigue Scale-Adolescent; FS-P, Fatigue Scale-Parent; HD, Hodgkin disease; LSS-A, Life Situation Scale for Adolescents; MFS, Multidimensional Fatigue Scale; MSAS (7–12, 10–18), Memorial Symptom Assessment Scale (for 7–12 and 10–18 age range); NORMS, healthy controls; NRS, Numerical Rating Scale; QOL, quality of life; RT, radiotherapy; T1, T2, etc., time point 1, time point 2, etc.; TC, testicular cancer; TRSC-C, Therapy-Related Symptom Checklist-Children; VAS, Visual Analogue Scale; VRS, Verbal Rating Scale.

TABLE 4. CONTROLLED STUDIES EVALUATING FATIGUE SEVERITY

Study	Aim(s)	Participants (mixed tumors unless stated)	Study design and fatigue assessments	Fatigue severity	Weight of Evidence D score
Aksnes et al. 2007 <sup>54</sup>	Examine fatigue, mental distress, and QOL in EBT survivors compared to matched controls	<ul style="list-style-type: none"> <li>• N=57 EBT survivors</li> <li>• Mean age at diagnosis within different cancer type subgroups: 16–25 years</li> <li>• Mean since diagnosis: 9–14 years</li> </ul>	<ul style="list-style-type: none"> <li>• Case-control (non-contemporaneous age- and gender-matched controls HD, TC, NORMS)</li> <li>• CFQ</li> </ul>	<ul style="list-style-type: none"> <li>• Mean total fatigue:</li> <li>• EBT survivors: 13.2</li> <li>• HD survivors: 13.4</li> <li>• TC survivors: 13.4</li> <li>• NORMS: 11.8</li> <li>• EBT survivors had significantly more fatigue than NORMS (<math>p=0.003</math>), but not more than other survivor groups</li> </ul>	Medium
Daniel et al. 2013 <sup>30</sup>	Compare adolescent and parent reports of fatigue in patients with and without cancer	<ul style="list-style-type: none"> <li>• N=102 with cancer on treatment</li> <li>• Mean age: 15.75 years</li> <li>• Mean since diagnosis: 20.4 months</li> <li>• N=97 controls; mean age: 15.55 years</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional observational (contemporaneous controls)</li> <li>• MFS</li> </ul>	<ul style="list-style-type: none"> <li>• MFS score in cancer and control groups, respectively: 58.54 and 71.72 (<math>p&lt;0.001</math>)</li> <li>• Total fatigue, general fatigue, and sleep/rest fatigue worse, but not cognitive fatigue</li> </ul>	High
Smith et al. 2013 <sup>31</sup>	Examine HRQOL of AYA patients and associated health-related characteristics	<ul style="list-style-type: none"> <li>• N=159</li> <li>• Age: 15–25 years</li> <li>• Subgroup of large AYA HOPE study with 523 cancer patients aged 15–39 at diagnosis</li> <li>• Since diagnosis: 6–14 months</li> <li>• 80% not on treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional observational (compared to age-range matched population norms)</li> <li>• MFS</li> </ul>	<ul style="list-style-type: none"> <li>• Mean MFS scores:</li> <li>• Ages 18–25: 61.3, significantly worse than reference healthy population score of 71.0 (<math>p=0.001</math>)</li> <li>• Ages 15–17: 59.8, not significantly different from ages 18–25 (no reference data for this age range)</li> </ul>	Medium

AYA, adolescent and young adult; AYA HOPE, Adolescent & Young Adult Health Outcomes & Patient Experience study; CFQ, Chalder Fatigue Questionnaire; EBT, extremity bone tumor; HD, Hodgkin disease; HRQOL, health-related quality of life; MFS, Multidimensional Fatigue Scale; NORMS, healthy controls; QOL, quality of life; TC, testicular cancer.



were worse in the two weeks after receiving chemotherapy and then improved until the next cycle. No longitudinal studies investigated fatigue severity over the longer period from treatment into survivorship. One small cross-sectional, observational study of three groups of adolescents during treatment ( $n=8$ ), 1–2 years after treatment ( $n=6$ ), and five or more years after treatment ( $n=8$ ) found that fatigue scores were highest during treatment, lowest during early remission, and higher again during late remission.<sup>18</sup>

### *Impact of fatigue*

Twenty-two studies reported the impact of fatigue on patients.<sup>17–19,23,33,34,37,39–43,48,55,68,72,73,80–84</sup> Distress caused by fatigue was the most commonly described impact, reported in 11 studies. The MSAS, a scale that allows comparison of the level of distress caused by each symptom, was used in six of these studies.<sup>17,33,34,68,72,73</sup> When symptoms were ranked in order of distress, fatigue was in the top half with only one exception.<sup>17</sup> One study reported that distress was correlated with the frequency and severity of fatigue.<sup>34</sup> The remaining five studies used diverse measures of distress,<sup>40,43,55,82,83</sup> and fatigue was one of the top four most distressing conditions in four of these studies.<sup>40,43,82,83</sup>

The second-most frequently described impact of fatigue was that it was a barrier to physical activity or exercise, which was reported in six studies.<sup>18,23,42,80,81,84</sup> Fatigue was the first<sup>80</sup> and second-most<sup>84</sup> significant barrier in one study each. Being unable to take part in exercise led to frustration and loss of confidence, with parents becoming “overprotective” and preventing their adolescents from taking part in activities that demanded energy.<sup>42</sup> Four studies reported fatigue as a barrier to other social activities,<sup>18,23,42,48</sup> including returning to school.<sup>48</sup> A negative impact on affective state, mood, or anxiety was described in three studies.<sup>19,23,37</sup>

### *Experience of parents*

Although 10 studies collected parent proxy reports of fatigue severity,<sup>30,37,38,47,49,59,60,74,75,77</sup> none investigated the experiences of parents of adolescent teenagers or young adults with cancer-related fatigue. Parent proxy reports of fatigue severity correlated more closely with those of their children for parents of cancer patients than for parents of healthy controls, which was attributed to the cancer patients’ parents being “physically closer” and “more attuned to the needs” of their children.<sup>30,59,61</sup> However, cancer patients’ parents appeared to be less adept than the patients themselves at perceiving changes in fatigue over time.<sup>60,77</sup> One study collected staff proxy reports of patient fatigue as well as parent proxy reports, and found that staff reports correlated less tightly than parent reports with patients’ self-reported fatigue.<sup>59</sup>

### *Fatigue correlates*

Factors correlating with the presence or severity of fatigue were reported in 27 studies, including five of the six scoring highest on the Gough’s Weight of Evidence Framework.<sup>30,38,47,49,51</sup>

Eleven studies highlighted an association between fatigue and physical symptoms, including poor sleep,<sup>35,37,57,61,74,75</sup> being part of a symptom cluster,<sup>33,70,73</sup> and nausea.<sup>29,61</sup> Al-

most all participants in the three studies that examined symptom clusters were receiving chemotherapy,<sup>33,70,73</sup> although there was no consistency in the specific symptoms found to cluster with fatigue, the symptoms tended to be chemotherapy-related. While receiving chemotherapy<sup>23,36,44,47,60,66</sup> or dexamethasone<sup>45</sup> both correlated with increasing fatigue, the evidence for a correlation between fatigue and hospital admission<sup>47,60,72</sup> or anemia<sup>46,60</sup> was conflicting. Even though patients associated fatigue with “doing too many things” or “being too active,”<sup>5,23</sup> there was a correlation between improved performance status and lower fatigue scores.<sup>46,78</sup>

Depression or low mood correlated with fatigue in five studies,<sup>30,38,59,61,85</sup> negative affect,<sup>29</sup> global distress,<sup>72</sup> anxiety,<sup>33,73</sup> and non-specific psychological conditions<sup>44,72</sup> were identified as correlates in a further five publications. Consistent with the link with physical and psychological symptoms, a high correlation with poor quality of life or satisfaction with life was reported in four studies.<sup>23,30,66,85</sup>

Although some of these correlations are intuitively likely to represent causal relationships—such as the relationship between fatigue and poor sleep quality—no studies addressed causality. However, one longitudinal study that observed a predictable fluctuation in fatigue during chemotherapy regimens of varying frequency<sup>23</sup> and a study involving planned periods on and off dexamethasone<sup>45</sup> both suggested causal relationships with fatigue.

### *Interventions to manage fatigue*

Table 5 details the five interventional trials for TYA cancer patients in which fatigue was used as an outcome measure.<sup>43,74,79,86,87</sup> Fatigue was not stated to be the primary outcome measure in any of the five. Three studies were uncontrolled<sup>79,86,87</sup> and three were feasibility studies.<sup>74,79,87</sup> Four involved evaluation of a structured activity intervention, and one investigated a self-care coping intervention. All of the interventions were standardized with a degree of individualization in accordance with each patient’s exercise capacity. Two uncontrolled trials found a statistically significant benefit from their interventions,<sup>79,86</sup> which involved intensive structured exercise in a gymnasium at weekly intervals for more than two months. The remaining two physical activity intervention studies involved bringing portable gym equipment to the patient’s hospital room and did not find any significant effect.<sup>74,87</sup> The self-care coping intervention was also ineffective.<sup>43</sup>

## **Discussion**

This review provides evidence that fatigue is one of the most prevalent and severe symptoms experienced by teenagers and young adults suffering from cancer, occurring in the majority of patients and particularly prevalent during cancer treatment. This finding is consistent with evidence in adults with cancer, for whom fatigue is now accepted as the most prevalent symptom.<sup>11</sup>

There were no studies comparing TYA patients’ fatigue with that of older adults with cancer. However, a number of publications compared fatigue in TYA patients to that in young children, with fatigue being more severe in the TYA population. This is consistent with the developmental sleep changes of adolescence. Healthy teenagers tend to develop

TABLE 5. STUDIES WITH FATIGUE INTERVENTIONS

Study	Aim(s)	Participants (mixed tumors unless stated)	Study design and intervention	Fatigue assessments	Results	Weight of Evidence D score
Atkinson et al. 2012 <sup>86</sup>	Determine the impact of a structured exercise intervention	<ul style="list-style-type: none"> <li>• N=55</li> <li>• Age: 15–25 years</li> </ul>	<ul style="list-style-type: none"> <li>• Uncontrolled trial</li> <li>• 2–3 sessions/week individual structured exercise in a hospital/private gymnasium with an exercise physiologist over 10 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Assessed pre- and post-intervention</li> <li>• Revised PFS, Ferrans and Powers QLI, measures of functional fitness</li> </ul>	<ul style="list-style-type: none"> <li>• Improvement in fatigue (<math>p \leq 0.0001</math>), as well as QOL and functional assessments</li> <li>• PFS scores decreased by 32%</li> </ul>	Medium
Hinds et al. 2000 <sup>43</sup>	Evaluate effects of an educational intervention designed to facilitate self-care coping	<ul style="list-style-type: none"> <li>• N=78</li> <li>• Mean age: 16.0 years</li> </ul>	<ul style="list-style-type: none"> <li>• Two-center randomized controlled trial</li> <li>• 40-minute intervention between T1 (1–12 days after diagnosis) and T2 (5–7 weeks after): information on self-care coping, video with strategies, and rehearsal of strategies</li> <li>• Control had equal time to discuss any topic</li> </ul>	<ul style="list-style-type: none"> <li>• Assessed at T1, T2, 3 months, and 6 months after diagnosis</li> <li>• Six outcome measures, including SDS (includes 5-point fatigue severity VRS)</li> </ul>	<ul style="list-style-type: none"> <li>• No difference in SDS score between groups at any time point</li> <li>• Fatigue 1 of 4 most distressing symptoms at every time point</li> </ul>	Low
Hinds et al. 2007 <sup>74</sup>	Evaluate the feasibility of using an enhanced physical activity intervention	<ul style="list-style-type: none"> <li>• N=11</li> <li>• Subgroup age: 13–18 years</li> </ul>	<ul style="list-style-type: none"> <li>• Two-center pilot randomized controlled trial</li> <li>• Pedaling a stationary bicycle exerciser for 30 minutes twice daily for 2–4 days of hospitalization with equipment brought to hospital room</li> <li>• Control spent equal time with researcher</li> </ul>	<ul style="list-style-type: none"> <li>• Assessed daily on days 1, 2, and 3</li> <li>• Patient, parent, and staff fatigue reports (FS-C, -A, -P, -S), wrist actigraphy, parent sleep diary, hemoglobin</li> </ul>	<ul style="list-style-type: none"> <li>• No difference between groups</li> </ul>	Medium
Keats et al. 2008 <sup>79</sup>	Assess feasibility of a physical activity intervention	<ul style="list-style-type: none"> <li>• N=10</li> <li>• Age: 14–18 years</li> <li>• Mean since diagnosis: 62.5 months</li> </ul>	<ul style="list-style-type: none"> <li>• Uncontrolled feasibility study</li> <li>• Weekly 90 minutes of group education and training for 8 weeks in gymnasium, then variety of non-competitive activities over 16 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Assessed at baseline, week 8, week 16, 3 months, and 1 year</li> <li>• PedsQL, MFS, Leisure Score Index, FitnessGram (a physical fitness test)</li> </ul>	<ul style="list-style-type: none"> <li>• Improvement in fatigue between baseline and 3 months (<math>p=0.01</math>), but post-intervention benefits not sustained at 3 months and 1 year</li> </ul>	Medium
Rosenhagen et al. 2011 <sup>87</sup>	Investigate feasibility and acceptability of sports therapy	<ul style="list-style-type: none"> <li>• N=13</li> <li>• Mean age: 15.3 years</li> </ul>	<ul style="list-style-type: none"> <li>• Uncontrolled feasibility study (control group gave acceptability data only)</li> <li>• Individualized exercise using ergometer in hospital room during isolation phase of SCT</li> </ul>	<ul style="list-style-type: none"> <li>• Assessed on days 1 and 14 and on discharge after SCT</li> <li>• QOL self-assessment, MFS</li> </ul>	<ul style="list-style-type: none"> <li>• Non-significant trend for fatigue improvement pre- and post-intervention</li> </ul>	Low

FS-A, Fatigue Scale-Adolescent; FS-C, Fatigue Scale-Child; FS-P, Fatigue Scale-Parent; FS-S, Fatigue Scale-Staff; MFS, Multidimensional Fatigue Scale; PedsQL, Pediatric Quality of Life Inventory; PFS, Piper Fatigue Scale; QLI, quality of life index; QOL, quality of life; SDS, Symptom Distress Scale; SCT, stem cell transplant; T1, T2, etc., time point 1, time point 2, etc.; VRS, Verbal Rating Scale.

fatigue and daytime sleepiness related to inadequate sleep.<sup>21</sup> At this age, longer sleep is needed, yet shifts in circadian rhythms result in later bed times; the amount of time spent sleeping is further limited by unhelpful sleep habits, such as caffeine consumption and social engagements.<sup>21</sup> Controlled studies have shown that fatigue in teenaged and young adult cancer patients is even higher than that in healthy controls.<sup>30,32,51,54</sup> The dual risk factors for fatigue development—having cancer and being within or soon after the teenaged years—appear to combine to create a particularly significant problem in this vulnerable patient group.

Cancer-related fatigue is not only present during or soon after treatment: several studies of TYA cancer survivors showed long-term continuation of fatigue many years after cancer diagnosis and treatment.<sup>32,52,54</sup> Given that TYA cancer patients have an approximately 80% five-year survival rate,<sup>6</sup> this means that large numbers of young people are contending with ongoing morbidity while attempting to rebuild their lives after a cancer diagnosis.

Not only is fatigue prevalent, severe, and persistent, there is consistent evidence that fatigue causes significant distress, with a negative impact on quality of life. Fatigue may be a particularly distressing symptom in teenagers and young adults because of its impact on functioning at an age when independence and social interactions are high priorities. The inherent social isolation resulting from the diagnosis of a serious disease at a young age that can require years of burdensome treatment is further compounded by the presence of fatigue. The level of distress may also reflect the developmental stage of teenagers and young adults, who are more able than children to understand the significance of their symptoms and underlying cancer, yet may be less able to control and rationalize their emotions than older adults.

Despite the increasingly strong and consistent evidence base confirming the magnitude of the problem, there are no published studies evaluating interventions whose primary aim is to treat or prevent fatigue. The few interventional studies to date are mostly uncontrolled or feasibility studies investigating physical activity. Exercise is recognized as an effective treatment in adults with cancer-related fatigue. The presence of fatigue hinders activity, which then leads to deconditioning (or loss of “fitness”). This in turn worsens the fatigue, so leading to a vicious cycle that perpetuates the symptom. Exercise or activity is believed to work, at least in part, by preventing deconditioning and the development of this vicious cycle. Although two of the four physical activity interventional studies did report significant findings, both were uncontrolled. Given the well-established placebo effect that occurs with subjective symptoms such as fatigue,<sup>88</sup> the strength of existing evidence for intervention effectiveness in the TYA age group is, as yet, poor.

In the context of physical activity being the only intervention for fatigue with any—albeit limited—supporting evidence in the TYA literature, a significant finding of this review is that fatigue itself is a key barrier to activity. There is mounting evidence that resting is perceived by patients, parents, and healthcare professionals as the best approach to managing fatigue. Studies have found that young patients feel that “being too active” or “doing too many things” may worsen fatigue;<sup>5,23</sup> that parents encourage rest;<sup>42</sup> and that in a mixed child and teenage population, healthcare professionals’ most commonly recommended treatment for fatigue was rest and relaxation.<sup>89</sup>

There is evidence that activity levels tend to decline during the teenaged years due to conflicting priorities, fear of injury, and a sense of embarrassment.<sup>90</sup> It is conceivable that TYA cancer patients may be particularly prone to such decline in activity; there may be perceived increased vulnerability to injury, and disease- or treatment-related bodily changes that could potentially cause self-consciousness.<sup>90</sup> Cancer-related fatigue, in combination with these normal teenage inhibitions, can therefore present a formidable barrier to activity, paradoxically the very intervention that appears to have the greatest potential to improve their fatigue. Furthermore, at this formative age, life-long habits are developed. Maladaptive behaviors such as inactivity are therefore even more likely to persist, perpetuating fatigue and its associated disability and adverse psychosocial sequelae long-term.

### *Strengths and limitations*

The main strength of this review is its breadth: studies were eligible if they investigated any aspect of cancer-related fatigue in TYA-aged patients, and even those with only a subgroup of patients aged 13–24 were included. The database search strategy was effective, with five articles found from other searches. The included studies, however, were heterogeneous and of relatively low quality, limiting the strength of the findings. Although experts in the field were contacted, literature not formally published in the form of journal articles (so-called “gray” literature) may have been missed. Exclusion of articles not in English may also have led to the omission of relevant articles.

### *Implications for clinical practice*

Clinicians should be aware of the prevalence and severity of fatigue in TYA cancer patients, as well as the significant distress it causes. It is possible that a degree of therapeutic nihilism has developed due the lack of clearly effective pharmacological interventions for fatigue.<sup>91</sup> Simply inquiring about the presence of fatigue in each clinical encounter may in itself be helpful, as this can openly acknowledge the problem and provide the possibility for peer and professional support.

Although the evidence base for exercise interventions is very limited, it is clear that encouragement of physical activity is likely to be helpful. In adults, it is well established that exercise improves cancer-related fatigue.<sup>15,92</sup> The wider benefits of keeping active during and after cancer treatment include increased well-being, functioning, and quality of life, as well as reduced cancer recurrence and mortality.<sup>93–96</sup> Clinicians, potentially lacking the time and knowledge to counsel TYA cancer patients about physical activity, should develop the skills to educate and address any misconceptions of TYA patients and their parents about the benefits of activity, should including confirming its potential to ameliorate rather than—as intuitively expected—worsen fatigue.

The correlation between fatigue and concurrent symptoms, such as poor sleep, is consistent with the evidence in adults that the management of sleep disorders<sup>97</sup> and other symptoms<sup>98</sup> can improve cancer-related fatigue. Rigorous control of concurrent symptoms, including education about sleep needs and habits in adolescence, may have a positive impact on fatigue.

### Implications for future research

This review has revealed many gaps in the literature. Further prevalence studies are needed with concurrent controls, using a longitudinal design to evaluate changes in fatigue and fatigue-related distress within a cohort from treatment into long-term survivorship. It would be valuable to compare fatigue severity and associated distress in TYAs and older adults. Future studies could usefully attempt to establish the directionality of relationships between fatigue and other factors. Determination of factors that cause, rather than are simply associated with, fatigue could helpfully guide fatigue management. Evidence for this review came from only five countries; further global research into TYA cancer-related fatigue is needed.

Use of dexamethasone in the TYA population appears to worsen fatigue by reducing sleep efficiency and increasing night-time awakenings.<sup>45</sup> Conversely, in adults, this drug may improve fatigue.<sup>99</sup> This conflicting evidence may indicate a genuine difference in the reaction to steroids of adolescents compared to older adults, and is worthy of further exploration.

Current research has established that cancer-related fatigue is a prevalent and distressing symptom in TYA cancer patients. It is essential that future research now focus on the development of interventions to manage fatigue, in order to limit the long-term suffering of this already vulnerable and burdened group of cancer patients. Physical activity—including determining its optimal forms and frequency—is a key research priority, as is assessing the impact of improving sleep hygiene and concurrent symptom control. Research considering parents' perspectives and experiences is also needed given that parental protectiveness may hinder the physical activity that could help ameliorate a TYA patient's fatigue. A deeper understanding of parents' views and attitudes could facilitate meaningful education of parents that, in turn, effectively increases the activity of TYA cancer patients.

### Conclusion

The fatigue experienced by teenagers and young adults with cancer is prevalent, persistent, and distressing. It has a negative impact on quality of life and social functioning that is particularly problematic at this formative age. The magnitude of the problem is established—it is now time to intervene.

### Acknowledgments

SB and AS were funded by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care East of England at Cambridgeshire and Peterborough NHS Foundation Trust.

### Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

### Author Disclosure Statement

No competing financial interests exist.

### References

1. Office of National Statistics. Mortality statistics: deaths registered in England and Wales (Series DR, 2012). Accessed October 16, 2014 from: [www.ons.gov.uk/ons/rel/vsobl/mortality-statistics-deaths-registered-in-england-and-wales-series-dr/2012/index.html](http://www.ons.gov.uk/ons/rel/vsobl/mortality-statistics-deaths-registered-in-england-and-wales-series-dr/2012/index.html)
2. Cancer Research UK. Teenage and young adult cancer incidence statistics. Accessed October 16, 2014 from: [www.cancerresearchuk.org/cancer-info/cancerstats/teenage-and-young-adult-cancer/incidence/](http://www.cancerresearchuk.org/cancer-info/cancerstats/teenage-and-young-adult-cancer/incidence/)
3. Bleyer A, O'Leary M, Barr R, Ries LAG (Eds). Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975–2000 (NIH Publication No. 06-5767). Bethesda, MD: National Cancer Institute; 2006.
4. Smith S, Case L, Waterhouse K, et al. A blueprint of care for teenagers and young adults with cancer. London: Teenage Cancer Trust; 2012.
5. Hinds PS, Hockenberry-Eaton M, Gilger E, et al. Comparing patient, parent, and staff descriptions of fatigue in pediatric oncology patients. *Cancer Nurs*. 1999;22(4): 277–88.
6. O'Hara C, Moran A, TYA National Cancer Intelligence Advisory Group. Survival in teenagers and young adults with cancer in the UK. London: National Cancer Intelligence Network; August 2012.
7. National Institute for Health and Clinical Excellence. Guidance on cancer services: improving outcomes in children and young people with cancer. London: National Institute for Health and Clinical Excellence; August 2005.
8. Mock V, Atkinson A, Barsevick A, et al. NCCN practice guidelines for cancer-related fatigue. *Oncology (Williston Park)*. 2000;14(11A):151–61.
9. Glaus A, Crow R, Hammond S. A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals. *Support Care Cancer*. 1996; 4(2):82–96.
10. Curt GA. Fatigue in cancer. *BMJ*. 2001;322(7302):1560.
11. Hofman M, Ryan JL, Figueroa-Moseley CD, et al. Cancer-related fatigue: the scale of the problem. *Oncologist*. 2007;12(Suppl 1):4–10.
12. Vogelzang NJ, Breitbart W, Cella D, et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. *The Fatigue Coalition. Semin Hematol*. 1997;34(Suppl 1):4–12.
13. Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist*. 2000;5(5):353–60.
14. Stone P, Richardson A, Ream E, et al. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. *Cancer Fatigue Forum. Ann Oncol*. 2000;11(8):971–5.
15. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev*. 2012;11:CD006145.
16. Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G. Psychosocial interventions for reducing fatigue during cancer treatment in adults. *Cochrane Database Syst Rev*. 2009;1:CD006953.
17. Collins JJ, Byrnes ME, Dunkel II, et al. The measurement of symptoms in children with cancer. *J Pain Symptom Manage*. 2000;19(5):363–77.



18. Ream E, Gibson F, Edwards J, et al. Experience of fatigue in adolescents living with cancer. *Cancer Nurs*. 2006; 29(4):317–26.
19. Gibson F, Mulhall AB, Richardson A, et al. A phenomenologic study of fatigue in adolescents receiving treatment for cancer. *Oncol Nurs Forum*. 2005;32(3):651–60.
20. Erickson JM. Fatigue in adolescents with cancer: a review of the literature. *Clin J Oncol Nurs*. 2004;8(2):139–45.
21. Crowley SJ, Acebo C, Carskadon MA. Sleep, circadian rhythms, and delayed phase in adolescence. *Sleep Med*. 2007;8(6):602–12.
22. Dahl RE, Lewin DS. Pathways to adolescent health sleep regulation and behavior. *J Adolesc Health*. 2002; 31(6 Suppl):175–84.
23. Erickson JM, Beck SL, Christian B, et al. Patterns of fatigue in adolescents receiving chemotherapy. *Oncol Nurs Forum*. 2010;37(4):444–55.
24. Erickson JM, MacPherson CF, Ameringer S, et al. Symptoms and symptom clusters in adolescents receiving cancer treatment: a review of the literature. *Int J Nurs Stud*. 2013;50(6):847–69.
25. Daniëls LA, Oerlemans S, Krol AD, et al. Persisting fatigue in Hodgkin lymphoma survivors: a systematic review. *Ann Hematol*. 2013;92(8):1023–32.
26. McMillan EM, Newhouse IJ. Exercise is an effective treatment modality for reducing cancer-related fatigue and improving physical capacity in cancer patients and survivors: a meta-analysis. *Appl Physiol Nutr Metab*. 2011; 36(6):892–903.
27. Chang CW, Mu PF, Jou ST, et al. Systematic review and meta-analysis of nonpharmacological interventions on fatigue in children and adolescents with cancer. *Worldviews Evid Based Nurs*. 2013;10(4):208–17.
28. Gough D. Weight of Evidence: a framework for the appraisal of the quality and relevance of evidence. *Res Paper Educ*. 2007;22(2):213–28.
29. Wesley KM, Zelikovsky N, Schwartz LA. Physical symptoms, perceived social support, and affect in adolescents with cancer. *J Psychosoc Oncol*. 2013;31(4):451–67.
30. Daniel LC, Brumley LD, Schwartz LA. Fatigue in adolescents with cancer compared to healthy adolescents. *Pediatr Blood Cancer*. 2013;60(11):1902–7.
31. Hamre H, Zeller B, Kanellopoulos A, et al. Serum cytokines and chronic fatigue in adults surviving after childhood leukemia and lymphoma. *Brain Behav Immun*. 2013;30:80–7.
32. Hamre H, Zeller B, Kanellopoulos A, et al. High prevalence of chronic fatigue in adult long-term survivors of acute lymphoblastic leukemia and lymphoma during childhood and adolescence. *J Adolesc Young Adult Oncol*. 2013;2(1):2–9.
33. Yeh CH, Chiang YC, Chien LC, et al. Symptom clustering in older Taiwanese children with cancer. *Oncol Nurs Forum*. 2008;35(2):273–81.
34. Yeh CH, Wang CH, Chiang YC, et al. Assessment of symptoms reported by 10- to 18-year-old cancer patients in Taiwan. *J Pain Symptom Manage*. 2009;38(5):738–46.
35. Erickson JM, Beck SL, Christian BR, et al. Fatigue, sleep-wake disturbances, and quality of life in adolescents receiving chemotherapy. *J Pediatr Hematol Oncol*. 2011; 33(1):e17–25.
36. Hockenberry MJ, Hooke MC, Gregurich M, McCarthy K. Carnitine plasma levels and fatigue in children/adolescents receiving cisplatin, ifosfamide, or doxorubicin. *J Pediatr Hematol Oncol*. 2009;31(9):664–9.
37. Hockenberry MJ, Hooke MC, Gregurich M, et al. Symptom clusters in children and adolescents receiving cisplatin, doxorubicin, or ifosfamide. *Oncol Nurs Forum*. 2010;37(1):E16–27.
38. Hockenberry MJ, Hooke MC, McCarthy K, Gregurich MA. Sickness behavior clustering in children with cancer. *J Pediatr Oncol Nurs*. 2011;28(5):263–72.
39. Hedström M, Haglund K, Skolin I, von Essen L. Distressing events for children and adolescents with cancer: child, parent, and nurse perceptions. *J Pediatr Oncol Nurs*. 2003;20(3):120–32.
40. Hedström M, Ljungman G, von Essen L. Perceptions of distress among adolescents recently diagnosed with cancer. *J Pediatr Hematol Oncol*. 2005;27(1):15–22.
41. Hedström M, Skolin I, von Essen L. Distressing and positive experiences and important aspects of care for adolescents treated for cancer. Adolescent and nurse perceptions. *Eur J Oncol Nurs*. 2004;8(1):6–17.
42. Chiang Y, Yeh CH, Wang KW, Yang CP. The experience of cancer-related fatigue in Taiwanese children. *Eur J Cancer Care (Engl)*. 2009;18(1):43–9.
43. Hinds P, Quargnenti A, Bush AJ, et al. An evaluation of the impact of a self-care coping intervention on psychological and clinical outcomes in adolescents with newly diagnosed cancer. *Eur J Oncol Nurs*. 2000;4(1):6–17.
44. Hinds PS, Nuss SL, Ruccione KS, et al. PROMIS pediatric measures in pediatric oncology: valid and clinically feasible indicators of patient-reported outcomes. *Pediatr Blood Cancer*. 2013;60(3):402–8.
45. Hinds PS, Hockenberry MJ, Gattuso JS, et al. Dexamethasone alters sleep and fatigue in pediatric patients with acute lymphoblastic leukemia. *Cancer*. 2007; 110(10):2321–30.
46. Lai JS, Cella D, Kupst MJ, et al. Measuring fatigue for children with cancer: development and validation of the pediatric Functional Assessment of Chronic Illness Therapy-Fatigue (pedsFACIT-F). *J Pediatr Hematol Oncol*. 2007; 29(7):471–9.
47. Mandrell BN, Yang J, Hooke MC, et al. Psychometric and clinical assessment of the 13-item reduced version of the Fatigue Scale-Adolescent instrument. *J Pediatr Oncol Nurs*. 2011;28(5):287–94.
48. McLoone JK, Wakefield CE, Butow P, et al. Returning to school after adolescent cancer: a qualitative examination of Australian survivors' and their families' perspectives. *J Adolesc Young Adult Oncol*. 2011;1(2):87–94.
49. Meeske K, Katz ER, Palmer SN, et al. Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. *Cancer*. 2004;101(9):2116–25.
50. Mulrooney DA, Ness KK, Neglia JP, et al. Fatigue and sleep disturbance in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study (CCSS). *Sleep*. 2008;31(2):271–81.
51. Smith AW, Bellizzi KM, Keegan TH, et al. Health-related quality of life of adolescent and young adult patients with cancer in the United States: the Adolescent and Young Adult Health Outcomes and Patient Experience study. *J Clin Oncol*. 2013;31(17):2136–45.
52. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *J Clin Oncol*. 2004;22(15):3139–48.

53. Zupanec S, Jones H, Stremmler R. Sleep habits and fatigue of children receiving maintenance chemotherapy for ALL and their parents. *J Pediatr Oncol Nurs*. 2010;27(4):217–28.
54. Aksnes LH, Hall KS, Jebsen N, et al. Young survivors of malignant bone tumours in the extremities: a comparative study of quality of life, fatigue and mental distress. *Support Care Cancer*. 2007;15(9):1087–96.
55. Azizi N, Mansour L, Tahmassian K, Mosavi F. Determining, ranking and comparing treatment stressors in children and adolescents with cancer in Tehran. *Iranian J Cancer Prevent*. 2012;5(3):138–43.
56. Corey AL, Haase JE, Azzouz F, Monahan PO. Social support and symptom distress in adolescents/young adults with cancer. *J Pediatr Oncol Nurs*. 2008;25(5):275–84.
57. Ameringer S, Elswick RK Jr, Shockey DP, Dillon R. A pilot exploration of symptom trajectories in adolescents with cancer during chemotherapy. *Cancer Nurs*. 2013;36(1):60–71.
58. Gibson F, Edwards J, Sepion B, Richardson A. Cancer-related fatigue in children and young people: survey of healthcare professionals' knowledge and attitudes. *Eur J Oncol Nurs*. 2006;10(4):311–6.
59. Hinds PS, Hockenberry M, Tong X, et al. Validity and reliability of a new instrument to measure cancer-related fatigue in adolescents. *J Pain Symptom Manage*. 2007;34(6):607–18.
60. Perdikaris P, Merkouris A, Patiraki E, et al. Evaluating cancer related fatigue during treatment according to children's, adolescents' and parents' perspectives in a sample of Greek young patients. *Eur J Oncol Nurs*. 2009;13(5):399–408.
61. Whitsett SF, Gudmundsdottir M, Davies B, et al. Chemotherapy-related fatigue in childhood cancer: correlates, consequences, and coping strategies. *J Pediatr Oncol Nurs*. 2008;25(2):86–96.
62. Varni JW, Burwinkle TM, Katz ER, et al. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer*. 2002;94(7):2090–106.
63. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *Eur J Cancer*. 1994;30A(9):1326–36.
64. Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. *J Psychosom Res*. 1993;37(2):147–53.
65. Baggott C, Gibson F, Coll B, et al. Initial evaluation of an electronic symptom diary for adolescents with cancer. *JMIR Res Protoc*. 2012;1(2):e23.
66. Enskär K, von Essen L. Prevalence of aspects of distress, coping, support and care among adolescents and young adults undergoing and being off cancer treatment. *Eur J Oncol Nurs*. 2007;11(5):400–8.
67. Enskär K, Carlsson M, Golsäter M, Hamrin E. Symptom distress and life situation in adolescents with cancer. *Cancer Nurs*. 1997;20(1):23–33.
68. Walker AJ, Gedaly-Duff V, Miaskowski C, Nail L. Differences in symptom occurrence, frequency, intensity, and distress in adolescents prior to and one week after the administration of chemotherapy. *J Pediatr Oncol Nurs*. 2010;27(5):259–65.
69. Williams PD, Williams AR, Kelly KP, et al. A symptom checklist for children with cancer: the Therapy-Related Symptom Checklist-Children. *Cancer Nurs*. 2012;35(2):89–98.
70. Baggott C, Cooper BA, Marina N, et al. Symptom cluster analyses based on symptom occurrence and severity ratings among pediatric oncology patients during myelosuppressive chemotherapy. *Cancer Nurs*. 2012;35(1):19–28.
71. Baggott C, Dodd M, Kennedy C, et al. Changes in children's reports of symptom occurrence and severity during a course of myelosuppressive chemotherapy. *J Pediatr Oncol Nurs*. 2010;27(6):307–15.
72. Miller E, Jacob E, Hockenberry MJ. Nausea, pain, fatigue, and multiple symptoms in hospitalized children with cancer. *Oncol Nurs Forum*. 2011;38(5):E382–93.
73. Atay S, Conk Z, Bahar Z. Identifying symptom clusters in paediatric cancer patients using the Memorial Symptom Assessment Scale. *Eur J Cancer Care (Engl)*. 2012;21(4):460–8.
74. Hinds PS, Hockenberry M, Rai SN, et al. Clinical field testing of an enhanced-activity intervention in hospitalized children with cancer. *J Pain Symptom Manage*. 2007;33(6):686–97.
75. Orsey AD, Wakefield DB, Cloutier MM. Physical activity (PA) and sleep among children and adolescents with cancer. *Pediatric Blood Cancer*. 2013;60(11):1908–13.
76. Hockenberry MJ, Hinds PS, Barrera P, et al. Three instruments to assess fatigue in children with cancer: the child, parent and staff perspectives. *J Pain Symptom Manage*. 2003;25(4):319–28.
77. Hinds PS, Hockenberry M, Rai SN, et al. Nocturnal awakenings, sleep environment interruptions, and fatigue in hospitalized children with cancer. *Oncol Nurs Forum*. 2007;34(2):393–402.
78. Hooke MC, Garwick AW, Gross CR. Fatigue and physical performance in children and adolescents receiving chemotherapy. *Oncol Nurs Forum*. 2011;38(6):649–57.
79. Keats MR, Culos-Reed SN. A community-based physical activity program for adolescents with cancer (project TREK): program feasibility and preliminary findings. *J Pediatr Hematol Oncol*. 2008;30(4):272–80.
80. Arroyave WD, Clipp EC, Miller PE, et al. Childhood cancer survivors' perceived barriers to improving exercise and dietary behaviors. *Oncol Nurs Forum*. 2008;35(1):121–30.
81. Cassano J, Nagel K, O'Mara L. Talking with others who "just know": perceptions of adolescents with cancer who participate in a teen group. *J Pediatr Oncol Nurs*. 2008;25(4):193–9.
82. Griffith KC, Hart LK. Characteristics of adolescent cancer survivors who pursue postsecondary education. *Cancer Nurs*. 2000;23(6):468–76.
83. Hinds PS, Quargnenti AG, Wentz TJ. Measuring symptom distress in adolescents with cancer. *J Pediatr Oncol Nurs*. 1992;9(2):84–6.
84. Lockwood R, Smith C. Physical activity during and after treatment for cancer: what do teenagers and young adults want from a service? Poster presented at the Teenage Cancer Trust 7th International Conference on Teenage and Young Adult Cancer Medicine, June 25–26, 2012, in London, United Kingdom.
85. Ruccione K, Lu Y, Meeske K. Adolescents' psychosocial health-related quality of life within 6 months after cancer treatment completion. *Cancer Nurs*. 2013;36(5):E61–72.

86. Atkinson M, Osborn M. A structured ten-week exercise intervention is associated with improvements in quality of life, fatigue, and functional status in adolescents and young adults with cancer. *Asia Pac J Clin Oncol*. 2012; 8(Suppl 3):abstract 321.
87. Rosenhagen A, Bernhörster M, Vogt L, et al. Implementation of structured physical activity in the pediatric stem cell transplantation. *Klin Padiatr*. 2011;223(3): 147–51.
88. de la Cruz M, Hui D, Parsons HA, Bruera E. Placebo and nocebo effects in randomized double-blind clinical trials of agents for the therapy for fatigue in patients with advanced cancer. *Cancer*. 2010;116(3):766–74.
89. Gibson F, Garnett M, Richardson A, et al. Heavy to carry: a survey of parents' and healthcare professionals' perceptions of cancer-related fatigue in children and young people. *Cancer Nurs*. 2005;28(1):27–35.
90. Grieser M, Vu M, Bedimo-Rung A, et al. Physical activity attitudes, preferences, and practices in African American, Hispanic, and Caucasian girls. *Health Educ Behav*. 2006; 33(1):40–51.
91. Spathis A, Fife F, Blackhall F, et al. Modafinil for the treatment of fatigue in lung cancer: results of a placebo-controlled, double-blinded, randomized trial. *J Clin Oncol*. 2014;32(18):1882–8.
92. Ibrahim EM, Al-Homaidh A. Physical activity and survival after breast cancer diagnosis: meta-analysis of published studies. *Med Oncol*. 2010;28(3):753–65.
93. Meyerhardt JA, Giovannucci EL, Holmes MD, et al. Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol*. 2006;24(22):3527–34.
94. Segal RJ, Reid RD, Courneya KS, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol*. 2003;21(9):1653–9.
95. Speck RM, Courneya KS, Masse LC, et al. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv*. 2010;4(2):87–100.
96. Holmes MD, Chen WY, Feskanich D, et al. Physical activity and survival after breast cancer diagnosis. *JAMA*. 2005;293(20):2479–86.
97. Zee PC, Ancoli-Israel S. Does effective management of sleep disorders reduce cancer-related fatigue? *Drugs*. 2009;69(Suppl 2):29–41.
98. de Raaf PJ, de Klerk C, Timman R, et al. Systematic monitoring and treatment of physical symptoms to alleviate fatigue in patients with advanced cancer: a randomized controlled trial. *J Clin Oncol*. 2013;31(6):716–23.
99. Yennurajalingam S, Frisbee-Hume S, Palmer JL, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *J Clin Oncol*. 2013;31(25): 3076–82.
100. Yellen S, Cella D, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*. 1997;13(2):63–74.
101. Piper BF, Dibble SL, Dodd MJ, et al. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. *Oncol Nurs Forum*. 1998;25(4):677–84.
102. McCorkle R. The measurement of symptom distress. *Semin Oncol Nurs*. 1987;3(4):248–56.

Address correspondence to:

*Anna Spathis, MSc  
Department of Palliative Care, Box 63  
Addenbrooke's Hospital  
Cambridge University Hospitals NHS Foundation Trust  
Cambridge CB2 0QQ  
United Kingdom*

*Email: aspathis@doctors.org.uk*

## Cancer-Related Fatigue in Adolescents and Young Adults After Cancer Treatment: Persistent and Poorly Managed

Anna Spathis, MSc,<sup>1,2</sup> Helen Hatcher, PhD,<sup>1</sup> Sara Booth, MD,<sup>2</sup> Faith Gibson, PhD,<sup>3,4</sup> Paddy Stone, MD,<sup>5</sup> Laura Abbas, BSc,<sup>1</sup> Matt Barclay, MSc,<sup>2</sup> James Brimicombe, BA,<sup>2</sup> Pia Thiemann, PhD,<sup>2</sup> Martin G. McCabe, PhD,<sup>6</sup> Rachel Campsey, BSc,<sup>7</sup> Louise Hooker, MSc,<sup>8</sup> Wendy Moss,<sup>1</sup> Jane Robson, BA,<sup>1</sup> and Stephen Barclay, MD<sup>2</sup>

Cancer-related fatigue is the most prevalent and distressing symptom experienced by adolescents and young adults (AYAs). An electronic survey was undertaken to ascertain current fatigue management and perceptions of its effectiveness. Eighty-five percent of responders (68/80) experienced fatigue, and it was worse more than 1 year after cancer treatment ended, compared to <1 year ( $p=0.007$ ). Forty-one percent received no fatigue management. Although advice to exercise was the most frequent intervention, the greatest impact of fatigue was on the ability to exercise and most did not find exercise advice helpful. Early intervention is warranted, supporting AYAs to persevere with increasing activity.

**Keywords:** fatigue, symptom control, quality of life, late effects

### Introduction

FATIGUE IS ONE of the most prevalent, severe, and distressing symptoms experienced by adolescents and young adults (AYAs) with cancer.<sup>1,2</sup> Healthy adolescents are inherently susceptible to fatigue. The developmental changes of adolescence mean that longer sleep times are needed, while accompanying shifts in circadian rhythm result in later bedtimes.<sup>3</sup> Sleep is further hindered by use of light-producing electronic devices in the bedroom, social commitments, and alcohol consumption.<sup>3,4</sup> AYA cancer patients experience even more severe fatigue than their healthy counterparts.<sup>5–7</sup> Young age and a cancer diagnosis, dual risk factors for fatigue, combine to create a particularly significant problem in this patient group.

Despite this, fatigue is a neglected symptom in AYAs, with no interventional studies focusing on fatigue management at this young age. Research evaluating interventions in older adults has begun to accumulate over the last decade. The

most promising approaches are exercise and psychosocial interventions such as education and treatment of concurrent symptoms, with little evidence for pharmacological management.<sup>8–11</sup> AYAs have unique needs that differ from those of adults and children, and it is well recognized that research outcomes in older adults cannot be extrapolated to the younger population. This has led to an international drive to develop evidence-based age-appropriate care.<sup>12,13</sup>

Preparatory research is needed to support the development of an AYA fatigue intervention that meets their needs. Although qualitative studies have provided insight into the unmet needs of this young group,<sup>14–17</sup> patients' needs have not been prioritized quantitatively, and there has been no evaluation of the impact on carers.<sup>1</sup> Furthermore, current practice in fatigue management is unknown. The objectives of this multicenter survey were to quantify the impact of fatigue on young patients and their carers, to find out how fatigue is currently being managed in the United Kingdom, and to ascertain perceptions of the effectiveness of such management.

<sup>1</sup>Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom.

<sup>2</sup>University of Cambridge, Cambridge, United Kingdom.

<sup>3</sup>Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom.

<sup>4</sup>University of Surrey, Guildford, United Kingdom.

<sup>5</sup>University College, London, United Kingdom.

<sup>6</sup>University of Manchester, Manchester, United Kingdom.

<sup>7</sup>The Christie NHS Foundation Trust, Manchester, United Kingdom.

<sup>8</sup>University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom.



## Methods

### Procedure

Participants were recruited from three Teenage and Young Adult Principal Treatment Centres (TYA PTCs) in the United Kingdom, and were required to have been diagnosed or treated with cancer at age 13–24 and to be 16–27 at the time of the survey.<sup>18</sup>

Electronic survey methods were used, following advice from TYA PTC service users. After priming by email, poster, and social media, a personalized email of invitation was sent to potential participants, containing a unique token number and links to the Participant Information Sheet and survey. Nonresponders were ascertained by noting unused tokens, and one reminder email was sent to nonresponders after 7 days. Approval was given by the National Research Ethics Service Committee East of England—Cambridgeshire and Hertfordshire (ref. 15/EE/0037).

### Outcome measures

Demographic data were collected from both responders and nonresponders. Participants completed two validated measures. The PedsQL™ Multidimensional Fatigue Scale (MFS) is a widely used 18-item scale validated in both adolescents and in young adults; scores are linearly transformed to a 0–100 scale, with lower scores representing worse fatigue.<sup>19</sup> The Quality of Life Visual Analog Scale (QOL-VAS) is a single-item measure of quality of life that captures a clinically significant change in quality of life more readily than multiple-item measures.<sup>20,21</sup>

The severity of 11 symptoms and the impact of fatigue were quantified using a 5-item verbal rating scale: “not at all,” “a little bit,” “somewhat,” “quite a bit,” and “very

much.” The successfulness of each treatment received for fatigue was rated using a 4-item scale: “entirely successful,” “somewhat successful,” “helped only a little,” and “no effect.” A “successfulness score” for fatigue treatment was generated by attributing 0, 1, 2, and 3 to the ratings “no effect,” “helped only a little,” “somewhat successful,” and “entirely successful,” respectively, for each treatment received and calculating a mean score. The former two ratings defined an unsuccessful treatment and the latter two a successful one. Selection of single or multiple best responses was used for a number of further questions, including defining the two symptoms most affecting daily life, views on the cause of the fatigue, and details of fatigue treatments received.

Participants indicating that fatigue had not affected them over the past month only provided demographic information and recorded the severity of the 11 symptoms, the 2 symptoms most affecting daily life, and the QOL-VAS. SPSS v22 was used for all analyses.

## Results

The survey link was sent to 197 eligible patients and 80 responded, equating to a 41% response rate. Across all data entry points, 1.8% were missing.

### Characteristics of participants

There were two main differences between survey responders and nonresponders. First, no patients currently receiving cancer treatment participated. Second, significantly more females than males responded, with 67% of responders and 47% of nonresponders being female. However, after excluding patients in the nonresponder group still receiving treatment, to compare responders and nonresponders off

TABLE 1. COMPARISON OF RESPONDER AND NONRESPONDER DEMOGRAPHIC DATA

	Responders (n=80)	All nonresponders (n=116)	p <sup>a</sup>	Nonresponders excluding those on treatment (n=93)	p <sup>a</sup>
Off/on treatment, n (missing data)	70/0 (10)	90/23 (3)	<0.001 <sup>b</sup>	90/0 (3)	NA
Age at survey in years, mean (SD, range)	22.1 (2.7, 17–27)	21.3 (2.7, 16–27)	0.06 <sup>c</sup>	21.5 (2.6, 16–27)	0.21 <sup>c</sup>
Age at diagnosis in years, mean (SD, range)	18.9 (3.1, 12–24)	18.2 (3.3, 9–24)	0.12 <sup>c</sup>	18.0 (3.2, 12–24)	0.06 <sup>c</sup>
Months since diagnosis, median (IQR)	31 (18–49)	31 (14–58)	0.85 <sup>d</sup>	37 (21–61)	0.19 <sup>d</sup>
Months since last treatment, median (IQR)	18 (10–32)	18 (5–46)	0.50 <sup>d</sup>	27 (11–52)	0.05 <sup>d</sup>
Months treatment duration, median (IQR)	8 (4–25)	NA	NA	6 (4–9)	0.006 <sup>d</sup>
Gender, n, male (%)	26 (33)	62 (53)	0.005 <sup>b</sup>	44 (47)	0.06 <sup>b</sup>
Diagnosis, n (%)					
Leukemia	20 (25)	20 (17)	0.44 <sup>b</sup>	12 (13)	0.11 <sup>b</sup>
Lymphoma	35 (44)	53 (46)		50 (54)	
Osteosarcoma/Ewing's	6 (8)	9 (8)		3 (3)	
Brain neoplasm	1 (1)	8 (7)		6 (6)	
Other	18 (23)	26 (22)		22 (24)	

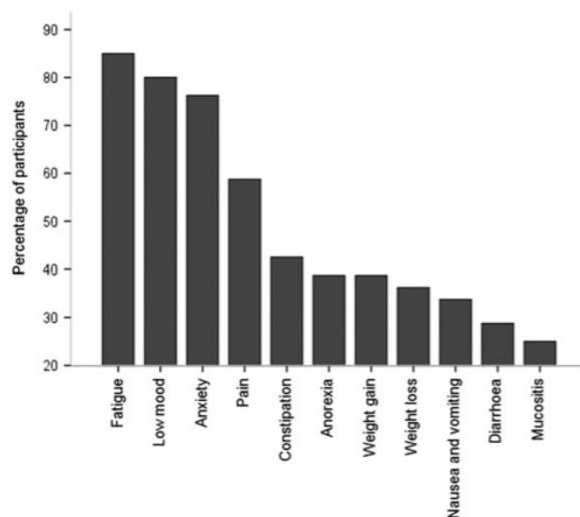
<sup>a</sup>p-Values comparing preceding column of nonresponders with responders and significant p-values in bold.

<sup>b</sup>Fisher's Exact Test.

<sup>c</sup>Independent samples t-test.

<sup>d</sup>Mann-Whitney U test.

IQR, interquartile range; SD, standard deviation.



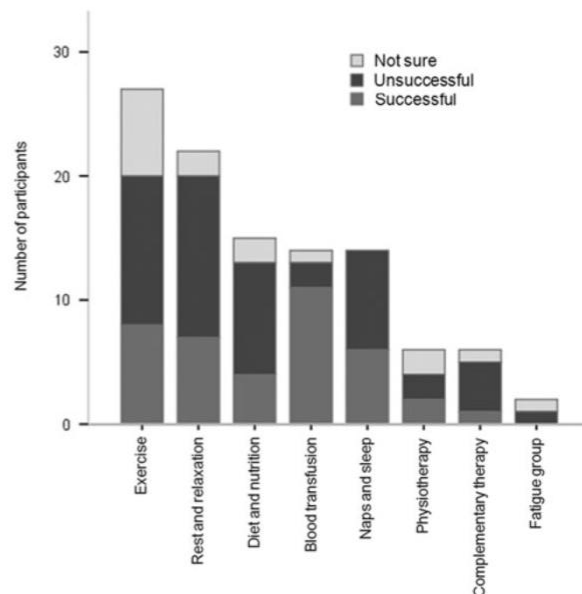
**FIG. 1.** Symptom prevalence bar chart.

treatment, there was no longer evidence of a gender difference between the two groups (Table 1).

#### Impact of fatigue

Fatigue was the most prevalent symptom, experienced by 85% (68/80) during the preceding month (Fig. 1). Fatigue was ranked as more severe than each of the other symptoms (Wilcoxon signed-rank test;  $p < 0.001$ , except anxiety  $p = 0.007$ ). The mean fatigue severity of the fatigued participants was 44.3 (standard deviation [SD] 20.5). Fatigue severity was worse more than 1 year after the last cancer treatment ( $M = 39.0$ ,  $SD = 19.7$ ), compared to  $< 1$  year ( $M = 53.8$ ,  $SD = 19.7$ ; independent samples  $t$ -test,  $t(56) = 2.8$ ,  $p = 0.007$ ). Fatigue was worse in females ( $M = 39.6$ ,  $SD = 19.3$ ) than males ( $M = 55.6$ ,  $SD = 19.6$ ;  $t(66) = 3.1$ ,  $p = 0.003$ ), but was not associated with other demographic variables, including cancer type or treatment duration. In a linear regression analysis, anorexia and low mood explained 50% of the variation in fatigue severity (adjusted  $R^2$  0.50,  $F$  change = 26.60,  $p < 0.001$ ). Gender no longer had a statistically significant relationship with fatigue after adjusting for anorexia and low mood. Fatigue (MFS) was an independent predictor of quality of life, after adjusting for the potential confounders, low mood, and anorexia (adjusted  $R^2$  0.42,  $F$  change = 7.13,  $p = 0.01$ ).

All participants, including those not experiencing fatigue, were asked which 2 out of 11 symptoms most affected daily life. Fatigue was chosen more often than any other symptom (Wilcoxon signed-rank tests,  $-7.87 < Z < -4.99$ , all  $p$ -values  $< 0.001$ ). The greatest impact of fatigue on aspects of daily life was on the ability to exercise, with 74% (50/68) experiencing "somewhat," "quite a bit," or "very much" impact. Attending school or work was hindered for 65% and socializing for 56%. Forty-five percent of participants (29/64) felt that their fatigue made the person most involved in their care "somewhat," "quite a bit," or "very much" upset, 42% (27/64) felt it caused frustration, and 41% (26/64) believed it limited rest time. Only 13% (8/64) thought that there was no negative impact.



**FIG. 2.** Stacked bar chart showing successfulness of each fatigue treatment.

#### Fatigue management

A minority of fatigued participants (19%, 13/68) believed that "something could be done" about fatigue, with many (38%, 26/68) believing it to be a symptom one "has to live with." Although 65% (44/68) had talked to a health carer about feeling fatigued; the most common reason for not talking was a belief that nothing could be done (60%, 9/15).

Forty-one percent (28/68) of the fatigued participants had not been recommended fatigue treatments. The remaining participants had been recommended a median of 2.5 treatments (range 1–7), most commonly advice to exercise (27/40) or to rest and relax (22/40). There was no difference in fatigue severity (MFS) between those recommended fatigue treatments and those not. Only blood transfusion was perceived as successful more often than unsuccessful (Fig. 2). Successfulness of fatigue treatment was lower in participants more than 1 year from last cancer treatment compared to those  $< 1$  year from treatment [ $t(30) = -2.93$ ,  $p = 0.006$ ].

All participants, irrespective of whether they had received fatigue treatment, were asked what they personally thought was the single best treatment. Most chose exercise (24%, 14/58), followed by diet/nutrition (12%, 7/58), rest/relaxation (12%, 7/58), naps/sleeping (10%, 6/58), blood transfusion (7%, 4/58), complementary therapies (5%, 3/58), physiotherapy (3%, 2/58), and fatigue group attendance (3%, 2/58). Thirteen of the 16 participants who recommended an active treatment (exercise or physiotherapy) had received an active treatment themselves; those who had received an active treatment were more likely to recommend an active treatment as being better than a rest-focused treatment (Fisher's Exact Test,  $p = 0.001$ ). However, no evidence was found that those who had received a rest-focused treatment (rest/relaxation, naps/sleeping, or complementary therapy) were more likely to recommend a rest-focused treatment ( $p = 0.62$ ).

## Discussion

This survey confirms that fatigue is the single most prevalent and severe symptom experienced by AYAs with a cancer diagnosis and has the most negative impact on daily life. Fatigue persisted long after the end of cancer treatment, being perceived as worse more than 1 year after the end of treatment, compared to during the first year following treatment.

Research to date has focused on the burden of fatigue during cancer treatment. Only one study has shown worse fatigue in AYA cancer survivors than controls,<sup>7</sup> and there have been no longitudinal studies evaluating fatigue changes over time.<sup>1</sup> One small, cross-sectional observational study has evaluated fatigue according to the time after the end of cancer treatment; there was a suggestion that fatigue in adolescents more than 5 years after treatment ( $n=8$ ) could be worse than those 1–2 years after treatment ( $n=6$ ).<sup>14</sup>

There may be a number of reasons for the persistence of fatigue well beyond cancer treatment. Resting is counterproductive as the inactivity caused by fatigue leads to a destructive spiral of muscle deconditioning, loss of cardio-respiratory fitness, and worsening fatigue.<sup>8,22</sup> Furthermore, AYA patients are at a formative age that puts them at particular risk of maladaptive behaviors such as activity avoidance.<sup>23</sup> Unhelpful health behaviors, such as inactivity, tend to become lifelong habits, increasing the potential for long-term disability. The finding that fatigue severity was worse more than 1 year after the end of treatment may reflect this deconditioning spiral. It could also be that, further from the end of treatment, the expectation that fatigue should be resolving drives a perception of worse fatigue.

These data reveal concerning therapeutic nihilism and under-management of fatigue. Over a decade ago, Stone et al. undertook an influential multicenter survey of older adults with cancer-related fatigue.<sup>24</sup> While the proportion of people believing that “something could be done” about fatigue remained comparably low (19% in this survey, 22% in Stone et al.), there is evidence of progress. Sixty-five percent fatigued participants in this survey had talked to a health carer about their fatigue; 59% had received some fatigue treatment and, of these, 68% had received advice to exercise (respective figures in older adults being 48%, 14%, and 4%).<sup>24</sup> Exercise was viewed as the best fatigue treatment and was most recommended to others. The fact that most participants found exercise advice unhelpful could be explained by the finding that fatigue has a particularly negative impact on the ability to exercise.

The main limitation of this study is the risk of selection bias. Although a nonresponder analysis was undertaken, fatigue severity was not measured in nonresponders. It is possible that people experiencing fatigue may have been more likely to participate, leading to fatigue overestimation. Greater selection bias further from cancer treatment could have contributed to the findings of worse fatigue and less successful fatigue management in those more than a year after cancer treatment. A longitudinal cohort study, powered to detect changes in fatigue over time, is needed to confirm the study findings.

Nevertheless, this study has a number of implications for clinical practice. The persistence of fatigue, potentially sustained by a spiral of inactivity and deconditioning, suggests that early fatigue intervention is warranted, before maladaptive rest-based behaviors become entrenched at this formative age. Given the impact of fatigue on the ability to

exercise, a fatigue intervention must find ways of engaging AYAs in persisting with increasing activity, despite the presence of fatigue. The negative consequences for carers suggest that it would be beneficial to incorporate family support into the intervention.

Considering the high prevalence and detrimental impact of fatigue, it is concerning that there has as yet been no research evaluating age-appropriate interventions. This survey provides evidence for the specific needs of fatigued AYAs and is supporting the design of future research aiming to develop an effective treatment for this important and debilitating symptom.

## Acknowledgment

This research was funded by Macmillan Cancer Support (grant No. 5592228).

## Author Disclosure Statement

No competing financial interests exist.

## References

1. Spathis A, Booth S, Grove S, et al. Teenage and young adult cancer-related fatigue is prevalent, distressing and neglected: it is time to intervene. A systematic literature review and narrative synthesis. *J Adolesc Young Adult Oncol*. 2015;4(1):3–17.
2. Baggott C, Dodd M, Kennedy C, et al. Changes in children's reports of symptom occurrence and severity during a course of myelosuppressive chemotherapy. *J Pediatr Oncol Nurs*. 2010;27:307–15.
3. Dahl R, Lewin D. Pathways to adolescent health sleep regulation and behavior. *J Adolesc Health*. 2002;31(6 Suppl): 175–84.
4. Hysing M, Pallesen S, Morten Stormark K, et al. Sleep and use of electronic devices in adolescence: results from a large population-based study. *BMJ Open*. 2015;5:e006748.
5. Daniel LC, Brumley LD, Schwartz LA. Fatigue in adolescents with cancer compared to healthy adolescents. *Pediatr Blood Cancer*. 2013;60:1902–7.
6. Smith AW, Bellizzi KM, Zebrack B, et al. Health-related quality of life of adolescent and young adult patients with cancer in the United States: the adolescent and young adult health outcomes and patient experience study. *J Clin Oncol*. 2013;31(17):2136–45.
7. Aksnes LH, Hall KS, Jebsen N, et al. Young survivors of malignant bone tumours in the extremities: a comparative study of quality of life, fatigue and mental distress. *Support Care Cancer*. 2007;15:1087–96.
8. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Syst Rev*. 2012; (11):Art. No. CD006145.
9. Goedendorp M, Gielissen M, Verhagen C, Bleijenberg G. Psychosocial interventions for reducing fatigue during cancer treatment in adults. *Cochrane Syst Rev*. 2009;1: CD006953.
10. de Raaf P, de Klerk C, Timman R, et al. Systematic monitoring and treatment in physical symptoms to alleviate fatigue in patients with advanced cancer: a randomised controlled trial. *J Clin Oncol*. 2013;31(6):716–23.
11. Spathis A, Fife K, Blackhall F, et al. Modafinil for the treatment of fatigue in lung cancer: results of a placebo-

- controlled, double-blind, randomized trial. *J Clin Oncol*. 2014;32(18):1882–8.
12. National Institute for Health and Clinical Excellence (NICE). Improving outcomes in children and young people with cancer. London: NICE; London: Teenage Cancer Trust, 2005.
  13. Teenage Cancer Trust. A blueprint of care for teenagers and young adults with cancer, 2nd ed. London: Teenage Cancer Trust 2016.
  14. Ream E, Gibson F, Edwards J, et al. Experience of fatigue in adolescents living with cancer. *Cancer Nurs*. 2006;29(4): 317–26.
  15. Chiang Y, Yeh C, Wang K, Yang C. The experience of cancer-related fatigue in Taiwanese children. *Eur J Cancer Care*. 2009;18(1):43–9.
  16. McLoone JK, Wakefield CE, Butow P, et al. Returning to school after adolescent cancer: a qualitative examination of Australian survivors' and their families' perspectives. *J Adolesc Young Adult Oncol*. 2011;1:87–94.
  17. Gibson F, Mulhall AB, Richardson A, et al. A phenomenologic study of fatigue in adolescents receiving treatment for cancer. *Oncol Nurs Forum*. 2005;32(3):651–60.
  18. Vindrola-Padros C, Taylor R, Lea S, et al. Mapping adolescent cancer services. *Cancer Nurs*. 2016;39(5):358–66.
  19. Varni JW, Burwinkle TM, Katz ER, et al. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer*. 2002;94:2090–2106.
  20. de Boer A, van Lanschot J, Stalmeier P, et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? *Qual Life Res*. 2004;13(2):311–20.
  21. Huschka M, Mandrekar S, Schaefer P, Jett J. A pooled analysis of quality of life measures and adverse events data in North Central Cancer Treatment Group lung cancer clinical trials. *Cancer*. 2002;109(4):787–95.
  22. Courneya K, Mackey J, Bell G, et al. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life measures. *J Clin Oncol*. 2003;21(9):1660–8.
  23. Sawyer S, Afifi R, Bearinger L, et al. Adolescence: a foundation for future health. *Lancet*. 2012;379(6736): 1630–40.
  24. Stone P, Richardson A, Ream E, et al. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. *Cancer Fatigue Forum*. *Ann Oncol*. 2000;11(8):971–5.

Address correspondence to:

*Anna Spathis, MSc*  
*Cambridge University Hospitals NHS Foundation Trust*  
*Addenbrookes Hospital*  
*Hills Road*  
*Cambridge CB2 8AR*  
*United Kingdom*

*E-mail: aspathis@doctors.org.uk*

## **7.2 Systematic literature review**

### **7.2.1 Eligibility criteria**

#### **7.2.1.1 Inclusion criteria**

- All study participants have malignant disease, or malignant group presented separately
- Evaluating any aspect of fatigue (or tiredness, exhaustion, lethargy)
- Majority participants age 13-24 years at the time of cancer diagnosis or treatment, or 13-24 age group presented separately
- At any time in relation to cancer treatment (before, during or after)
- Measuring prevalence of fatigue
- Measuring impact of fatigue
- Evaluating correlates to fatigue
- Evaluating any intervention for fatigue, non-pharmacological or pharmacological
- Examining the experience of the carers of fatigued patients
- Quantitative and qualitative research methods
- Studies within peer review journals
- From January 1981 to November 2013
- Based within any country
- Title, abstract and main paper available in English

#### **7.2.1.2 Exclusion criteria**

- Not diagnosed or treated for cancer aged 13-24
- Literature reviews
- Case reports of five or fewer patients
- Retrospective case note review
- Phase 1/2 clinical trials
- Clinical trial of investigational medicinal produce with ten or fewer patients
- Studies without any original empirical data
- Laboratory data only
- Benign tumours
- Guidelines, comments, editorials
- Studies evaluating treatment for an adverse effect of cancer treatment
- Grey literature, except for the TCT conference

## **7.3 Fatigue in Focus multicentre survey**

### **7.3.1 Priming process**

#### **7.3.1.1 *Standardised priming email***

**This was allowed to be amended slightly by healthcare staff at each site**

We are setting up the first UK survey focusing on fatigue in young people who have had cancer. This is a really important survey as young people keep telling us that fatigue is a big problem, but there has not been much research on this yet.

Please look out for an email about this survey early next year. It'll be quick and easy to complete, on your phone or computer, and will just take a few minutes.

We would really appreciate it if you could take part. We need lots of people to join in for the survey to be useful. Everyone who completes it will be put into a draw to win an iPad or three £50 Amazon vouchers!

The main thing is we want to learn from your experiences and use it to help other patients. Help us understand fatigue to help us treat it.



## FATIGUE STUDY FOR YOUNG PEOPLE WITH CANCER

Win an iPad



We are setting up the first UK survey focusing on fatigue in young people who have, or have had, cancer. This is a really important survey as young people keep telling us that fatigue is a major problem, but there has not been much research on this yet.

Please look out for an email about this survey, which will be sent out just after Easter. It'll be quick and easy to complete, on your phone or computer, and will just take a few minutes. Want to take part, but haven't given us your email address? Just email Wendy on **wendy.moss@addenbrookes.nhs.uk**, and she'll make sure you're included. If you're wondering where the email is, you could give your junk box a quick check.

We would really appreciate it if you could take part. We need lots of people to join in for the survey to be useful. Everyone who completes it will be put into a draw to win an iPad or three £50 Amazon vouchers!

The main thing is we really want to learn from your experiences and use it to help other patients. Please help us understand fatigue to help us treat it. Thank you.



Jane Robson  
Teenage Cancer Trust Lead TYA Nurse



Helen Hatcher  
Consultant, TYA Lead



### Would you like to take part?



We would like to hear from you if you were diagnosed between the ages of 13 and 24 years old **and are now 16-27 years**. You can be on treatment or have finished treatment.

### 7.3.2 Survey covering email

#### Fatigue in Focus. Help us understand it to help us treat it.

Dear (*insert patient first name*),

I wonder if you could help us with some important research. We would like to invite you take part in the first UK survey focusing on fatigue in young people who have had cancer.

Young people keep telling us fatigue is a big problem, but there has not been much research on this yet. We want to learn from your experiences, and use it to help other cancer patients. If you were able to complete this short survey, we would appreciate it so much.

The survey is easy to complete, just click the link below. We have made it as brief as possible – it will take about 4-8 minutes of your time. A participant information sheet is attached to this email, giving you more detailed information.

Everyone who completes the survey will be put into a draw to win an iPad or three £50 Amazon vouchers. The survey is anonymous and there is no way you can be identified from the information you provide.

We need to focus on fatigue. Help us understand it to help us treat it.

Thank you very much indeed for considering taking part.

Dr Helen Hatcher  
Consultant medical oncologist and TYA service lead  
On behalf of the Fatigue in Focus survey team



## **Fatigue in Focus Survey**

### **Information sheet for participants**

#### **What is the Fatigue in Focus survey about?**

This is the first survey in the UK focusing on fatigue in young people who have, or have had, cancer. Many young people have told us that they are suffering from fatigue or tiredness. Although it seems to be a big problem, there has been very little research in this area. We need to know more about fatigue, both to understand the effect it has on people's lives, and also to help us find an effective treatment.

#### **Why have I been chosen?**

We have emailed all the young people known to three Teenage and Young Adult (TYA) Cancer Service, in Cambridge, Manchester and Southampton, for whom we have an email address.

#### **What would taking part involve?**

This is an electronic survey. Taking part is therefore quick and easy. You just need to click on the link in the email that this sheet was attached to, and it will open up the survey. You can complete it on your computer or phone, and it may take up to 10 minutes to complete.

You give your consent to take part in this research by ticking a box saying 'I agree to take part in this survey' on the first page of the survey, and then pressing the 'submit' button at the end of the survey.

Everyone who takes part in the survey will be entered automatically into a prize draw for an iPad and three £50 Amazon vouchers.

#### **What will happen to the study findings?**

The findings will be presented at a conference for professionals and for people who have had cancer. They will be published in a professional journal. We also plan to email a brief summary of the results to everyone who has taken part in the survey. If people want more information, this email will contain the contact details of a person who can send you the full report of the survey.

#### **What difference will the study make?**

The study will allow us to understand more deeply the experience of young people suffering from fatigue. This will then help us develop an effective treatment for fatigue.

**Do I have to be fatigued or tired to take part?**

No. We would like everyone to complete the survey, to give us an idea of how common fatigue is. As it is an electronic survey, the questions change according to your answers. So if you are not fatigued, you will not be asked questions about fatigue.

**What about confidentiality?**

It is important to understand that responses in this survey will be strictly confidential. It will not be possible for anyone to link survey responses to individual participants. The research team locally, who sent this email and information sheet, will know whether or not you have completed the survey, but they cannot access your responses. They need to know you have taken part, so that one email reminder can be sent, and also so that participants can be entered into the prize draw.

**Do I have to take part?**

There is no need to take part if you don't want to. Choosing not to complete the survey will not affect anything. Whether or not you still have contact with your TYA service, it won't change your care in any way.

**Are there any risks from taking part?**

No, we do not think there are any risks. When we set up this survey, patients advised us to make it short, as fatigue can make it harder to complete tasks. We have taken this very seriously, and have done our best to make this survey easy to complete and as brief as possible.

**Who has reviewed this survey?**

This study has been reviewed and approved by an ethics committee, NRES Committee East of England – Cambridgeshire and Hertfordshire (reference number 15/EE/0037).

**What do I do now?**

If you want to take part, just click on the survey link in the email we sent you. This will connect you directly with the electronic survey.

**Details of the research team?**

Principal/Chief Investigator: Dr Anna Spathis, [anna.spathis@addenbrookes.nhs.uk](mailto:anna.spathis@addenbrookes.nhs.uk)

***Thank you very much indeed for  
considering taking part in this survey.***

### 7.3.4 IT process instructions

#### Fatigue in Focus survey: IT instructions FINAL 16.4.15

We recommend initially trying this whole process using a test Excel spreadsheet (for example, containing email addresses of immediate colleagues)

##### **Section A: Survey email**

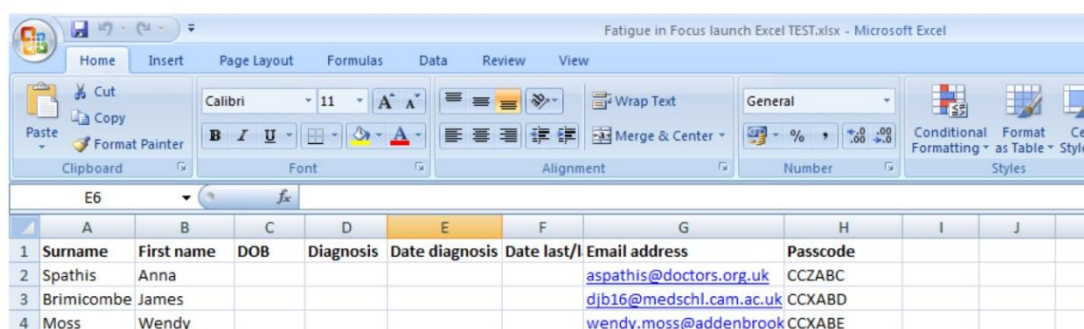
1. Create an Excel database containing information on all patients that fulfil the eligibility criteria, ensuring it has the following column headings in the first row:

- Surname
- First name
- DOB
- Diagnosis
- Date diagnosis (month, year is sufficient)
- Date last/latest treatment (month, year is sufficient)
- Email address
- Passcode (just the heading at the moment)

2. This spreadsheet should be on sheet 1 of the Excel file, with all other sheets empty. If this is not the case, paste all the patient data into a new Excel file. Save file as '**Fatigue in Focus survey Excel FINAL**'.

3. When the participant list is finalised, paste the passcodes sent by James Brimicombe, in alphabetical order, into the passcode column. You will have more passcodes than needed and the extra codes can be deleted.

**Be careful not to give two participants the same passcode.** Make a note of the total number of participants that will be sent the survey email. Consider adding your own name and email address (without token) to the bottom of the patient list, to give you evidence of successful sending of the survey.



The screenshot shows an Excel spreadsheet titled 'Fatigue in Focus launch Excel TEST.xlsx'. The spreadsheet has columns A through J. The first row (row 1) contains the following headers: A: Surname, B: First name, C: DOB, D: Diagnosis, E: Date diagnosis, F: Date last/I, G: Email address, H: Passcode. Rows 2 through 4 contain patient data:

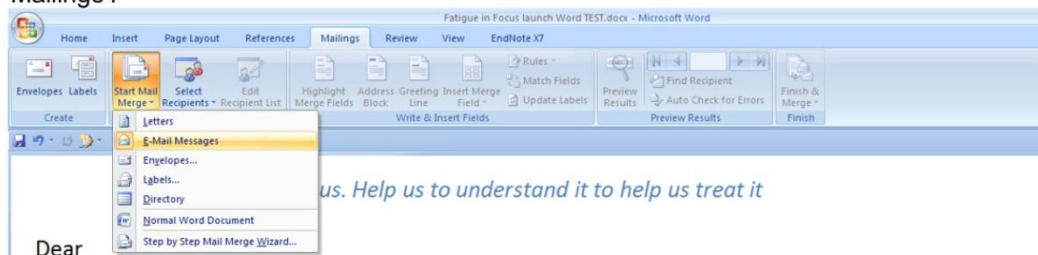
	A	B	C	D	E	F	G	H	I	J
1	Surname	First name	DOB	Diagnosis	Date diagnosis	Date last/I	Email address	Passcode		
2	Spathis	Anna					<a href="mailto:aspathis@doctors.org.uk">aspathis@doctors.org.uk</a>	CCZABC		
3	Brimicombe	James					<a href="mailto:djb16@medschl.cam.ac.uk">djb16@medschl.cam.ac.uk</a>	CCXABD		
4	Moss	Wendy					<a href="mailto:wendy.moss@addenbrook">wendy.moss@addenbrook</a>	CCXABE		

4. Open a new Word document and paste in the survey 'covering email' (V1.3, with names of local clinicians inserted), and save as '**Fatigue in Focus survey Word FINAL**'.

5. Check that the hyperlink to the PIS ("An information sheet with more details about the survey is available [here](http://www.phpc.cam.ac.uk/pcu/files/2015/03/Fatigue-in-Focus-A093524-PIS-CAMBRIDGE-.pdf)") is working. If it is not, create the hyperlink as follows:

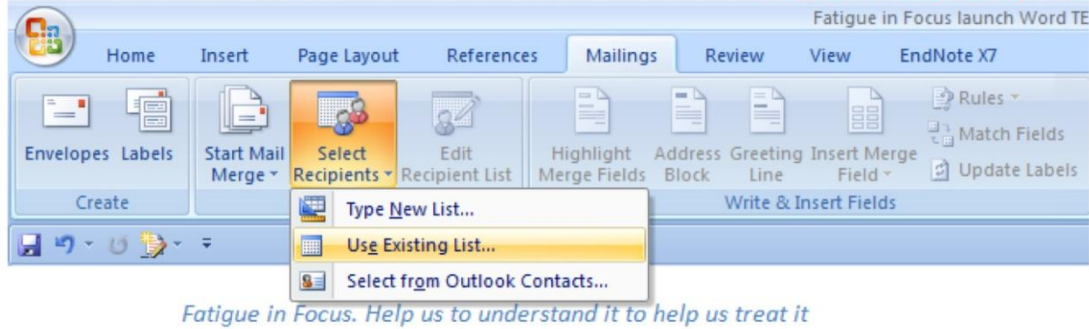
- Highlight the word '**here**', then press '**control**' and '**K**' at the same time.
- Under 'address', copy and paste this text: <http://www.phpc.cam.ac.uk/pcu/files/2015/03/Fatigue-in-Focus-A093524-PIS-CAMBRIDGE-.pdf>

6. Go to 'Mailings' and click on 'Start Mail Merge', then 'E-mail messages'. All the following steps occur within 'Mailings'.

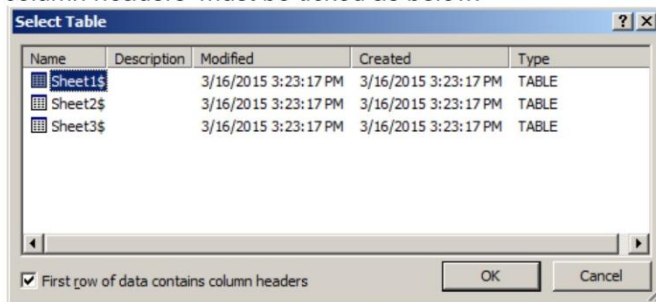




7. Click on 'Select Recipients', then 'Use Existing List'. Browse for **Fatigue in Focus survey Excel FINAL** file.

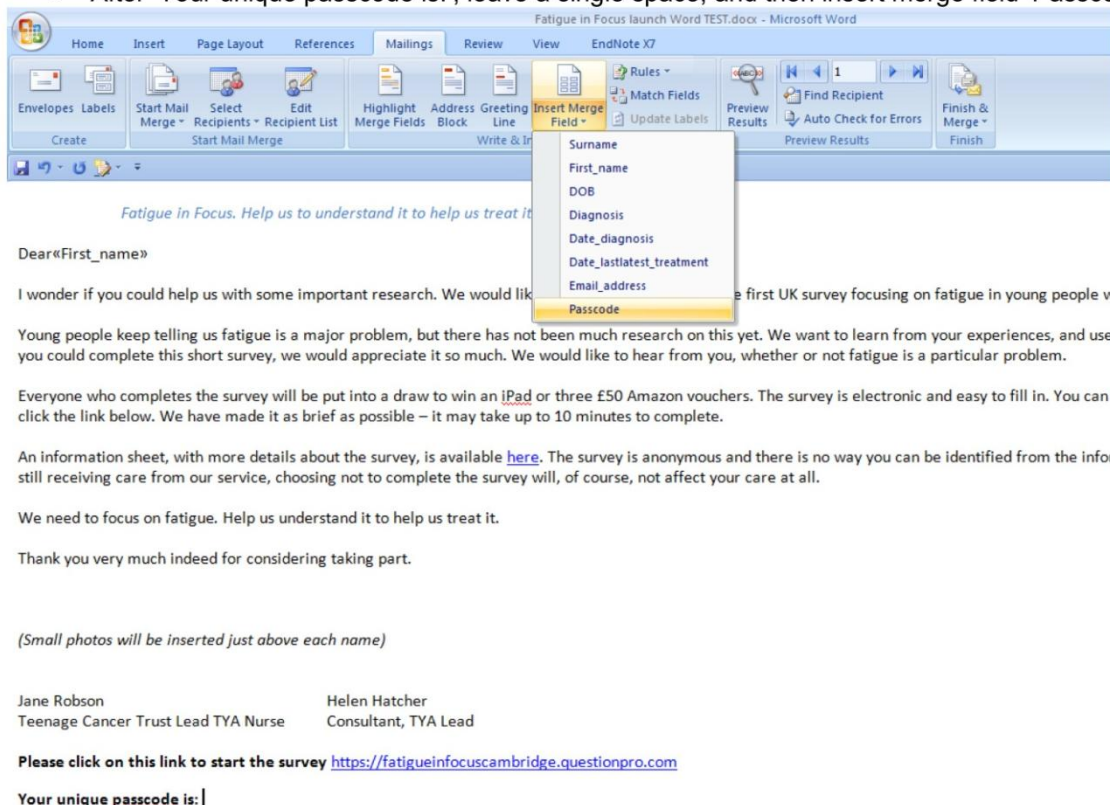


8. You will be asked to select a table. Click on sheet 1, then OK. Note that the 'First row of data contains column headers' must be ticked as below.



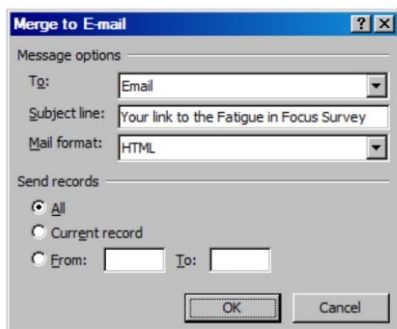
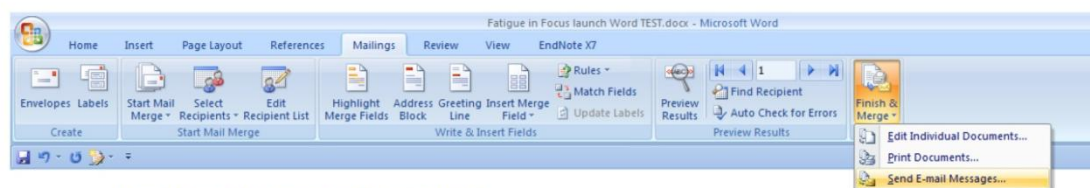
9. Click on 'Insert Merge Field', and insert the appropriate fields in the correct places in the Word document:

- After 'Dear', leave a single space, and then insert merge field 'First\_name'
- After 'Your unique passcode is:', leave a single space, and then insert merge field 'Passcode'



10. Finally, click on 'Finish & Merge', then 'Send E-mail messages' to the "EMAIL address" column. Enter 'Your link to the Fatigue in Focus survey' into the subject line, with HTML format and ALL records selected.

When you click 'OK', individual emails will be sent to each email address in the Excel spreadsheet. The survey has been sent!



11. Collect the email address of all survey emails that 'bounced', which will be used in step 14 below.

### **Section B: email to non-responders only (one week later)**

12. Within 24 hours of needing to send the non-responder email, James Brimicombe will send you an Excel file containing the original list of passcodes, with 'NON-RESPONDER' inserted for each patient in a new adjacent column if appropriate. Open the original Excel file ('Fatigue in Focus survey Excel FINAL'), and make sure the patients are still in alphabetical order based on passcode. Paste the new 'RESPONDER' column into the spreadsheet, carefully aligning it with the correct passcodes. [It may be wise to paste in two new columns, TOKEN (ie Passcode) and RESPONDER so that you can visually check that everything lines up. When satisfied it does, the TOKEN column can be deleted].

Passcode	TOKEN	RESPONDER
CABVRM	CABVRM	
CADXMK	CADXMK	NON-RESPONDER
CAMJGP	CAMJGP	NON-RESPONDER
CATBFB	CATBFB	
CAWKSR	CAWKSR	
CAWVQR	CAWVQR	NON-RESPONDER
CBBHLB	CBBHLB	NON-RESPONDER
CBBLYH	CBBLYH	
CBDQPB	CBDQPB	
CBPFSP	CBPFSP	NON-RESPONDER
CBPZMK	CBPZMK	
CBTFFM	CBTFFM	NON-RESPONDER
CBWFYD	CBWFYD	
CBWTAH	CBWTAH	
CCBJEF	CCBJEF	
CCBNTK	CCBNTK	
CCBYLM	CCBYLM	NON-RESPONDER
CCFDGR	CCFDGR	
CCHAMK	CCHAMK	

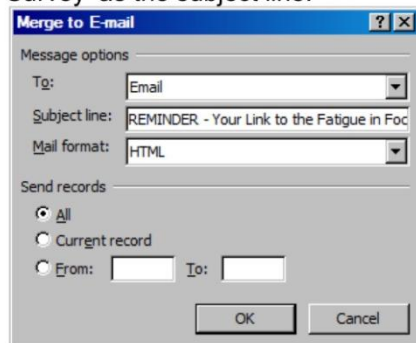
13. Save this file as '**Fatigue in Focus REMINDER Excel**', so now you have two Excel files, one used to send the first survey email in section A above, and one which you will now work on to send the reminder email.

14. Delete from the '**Fatigue in Focus REMINDER Excel**' spreadsheet all the participants whose original survey email 'bounced' (see point 11 above), unless their email clearly has an obvious typing error that needs correcting.

14. Now sort the spreadsheet according to whether the participant is a 'Responder' or a 'Non-responder'. **Delete the responders only**. This file now contains data just on those people who did not respond and whose email did not bounce.

15. Open a new Word document and paste in the survey 'reminder email' (V1.0, adapted to the site by putting in names of local clinicians), and save as '**Fatigue in Focus REMINDER Word**'.

16. Then, using these two REMINDER Excel and Word files, follow steps 5-10 exactly as before, to send reminder emails to non-responders. This time, use 'FINAL REMINDER – Your link to the Fatigue in Focus Survey' as the subject line.



### Section C: data the central study team will need from you

17. All data from the survey will be accessed centrally when participants submit the survey. However, we will need some additional data from you, to undertake our data analysis. We will need:

- The total number of people excluded from the survey by the PI (ie those meeting our one exclusion criterion)
- The total number of participants sent the survey email
- The total number of emails that bounced
- The total number of participants sent the reminder email

18. In addition we will need to do a simple analysis of non-responder demographics. When data collection ends (three weeks after the final site sends out the survey), James Brimicombe will send you another Excel file, similar to that in step 12, this time marking the people who never responded (even after the reminder email). Please paste these columns into your '**Fatigue in Focus REMINDER Excel**' file, as you did in step 12. Again, sort according to whether a responder or not. Please delete:

- The rows containing responders
- The columns containing name, address, email address or other patient identifier.

Please name this Excel file '**Fatigue in Focus Non responder demographics**'. It should just contain columns for: DOB, diagnosis, data of diagnosis (month, year), and data last/latest treatment (month, year) for each of the non-responders. Please email this file using your nhs.net email address, to Anna Spathis using the following address: [anna.spathis@nhs.net](mailto:anna.spathis@nhs.net).

*Please don't hesitate to email Anna Spathis on [anna.spathis@addenbrookes.nhs.uk](mailto:anna.spathis@addenbrookes.nhs.uk) (or call 07970787657) for general questions on the survey or James Brimicombe on [djb16@medschl.cam.ac.uk](mailto:djb16@medschl.cam.ac.uk) for technical help.*

***Thank you so much for all your hard work on this survey.  
We appreciate it so much.***



### 7.3.5 Research Ethics Committee approval

*Decision and signature pages only*



## Health Research Authority

### NRES Committee East of England - Cambridgeshire and Hertfordshire

Rolling Mill Road  
Jarrow  
Tyne and Wear  
NE32 3DT

Telephone: 0191 4283564

29 January 2015

Dr Anna Spathis  
Consultant in Palliative Medicine  
Cambridge University Hospitals NHS Foundation Trust  
Department of Palliative Care  
Cambridge University Hospitals NHS Foundation Trust  
Hills Road, Cambridge  
CB2 0QQ

Dear Dr Spathis

<b>Study title:</b>	<b>Fatigue in Focus Survey: a national electronic survey of the prevalence, impact and management of fatigue in teenage and young adult cancer patients</b>
<b>REC reference:</b>	<b>15/EE/0037</b>
<b>Protocol number:</b>	<b>A093524</b>
<b>IRAS project ID:</b>	<b>170308</b>

The Proportionate Review Sub-committee of the NRES Committee East of England - Cambridgeshire and Hertfordshire reviewed the above application in correspondence.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Miss Kathryn Murray, [nrescommittee.eastofengland-cambsandherts@nhs.net](mailto:nrescommittee.eastofengland-cambsandherts@nhs.net). Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

#### **Ethical opinion**

On behalf of the Committee, the sub-committee gave a **favourable ethical opinion** of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

## User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

## HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

With the Committee's best wishes for the success of this project.

15/EE/0037
------------

Please quote this number on all correspondence
--

Yours sincerely



**Mr David Grayson**  
**Chair**

Email: [nrescommittee.eastofengland-cambsandherts@nhs.net](mailto:nrescommittee.eastofengland-cambsandherts@nhs.net)

*Enclosures:*

*List of names and professions of members who took part in the review  
"After ethical review – guidance for researchers" [SL-AR2]*

*Copy to: Mr Stephen Kelleher, Research and Development Office Addenbrookes Hospital*



### 7.3.6 Survey questionnaire

#### **Fatigue in Focus Survey**

##### **Survey questions**

Please note: this is an electronic survey, and has been formatted carefully to ensure that it is 'user-friendly'. The questions contained within the survey are pasted below for ease of access of those reviewing the study.

The responses to some questions will change subsequent questions, so this full version is longer than the one any individual participant will complete. The link to the electronic survey is available at the end of the survey covering email.

This on-line questionnaire has been designed for people aged between 16-24, so we can better understand the experience of fatigue in people who have had cancer. Fatigue means a feeling of overwhelming tiredness or loss of energy.

Please remember there are no right or wrong answers to any of the questions – we only want your opinions. The answers you give will be completely confidential. We have tried hard to make the survey as short as possible, and it takes 4 to 8 minutes to complete.

Thank you very much for your help.

☐ I agree to take part in this survey (TICK TO CONTINUE)

## **Section A : How you are feeling**

**This section is about how you have been feeling over the last month.**

**1. How much has each of following symptoms affected you over the past month?**

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Pain *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Nausea and vomiting *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Diarrhoea *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Constipation *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Fatigue *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
No appetite *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Weight loss *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Weight gain *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Mucositis (sore mouth) *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Low mood *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anxiety *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**2. Please mark which two symptoms are affecting your daily life the most.**

\*

- ☐ Pain
- ☐ Nausea and vomiting
- ☐ Diarrhoea
- ☐ Constipation
- ☐ Fatigue
- ☐ No appetite
- ☐ Weight loss
- ☐ Weight gain
- ☐ Mucositis (sore mouth)
- ☐ Low mood
- ☐ Anxiety

**3. Please select the number between 0-10 that best represents your quality of life during the last month**

Worst possible quality of life	Best possible quality of life
0	10
<div></div>	

*(If scored 'not at all' for fatigue in question 1 above, the survey will now jump to question 15 after clicking 'Next Page')*

## **Section B : Your experience of fatigue**

**Everyone is different, and we would like to know what fatigue is like for you. This first question is the longest one in the survey. We really appreciate your effort filling it in, as it gives us particularly useful information.**

### **4. In the past one month, how much of a problem has this been for you...?**

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel tired	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I feel physically weak (not strong)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I feel too tired to do things that I like to do	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I feel too tired to spend time with my friends	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I have trouble finishing things	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I have trouble starting things	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I sleep a lot	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
It is hard for me to sleep through the night	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I feel tired when I wake up in the morning	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I rest a lot	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I take a lot of naps	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I spend a lot of time in bed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

### **4. (continued) In the past one month, how much of a problem has this been for you...?**

	Not at all	A little bit	Somewhat	Quite a bit	Very much
It is hard for me to keep my attention on things	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

It is hard for me to remember what people tell me	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
It is hard for me to remember what I just heard	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
It is hard for me to think quickly	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I have trouble remembering what I was just thinking	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I have trouble remembering more than one thing at a time	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**5. How often in the past month have you experienced fatigue?**

- ☐ Every day
- ☐ On most days
- ☐ At least once a week
- ☐ Only a few days each month
- ☐ Hardly ever

**6. What do you think has caused your fatigue?**

- ☐ Mainly your illness
- ☐ Mainly your treatment
- ☐ A combination of both
- ☐ Other (please specify)

**7. Do you think something can be done about fatigue, or is it something you have to live with?**

- ☐ Something can be done
- ☐ Must live with it
- ☐ Not sure

### **Section C : Talking with your healthcare team**

**This section is about the conversations you have had with the doctors or nurses or other professionals involved in your care.**

**8. Have you ever talked with your healthcare team about feeling fatigued?**

**\***

- ☐ Yes
- ☐ No
- ☐ Can't remember

**EITHER:**

***You talked with your healthcare team about being fatigued***

**9. What treatment, if any, was recommended? Tick all that apply**

**For each one ticked: How successful was this treatment?**

	Recommended	How successful was this treatment?
Blood transfusion	<input type="checkbox"/>	-- Select --
Diet or nutrition	<input type="checkbox"/>	-- Select --
Exercise	<input type="checkbox"/>	-- Select --
Rest and relaxation	<input type="checkbox"/>	-- Select --
Physiotherapy	<input type="checkbox"/>	-- Select --
Attending a fatigue group	<input type="checkbox"/>	-- Select --
Taking naps or sleeping more	<input type="checkbox"/>	-- Select --
Complementary therapies	<input type="checkbox"/>	-- Select --

☐ *If NO treatments were recommended, please tick this box*

**9b. What do you personally think is the best treatment for fatigue?**

-- Select --

**OR**

***You didn't talk with your healthcare team about being fatigued***

**9. Why did you not talk about your fatigue? Mark all that apply**

- ☐ You thought it was inevitable
- ☐ It did not seem important enough to you
- ☐ You believed nothing could be done
- ☐ You thought people might think you were lazy or complaining
- ☐ You feared your treatment would be changed or stopped
- ☐ Your doctor or nurse never asked you about it
- ☐ You didn't want to bother the doctor or nurse
- ☐ Other reason (please state)

## **Section D : The effect of fatigue on your life**

**We would like to understand what effect fatigue has had on your life and on the people around you.**

### **10. How much do you think fatigue affects the following aspects of your life?**

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Ability to socialise	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ability to exercise	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ability to attend school/study/work	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ability to be independent	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ability to enjoy life	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Relationship with family	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Relationship with friends	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

### **11. Do you think the effect of fatigue on your life is understood by the people around you?**

	Not at all	A little bit	Somewhat	Quite a bit	Very much
By healthcare professionals	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
By family	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
By friends	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

### **12. In your day-to-day life since you were diagnosed with cancer, who has been most closely involved in your care?**

- ☐ Parent
- ☐ Another relative
- ☐ Friend
- ☐ No-one



**13. What effect do you feel your fatigue has had on this person?**

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Made him/her upset	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Caused frustration	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Limited his/her time to rest	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
No effect	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Not sure	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**14. Is there anything else you would like to tell us that we did not ask?**

**Section E : About You**

**15. What is your month and year of birth?**

**16. Are you male or female?**

- ☐ Male
- ☐ Female

**17. When were you diagnosed with cancer?**

**18. What type of cancer do you have or have you had treated?**

- ☐ Leukaemia

- ☐ Lymphoma
- ☐ Brain
- ☐ Osteosarcoma
- ☐ Ewing's
- ☐ Neuroblastoma
- ☐ Wilms
- ☐ Other



**19. When was your last or latest treatment?**

**Thank you for completing this survey. If you have any concerns, anxieties or comments you should contact Dr Anna Spathis on 01223 274404 or [anna.spathis@addenbrookes.nhs.uk](mailto:anna.spathis@addenbrookes.nhs.uk)**

7.3.7 Non-responder analysis comparative histograms

Figure 7.1 Comparative histogram of age at survey for responders and all non-responders

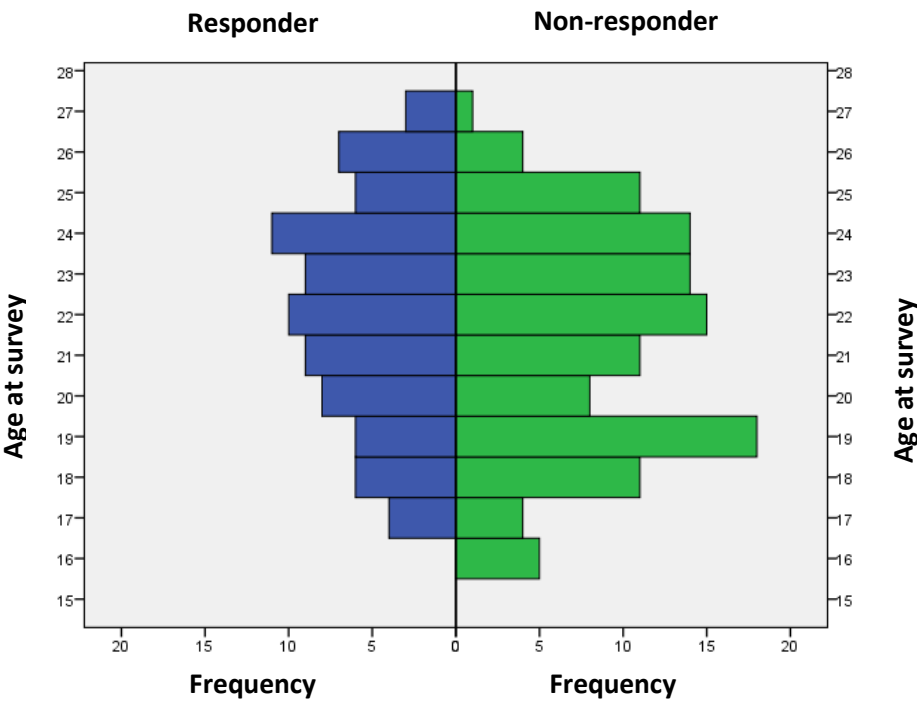


Figure 7.2 Comparative histogram of age at diagnosis for responders and all non-responders

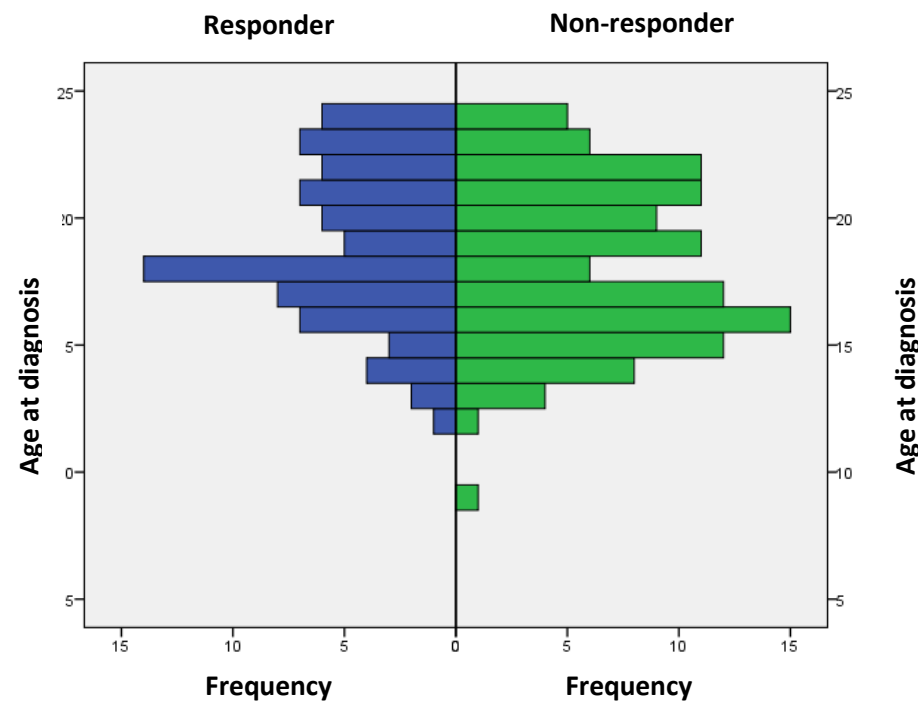
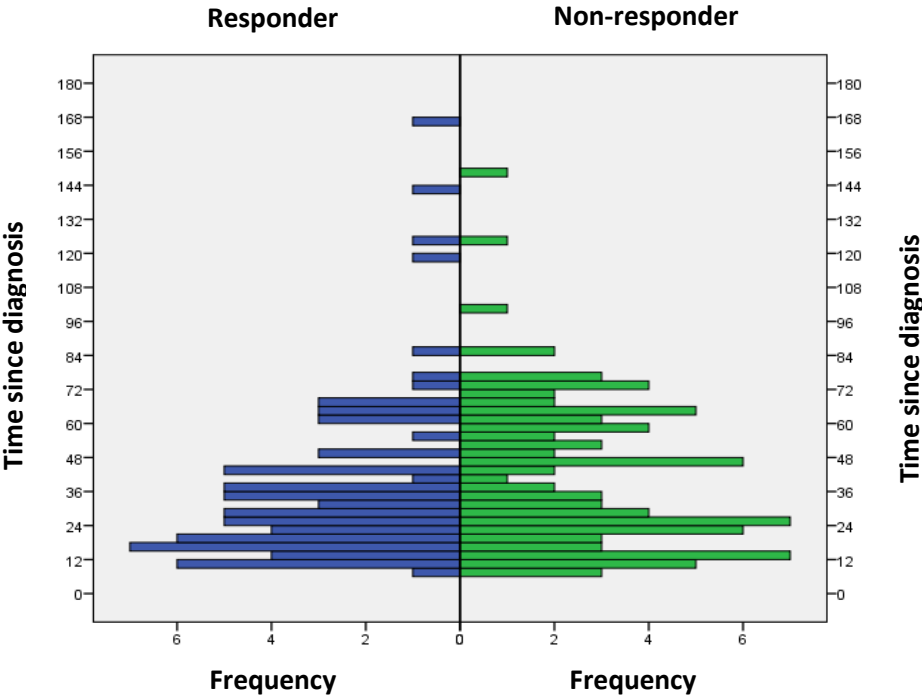


Figure 7.3 Comparative histogram of time since diagnosis for responders and all non-responders



### 7.3.8 Regression diagnostic plots

#### 7.3.8.1 Diagnostic plots for predictors for fatigue severity

Figure 7.4 Frequency of standardised residuals (dependent variable MFS)

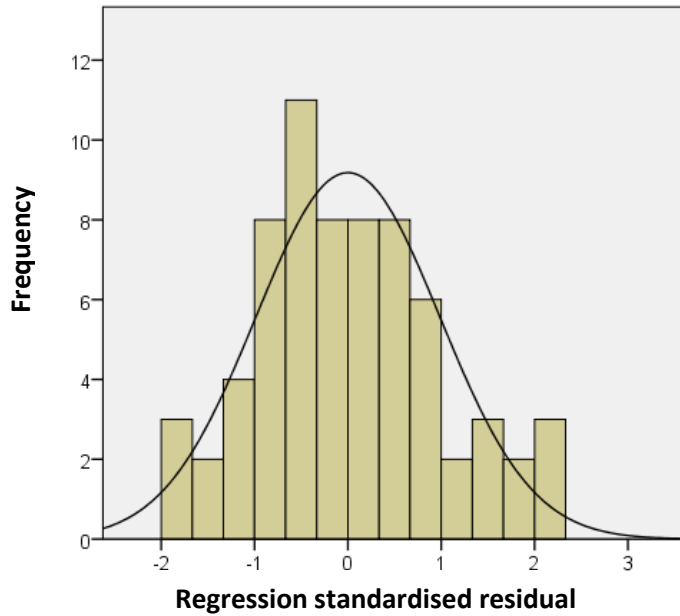
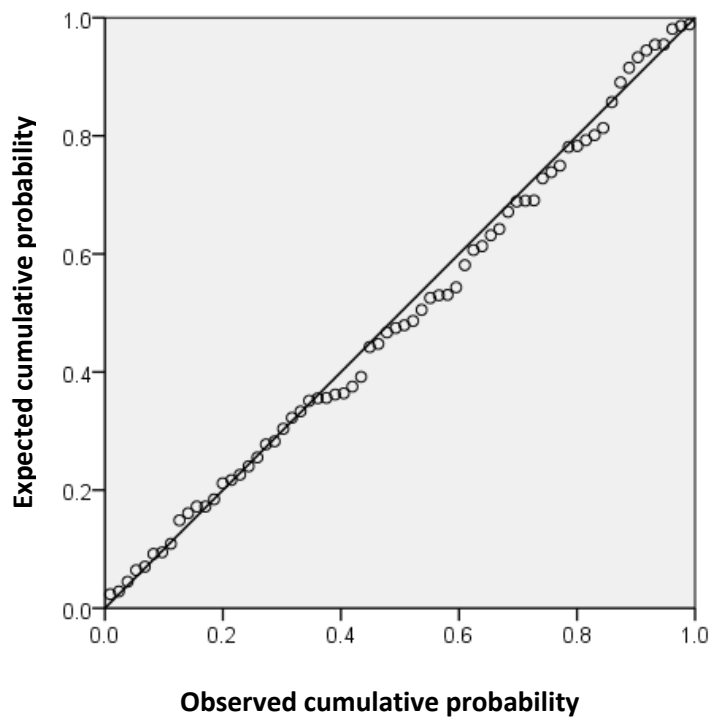
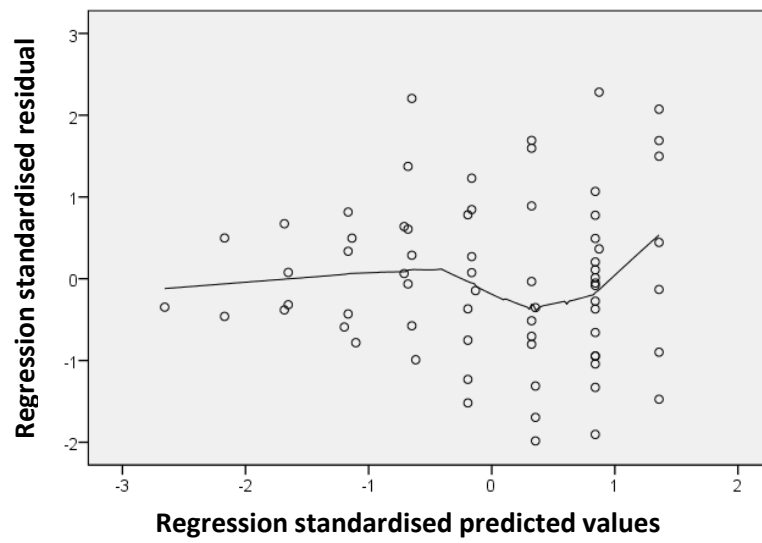


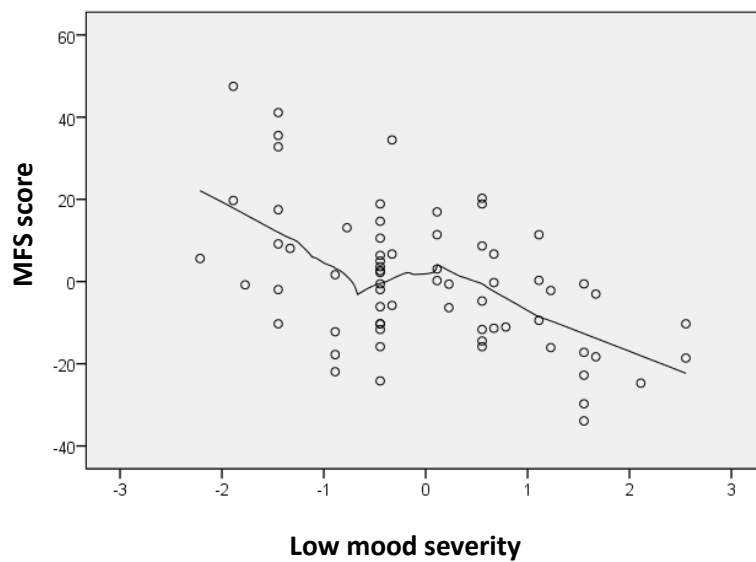
Figure 7.5 Normal P-P plot of regression standardised residuals (dependent variable MFS)



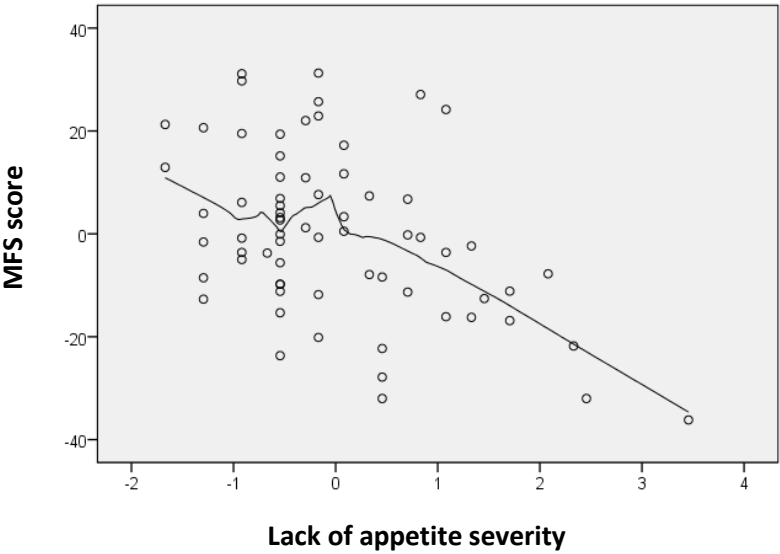
**Figure 7.6 Scatterplot of standardised residuals and predicted values with Loess line (dependent variable MFS)**



**Figure 7.7 Scatterplot of residuals of MFS and low mood severity with Loess line**



**Figure 7.8 Scatterplot of residuals of MFS and lack of appetite severity with Loess line**



**7.3.8.2 Diagnostic plots for predictors for quality of life**

**Figure 7.9 Frequency of standardised residuals (dependent variable QOL NRS)**

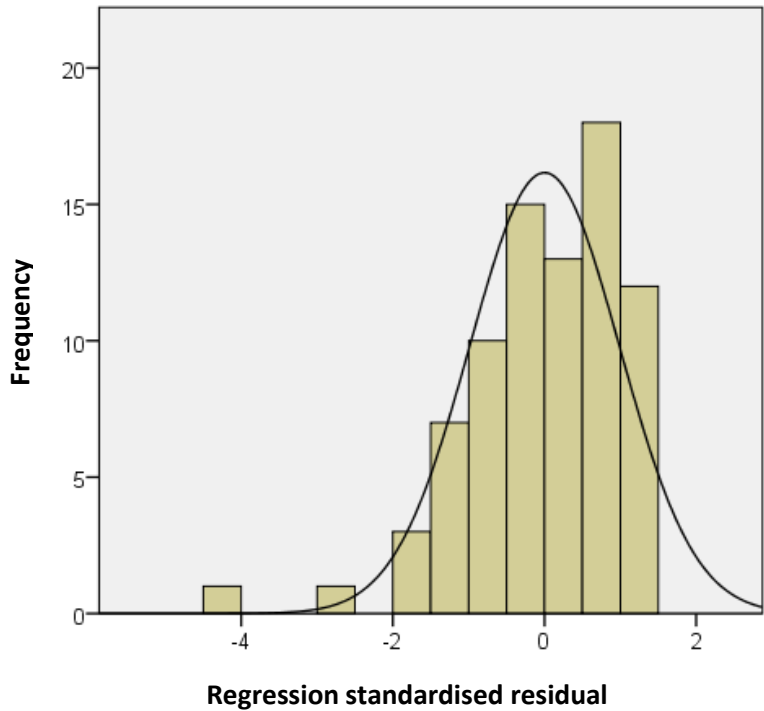


Figure 7.10 Normal P-P plot of regression standardised residuals (dependent variable MFS)

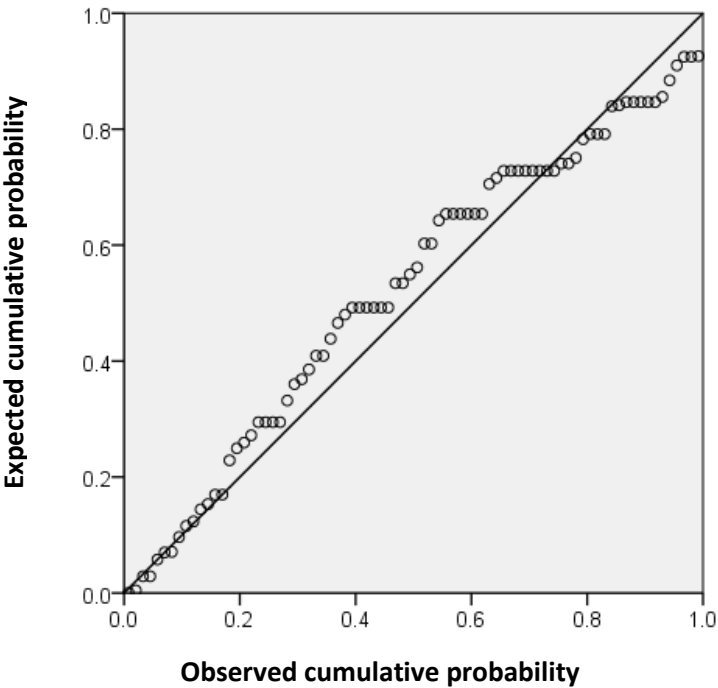


Figure 7.11 Scatterplot of standardised residuals and predicted values with Loess line (dependent variable QOL NRS)

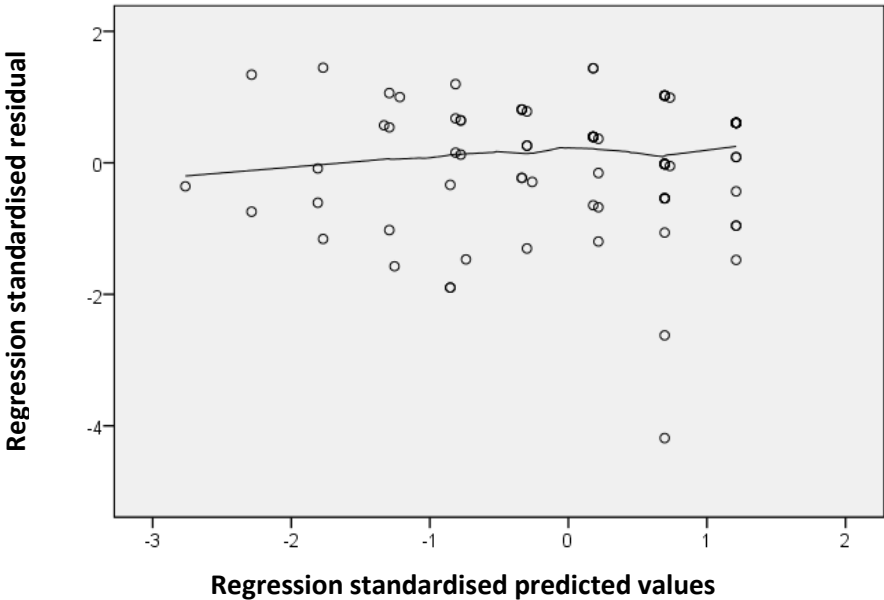




Figure 7.12 Scatterplot of residuals of QOL NRS score and low mood severity with Loess line

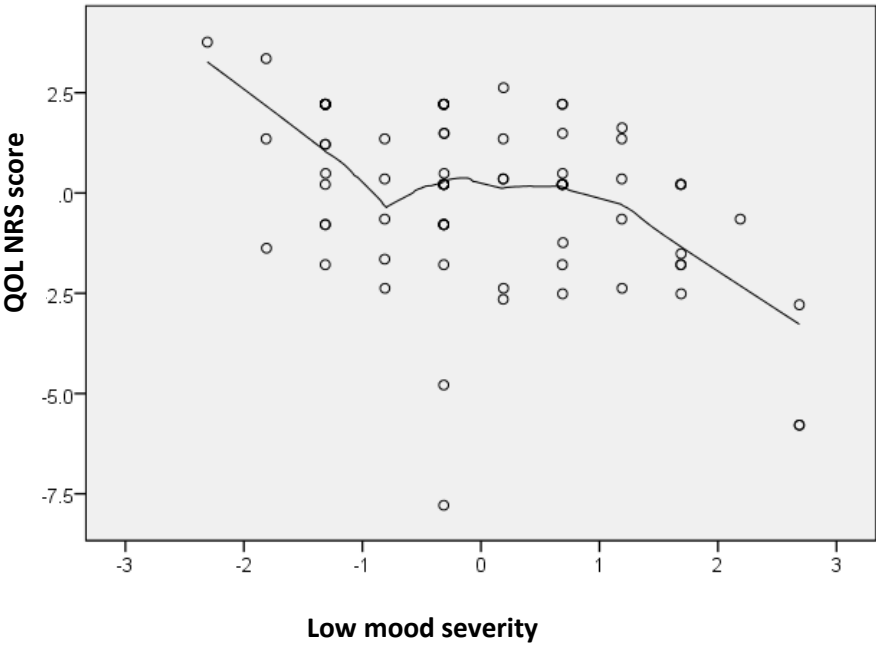
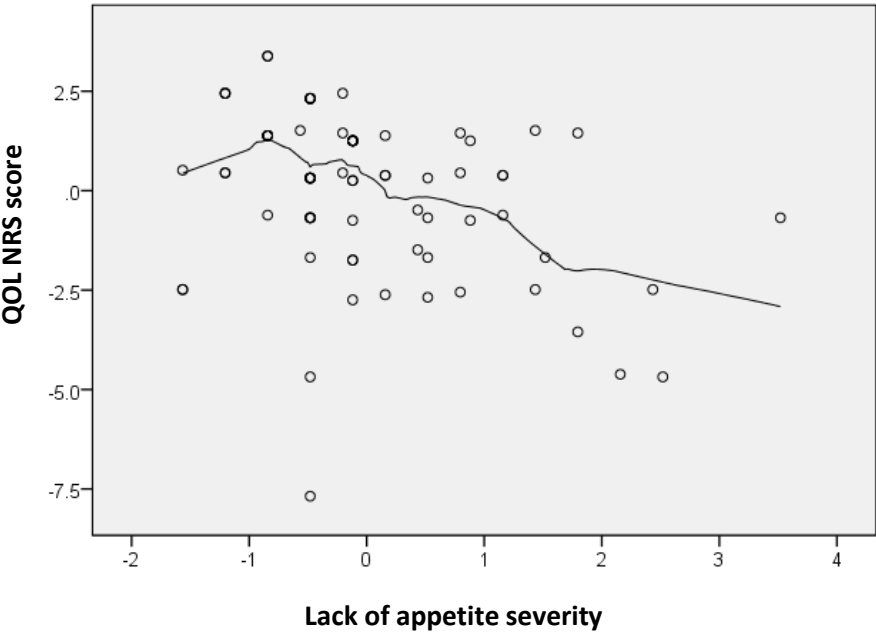


Figure 7.13 Scatterplot of residuals of QOL NRS and lack of appetite severity with Loess line



### 7.3.9 Symptom cluster based regression model

**Table 7.1 Linear model of predictors of fatigue severity using cluster level mean symptom scores**

	B	SE B	Beta	p	Tolerance	VIF
<b>Step 1</b>						
Constant	68.12 (56.63, 77.95)	4.70	-	-	-	-
Lack of appetite cluster	-13.71 (-18.16, -9.63)	2.43	-0.57	<0.001	-	-
<b>Step 2</b>						
Constant	82.63 (72.38, 91.92)	4.92	-	-	-	-
Lack of appetite cluster	-9.62 (-13.41, -5.91)	2.22	-0.40	<0.001	0.87	1.15
Low mood cluster	-7.54 (-10.31, -4.60)	1.48	-0.47	<0.001	0.87	1.15
<b>Step 3</b>						
Constant	84.27 (74.06, 94.44)	5.36	-	-	-	-
Lack of appetite cluster	-9.00 (-12.78, -5.30)	2.37	-0.38	<0.001	0.77	1.30
Low mood cluster	-7.06 (-10.29, -3.70)	1.61	-0.44	<0.001	0.74	1.35
Pain cluster	-2.27 (-7.66, 2.80)	2.90	-0.082	0.44	0.68	1.46

Step 1 adjusted  $R^2$  0.33, Step 2 adjusted  $R^2$  0.52 (F change=25.8,  $p<0.001$ ), Step 3 adjusted  $R^2$  0.50(F change=0.61,  $p=0.44$ )

**Table 7.2 Linear model of predictors of quality of life using cluster level mean symptom scores**

	<b>B</b>	<b>SE B</b>	<b>Beta</b>	<b>p</b>	<b>Tolerance</b>	<b>VIF</b>
<b>Step 1</b>						
Constant	12.15 (10.05, 12.52)	0.71	-	-	-	-
Lack of appetite cluster	-0.89 (-1.25, -0.34)	0.31	-0.31	0.006	0.77	1.30
Low mood cluster	-0.48 (-1.14, -0.30)	0.21	-0.26	0.028	0.74	1.35
Pain cluster	-0.80	0.38	-0.24	0.041	0.68	1.46
<b>Step 2</b>						
Constant	8.61 (5.14, 10.70)	1.49	-	-	-	-
Lack of appetite cluster	-0.51 (-0.98, 0.003)	0.33	-0.18	0.13	0.63	1.59
Low mood cluster	-0.19 (-0.86, 0.075)	0.23	-0.10	0.42	0.57	1.75
Pain cluster	-0.70	0.37	-0.21	0.061	0.68	1.48
Fatigue severity (MFS)	0.042 (0.011, 0.074)	0.016	-0.36	0.010	0.48	2.09

Step 1 adjusted  $R^2$  0.38, Step 2 adjusted  $R^2$  0.43 (F change=7.12,  $p=0.01$ )

95% bias corrected and accelerated confidence intervals reported in parenthesis

### 7.3.10 Survey supplementary qualitative data

*Verbatim as typed by participants, with minor amendments to spelling and punctuation*

<b>Lack of understanding</b>
<p>Think my partner gets frustrated at the fact and doesn't understand fully. She thinks I'm too lazy sometimes.</p> <p>I brought up my fatigue with doctors. Nothing was suggested apart from trying to rest and gentle exercise. However I started having private alternative therapy and my oncologist recommended I keep having it.</p> <p>Fatigue is rarely discussed after finishing chemo and, when it is, staff tend to say that it has nothing to do with past treatment and don't offer treatment or suggestions to help. Although mine has worsened with the side effects of [condition] and its medication, staff still don't seem to grasp the huge effect this has on my life and struggle to signpost me anywhere. I feel that for longer term survivors (3 years plus from end of treatment) there is very little support and awareness about how all late effects (fatigue included) still impact your life even though you 'look so well'.</p>
<b>Emotional impact</b>
<p>Basically, fatigue is ruining my day to day life... I feel like I don't see my family much or my friends and I always need to sleep. It's depressing.</p> <p>From my perspective, when I feel fatigued first I would say it a matter of me taking on a lot more mentally than I can achieve... Anxiety is a factor in me staying awake during the night when I wake up... Additionally, it makes me feel guilty when I feel too fatigued to do something like cooking myself a meal that I know I need to eat, and asking someone else to do it for me.</p>
<b>Impact on work</b>
<p>My main fatigue is from all the side effects from the treatment of cancer. Since my transplant 10 years ago I never recovered my strength and it has gone downhill even more. I can't work 9-5 and I have tried but it has a consequence on my body. I have tried different career paths and I haven't found something suitable. My mother and partner have to support me and I know they don't mind but I do because having a job and an income makes you feel like a person.</p>
<b>Perception activity is helpful</b>
<p>I think healthcare professionals recommend resting or taking regular naps as the best way to lessen the fatigue but I have personally found a healthy balanced diet and frequent gentle exercise to be a much better answer. The more you do the more you feel capable of doing, but doctors don't tend to encourage this in my experience.</p> <p>I'd like a fatigue support group post treatment as it would be nice to catch up with other patients again to discuss how we are all feeling now, and if there's any physio or complimentary therapies that can be recommended.</p>
<b>Requests for more research</b>
<p>Please look at the other aspects of fatigue, for example: spots appearing on the face and body through being drained, people's image changing because they're extremely tired. It also affects the physical appearance as well as the mental.</p>

## 7.4 Fatigue Intervention Co-design Study

### 7.4.1 Patient information sheet



### **Fatigue Intervention Co-design Study** **Information sheet for participants (patients)**

#### **What is this study about?**

Many young people treated for cancer have told us they are suffering from fatigue or tiredness. They are frustrated there is no effective treatment for this problem, and have asked us to do this research. This is the first study aiming to find a treatment that helps fatigue in teenagers or young adults who have, or have had, cancer. We value your experience and want to work together as a team with you to design the treatment.

#### **Why have I been chosen?**

You have been invited to consider taking part because you have told us that fatigue has been a problem for you since you had treatment for cancer. We aim to work with about ten young people in all, and would like to involve people with a range of ages and cancer types.

#### **What would taking part involve?**

You could take part alone, or can choose to involve one or both of your parents. We would like to include parents too, as our earlier research shows that not enough is known about parents' experiences and views. The study has three steps.

Step 1 We'd arrange for you to meet a researcher at a time and place that suits you. You would share ideas about designing a treatment. For example, we know from previous research that being active can help fatigue, but we don't know what sort of activity would suit people best. If one or both of your parents took part, their meeting with a researcher would be separate from yours. We also plan to run two focus groups, one for young people, and the other for their parents. Meeting as a small group can lead to interesting discussions that help us work out what type of treatment will work best.

Step 2 After this, a fatigue treatment will be developed, based on the information from the interviews and focus groups. When it is ready, you can try out the treatment you helped design. It is likely to involve giving information about fatigue, thinking about conserving energy, and finding ways to be more active. For some people, it could include exercise. The details of the treatment will be different for each person, as everyone has unique needs. A healthcarer would meet you at your home or in hospital on one to three occasions, and would work with you to try to help your fatigue.

Step 3 We'd meet you on one more occasion, again at a time and place that suits you, to get your feedback. This will help us improve the treatment so that it suits people even better.

#### **What will happen to the study findings?**

This study is part of an educational project. The findings will be used to design a fatigue treatment that we then plan to test out in a future larger study, to find out whether it is effective. We also plan to publish the Patient information sheet, version 1.4, 3.05.16

results in a professional journal. If you are interested, we can email a summary of the results to you after the study ends.

**What difference will the study make?**

The study is the first step in developing an effective treatment for fatigue in young people who have, or have had, cancer.

**What about confidentiality?**

The research team and anyone monitoring the study, such as members of the hospital Research and Development department, may need to look at your clinical notes. We will follow good ethical and legal practice, and will make sure all information about you is kept confidential. The interviews and focus groups will be recorded and kept securely. If we include something you tell us in our study reports, it will be anonymous, and there will be no way people could connect the quote with you.

**Do I have to take part?**

There is no need to take part if you don't want to. Choosing not to be involved, won't affect your care in any way. If you start the study and then want to withdraw, you can do this at any time without giving a reason and, again, it won't affect your care at all.

**Are there any risks from taking part?**

No, we don't think there are any risks. The fatigue treatment is safe, and will not involve taking any medicines. We do understand that being fatigued can make it harder to do things like taking part in research. We will do our best to make this study as easy as possible for you, for example, meeting you rather than expecting you to travel, and making meetings short if you want. If you do decide to travel to the hospital, we would pay your expenses. Should you feel upset by any aspect of the study, please contact Anna Spathis or Amy Chapman using the numbers or email addresses below. If necessary, your clinical care team may be involved. Also, you can contact the Patient Advice and Liaison Service at Addenbrooke's Hospital on 01223 216756.

**Who has reviewed this survey?**

This study has been reviewed and approved by the London-Chelsea Research Ethics Committee (reference number 16/LO/0575).

**What do I do now?**

If you want to take part, just tell one of your usual healthcare team. They will let us know, and then we'll get in touch.

**Details of the research team**

Chief Investigator: Dr Anna Spathis, 01223 274404, [anna.spathis@addenbrookes.nhs.uk](mailto:anna.spathis@addenbrookes.nhs.uk)

TCT Youth Support Co-ordinator: Amy Chapman, 01223 274243, [amy.chapman@addenbrookes.nhs.uk](mailto:amy.chapman@addenbrookes.nhs.uk)

***Thank you very much indeed for considering taking part in this study.***

Patient information sheet, version 1.4, 3.05.16

## 7.4.2 Parent information sheet



### **Fatigue Intervention Co-design Study**

#### **Information sheet for participants (parents)**

#### **What is this study about?**

Many young people treated for cancer have told us they are suffering from fatigue or tiredness. They are frustrated there is no effective treatment for this problem, and have asked us to do this research. This is the first study aiming to find a treatment that helps fatigue in teenagers or young adults who have, or have had, cancer. We value your experience and want to work together as a team with you to design the treatment.

#### **Why have I been chosen?**

You have been invited to consider taking part because we are aware that fatigue has been a problem for your son or daughter since his or her treatment for cancer. We aim to work with about ten young people and also about ten parents of young people who have had cancer treatment.

#### **What would taking part involve?**

We would like to include parents too, as our earlier research shows that not enough is known about parents' experiences and views. The study has three steps.

Step 1 We'd arrange for you to meet a researcher at a time and place that suits you. You would share ideas about designing a treatment. For example, we know from previous research that being active can help fatigue, but we don't know what sort of activity would suit people best. Your meeting with a researcher would be separate from your son's or daughter's meeting. We also plan to run two focus groups, one for young people, and the other for their parents. Meeting as a small group can lead to interesting discussions that help us work out what type of treatment will work best.

Step 2 After this, a fatigue treatment will be developed, based on the information from the interviews and focus groups. When it is ready, your son or daughter would be able to try out the fatigue treatment that you will have all helped us design. It is likely to involve giving information about fatigue, thinking about conserving energy, and finding ways to be more active. For some people it could include exercise. The details of the treatment will be different for each person, as everyone has unique needs, but it can be at home or in hospital, and is likely to involve meeting a healthcareer on one to three occasions. Parents will also meet the healthcareer for support and information, as part of the treatment.

Step 3 We'd meet you on one more occasion, again at a time and place that suits you, to get your feedback. This will help us improve the treatment so that it suits people even better.

#### **What will happen to the study findings?**

This study is part of an educational project. The findings will be used to design a fatigue treatment that we then plan to test out in a future larger study, to find out whether it is effective. We also plan to publish the Participant (parent) information sheet, version 1.4, 3.05.16



results in a professional journal. If you are interested, we can email a summary of the results to you after the study ends.

#### **What difference will the study make?**

The study is the first step in developing an effective treatment for fatigue in young people who have, or have had, cancer.

#### **What about confidentiality?**

The research team and anyone monitoring the study, such as members of the hospital Research and Development department, may need to look at your son's or daughter's clinical notes. We will follow good ethical and legal practice, and will make sure all information is kept confidential. The interviews and focus groups will be recorded and kept securely. If we include something you tell us in our study reports, it will be anonymous, and there will be no way people could connect the quote with you.

#### **Do I have to take part?**

There is no need to take part if you don't want to. Choosing not to be involved, won't affect your son's or daughter's care in any way. If you start the study and then want to withdraw, you can do this at any time without giving a reason and, again, it won't affect care at all.

#### **Are there any risks from taking part?**

No, we don't think there are any risks. The fatigue treatment is safe, and will not involve taking any medicines. We will do our best to make this study as easy as possible for you, for example, meeting you rather than expecting you to travel, and making meetings short if you want. If you do decide to travel to the hospital, we would pay your expenses. Should you, or your son or daughter, feel upset by any aspect of the study, please contact Anna Spathis or Amy Chapman using the numbers or email addresses below. If necessary, your son's or daughter's clinical care team may be involved. Also, you can contact the Patient Advice and Liaison Service at Addenbrooke's Hospital on 01223 216756.

#### **Who has reviewed this survey?**

This study has been reviewed and approved by the London-Chelsea Research Ethics Committee (reference number 16/LO/0575).

#### **What do I do now?**

If you want to take part, just tell one of your son's or daughter's usual healthcare team. They will let us know, and then we'll get in touch.

#### **Details of the research team**

Chief Investigator: Dr Anna Spathis, 01223 274404, [anna.spathis@addenbrookes.nhs.uk](mailto:anna.spathis@addenbrookes.nhs.uk)

TCT Youth Support Co-ordinator: Amy Chapman, 01223 274243, [amy.chapman@addenbrookes.nhs.uk](mailto:amy.chapman@addenbrookes.nhs.uk)

***Thank you very much indeed for considering taking part in this study.***

Participant (parent) information sheet, version 1.4, 3.05.16



### 7.4.3 Healthcare professional information sheet



Cambridge University Hospitals  
NHS Foundation Trust

## Study information for healthcare staff v0.1 9.02.16

---

Study title: Fatigue Intervention Co-design Study in teenagers and young adults with cancer

Dear Dr.....

I am writing to let you know that your patient..... has kindly agreed to participate in a research study. This small qualitative study is aiming to design an intervention that increases participants' confidence in managing cancer-related fatigue. Patients and, if they agree, their parents will work with us to co-design a non-pharmacological treatment. They will then receive the prototype intervention and give us further feedback to help in the design process.

The intervention will be based around provision of education about fatigue, promotion of activity, and conservation of energy. It will be delivered by an Allied Healthcare Professional over a few weeks, in a place of their choice. Participants are aware that, at this stage, we will not know whether or not the intervention is effective. That will be tested in a future larger controlled study. However, we anticipate that it will be entirely safe.

Please do not hesitate to contact me on 01223 274404 or by email using the address at the bottom of this letter if you have any queries.

Yours sincerely,

Anna Spathis

Chief Investigator  
Consultant in Palliative Medicine  
Email: [anna.spathis@addenbrookes.nhs.uk](mailto:anna.spathis@addenbrookes.nhs.uk)

#### 7.4.4 Information for Facebook

**\*This the content of the information, but the exact wording may be amended slightly\***

Are you suffering from fatigue? And have you completed cancer treatment?

If so, would you like to take part in some research that will help us design a treatment for fatigue?

For many years, young cancer patients have been telling us about their fatigue. It affects people in many ways, from feeling weak to having difficulty thinking or concentrating. Although it is such a common and distressing problem, there has been no research to find a treatment specifically for young people.

Research in older patients shows the benefits of building up activity, while at other times resting and conserving energy. Support and information about fatigue can also help. However, we need to find out what young people really want. The best way of doing this is to work together to design a treatment.

We need your help!

Taking part would involve meeting us one-to-one and in a small focus group. Then you'd get the treatment you had helped design. After that, we'd meet once more to get further advice from you. We'd also like to include a few parents in this research.

If you'd be interested, please let us know. We'd really appreciate your help, so we can work together to design the best possible treatment.

*Thank you for considering taking part.*

*Let's work together to treat fatigue!*

## 7.4.5 Patient consent form



Cambridge University Hospitals  
NHS Foundation Trust

### Consent form (patient) v0.1 9.02.16

Project title: Fatigue Intervention Co-design Study in teenagers and young adults with cancer

Chief Investigator: Dr Anna Spathis

Participant ID number:

**If you agree to each sentence below, please initial each box.**

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary, and I'm free to withdraw at any time without giving reason and without my medical care being affected.
3. I understand that relevant sections of my medical notes may be looked at by the research team, or by monitors or auditors of the research. I give permission for this access.
4. I understand that my GP will be informed that I'm taking part in the research and will be sent details of the study. I give permission for my GP to be notified.
5. I understand that if the researchers have concerns about me during the study, they may need to share relevant information with my clinical team. I agree to this.
6. I understand that the interviews and the focus group will be tape-recorded and I agree to this.
7. I consent to the use of quotations of what I have said in the interview in published reports, providing the quotations are anonymised and I will not be identifiable.
8. I agree to take part in this study.
9. I understand that one or both of my parents will be invited to take part (sign one box only)
  - I give permission for the following person/people to be contacted  
.....
  - I do not give permission for my parents to be contacted

\_\_\_\_\_  
Name of participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

#### 7.4.6 Parent consent form



Cambridge University Hospitals  
NHS Foundation Trust

### Consent form (parent) v0.1 9.02.16

---

Project title: Fatigue Intervention Co-design Study in teenagers and young adults with cancer

Chief Investigator: Dr Anna Spathis

Participant ID number:

**If you agree to each sentence below, please initial each box.**

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary, and I'm free to withdraw at any time without giving reason and without the medical care of my child being affected in any way.
3. I understand that if the researchers have significant concerns about me during the study, they may need to share relevant information with my GP. I agree to this.
4. I understand that the interviews and the focus group will be tape-recorded and I agree to this.
5. I consent to the use of quotations of what I have said in the interview in published reports, providing the quotations are anonymised and I will not be identifiable.
6. I agree to take part in this study.

\_\_\_\_\_  
Name of participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

#### 7.4.7 Research Ethics Committee approval

*Decision and signature pages only*



## Health Research Authority

### London - Chelsea Research Ethics Committee

Research Ethics Committee (REC) Bristol Centre  
Level 3, Block B  
Whitefriars  
Lewins Mead  
Bristol  
BS1 2NT

Telephone: 02071048055

**Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval**

26 April 2016

Dr Anna Spathis  
Department of Palliative Medicine  
Addenbrookes Hospital  
Cambridge  
CB2 0QQ

Dear Dr Spathis

<b>Study title:</b>	<b>Fatigue Intervention Co-design Study in Teenagers and Young Adults with Cancer</b>
<b>REC reference:</b>	<b>16/LO/0575</b>
<b>Protocol number:</b>	<b>A093987</b>
<b>IRAS project ID:</b>	<b>202256</b>

The Research Ethics Committee reviewed the above application at the meeting held on 11 April 2016. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Miss Alik Sifostratoudaki, [nrescommittee.london-chelsea@nhs.net](mailto:nrescommittee.london-chelsea@nhs.net). Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

## Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

## Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

1. Please update the Participant Information Sheet to state that if the participant decides to withdraw from the study, their care will not be affected.
2. Please update the Participant Information Sheet to clearly state that that the interviews and focus groups will be separate experiences to the intervention. The PIS should state that an intervention will be developed based on the interview data and when this is ready, the participants will receive the intervention.
3. Please update the Participant Information Sheet to include more information about how you would proceed if a participant finds something distressing during the interview or the intervention. Please provide contact numbers and email addresses for the research team and whether you will contact the clinical care team.
4. Please update the Participant Information Sheet to include examples of what the intervention may be (e.g exercise).
5. Please re-phrase the sentence 'The research team and any monitors of the research' in the Participant Information Sheet. Please detail exactly who the 'monitors of research' will be.
6. The Participant Information Sheet should be updated to clearly state that the interviews/focus groups will be recorded and all data will be anonymised. The Committee also noted that the Consent form should include a point about whether participants are happy to be recorded.
7. Please update the Participant Information Sheet to state that this study is part of an educational project.
8. The Committee noted that the sentence 'The study is an important first step in developing an effective treatment for fatigue in young people who have, or have had, cancer.' may appear coercive. Please remove the word 'important'.

**You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.**

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).*



The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

### **User Feedback**

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

### **HRA Training**

We are pleased to welcome researchers and R&D staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

<b>16/LO/0575</b>
-------------------

<b>Please quote this number on all correspondence</b>
---

With the Committee's best wishes for the success of this project.

Yours sincerely



**Dr Shelley Dolan**  
**Chair**

E-mail: [nrescommittee.london-chelsea@nhs.net](mailto:nrescommittee.london-chelsea@nhs.net)

*Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments*

*"After ethical review – guidance for researchers" [SL-AR2 for other studies]*

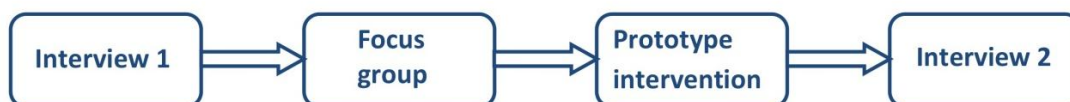
*Copy to: Mr Stephen Kelleher, Addenbrookes Hospital NHS Trust*

## 7.4.8 Patient interview and focus group schedule



### Fatigue Intervention Co-design Study

#### Interview and focus group schedules (patients)



#### Interviews

##### Introduction

Points to include:

- Check understanding of purpose and design of study, and find out if have any questions
- Emphasize confidentiality
- Explain that there are no right or wrong answers; we want to learn from participants' experiences and views.

##### **Interview 1 topic guide (before intervention)**

The interviews are semi-structured and iterative, so the content may vary. Questions can be rephrased into a language appropriate to each individual. Questions will include the following:

- Tell me about your illness and how it has affected you.
- What do you find most distressing about your fatigue?
- How has it affected your parents? What has their experience been?
- What are your views about the three main elements of the intervention? (*Explain these*)
- What do you think would work best for people? And work best for you? What would help you function better?
- What is the intervention missing? What other ingredients would you want included? Would you like the intervention to include a webcast, a Fitbit, a specific app?
- Would you like a way of measuring your progress? What would work best?
- What should we call the intervention?
- What is the best timing relative to cancer treatment?
- Anything else? Tell us what 'good fatigue care' should look like.

##### **Interview 2 topic guide (after intervention)**

Questions will include the following:

- Tell me about your experience of receiving the intervention
- What worked well? What didn't work so well?
- What would you keep in the intervention? What would you change? What would you add?
- Do you feel the intervention has had any effect on your fatigue? If yes, why? If no, why?
- Do you think the intervention has any effect on your parent(s) (if involved)?
- Would you like a copy of the study results when they are published?



## **Focus group**

### **Introduction**

Points to include:

- Introductions, confidentiality within group
- Explain who participants can talk to if their involvement in the group causes distress or if they have concerns about the study
- Explain that there are no right or wrong answers; we want to learn from participants' experiences and views
- Emphasize that the purpose is not to reach consensus but to have a debate and explore a range of opinions.

### **Focus group topic guide**

During the focus group, themes that have emerged from the first interview will be described to participants (while maintaining confidentiality). Then questions will be asked to try to encourage debate and expression of a range of views, in order to gain further insight beyond that from the first interviews. This will be a particularly iterative and flexible process, and it is not feasible to predict questions before the first interviews have occurred. Examples of types of question may be as follows:

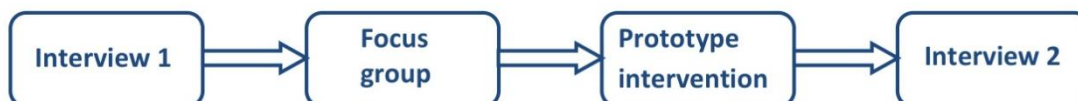
- We have been hearing from you in your individual interviews that sometimes your fatigue is like a weakness or lack of energy, but at other times or for other people it affects memory and concentration. Could you tell us more about that? What are your thoughts about why it varies like this?
- Some people think their parents over-react to their fatigue and do everything for them, but at other times parents don't seem to get just how bad it is. How can we make sense of this?
- Overall most people seem to want to receive the intervention at home. Do you think we should still allow it to be flexible, so people can be seen in outpatients? Or somewhere else?
- From what we've been hearing from you, the intervention is beginning to look like this.... (*say*). What are your thoughts about this? Do you think we're on the right lines? Or are we missing something?
- Anything else you would like to talk about?

## 7.4.9 Parent interview and focus group schedule



### Fatigue Intervention Co-design Study

#### Interview and focus group schedules (parents)



#### Interviews

##### **Introduction**

Points to include:

- Check understanding of purpose and design of study, and find out if have any questions
- Emphasize confidentiality
- Explain that there are no right or wrong answers; we want to learn from participants' experiences and views

##### **Interview 1 topic guide (before intervention)**

The interviews are semi-structured and iterative, so the content may vary. Questions can be rephrased into a language appropriate to each individual. Questions will include the following:

- Tell me about your son's/daughter's illness and how it has affected you son/daughter.
- How has it affected you? What impact does it have on daily life? How does it make you feel?
- What impact does it have on the lives of others in your family?
- How well do you feel you understand your son's/daughter's fatigue? And do you understand the most helpful ways of managing it?
- What are your views about the three main elements of the intervention? (*Explain these*)
- What, out of this, do you think would be helpful for you? Is the intervention missing anything that you would helpful?
- Do you have a view about what we call the intervention?
- What are your views about the best timing relative to cancer treatment?
- Anything else? Tell us what 'good fatigue care' should look like.

##### **Interview 2 topic guide (after intervention)**

Questions will include the following:

- Tell me about your son's/daughter's experiences, and yours, of receiving the intervention.
- What worked well for your son/daughter? What didn't work so well for your son/daughter?
- What worked well for you? What didn't work so well for you?
- What would you keep in the intervention? What would you change? What would you add?
- Do you feel the intervention has had any effect on your son's/daughter's fatigue? If yes, why? If no, why?
- Would you like a copy of the study results when they are published?

Interview and focus group schedules (parents) V1.0 16.3.16

## **Focus group**

### **Introduction**

Points to include:

- Introductions, confidentiality within group
- Explain who participants can talk to if their involvement in the group causes distress or if they have concerns about the study
- Explain that there are no right or wrong answers; we want to learn from participants' experiences and views
- Emphasize that the purpose is not to reach consensus but to have a debate and explore a range of opinions.

### **Focus group topic guide**

During the focus group, themes that have emerged from the first interviews will be described to participants (while maintaining confidentiality). Then questions will be asked to try to encourage debate and expression of a range of views, in order to gain further insight beyond that from the first interviews. This will be a particularly iterative and flexible process, and it is not feasible to predict questions before the first interviews have occurred. Examples of types of question may be as follows:

- Some parents describe feeling that it's most helpful to let their son/daughter rest, whereas others keep trying to encourage them to get on and do things. What do you think causes this range of opinion? How can we make sense of this?
- Some people think their parents over-react to their fatigue and do everything for them, but at other times parents don't seem to get just how bad it is. How can we make sense of this?
- Overall most people seem to want to receive the intervention at home. Do you think we should still allow it to be flexible, so people can be seen in outpatients? Or somewhere else?
- From what we've been hearing from you, the intervention is beginning to look like this.... (*say*). What are your thoughts about this? Do you think we're on the right lines? Or are we missing something?
- Anything else you would like to talk about?

#### 7.4.10 Final node structure

Name of node	Number of sources	Number of references
<b>Experience of fatigue</b>	40	628
Concept and importance of fatigue	11	18
Fatigue pattern	12	20
Sleep pattern change	11	18
Factors that help fatigue	23	71
Factors that worsen or don't help fatigue	22	41
Concerns about activity	9	20
Physical impact	6	9
Emotional impact	19	38
Emotional impact on family	7	12
Cognitive impact	19	39
Relative importance impact type	10	16
Impact on work, education	15	22
Impact on social functioning	20	51
Impact on family social functioning, regression	12	24
Info needs, what to expect	15	25
Info needs, how much to push self	14	27
Info needs, how much to push YP	11	23
Info needs, other	16	35
TYA characteristics, need for normality	22	65
Misunderstandings, tension	25	54
<b>Intervention principles</b>	40	377
Approach, motivation	18	56
Flexibility	8	10
How specific	16	43
Involvement of family	15	36
Activity goals, feedback, app	20	60
Energy conservation	14	38
Education content	26	56
Education mode, video	14	32
Diet advice	9	17
Sleep advice	8	10
Psychological support	10	19
<b>Intervention practicalities</b>	35	244
Intervention name	13	29
Timing relative to end of cancer treatment	21	47
Frequency length of contact	10	19
Location intervention	16	39
Location activity	6	9
One to one, family, group, chat room	11	24
Mode communication	13	27
Which therapist(s)	1	8
Helpful aspects prototype	7	24
Unhelpful aspects prototype	6	18

#### 7.4.11 Intervention prototype guidance for Allied Health Professional

##### **Intervention prototype**

This has been informed by:

Patient and parent individual interviews (n=21)

Patient and parent focus groups (n=2)

Research team discussion in intervention co-design meeting (n=1)

##### Intervention name

Road to Recovery: Fatigue Support (R2R)

##### General points

The intervention needs to be very flexible and individualised.

There is often a degree of tension in the home, with a perception of being considered 'lazy'; young people want parents to be involved and informed.

Participants describe cognitive fatigue as often more problematic than physical fatigue.

Positivity, psychological support and building confidence in self-management all underpin the intervention.

##### Content

###### *1) Education/guidance*

Guidance in electronic and, where possible, video format. While in process of developing our own videos (peer-produced), consider Evans Health Lab video (young people) and Macmillan fatigue booklet (parents).

Content for young people to include: managing expectations, impact especially emotionally, sleep needs and improving pattern, diet/nutrition.

Content for parents to include: all of above, also how much to 'push'.

###### *2) Exercise/activity*

Activity of young person's choice, but avoiding need to pay – consider 'exercise referral'.

Structured incremental activity, with specific daily/weekly goals, and clarity about intensity.

Monitor/feedback using health Apps (aim to identify 'top 5' valued Apps); health App may include calories/diet element if relevant.

###### *3) Energy conservation*

Analysing priorities, recognising that may not want to avoid 'boom and bust' eg if a night out is a priority.

Support with pacing and planning, coping with variation in energy, strategies to 'top up' energy.

Include short relaxation techniques eg short mindfulness.

##### Process

Find mutually convenient location: probably public place, not home or hospital.

Aim for at least one face-to-face meeting. After this (and potentially at introduction stage) can communicate by video link eg Facetime. Generally not to use telephone, unless an individual's preferred option.

Frequency to be mutually determined, potentially up to weekly contact in relation to achieving incremental goals.

Give individual Tip List (up to 10 items) as PDF to download on phone.

One letter (minimum) will be sent to the young person, with a copy to oncologist/haematologist.

Intervention length from first contact can be up to 3 months.

### 7.4.13 Framework 1: Participant experiences

	1a. Fatigue pattern and influences	1b. Impact of fatigue	1c. Unmet information needs	1d. Tensions and misunderstandings
TYA1	Non-strenuous exercise, like walking in nature, is calming. Suggests giving control: <i>'wiser to let people make the mistakes and learn themselves, so over exert themselves, because then they can work out their boundaries'</i> . Talking to friends and 'community' is also important. <i>'Emotional and psychological things that weigh you down, they also can contribute'</i> . Depression may manifest as fatigue. Attributes insomnia to poor bedtime routine. Perceives 'overlap' between fatigue and PTSD, PTSD symptoms including <i>'being numb and not able to focus'</i> .	The most upsetting impact of fatigue is effect on <i>'my mind'</i> , particularly memory and concentration hardest. <i>'I would be OK with [physical stuff] not changing, but... I would be distraught if I could not improve my mind. A young body can be pushed hard. ...with my body I can push myself...'</i>	Would like to know how much to push oneself with exercise as finds walking too long 'counterproductive'.	Did not realise that fatigue was not just physical; psychological component too. Perceives parents <i>'think I'm making it up'</i> . <i>'They're like you're off treatment so now go back to normal'</i> . <i>'And so of course they attribute what I would call fatigue to either laziness, or lack of willpower... I have spoken to them and tried to explain that it is not laziness'</i> .
TYA2	Experiencing worse fatigue than during treatment; fatigue persisting well after the end of cancer treatment: <i>'I can't seem to shake it off....'</i> Finds fatigue very unpredictable. Sceptical about advice to exercise as it seems to make fatigue worse, although at times it has been helpful. <i>'At the moment exercise just seems to make it worse. I just end up drained rather than like bouncing.... If I over exercise I just like die at the end and the next day I just can't do anything'</i> . The mindfulness App ['Headspace'] is very helpful.	Impact is more than tiredness or sleepiness: <i>'It's not really sleepy it's just like... a ton of brick pressing on you...when you're so tired that you can't sleep... and everything slows down and all I want to do is just get onto the sofa and lie down'</i> . Particular impact on ability to concentrate and 'find words'. <i>'I zone out... I just have to keep nodding and trying to like think of the end word they've said so I can say something about that'</i> . Fatigue being worse in the evenings makes it harder to meet friends and poor memory leads to forgotten social arrangements. Cognitive impact worse than physical. Fatigue unpredictability makes it hard to make	Need to know what to expect, particularly how long it will last. <i>'I was expecting it to get better 'cause I wasn't having all the treatment, but it didn't, it got worse'</i> . Wants information on <i>'what is normal... this time out of treatment.'</i> More information would have helped make realistic plans for future work. <i>'It just helps with kind of thinking what actually is realistic with what you can do afterwards'</i> . Would have liked detailed information on exercise intensity and when <i>'the point'</i> to stop is: <i>'it's quite hard to know whether to just go for it or like do a little bit and often'</i> . Acknowledgement of fatigue 'it happens' is inadequate; wants <i>'practical'</i>	Frustrated by how reliant has become on family for activities of daily living. <i>'I don't really want the reliance..'</i> Experienced sense of abandonment on leaving hospital <i>....you leave the hospital... 'You are not really getting the same level of support that you were before, and it just seems like the fatigue is the inevitable consequence, and you just have to deal with it'</i> .

	1a. Fatigue pattern and influences	1b. Impact of fatigue	1c. Unmet information needs	1d. Tensions and misunderstandings
		[continued from previous page] plans: <i>'so it's quite hard to plan things and I'd rather not plan things otherwise I'm always cancelling them'</i> . Fatigue makes pain more severe and harder to cope with. Worried about impact on ability during a job interview. Hard to say: <i>'...Oh sorry, I forgot the question...'</i>	[continued from previous page] solutions' or 'strategies', <i>'because it's really hard to know whether doing something is good or just counterproductive'</i> . Wants information on how to talk to employers: <i>'....rather than just be like I'm really tired, which kind of sounds like you're just being lazy'</i>	
TYA3	Variability of fatigue is particularly hard to cope with: <i>'I have a couple of days of a major rush, and then all of a sudden it is knocked out of me and it will take a good five days to get back up again'</i> . Describes it as being on a 'roller coaster'. Finds snacking, a 'sugar rush', can be helpful.	Fatigue causes irritability, and makes him 'say things I don't mean'. <i>'...because my body is so tired, and doesn't want to go any longer, sometime [parent] can say a simple sentence, and I will blow it out of proportion..'</i> Feels more forgetful, and that <i>my brain isn't functioning... how most of my friends' brains are...</i> Cognitive worse than physical fatigue. Too tired even for TV. Forgets dates: <i>You say, oh yeah, I'll meet you [day]... and you get like a really awful text... where are you?</i> Feeling of burdening friends with the fatigue ( <i>'he needs to nap'</i> ).	Concerned that exercise may make fatigue worse, particularly walking up stairs. Needed information about diet, <i>'I had no idea where to start with diet'</i> .	<i>'Family as well... now you're off chemo it's like oh, you must be fine... So it does cause arguments, a lot of arguments... I get seen as being lazy... my siblings are older and my brother especially, she doesn't understand how tired I do get. And it's very much like we end up arguing then because it's like why can you be this tired you don't do anything all day... I think he doesn't understand that just because my chemo has stopped doesn't mean that all the post stuff does stop too'</i> .
TYA4	Pacing can be helpful, for example resting during the day before an evening event. Activity, including during cancer treatment, valuable, best as 'smaller shorter stints'. <i>'If you can get out of bed and even just go for a walk or something, I do think it helps.'</i>	Describes having to leave evenings out early, whereas <i>'before I would probably be out until whatever time'</i> . Would like to return to <i>'night-clubbing'</i> .		

	1a. Fatigue pattern and influences	1b. Impact of fatigue	1c. Unmet information needs	1d. Tensions and misunderstandings
TYA5	Tries to 'sleep it off' but this doesn't help fatigue, and may be counter-productive.	Fatigue leads to a sense of lack of energy. Unable to work or meet friends: <i>'If I've been invited out by a mate or something... I rarely actually go because I would just be too knackered'.</i>		In the interview reacted, half-joking, in a way that implied she felt he was been seen as lazy. <i>'That makes me sound outright lazy though'.</i>
TYA6	Feels daily routine with having to 'do things' helps fatigue and sleep. Broke vicious cycle of poor sleep worsening fatigue by 2 nights of sleeping tablets. <i>'If I spend most of the day in bed, I am more tired, whereas if I get up and do something' then energy improves.</i> Describes impact of emotional state; compared to being ill when younger; at this age knowing too much causes 'worry' which affects sleep and fatigue. Activity helpful.	Impact includes having to cancel social plans, and feeling memory is much less good.	Needed information on how to improve sleeping pattern.	Feels fatigue is misunderstood: <i>...it's not just tired...</i> Is aware that the fatigue and related frustration has an impact on family. Family feel upset also when <i>'I've got plans and I have to cancel them'</i> . Peers also do not understand: <i>'I do think if you don't know ... if you haven't experienced fatigue or know what it is, you don't understand fully, you would just think, oh you just need a little nap, or something...'</i>
TYA7	Finds exercise really helps fatigue, any activity, including walking. Started exercise during treatment. Impacted on mental wellbeing; as it was <i>'something positive'</i> . <i>'I found it kind of like helped my mind as well, but helped the tiredness, because I felt that the days where I was just at home in bed feeling sorry for myself... you actually made yourself feel worse'</i> . Diet made no difference.	Aware of the psychological impact of fatigue, <i>'it brings you down as well, because your body doesn't really feel up to a lot of things'</i> . Also impact on concentration, leading to <i>'doing things wrong'</i> at work; at worst times was not even able to <i>'watch a film'</i> (audio easier than video). Fatigue hinders feeling 'normal', <i>'you want to act as if nothing's happened so you put your all into everything as if nothing [had happened]...'</i>	Finding it hard to understand <i>'what's just general tiredness and what's fatigue'</i> . Wanted more information on how to stay active and fit during cancer treatment. Advice would need to be guidance rather than specific, as everyone's needs are different.	Feels parents do not understand, <i>'They're just like get on with it'</i> . Similarly employer: <i>'...I have made them aware... But I don't think they get it'</i> Also friends when cannot go out: <i>'my friend got annoyed at me'</i> , <i>'So the other day I did get quite tense in that I swore at mum... she was just like, 'Well anyone would feel like that on a normal day at work'. I was like, 'You don't get it', and then I tried to explain it more'.</i>



	1a. Fatigue pattern and influences	1b. Impact of fatigue	1c. Unmet information needs	1d. Tensions and misunderstandings
TYA8	Feels being active is helpful <i>'fatigue was getting better anyway, just through me doing more'</i> . Believes that <i>'fatigue breeds fatigue'</i> and solution is to build up activity, rest making things worse. Important not to push <i>'it too hard and I was dying sort of thing the next day'</i> . Describes continuing at school through chemotherapy, which kept his, <i>'brain active and therefore in a better state than others'</i> .	Fatigue has huge impact on cognition, particularly concentration, memory and writing. Cognitive impact is worse than physical. <i>For me the physical isn't too bad, as I've found ways of controlling it, and improving it [activity], but the mental stuff I found tricky. Hard during exams, I'd think of the next point... but by the time I got to it, I'd forgotten it.</i> Impact on exam results, worse the days when <i>'tired and couldn't think straight'</i> . Definite social impact, not <i>'going out'</i> .	Is uncertain about how much to exercise, as a lot of walking <i>'can have quite an effect a few days afterwards'</i> . <i>'I kept getting mixed messages from one doctor and another about how hard I should push myself, how much I should do.'</i>	<i>'My mum threw my duvet down the stairs to get me out of bed.'</i>
TYA9	Perception that <i>'rest'</i> and <i>'time'</i> have made fatigue better. Diet made no difference.	Cognitive fatigue worse than physical fatigue, as it can't be seen. <i>'I can't concentrate enough on anything, and I can't read, because by the time I have registered one word, and moved onto the next, I can't string them together'</i> . Really worried about doing exams with <i>'memory problems'</i> .	Was not given verbal information about fatigue; only accessed information from a charity website. Feels parents have information needs and should have a written summary: <i>'best if they have the information... so they know what's going on...'</i>	Invisibility of fatigue causes misunderstandings, just being <i>'disorganised'</i> . <i>'The most stressful part... I will be sitting in school and I just can't do anything, and it looks like I'm not trying'</i> . Pressure from family to get back to normal life, including school/job. <i>'...my parents are saying 'just get up earlier' but I can't, because I am so tired all the time... and they don't understand'</i> .
TYA10	Feeling more fatigued months after end of cancer treatment than at the time of ending treatment, <i>'which I'm very shocked by'</i> . Activity helps fatigue and having a goal to aim for. <i>'Long walks... up my energy levels'</i> . Being active also reduces day time sleep. Yoga also helpful, as incorporates activity, relaxation and mindfulness, <i>'it is not just your body, it is the mind as well that it really helps with'</i> . However, just exercising the mind and not the body <i>'is not enough'</i> .	Fatigue leads to being <i>'overemotional'</i> Describes impact of fatigue on memory and concentration, <i>'I might need reminding several times to do something'</i> . Considers <i>'mental fatigue'</i> main problem, not <i>'physical'</i> . <i>I just assumed it would be my body... my body could get up and do another day, but mentally I can't seem to get going'</i> . Huge impact on family. <i>I think everybody has just been quite exhausted by the whole thing, it has taken its toll on everybody... my [sibling] didn't go to university because she was looking after me...</i>	Would have liked family to have had more information <i>'I think it could have been understood a lot earlier on by family and people around me if they had perhaps had some information'</i> .	Emotional impact of fatigue can lead to conflict within the family. <i>'When I'm tired, I am very moody and agitated, and I will lash out... And it can cause issues at home, because I will have a falling out with my [family], or I will snap at somebody'</i> . Describes manager at work being surprised at not wanting to increase hours. Feels family think of fatigue in physical terms, not understanding what it really is. <i>'They just think, oh well, she has had a long day, so she just needs to have some sleep'</i> .

	<b>1a. Fatigue pattern and influences</b>	<b>1b. Impact of fatigue</b>	<b>1c. Unmet information needs</b>	<b>1d. Tensions and misunderstandings</b>
TYA11	Relates daytime tiredness to difficulty sleeping, sometimes only two hours at night.	Really frustrated by reduction in concentration. Hardest part is <i>'not wanting to do anything'</i> , because of not <i>'having the energy to get up and do it'</i> .	Perceives that exercise can be harmful: <i>'I can't do too much because I injure myself too badly... If I walked any more I would hurt myself'</i> .	Internal misunderstanding, thought meaning of 'fatigue' was not being able to eat enough.
TYA12	Fatigue very variable day to day. Not sleeping much. Aware that light from electronic devices can hinder sleep but <i>'I have to be honest, I do do that. I do check my phone and that'</i> .	Has been told by family that she is more angry than before. Very aware of reduction in concentration, impacting on education and socially, <i>'I found myself losing concentration... about five minutes later, I realised I had not listened to a word anyone had said...'</i>	Wanted to know how long fatigue would last, but was given wide range of possibilities, and the cause: <i>'I would have wanted to know if when I am feeling knackered whether it was because of my treatment or not'</i> . Needed also to know how much to push herself physically.	Frustrated by variation in fatigue. Does not think University understands and frustrated her parents are pushing her to get on with University work. <i>'She is proper ratting on me, on my case, all the time.'</i>
TYA14	Resting can be helpful. <i>'Working myself up to doing things isn't very helpful... It build up into too much and I stop being able to do even the littlest things anymore.'</i> Feels that being active can make her ill; can become <i>'deathly ill from doing too much'</i> .	Fatigue leads to being more emotional. It also leads to <i>'brain fog'</i> . Physical impact probably worst, but <i>'closely followed'</i> by psychological.	Needed easily accessible information about <i>'brain fog'</i> .	<i>'I don't feel like people get it; they're just not very informed most of the time and it's hard to communicate... lack of understanding from my point of view'</i> .

	1a. Fatigue pattern and influences	1b. Impact of fatigue	1c. Unmet information needs	1d. Tensions and misunderstandings
PAR2	Fatigue persists and has progressively worsened after the end of cancer treatment. Feels that fatigue is very closely related to his mood. Is aware of <i>'habits forming'</i> in relation to fatigue, such as relying on siblings for help.	Fatigue is the <i>'biggest problem'</i> with the main effect being on cognition and concentration, particularly in social contexts. Impact of fatigue becomes greater the longer from cancer treatment, not necessarily because the fatigue is actually worse, but because the YP is trying to get back into normal life. The variability of fatigue has a negative impact on the family as well as the YP. Emphasises the enormous social impact of fatigue and it being difficult to <i>'reintegrate'</i> . Part of emotional impact of fatigue is that <i>'the fatigue is a constant reminder of where he has been [cancer diagnosis and treatment].'</i> Fatigue particularly hard at this age <i>'because up until now his body has never not worked'. 'It's a very tricky age for this all to be happening'</i> . Loss of control is particularly difficult at this age.	It is particularly difficult to cope with uncertainty of fatigue trajectory: <i>'But it isn't really substantially better now, six months later, and so when he is looking ahead, he doesn't know, and nobody can tell her'</i> . Would have liked to have known what to expect. Day to day unpredictability also particularly hard. <i>'It doesn't have any rhyme or reason'</i> . Uncertainty about how much should have pushed [TYA2], and questioning self on hearing other parents' approaches in the focus group. Felt [TYA2] was particularly frustrated that no-one could give a timescale for the fatigue, and help manage his expectations. Feels much more information is needed about psychological aspects of fatigue.	<i>'I mean, everybody in our house is unseated'</i> . Describes that if, for example, siblings do not believe in the fatigue, it can lead to conflict. . Alludes to invisibility of fatigue, <i>'somebody who has had a limb amputation, you would be seeing it'</i> . Describes great need of [TYA2] to <i>'feel believed'</i> . <i>'...friends ...compatriots are just not on the same page'</i> . Great reliance on family, particularly siblings: <i>'...has been a servant to [TYA2] nonstop... sits on the sofa and ...just shouts [name] and expects him to jump.... we've had some terrible blow ups because of [sibling] all because [TYA2] has been asking him to do stuff'</i> .
PAR3	Reports that [TYA3] feels better when she makes an effort and <i>'does something'</i> . Having <i>'nothing to do'</i> makes the fatigue worse. <i>If you do nothing, it makes you even more tired and exhausted.</i>	Frustration caused by fatigue leads to irritability and anger. Relates some of this to social isolation caused by fatigue. Also aware that [TYA3]'s memory is less good.		Emotional impact of fatigue affects family: <i>'...she gets quite angry with the world, and then she sort of has a go at me and I have a go back'</i> . Describes <i>'double-edged sword'</i> of social networking, as aware of what peers are able to do. Exhausted by dependence of TYA3's, including driving long distances. Feels sibling misunderstandings particularly bad.
PAR4	Belief that fatigue is a <i>'state of mind'</i> , where feeling emotionally positive and enjoying oneself can make the fatigue improve. Also <i>'getting up and doing something'</i> helped with difficulty sleeping.	Felt that fatigue made it much harder for [TYA4] to learn new things, particularly in a work context; this led to considerable distress.	<i>'I guess the biggest thing is that you don't know what normal is, so you don't know how [TYA4] should be, you don't really know what to expect'</i> . Would have been useful to get more information from other parents in a similar situation.	Tension between partners as to how hard to push <i>'....my wife would be saying to me 'Don't push her, don't push her'. And I would say 'Well she is strong enough to say 'no' when she is not.'</i>

	1a. Fatigue pattern and influences	1b. Impact of fatigue	1c. Unmet information needs	1d. Tensions and misunderstandings
PAR5		Fatigue is the biggest problem of many; causes frustration, low mood and irritability. Particular frustration when <i>'she sees her mates' lives going forward, like cars, jobs, girlfriends. She has sort of come to a bit of a standstill'</i> . Impact on concentration, not memory. Friends <i>'not coming round any more'</i> . Parental dependence.	Would like to be given ideas for how to support [TYA5] when she is frustrated with the fatigue.	<i>'...it can have a knock-on effect because she feels so tired all the time, and takes it out on me, quite understandably.</i> Describes an impact on all family members including grandparents.
PAR6	During holidays she <i>'is sleeping later in the day, and then she is finding it really difficult to sleep at night'</i> . Describes tending to watch TV in the bedroom, leading to getting to bed early but sleeping late. Learned that <i>'energy breeds energy'</i> from her own mother. Being active is helpful: <i>'she finds that when she actually gets up and does something it gives her more energy.... what she was doing was just spending the day in bed, and it was just making her feel worse.'</i>	Fatigue causes significant mood swings. <i>'She gets frustrated a lot more with the mental side of things than she does with the physical side...'</i> Particularly aware of social impact. <i>'It is quite upsetting to see her sort of separating herself from her friends, because she doesn't feel she can keep up with them'</i> . Impact on education, falling asleep revising. Social impact causes anger: <i>'because of the amount of stuff she's missed....missing out quite a bit on seeing friends, and socialising like a normal 17 year old'</i> . Impact also on not being able to make family plans: <i>'you don't know how they'll be feeling from one day to the next'</i> .	<i>'We have not actually been given any information about fatigue. ...how much do we put down to the treatment that she has had, and how much do we put down to just her being 17?'</i> Fatigue has led [TYA6] to feel anxious, as she did not know it would continue after the end of cancer treatment. Wanting to push [TYA6], while it is also <i>'hard to push...too much'</i> . <i>'So maybe we could have pushed her a bit more, maybe we have pushed her too much, we don't really know'</i> . Needs more information about sleep: <i>'now she's just not sleeping at all...at what point should I think it's not just fatigue, it's something else'</i> .	Mood swings lead to tensions within the family. Describes feeling upset and frustrated, particularly seeing [TYA6] becoming socially isolated. <i>'She sees all her friends all doing normal things, they've all got partners and jobs, they're all going off to university, and she's still sort of there...'</i> Effect on parents: <i>'It does have an impact... I can't really make plans to go and see friends and family, because I have got to basically work around [TYA6]'s fatigue'</i> .
PAR7	<i>'....obviously the more you sit still, whoever you are and whatever you have done, the more you feel tired'</i> . Exercise has been particularly helpful for [TYA7], both physically and psychologically. <i>'It is like psychological, isn't it ...if it is helping in your head, then it helps the rest of your body... I think your mood will make you more tired'</i> .	Describes [TYA7] as getting very frustrated at times, sometimes leading to anger.	Found it hard to differentiate between fatigue and <i>'normal tiredness'</i> . [TYA7] had accessed information from the Macmillan fatigue booklet, but was not age appropriate: <i>'it always aims at breast cancer more than anything...'</i>	

	1a. Fatigue pattern and influences	1b. Impact of fatigue	1c. Unmet information needs	1d. Tensions and misunderstandings
PAR8	<i>'To me, exercise never worsens fatigue. Fatigue breeds fatigue in my head.'</i> Strong views that parents are the key to successfully managing fatigue, <i>'the mums almost keep them ill...'</i>	Feels that the psychological impact of fatigue is worse than physical: <i>'It seems easier for them to force themselves to do something physical...the mental thing might lead to... aggression'</i> . Describes pronounced regression, with <i>'wanting his blanket back'</i> . <i>'... little bald headed who even looks like a baby... he acted exactly like a young child'</i> .	Described accessing a variety of leaflets, including from Macmillan, relating to fitness, but they <i>'were aimed at older people'</i>	Describes social networking potentially making it harder as <i>'you are seeing what everyone's doing and you're not doing'</i> .
PAR12	Describes poor sleep, and acknowledges influence of light from electronic device.	Perceives poor concentration problematic, and leading to procrastination. <i>'....really difficult to sort of sit in front of the laptop and apply herself.'</i>	Would have wanted an 'exercise plan', as [TYA12] went from no exercise to going for a run: <i>'I thought she was going to die, he was so out of breath, and was going to pass out. But of course she had gone from nothing, to go for a run'</i> .	Aware of being seen as <i>'nagging'</i> her daughter to get on with University work. <i>There have been tensions...It has been tense because we have adapted to life without her, and now she is there, and everybody is centred around [TYA12], and probably her [sibling] has felt a little bit shut out..... So it is definitely tense'</i> .
PAR13	Feels that [TYA13] perceives that the gym makes him more tired.	Feels psychological impact of fatigue for [TYA13] has been worse than physical.	<i>'The problem... is you don't know how much of it is normal for their age'. 'And I needed someone to tell me that...'</i>	Sense of invisibility of fatigue. <i>'So to look at him, he didn't really look any different...'</i> Arguments occurred when trying to help him <i>'feel more normal'</i> by getting dressed, but he did not want to. <i>'So it was getting him to do things... because he would say things like 'You don't understand, I have been through a lot'</i>
PAR14	Rest, relaxation, avoiding stress are all helpful. <i>'...being happy and having fun can actually give you a boost of energy'</i> .	Fatigue can cause a severe downward spiral of depression. It leads also to [TYA14] <i>'not being able to speak any words at all'</i> .	Needs guidance on how young person can <i>'take control'</i> again.	Felt healthcareers did not understand the fatigue as well as they did, and this led to conflict. Perceives that pushing to be active can be harmful: <i>'harmful to young people because adults can push them into doing more than they are physically capable of when they don't recognise their fatigue, with potentially long term, permanent consequences'</i> .

#### 7.4.14 Supplementary qualitative data

Theme A1: TYA developmental stage compound the impact of fatigue	
Hindering cognition	
Effect on memory and concentration	<p>... like I have started to listen to tapes, because also I couldn't focus on films and things like that. [TYA7, phase A]</p> <p>My TV is in my cupboard collecting dust. I haven't watched TV in... we are into the seventh month, seven months, eight months last December. [TYA3, phase A]</p> <p>...like I just can't remember things any more. [TYA2, phase A]</p> <p>Both really because her memory is not very good at the moment and she has a fantastic memory and it's just like sometimes she just forgets, the silliest things, you know, what she went upstairs for, that sort of thing. I do that, but I'm nearly sixty, you know. [PAR3, phase A]</p>
Impact on work, education and socially	<p>Whereas I'd find at the start of the exam I was alright. But as I went on I would start writing the paragraph, think of the next point as you do but by the time I got to it I'd forgotten it. That was a bit of a pain. [TYA9, phase A]</p> <p>And sometimes actually I kept doing things wrong on the tills, and I think that could be a struggle. [TYA7, phase A]</p> <p>But he is finding it really, really difficult to sort of sit in front of the laptop, and apply himself, and is procrastinating and putting it off. [PAR12, phase A]</p> <p>Yeah, I think like especially when I'm having conversations with people and I just like forget stuff and it looks like I'm being really rude or just not listening, but like I genuinely like forget stuff all the time. [TYA2, FG, phase A]</p> <p>Do you say, 'Oh, yeah, I'll meet you Thursday', or whatever and then Thursday comes and you get like a really awful text... 'Where are you? Was I meant to be meeting you today?' [TYA3, phase A]</p>
Cognitive fatigue versus physical fatigue	<p>And I don't feel physical fatigue without the mental stuff, I feel the mental... sometimes without the physical, but usually both of them with the mental more obvious to me, because it is the part of me that I use more than I use my body. [TYA9, phase A]</p> <p>What I found with [TYA6] is that sometimes when she's having an active day she tends to handle that more than if she's having a mental day. Like when she was studying for her exams, for example, that wiped her out a lot more... [PAR6, phase A]</p> <p>Yeah, with this age group it's more probably important mentally... and also like just having conversations with friends otherwise you're kind of out of it, if you just get so tired in the conversation you're just sitting there like unable to speak. [TYA2, FG, phase A]</p>

	<p>...it was so interesting is that the cognitive aspects of fatigue, concentration and memory are a bigger problem and they want us to focus more on this. [RES, CDM, phase B]</p> <p>... I was fascinated to hear this from parents and also in a sense from young people of actually... it is the cognitive side of the fatigue that's particularly bad and 'we do want support with that'. And if that's psychological support 'we want that'. So they didn't feel like the stigma around support or psychological support because they're getting the fact that this is affecting how they think, and their memory and concentration. [RES, CDM, phase B]</p>
<b>Exacerbating emotional reactivity</b>	
'Anger' and 'frustration'	<p>Yeah, I agree, my hearing's completely off but then when you're tired, or when I'm tired or if I'm struggling to hear things then I end up like aggravated and angry because it's like I'm trying to process what people are saying but I can't hear them, if that makes any sense. [TYA3, FG, phase A]</p> <p>I know that when I am tired like I would say [like] most of my year group, you end up ratty, you end up angry for no reason. And instead of me knowing... to kind of just mellow, because I am already wound up, because my body is so tired, and doesn't want to go any longer, sometimes mum can say a simple sentence, and I will blow it out of proportion... [TYA3, phase A]</p> <p>Yes, because if she is tired she gets muddled or she can't remember things that frustrates her. She does get very angry with herself and other people. [PAR3, phase A]</p> <p>She gets frustrated sometimes. She has got really frustrated with it, where she has just felt that she is more tired than she should be at her age... [PAR7, phase A]</p> <p>And she gets very frustrated because she sometimes can't do what she used to do and sometimes it makes her feel inadequate. And I get the sense that she doesn't feel she's as much of a person, if that makes sense. [PAR5, phase A]</p>
Effect on mood	<p>...you can start to lose hope and lose hope of never being able to actually achieve that independence and that really spirals you down into depression and it can be really serious depression because you know. [PAR14, phase A]</p> <p>It is like mood swings really, yes. Because like you say one minute her and her sister will be laughing their heads off, and then the next minute she will be like 'Right I am tired now [sister], go to your room'. [PAR6, phase A]</p>
<b>Hampering the need to conform</b>	
TYA perspectives	<p>I think that just comes with our age as well, when you're under 25 your brain is still trying to keep up with what everyone else is doing... [TYA3, FG, phase A]</p> <p>Yeah, like going out at the weekends and just even generally doing stuff in the day, you kind of put your all and I generally don't say, 'No,' because I have huge fear of missing out. So like I'll go out continuously, like at weekend... you want to act as if nothing's happened... [TYA7, FG phase A]</p>

Parent perspectives	<p>Whereas before she was getting very annoyed and frustrated because she was watching Facebook and all her friends going out, partying and out with their boyfriends and this and that and she said, 'I can't do that.' [PAR3, FG, phase A]</p> <p>...like you said, on Facebook she sees all these people that she knew from school that she should be in a friendship group that she would have been friends with. So she sees them all doing normal things, they've all got partners and jobs, they're all going to college, they're all going off to university and she's still sort of there... that's where her anger is coming from because of the amount of stuff she's missed. [PAR6, FG, phase A]</p>
<b>Dependence and demotivation</b>	
Regression to dependence	<p>...and you have this bald headed who even look like a baby but they, he acted exactly like a young child. [PAR8, phase A]</p>
Demotivation	<p>...have days where I don't do anything, it kind of hits me, and I get quite achy and tired, and I am just de-motivated, and I just can't really... [TYA7, phase A]</p> <p>Literally not even getting dressed and I'm like, you need to motivate you to do something. [PAR3, phase A]</p> <p><i>But she's sort of lost that motivation to get out because she's been so tired.</i> [Interviewer] Yeah, I think that's what it is. She doesn't seem motivated. And she, obviously the tiredness isn't helping. [PAR5, phase A]</p>



Theme A2: TYA developmental characteristics influence intervention design	
Intervention approach	
Motivation and confidence	<p><i>And what is the secret to regaining that hope? [Interviewer]</i></p> <p>I guess understanding that the little things that you do like taking control of things are actually important. [TYA14, phase A]</p> <p>Yeah, I mean I'm trying to work it out myself what... how you could help someone, because I think what's needed is almost like a catalyst or a way of moving the progress forward, or like understanding in all sorts of individuals, what would help them move forward. [TYA1, phase C]</p> <p>I don't like this passive, 'fix me' attitude. It's all, it's a two-way thing, the doctors will do their thing and nurses will do their thing and then you have to do your thing, you have to do your part. [PAR 8, phase A]</p> <p>...definitely the best way for people I think to get over [fatigue] is to keep them motivated. [TYA8, phase A]</p>
Health coaching	<p>I was almost saying 'this might be normal for you, it might be normal to stay up to 3 or 4 watching American football, because that's the time it's on with the time difference. That's OK, but it is going to have an impact.' And I didn't think there was going to be any change there. But obviously it's clicked in his mind, and he thought, 'That is a problem for me and I'm going to change it.' So I think that is what he changed, without me saying, 'You need to change this. I was just identifying what the link was really.' [HCP, phase C]</p>
Individualised, own goals	<p>... so kind of set a goal with them. So if you say to someone like me, so where do you want to be in three months time, and I just turn around and be like, 'Well I don't know,' then you kind of start digging and find out what they like, what they want to do, if they go to school, things like that. And then they'll set themselves their own goal without even thinking about it. [TYA3, phase C]</p> <p><i>And so is what you're saying [TYA3], just to check I've understood, that it's actually most important for the person themselves to set their goal, and to work out the plan to get there, rather than actually, whoever it is, whether it's [HCP] or whoever it is in future treatment, writing down a plan for somebody? [Interviewer]</i></p> <p>Yes, because it's then set to what your body wants not what their body wants. And like everyone's body is different, so you might give a young 14 year old the same thing as me and I might be fine with it, but she might be struggling. [TYA3, phase C]</p> <p>...the end goal of playing basketball again, so that's my motivation from within me, rather than most people won't have an end goal set that will want them to be motivated. So I don't know if it's just ringing up and setting goals [TYA8, phase A]</p> <p>...the worst thing you can do is sort of shame them into a state of being motivated or saying 'you should do something' because there's probably a really good reason why people feel demotivated. [TYA1, phase C]</p>

	<p>And I am not really part of the camp that says that you should just give people some instructions, and they have to take it like a bitter pill. [TYA1, phase A]</p> <p>...was there something that all this time you've been ill you've been thinking 'I wish I could do that'? And, 'Let's aim for that...' [PAR 8, phase A]</p> <p>But I do think having an end goal is something that... like, I knew I wanted to get back into a full time job, and that's what I've worked towards, and that's what I'm doing. [TYA10, phase C]</p> <p>The other really big theme is that the intervention must be flexible and individualised and almost nothing they want completely planned. [RES, CDM, phase B]</p>
Positive approach	<p>I think anything that's offered to him in a positive way is to be taken, because he is very disabled in many ways at the moment; he doesn't want to think he is but he is. So I think positive things are great. [PAR2, phase A]</p> <p>Well I think, I always try and work it backwards from the point where you are at, to bring... I try and get [TYA4] from where I think she actually is to the best place she can be with sort of like positive thinking, motivation. And I very much, we focus on the good things, we don't focus on the bad things. [PAR4, phase A]</p> <p>Again, focus on the recovery not the illness. You've got to always think about your recovery, recovery, what can you do. [PAR 8, phase A]</p>
<b>Intervention content: activity</b>	
Specific, structured regular support	<p>I would love to just have someone say, 'This is what you should do this day, this is what you should do this day'. And then it just means that it is something to focus on as well, isn't it, rather than you have got something to keep your mind onto, and it should be more or less achievable, shouldn't it? ...Yes if I could have a regimented plan it would be loads easier, loads easier to get back into it. [TYA12, phase A]</p> <p>Yes, like it felt kind of like any conversation I've had was a consultation, yes, in a consultation, because it's kind of like, 'Oh, how are you doing, how are you coping?' But then that's kind of like the things that you go through, it kind of just felt like a general... [TYA7, phase C]</p> <p><i>Chat? [Interviewer]</i></p> <p>Yes, rather than kind of picking out things that are the worst to then go, 'Right, let's kind of take this and ...' I don't know. [TYA7, phase C]</p> <p>...I guess the main thing I kind of thought was lacking maybe was like a plan going forward. I don't know what... I just thought she might kind of help me create like a plan going forward for what worked, what didn't work. But it just more seemed to be a kind of general chat. [TYA2, phase C]</p> <p>...so the message was a bit hazy, whereas if you just say... all I wanted to see was right you can do this, you can do this... [TYA8, phase A]</p> <p>I was quite surprised because I perhaps wasn't prepared for the bluntness or the actual needing facts rather than talking around things if you see what I</p>

	<p>mean... So I would say that they did want more specifics and absolute detail rather than more generic advice. [HCP, phase C]</p> <p>... there they really want... 'What do I need to do today, what do I need to do tomorrow, what do I need to... where will I be at the end of the week, where will I be at the end of the next week, how will I know how I'm doing and how often can we be in touch to talk about how I'm doing?' So it's really specific and defined which I think is not surprising but interesting. [RES, CDM, phase B]</p> <p>And then going on to activity, they want a very clear plan of what they're going to do, most people said this. What they're going to do each week rather than just say, you know, 'Exercise until you feel that your body's had enough,' is just not good enough because actually they can push themselves, young bodies... [RES, CDM, phase B]</p> <p>...what they want is very definite and it's all trial and error at the moment and so people are... some of the young people are literally just breaking themselves by doing far too much but they've got nothing to go on... [RES, CDM, phase B]</p>
Activity goals	<p>You've got to set an overall goal and then you've got to set a weekly goal, a monthly goal, and lower so if you don't... 'cause if you set one say, 'You've got [to] reach this,' and you don't reach that you're going to be, phew! Whereas if you're setting them and you're constantly getting that buzz, so you're losing weight, so you lose a pound this week you feel good and you keep going... [TYA8, FG, phase A]</p> <p>You could do a sort of chart thing so like if you're going to do it with [HCP] we try different things each week and then she just rings us or emails us and says, 'Did you do such and such, did you manage to do that?' And it's like... like I set a week thing, everyday I've got something on so like Monday morning you go and walk the dogs, Tuesday go and do the [local activity], I've always got something on. [TYA3, FG, phase A]</p> <p>But I do think having an end goal is something that ... like, I knew I wanted to get back into a full time job, and that's what I've worked towards, and that's what I'm doing. [TYA10, phase C]</p> <p>There's also the reassessment point then, isn't it? Because it's sort of checking back with them saying, 'Okay, so you managed that really easily so this week actually we can move those a bit,' Or actually, 'You haven't managed that...', really tailored week by week. [HCP, CDM, phase B]</p>
Monitoring progress	<p>I know in my heart that I do, and I am making a difference, but when your brain is already in overdrive, and then you are already feeling low, something that is not visible straightaway... [TYA3, phase A]</p> <p>An App to keep track of the good days and bad days would probably help me to make progress I think, in help like keeping control of the good and the bad days. I think it'll show me how many I'm having actually per month and per week. [TYA6, phase A]</p> <p>Also in terms of having something to measure your progress by. It would be</p>

	<p>quite nice to have a little like, I guess mentally, to have a little like reminder or thing. Rather than just thinking, I mean to actually see it written down, like, 'You've walked this many steps and you've done this...' I guess that's why an App might be quite helpful because it's like a day to day thing. [TYA2, phase A]</p> <p>So they could compare with each other and you can congratulate each other, you know, you can send little 'well done' and things like that if they've done a particularly... or you could have a set goal, you can have goals on this Map My Walk. [PAR8, phase A]</p>
<b>Intervention content: energy conservation</b>	
Irrelevance of energy conservation, pacing	<p>Yeah, like going out at the weekends and just even generally doing stuff in the day, you kind of put your all. And I generally don't say, 'No, 'because I have huge fear of missing out. So like I'll go out continuously, like at weekend and then it'll come down to like Monday or Tuesday or whatever and you just like proper feel it like catching up with you. But I still try and like continue... you want to act as if nothing's happened so you put your all into everything... [TYA7, FG, phase A]</p> <p>If you want to do stuff then you just get the fatigue anyway, so you kind of... you make the sacrifices and you say, yeah, I'll get that fatigue... [TYA2, FG, phase A]</p> <p>It depends on the person. Like there are some things that are more important than being a bit tired 'cause we're always a bit tired that's why we're doing this study. [TYA1, FG, phase A]</p> <p>I still get a feeling that sometimes she tries to run before she can walk, and I kind of try and get her to, you know, take time out... pace herself a little bit [PAR6, phase C]</p> <p>I wouldn't say he used relaxation techniques particularly. He'd just go to bed. [PAR8, phase A]  <i>It's not a massive teenage thing? [Interviewer]</i>  No, not really. [PAR8, phase A]</p> <p>...the key reason why I don't pace myself is because I get disconnected from that. [TYA1, phase A]</p> <p>...so energy conservation I think for the parents was a huge concept, inevitably, and frustration at adolescents tending not to plan and the inevitable being boom and bust.... My sense from your focus group is that 'boom and bust' isn't something they actually recognised which is a word that they use with older people... [RES, CDM, phase B]</p> <p>...so that if they had a big night out they would just expect that they'll be, you know, floored the next day, and that's something that they're willing to do, to live with. [RES, CDM, phase B]</p> <p>'I'm young, I'm not prepared to do this, I'm not prepared to stop going night-clubbing...' [RES, CDM, phase B]</p>

Mindfulness or other meditative techniques	<p>... your brain is already in overdrive, [TYA3, phase A]</p> <p>[Mindfulness] it's very in at the moment so... we could use that again. [HCP, phase C]</p> <p>[TYA12] said he was doing the Headspace App, which is the mindfulness App, and really took on board some information and was doing really well. [HCP, phase C]</p> <p>[TYA1] also did talk about mindfulness and relaxation and having taster session on the ward, for people to go in and actually try. [HCP, phase C]</p> <p>So part of exercising the mind now is to allow it to be quiet. [TYA1, phase A]  <i>...So something about almost... I don't know if you use that word 'mindful', about being in a still, calm, aware place...? [Interviewer]</i>  ...I prefer the idea of moving meditations like Tai Chi. [TYA1, phase A]</p> <p>For me the benefit [of yoga] is massive. [TYA10, phase A]</p>
<b>Intervention content: information needs</b>	
'How hard to push'	<p>I did it the other day when I went for a run, and I came back, I pushed myself as hard as I can. I came back, I weren't nearly sick, but I was like really ill, like feel myself ill... Yes, someone who knows what they are talking about really, in terms of how hard they can push you without, well, killing myself basically. [TYA12, phase A]  <i>Yes. And finding I guess that medium ground, that safe ground, for knowing that...[Interviewer]</i>  ...push yourself to the extent where you are improving, you are getting better, but not to the extent where you feel crap afterwards like I did. [TYA12, phase A]</p> <p>...she told me that I wasn't allowed to push myself to my limit... So I think in the long term it'll probably help me a bit, like, because she's given me advice on making sure I don't mess myself up basically. [TYA12, phase C]</p> <p>It's quite hard to know whether to just go for it, or like do a little bit and often. [TYA2, phase A]</p> <p>And she was just writing about pushing it a bit, and that does happen. Like if you do stretch yourself, and spend all day out, and then spend time with friends, then it's kind of normal for that to happen. It doesn't mean it has just suddenly come back. [TYA2, phase C]</p> <p>So maybe we could have pushed her a bit more, maybe we have pushed her too much, we don't really know. [PAR6, phase A]</p> <p>...when you set some initial guidance young people think, 'Well, that's just too easy,' on day one, day two and so they then go and do ten times too much on day three and they can't move... [HCP, CDM, phase B]</p>

<p>'What to expect'</p>	<p>And I also wanted to know if that was still normal, or whether it was just totally... I don't know whether other patients at my stage, at my time out from treatment, who had my kind of treatment, were actually at that level that I was, or whether someone managing much better. [TYA2, phase C]</p> <p>So there was still some residual lethargy, and not having... The problem with children that age, he was just 18, is you don't know how much of it is normal for their age... We have got a decent size garden, so the dog can run around and everything, and I will say 'Oh I thought you would take him for a walk'. And he said, 'I will when I get dressed' and it is lunch time. But again is that a normal teenager? [PAR13, phase A]</p> <p>I guess the biggest thing is that you don't know what normal is, so you don't know how [TYA4] should be, you don't really know what to expect. And then if she was tired, then there is obviously that worry about why she was tired, and again whether that was normal, or what that was all about. [PAR4, phase A]</p> <p>But sometimes as I say it is very hard to sort of differentiate between normal fatigue, and just normal tiredness. [PAR7, phase A]</p> <p>Parents' information needs came through as a big theme as they just want to know much more... [RES, CDM, phase B]</p>
<p>How to talk to employment or education staff</p>	<p>But I guess ultimately it would be about education. So it has got to be about being able to educate companies or managers to understand the benefits of it [people with cancer working]... [PAR4, phase A]</p> <p><i>...is there some way that if we, with the young person's consent, we can join them in a meeting with their managers, and try and support and explain things, and try to negotiate, and educate in other words, in a very gentle non-patronising way the managers... [Interviewer]</i></p> <p>...having spent more time dealing with fatigue I guess the main thing is that it's important to have those around you, for example, work or university or school, be supportive and give you sort of extra time to do things if you need that. ...encourage those that have chronic fatigue... to feel that it's okay for them to ask for, I guess 'special treatment' is one way of putting it. I mean in that it's sometimes like ...because my lecturers are wonderful. They gave me extra time for everything, even though I don't always need it. And it allows me to not be stressed and then in itself helps me to stay well and it's not as exhausting because it takes a weight off. [TYA1, phase C]</p> <p>I had sent this e-mail about having to make reasonable adjustments, and they just said it is possible to do the first year on a part-time basis which I think just would make all the difference and actually enable me to do it rather than just to fall at the first hurdle or whatever. ...I only found out about Working With Cancer through [charity], and it might be helpful to have a kind of... a place where people can go for more information... I didn't mention anything about cancer, I just said, 'Oh, I have had some medical treatment, and it would work better for me to come in later and avoid the tube and the rush hour and everything.' And they said, 'That's fine.' [TYA2, phase C]</p>

	<p>I think she also gave her some good advice about employment law, which of course is partly relevant with the fatigue, because it's the fatigue that is causing him the problems. [PAR2, phase C]</p> <p>...[information] around work, so getting back into work or university, more specifics around what they need to be doing, but on an individual basis. [HCP, phase C]</p> <p>And just saying to him [TYA2] that it's OK to have a conversation with work to say this is what is happening with me, because he hadn't actually told them what was going on for him, and didn't want that to influence them in any way, their perception of him. He did have a conversation with the guy, and they were very supportive, and have given him a later starting time, so he didn't have to battle with the tube journey. So I think that may have been helpful. [HCP, phase C]</p> <p>But then it was the more everyday things that caused the real concern like, 'How am I going to get up to go to work every day?' for those that are starting jobs or, 'How am I going to cope with being in eight hours' worth of lectures?' [RES, CDM, phase B]</p>
<b>Intervention practicalities</b>	
Name of intervention	<p><i>But not with the word treatment in there because treatment sounds like...?</i> [Interviewer]</p> <p>...Because that just puts a downer on it. [TYA11, phase A]</p> <p>...for me I just think anything that sounds a bit negative... but I would rather it was called like... like use a word like 'recovery' than... [TYA8, FG, phase A]</p> <p>Yeah, because then it would still have the same legitimacy because it would suggest that you are not quite recovered yet. [TYA1, FG, phase A]</p> <p>I think I would include 'fatigue', because I think it is then something that people relate to. I think if it is quite open in 'wellbeing', some people will just brush it under the carpet. [TYA7, phase A]</p> <p>Just don't have negative... if you call it 'fatigue'... you're making it sound like it's bad... [TYA8, FG, phase A]</p> <p>But then if you do do it then you're adding like medical legitimacy to it. [TYA2, FG, phase A]</p> <p>What I mean is so you want to call it 'fatigue' because it gives it more legitimacy, or you could just call it 'fatigue' to people and then you can call it 'road to recovery' because that's what you want to focus on. [TYA1, FG, phase A]</p>
Videos not leaflets	<p>I'd like if it is a video, it is easier to pay attention to everything you are listening to. [TYA9, phase A]</p> <p>...you know that's the first that they think at that age, this generation, that's where they go for information, I mean I wouldn't think of that but so... I mean and then again it's dealing with your peers, isn't it, it's getting information from peers...? [PAR2, FG, phase A]</p>

	<p>Just like a video on fatigue, just like common side effects and like what it might affect. [TYA2, FG, phase A]</p> <p>I think what [TYA2] is saying is like I agree so much, I think we should do it though... Do a video, I think we should do it as a group because it just is a doctor, as soon as a people person opens that, I don't know if you guys do it? Hold on a minute, who actually read all the leaflets you get when you're first diagnosed... [TYA3, FG, phase A]</p> <p>I purposely didn't read them 'cause actually when I tried reading one of them... [TYA1, FG, phase A]</p> <p>Every single one of them. [TYA2, FG, phase A]</p> <p>I got that many... I got hundreds... [Multiple speakers concurrently]</p> <p>I got them all but they're no use... all weird language... [TYA8, FG, phase A]</p> <p>So I think that we should do the video because it's more catchy, like if you see a group of young people saying this is exactly how it is. There's no medical terms in there, we're just going to say exactly how it is. Whereas you open a tab and it's got like a doctor standing there it's like, 'My name is such and such and...' That's boring, log off... [TYA3, FG, phase A]</p> <p>Short, it's got to be short. [TYA8, FG, phase A]</p> <p>Why don't we do clips... [TYA3, FG, phase A]</p> <p>If you're going to go for the young generation. Does anyone here not have Facebook? Well, that's a 'no'... You need to go for that because it's like Facebook, like they've proven... one little click or one little picture can go a long way. [TYA7, FG, phase A]</p> <p><i>Okay, just get this in my head, so are we talking about making one film, or making a couple, people looking at different... [Interviewer]</i></p> <p>Do a series on... Short, like five or ten minutes each. [TYA1, FG, phase A]</p>
Intervention timing	<p>Yes, I think ongoing from the start really. And I think once you have had a chance to get it into your head what is happening, and I think maybe a few weeks, a month or so into your treatment, I think it is good to start that. [TYA4, phase A]</p> <p>Definitely before I had finished... The sooner the better with that probably. [TYA5, phase A]</p> <p>When you have finished cycle five, going into cycle six, is roughly when you would say do it. Because then they have got that last little bit to do, but you can get into a routine. [TYA11, phase A]</p> <p><i>And then you can get into a positive thing of right I am moving forward now? [Interviewer]</i></p> <p>Yes, yes. You haven't then got to try and cope with it on your own at home with no help. [TYA11, phase A]</p> <p>From my end it would have been straight after I finished my last bit of chemo... Give you something to focus on as well wouldn't it? That is why as soon as I finished having someone to think, 'This is what you need to do this day, this is what you need to get done by the end of this week.' That would have been helpful, I would say. [TYA12, phase A]</p> <p>Well, I think that it should be done either just before discharge, or on discharge. Because if we had some information to take home with us, it might have been easier for us to put something in place for her when we got home... So I think some sort of advice before taking her home would have been very helpful. [PAR6, phase A]</p>



	<p>...this needs to be early and a feeling of this actually needs to start during treatment... because of the sense of hiatus, of life has been hospital , and then all of a sudden there's a hole and happily wanting to put this into it. [RES, CDM, phase B]</p>
Intervention location	<p>Yes, I would have someone come at home, but I just always... I don't know, sometimes I find it nicer to go out. [TYA7, phase A]</p> <p>Personally for me it's just like I have spent so much time [at home] anyway... And it's not that I have got anything private to say, it's just nice to kind of be removed from that setting. And it's also quite nice to actually get out a bit, especially when I was just after treatment, I hadn't really had many chances to get out. And yes I guess it's just... rather than you having to get a time and try and make sure [family members] don't come in, or what have you. And it is just nice to have a specific time just to focus on that, and I guess it's nice to go out for that, well for me... But yes with [HCP] we just met at a cafe nearby which was fine, and nicer than going into [town]. So I think going into [town] might be quite tiring, but it's definitely nice not to have it at your house. [TYA2, phase C]</p> <p>Oh no, you can visit [home], no it's fine. I just don't think it is conducive for combating fatigue, because in order to combat fatigue you would have to do a bit of exercise. [TYA1, phase A]</p> <p>No, not at the hospital... Hospital is too much of a reminder, with cancer. So the hospital is, like I dread coming to hospital, and I haven't even come to see the ward. [TYA3, phase A]</p> <p>From [TYA6's] perspective I would say anywhere but the hospital. So here would be a good place, or home. But... the last thing a patient wants to do is come to hospital if they don't need to be here. So yes, I would say to avoid being on a ward or anything like that... [PAR6, phase A]</p> <p>In terms of pragmatic, practical things, this was another surprising thing... young people want to leave home to meet somebody to get support with their fatigue because home's actually where they're stuck all the time... [RES, CDM, phase B]</p>
Location and types of activity	<p>I meant exercise that isn't too strenuous, but so that I move all my different body parts, so like yoga or Tai Chi, following like a YouTube video, and going for walks in nature. And I think it is not just that it is walking, it is the setting as well, it is calming. [TYA1, phase A]</p> <p>Because I think you don't always feel like getting up and going out. So I know a lot of the time I wouldn't have felt like going to a gym, but if it is there you can do it in front of the TV or something, in the privacy as well of your own home. [TYA4, phase A]</p> <p>Yes, because it's then set to what your body wants not what their body wants. And like everyone's body is different. So you might give a young 14 year old the same thing as me and I might be fine with it, but she might be struggling, or he might be struggling. And I think it just is you need to kind of just sit down with them, just jot things and do a mind map and things like that of just what they want out of this. [TYA3, phase C]</p>

Discipline of intervention provider	<p>For some people [a conversation with a sleep specialist] could be helpful, because I did find it really hard when I was having sleepless nights. [TYA6, phase C]</p> <p>I don't think I have got anything specific [to add to the intervention] apart from psychological help. [PAR3, phase C]</p> <p><i>From a psychologist do you think? [Interviewer]</i></p> <p>Yes. Yes, well a sort of counselling type thing, whether that is a psychologist or something else. [PAR3, phase C]</p> <p>Another thing was that I was fascinated to hear this from parents and also in a sense from young people of actually how it is the cognitive side of the fatigue that's particularly bad and, 'We do want support with that' and 'if that's psychological support we want that.' So they didn't feel the stigma around support or psychological support because they're getting the fact that this is affecting how they think and their memory and concentration. So that's another missing element. [RES, CDM, phase B]</p>
-------------------------------------	---

Theme B1: TYAs experience pervasive tensions and misunderstandings	
Internal tensions	
Mismatch reality and expectations	<p>Well, because during chemo it would get really bad and then it would always ease up. But ever since the surgery it just didn't ease up so I was kind of expecting it... to get better 'cause I wasn't having all the treatment, but it didn't, it got worse. [TYA2, phase A]</p> <p>I would say now, fatigue is a much bigger problem. [PAR2, phase C]  <i>And do you feel that is because [TYA2]'s fatigue is, if one can quantify it, actually worse in itself, or because... it is impacting more on his life because he is getting more back into normal life? [Interviewer]</i>  I think it's the latter. [PAR2, phase C]  <i>Yes. So it's the expectations. [Interviewer]</i></p>
Tensions within family	
Parents perceive as 'lazy' or 'disorganised'	<p>Yes, because I am tired, because I am just drained mostly. So it does cause arguments, a lot of arguments. But it is also... you can be seen, like me personally, I get seen as being lazy, because I am not ready to go back to work, I am not ready to go back to college and things like that. [TYA3, phase A]</p> <p>...my parents are saying 'Just get up earlier', but I can't, because I am so tired all the time anyway. And they don't understand how tired I am all the time. And I don't know, because it affects my concentration and my memory and stuff as well. And they find it really frustrating that I don't remember things... And it is just kind of frustrating that they don't understand, they just think that I am being disorganised. [TYA9, phase A]</p> <p>...conflict of home... came up very strongly with a sense of young people that parents attributing... are basically saying on some level that they're lazy and they just need to pull themselves together which, obviously, is distressing. [RES, CDM, phase B]</p>
Parents misunderstand	<p>Like when I was a bit younger, I think they [parents] understood it quite a lot but I don't think they got how, like I don't think they understood, it's not just tired, it's I have to, feel like I have to sleep otherwise I can't move. [TYA6, phase A]</p> <p>They just think, 'Oh well she has had a long day, so she just needs to have a sleep.' [TYA10, phase A]</p> <p>...they just assume that I have got back to normal maybe, just a tiny bit more tired or things. They just don't seem to get that it still affects my life. [TYA9, phase A]</p> <p>And then at home, I don't actually think I have ever... I have had arguments, well, not arguments, but tension, where I have kind of said, 'You don't understand.' ...because I do quite a lot, I do see my friends a lot, and I do go out for dinners and I go out for nights out and things. So for them they are like well she is getting on with normal life, surely she is fine? [TYA7, phase A]</p>

	<p>...he [TYA2] said, 'There are so many people whose parents are saying to them 'Now come on, now you have got to sort of deal with this.' [PAR2, phase C]</p> <p>It's when I'm like tired and I'm like, I really just need to like... sometimes I get told like, well you've just been to work so anyone... they're just like, 'Get on with it and like...' [TYA7, FG, phase A]</p> <p>Yeah. [TYA1, FG, phase A]</p> <p>I don't know I feel... either they care, it kind of feels like they don't actually like... I don't know, I can't explain it. [TYA7, FG, phase A]</p> <p><i>I think you're explaining it really well, I get what you're saying there's just that lack of... [Interviewer]</i></p> <p>Subtlety. [TYA1, FG, phase A]</p> <p><i>A lack of understanding maybe? [Interviewer]</i></p> <p>You don't want someone to tiptoe around you but then you don't want someone to not understand... [TYA7, FG, phase A]</p> <p>I think in terms of fatigue, I am not sure how much she [mother] knows about, like if she knows I feel fatigued or not. [TYA12, phase A]</p>
<b>Tensions beyond family</b>	
Friends misunderstand	<p><i>Do you think people of your age who haven't been through your kind of experience, do you think they get it? [Interviewer]</i></p> <p>I do think if you don't know... if you haven't experienced fatigue or know what it is, you don't understand fully. You would just think, 'Oh you just need a little nap,' or something. [TYA6, phase C]</p> <p>A few of my friends that I haven't known for as long, they do always just think, 'Oh you're just tired, you'll be fine. But I haven't really, like, sat down and explained it to them properly, because like... I don't know, I just haven't. It hasn't come up in conversation yet. [TYA6, phase C]</p>
Perception of abandonment	<p>I don't think there is enough support though. There is around the hospital, like I have had loads of support out of my treatment, but I don't think there is enough support in the community to get people back on their feet. [TYA3, phase A]</p> <p>...when I first got told that my treatment was over that was it, it was done, there was no safety net and my safety net was here. [TYA3, FG, phase A]</p> <p>...finishing treatment, and leaving here and not seeing anybody, that might feel like that's kind of a difficult time. [HCP, phase C]</p>

Theme B2: Fatigue related tensions have a detrimental impact on family	
Internal tensions	
How much to push TYA	<p>I thought there must be a button we could press that could do this easier. So he probably thinks I am nagging him, but I am probably shielding him from other people who want to see and achieve what he is capable of achieving, which I do understand that, but as I say part of me really couldn't care less. But I don't want him to think that, because I still want to keep his motivation going. So it is difficult as a mum. [PAR12, phase A]</p> <p>It is quite upsetting sometimes to see her sort of separating herself from her friends, because she doesn't feel that she can keep up with them. And so sometimes it is difficult not to get annoyed at her, or not to tell her just, 'Get up it is your friends. Tomorrow you are going to be crying, because you didn't go out today, try and make that effort.' So it is quite frustrating. [PAR6, phase A]</p> <p>So it was getting him to do things, and trying to make him accept... because he would say things like 'Oh you don't understand, I have been through a lot, I'm tired, I can't,' But then with some help and encouragement he would do things. [PAR13, phase A]</p>
Tensions within family	
Conflict with siblings	<p>And then I think also maybe that's where parents, it isn't so much a problem because they are there anyway at a greyer stage in their lives. Also they've had ups and downs with their children. But that's where siblings can be thinking, 'Well, what's this about? They are not being truthful,' and then you can lose an element of trust... And because you can call into trust whether, it's trust comes in, I mean I've seen it so many times over the last year, you know, 'Well how can it be that he's this, this time and that the next?' whatever it is. 'How can he be in this state now and that state next moment?' ...So then what does it do? It unseats him and everybody's unseated. I mean everybody in our house is unseated. [PAR2, phase A]</p> <p>[TYA12] has been independent for three years, and been living away from home, and now he is living under our roof, and on our sort of terms. But it has been tense, because we have adapted to life without him, and now he is there, and everybody is centred around [TYA12] and probably my son has felt a little... his brother has felt a little bit shut out. He is 16, he was doing his GCSEs, so that has not had a great effect on him, the timing of it. ...So it definitely is tense. [PAR12, phase A]</p>
Impact on family plans	<p>When she was quite poorly and she obviously had a lot of fatigue and a lot of tiredness, it just, everything stopped. You just didn't do anything. We would get up and go, 'Well what are we doing today?' 'Don't feel well, don't feel like it, I'm too tired.' So we didn't. [PAR3, phase A]</p>

Tensions beyond family	
Others misunderstand	<p>Yeah, they [extended family] don't really understand it. They did when she was really poorly because she was poorly but now she is well, you know, they don't really get it. [PAR3, phase A]</p> <p>I think sometimes she might push herself a bit too far, because she has done too much of being normal... well saying normal, and never moaning too much about it to friends, that people then think, 'Oh she is absolutely fine.' So I think when it does come to going out that she feels tired, because she has never said anything about anything really, and never really moaned in the past, that they just expect her sometimes just to bounce right back up. [PAR7, phase A]</p> <p>And it just seems to impact, you know, on the whole family because my mother worries as well and she's [age] and she could do without the worry. So I try not to talk to her about it if I can help it, because I don't want to worry her too much. [PAR5, phase A]</p>

Theme C1: Fatigue may perpetuate with vicious cycles	
Activity	
Impact of activity on fatigue	<p>...sometimes like I feel really tired and then I think, oh, I'll go and do something and then I actually feel a bit better afterwards. [TYA2, phase A]</p> <p>I find if I stay in bed the whole day... the next day I feel worse both mentally and physically whereas if I got up and went to the gym the next day... I felt more energetic. [TYA8, FG, phase A]</p> <p><i>What would you say is the biggest thing that's helped you cope with it [fatigue] so well yourself? [Interviewer]</i></p> <p>Well, everyone's different, but I'd say like for me, it's exercise. [TYA7, phase C]</p> <p><i>Keeping active? [Interviewer]</i></p> <p>Yes, I mean, it doesn't have to be like a run, it can be like a walk somewhere or, I don't know. Yes, I'd say it's kind of like that, make sure you're active and stuff. [TYA7, phase C]</p> <p><i>And you found that actually being active generates energy in itself? [Interviewer]</i></p> <p>Yes. [TYA 7, phase C]</p> <p>I'm not sure I fully understand how I've managed to minimise my fatigue, but I do think it has a lot to do with, like, physical activity... go to a class every week and to see an improvement in your level of fitness that way, I think that would massively help. [TYA10, phase C]</p> <p>[TYA6] always says to me, 'I always feel better when I'm doing something.' So even when she feels like she really can't do anything, she always feels better if she gives that little bit of effort and gets up and does something. [PAR6, FG, phase A]</p> <p>[TYA3] says that too. [PAR3, FG, phase A]</p> <p>She finds that when she actually gets up and does something it gives her more energy, as opposed to when she's feeling fatigued... before, what she was doing was just spending the day in bed, and it was just making her feel worse. ...So what she is trying to do is when she does feel tired in the afternoon, rather than go for a nap, go for a little run on the treadmill, and it kind of boosts her energy up again. [PAR6, phase C]</p>
Thoughts	
Impact of mood on fatigue	<p>I believe it [fatigue] is a state of mind. [PAR4, FG, phase A]</p> <p>...it seems to me it goes hand in glove with his mood... Today for instance we walked around [place name], we go every day, we walk, but today we did a very short walk and he just kept saying, 'I'm so tired. I'm so tired.' But I feel that there's potentially some overlap, which would not be unreasonable, with his mood. [PAR2, phase A]</p> <p>...emotional and psychological things that weigh you down, they also can contribute to physical fatigue. [TYA1, phase C]</p>

	<p>It's hard to tell but I think a lot of it is psychological because the minute he stopped treatment because we've been one month out of treatment now, he was suddenly active. Like the next day almost... [PAR8, phase A]</p>
<b>Sleep</b>	
Change in sleep	<p>She would have had to have gone home and gone 'I have got to have an afternoon nap'. So she would have a sleep in between, where she may not necessarily have done that before. [PAR7, phase A]</p> <p>I would probably have a sleep, and then I would be alright afterwards. [Partner] used to laugh at me, because I would have an afternoon or evening nap, and then I would be alright again afterwards. [TYA4, phase A]</p> <p>I do end up just trying to sleep it off most of the time. But that doesn't really work though. [TYA5, phase A]</p> <p><i>...Okay, and do you think... your way of managing it in terms of just going back to sleep, do you think that's almost counter-productive? Is that what you are saying, like it has the opposite effect? [Interviewer]</i></p> <p>Sometimes, yeah, I think when I do eventually get up, I sometimes feel worse for it I think. [TYA5, phase A]</p>
Unhelpful sleep habits	<p>But I know he struggles to get to sleep, but whether that's because of his lifestyle, and if he doesn't get in from work until perhaps sort of 10, 11 o'clock, he doesn't want to go straight to bed necessarily. [PAR12, phase C]</p> <p>It is very difficult to get involved in that, because she spends so much time in her room, and then I do say to her 'Get an early night, because you will feel better for it in the morning'. But an early night for [TYA6] is going up to her bedroom by 8:00pm, but watching television until about 2:00am. So it is not really an early night. [PAR6, phase A]</p> <p><i>...what they've found is that the light from the phone is one of those wavelengths that really wakes up the brain, if that makes sense, even more than TV. [Interviewer]</i></p> <p>I have to be honest, I do do that. I do check my phone and that. [TYA6, phase C]</p>
Anxiety and sleep	<p>...last time I was ill when I was younger, I found when I got to this well, this stage of being this, well, my fatigue would get less. But this time I find it's a bit more because I've known a lot more information about my care... and it's just knowing too much has worried me a lot more. So I haven't really slept at all... I'll go to bed early but I won't go to sleep until two o'clock and then I'll be awake every day at 04:00. And it's like the hot weather as well. It's quite, it does make you a lot more fatigued. [TYA6, phase A]</p> <p>I did find it really hard when I was having sleepless nights, I found it really hard. And obviously a sleep specialist would help you get sleep, and then... it wasn't until I started getting sleep that I thought I have to start getting my life back. [TYA6, phase C]</p> <p>Yeah, and also its if I don't sleep enough it gets really bad, like if I wake up early I feel like exhausted as soon as I get up. And then I just have to lie down all morning. [TYA2, phase A]</p>



	<p>With the sleep [TYA12] I think has been struggling with his sleep. Because he won't talk to anybody about what has gone on in here really. [PAR12, phase A]</p>
Small changes to improve sleep	<p><i>So, what came first? Was it the sleep and then you enrolled on the course?</i>  <i>[Interviewer]</i>  Well one night... there were a couple of nights where I was just, like, I'm just too tired, so I did... I have a couple of... some medication that was helping me. But I really didn't want to take it at first, but I took it for, like, two nights, and then I was really well rested. And then I just woke up that day and was, like, I need to do something. [TYA6, phase C]  <i>That's really interesting. So it was actually taking that medication that got rid of the, sort of, vicious circle you were in of being too tired to do other things.</i>  <i>[Interviewer]</i>  Yeah. [TYA6, phase C]  <i>And you only took the medication for a couple of days?</i> <i>[Interviewer]</i>  Yeah, I only took it two nights because I'm not really a medication kind of person, I don't like it. [TYA6, phase C]  <i>Good for you, yeah. So you made that decision to just break the cycle you were in, get a bit more rest. And then do you feel that the [course] has helped your sleep, just because you are in a... regular rhythm of life?</i> <i>[Interviewer]</i>  Yeah definitely. I find, like, if I have a lie in in the morning, or if I spend most of the day in bed, I am more tired. Whereas if I get up and do something I feel like at night I get a proper sleep because in the day I'm really energetic... [TYA6, phase C]</p>

Theme C2: Responses to fatigue relate to outcomes	
Positive outcomes	
Positive approach to activity	<p>And it was just things like if you are feeling a bit tired, maybe go for a walk. I know on bad days, I just used to literally go around the block, because also the fresh air and everything, I used to like standing outside, because it made me feel a bit better. But I kind of started to do the exercise, and it kind of just started to help, so I just did it more and more. [TYA7, phase A]</p> <p>But exercise regularly and I'd say that it really helps. [TYA8, FG, phase A]</p> <p><i>Do you have anything else that you think would contribute to what good fatigue care looks like? [Interviewer]</i></p> <p>...I think just really stay as active as you can throughout your treatment even if you don't always feel like it, it can sometimes help. [TYA4, phase A]</p>
Parents' positivity	<p>I believe that what doesn't kill you makes you stronger and I think that is the principal we've worked on and luckily for me [TYA4] seems to have the same mentality, she's just eating it up. [PAR4, phase C]</p> <p>...another thing I did as a mum actually, partly for my other ones, was we stayed normal, right. So this going six months off work, forget that, that's not even. So like the older two were due to go on holiday at the end of that first month and straightaway the oldest one said, 'Well we can't do that now,' and I said, 'You absolutely go, you have a good time and you come back and you tell him what a good time you've had, that's what you do.' So I gave them permission to [go]. [PAR8, phase A]</p>
Negative outcomes	
Activity fear avoidance beliefs	<p>It is a good thing that I am trying to be active, but I can't do too much because I injure myself too badly. [TYA11, phase A]</p> <p><i>Do you feel that resting is helpful? [Interviewer]</i></p> <p>Kind of. It helps sometimes and other times it just can't be helped. [TYA14, phase A]</p> <p>What did we say on the thing about what helps? [PAR14, phase A, referring to document written by TYA14]</p> <p><i>Those things: rest, food and not adding to fatigue with stress and activity. [Interviewer, reading the document]</i></p> <p>...It might be good [in the intervention] to provide ways that you can find out what's best for you, like saying the different things that people find are the least stressful for them, or the best ways that they can rest. [TYA14, phase A]</p>
Low self-efficacy	<p>I know I would sit there and listen to it and think, 'Yeah, that's a good idea,' but I probably wouldn't actually stick to it. [TYA5, phase A]</p> <p>I would just say I am tired and I don't think a lot can be done about it...</p> <p><i>Any ideas about what good fatigue management would look like? [Interviewer]</i></p> <p>I don't think so, no. I don't think that I have been that brilliant at managing it. No, I can't think of anything. [TYA5, phase A]</p>

	<p>Working myself up to doing things isn't very helpful; it's helpful to a certain extent, but then you know, it builds up into too much and I stop being able to do even the littlest things any more. [TYA14, phase A]</p> <p>...then you can start to lose hope, and lose hope of never being able to actually achieve that independence. [PAR14, phase A]</p>
--	---

#### 7.4.15 Triangulation of qualitative data between sources, time points and methods

Between sources: TYAs and parents	
Also it's quite unpredictable, 'cause some days are way worse than others. So it's quite hard to plan things and I'd rather not plan things otherwise I'm always cancelling them. [TYA2, phase A]	I guess the one huge difficulty is that fatigue is not, it goes up and down, it's the variability and I think that's very difficult for everybody concerned, it's very difficult for [TYA2], but it's also very difficult for everybody in the family. [PAR2, phase A]
When I think about it now going back to when I first got told that my treatment was over that was it, it was done, there was no safety net and my safety net was [hospital]. [TYA3, FG, phase A]	It's a more positive attitude and actually had that all the way through her treatment until it ended and then there was nothing. I mean you get loads of support in this hospital, I know it's fantastic but it felt like there was nothing. [PAR3, FG, phase A]
I feel like a couple of years ago, or even just a year ago, meeting with someone and getting that help would have been... it would have been the ideal thing for me really. [TYA6, phase A]	However, a year ago or 18 months ago, when she was sort of in the middle of it, or just after treatment, I think it would have been very useful to have some sort of intervention, definitely. [PAR6, phase A]
I used to walk on the treadmill for about an hour... I found it kind of like helped my mind as well, but it helped the tiredness, because I felt that the days where I was just at home in bed feeling sorry for myself, it didn't really help much, and you actually made yourself feel worse. [TYA7, phase A]	So she just thought if I keep moving, it may help with the tiredness... So yes, like lift yes, just lifts her that bit. [PAR7, phase A]
<i>Do you feel that resting is helpful? [Interviewer]</i> Kind of. It helps sometimes. [TYA14, phase A]	<i>What did we say... about what helps? [Interviewer]</i> Those things, rest, food and not adding to fatigue with stress and activity. [PAR14, phase A]
But now all my Uni (sic) work getting back, she is proper ratting on me, on my case, all the time. ...yes, she has been proper naggy (sic) about that. [TYA12, phase A]	So he probably thinks I am nagging him... But I don't want him to think that, because I still want to keep his motivation going. So it is difficult as a mum. [PAR12, phase A]
Yeah, I agree, my hearing's completely off but then when you're tired, or when I'm tired or if I'm struggling to hear things then I end up like aggravated and angry because it's like I'm trying to process what people are saying but I can't hear them, if that makes any sense. [TYA3, FG, phase A]	She's lonely, she's frustrated, she's like bad tempered, what do I do 'cause every time I open my mouth I'm wrong. It doesn't help if I suggest she has jelly and ice cream, still wrong. [PAR3, FG, phase A]
It is not that sort of bad food, it is just eating heavy loads of food I guess. TYA12, phase A] <i>And carbs? [Interviewer]</i> Yes. Big pastas, baguettes, that sort of thing, yes exactly. [TYA12, phase A]	We don't have the best diet, too high in carbs, and too much bread and potatoes and stuff. So [TYA12] is conscious of the fact that we probably don't eat as well as we should, and she would say, 'That was my fault.' And I hold my hands up and say, 'It is true.' [PAR12, phase A]

Between sources: TYAs and healthcare professional providing prototype intervention	
I personally wouldn't mind seeing a psychologist if I knew what kind of psychology they were specialising in or what kind of treatment... I'm really interested at the moment in something called thematic therapy. [TYA1, phase C]	And I think [TYA1] would find it helpful to see a psychologist, but purely for a debate, rather than anything. [HCP, phase C]
<p><i>How important is it to have those times where, okay, it might exhaust you for days afterwards but how important is that to still experience those things? [Interviewer]</i></p> <p>You have got to do it. [TYA8, FG, phase A]</p> <p>Whilst you're young I think, well I'd do anything now... So I'm going out enjoying myself, I go to the pub, I go out clubbing and things like that but then I also think like when Sunday comes that's like you sleep all day. Non stop. [TYA3, FG, phase A]</p>	<p>I got very much a sense that people, particularly around the 'boom or bust' or the activity pacing, that's a real challenge for young people because they want to feel normal and want to do the things that other people want to do... It was almost saying, 'That doesn't fit with my life' and there was less of a willingness I think to change that I guess... [TYA3] was saying I'd rather not do that if it means that I can't be up all night and I'd rather not do it. [HCP, phase C]</p>
Between time points: phase A and phase C	
The only thing I got told at the beginning was the fatigue breeds fatigue, which is true. Like if I spent a week doing nothing, and staying in bed, my fatigue would get worse, whereas if I get up and walked, or even something small like just a five minute bike ride or something, if I did that every day I would feel much better. [TYA8, phase A]	Me and my mum were still quite keen on the whole fatigue breeds fatigue thing and the fact that I'm just getting on with things and really just... Every day I'm doing something rather than just laying in bed. I think as a whole six months down the line... sorry, four or five months down the line, so it massively improved. [TYA8, phase C]
But of course as soon as you think, 'Right, I'm back to normality,' then you've got this whole business of, 'If life is normal then it suddenly becomes even more apparent the stuff you can't do.' [PAR2, phase A]	<p>I would say now, fatigue is a much bigger problem. [PAR2, phase C]</p> <p><i>And do you feel that is because [TYA2's] fatigue is, if one can quantify it, actually worse in itself, or because there is a bigger mismatch between... it is impacting more on his life because he is getting more back into normal life? [Interviewer]</i></p> <p>I think it's the latter. [PAR2, phase C]</p> <p>Yes. So it's the expectations. [Interviewer]</p>
Between data collection methods	
I forget everything. The only things I don't forget are things that I shouldn't remember. Like door codes. [TYA3, phase A]	Do you say, 'Oh, yeah, I'll meet you Thursday...' and then Thursday comes and you get like a really awful text... 'Where are you? Was I meant to be meeting you today?' [TYA3, FG, phase A]
So from a really selfish way, I wasn't just managing [TYA4], I was managing myself, yes? So it was like right if I focus on getting [TYA4] to go and work for a couple of days, and she actually comes back and she says, 'Yes dad I am alright,' from that I could get a strength. [PAR4, phase A]	I think I did it for me, right, if I'm honest... So on [TYA4's] worst days, that was it, that's 'game over' as far as I was concerned. I didn't know what to do. So I had to encourage her to be strong as much for me as anyone, because I could deal with it when she was smiling and saying, 'Yeah, I'm all right, dad.' [PAR4, FG, phase A]

