Title: Hypo-METRICS: Hypoglycaemia – MEasurement, ThResholds and ImpaCtS – A multi-country clinical study to define the optimal threshold and duration of sensor-detected hypoglycaemia that impact the experience of hypoglycaemia, quality of life and health economic outcomes: the study protocol.

Short Title: Hypo-METRICS: Hypoglycaemia – MEasurement, ThResholds and ImpaCtS- study protocol

Authors:

Patrick Divilly (1), Natalie Zaremba (1), Zeinab Mahmoudi (1, 2), Uffe Søholm (1, 3), Daniel J. Pollard (4), Melanie Broadley (3), Evertine J. Abbink (5), Bastiaan de Galan (5,6,7), Ulrik Pedersen-Bjergaard (8,9), Eric Renard (10,11), Mark Evans (12), Jane Speight (13,14), Alan Brennan (4), Rory J. McCrimmon (15), Matthias Müllenborn (16), Simon Heller (17), Alexander Seibold (18), Julia K. Mader (19,20), Stephanie A. Amiel (1), Frans Pouwer (3,), Pratik Choudhary (1, 21) for the Hypo-RESOLVE Consortium

Author's affiliations:

1. Department of Diabetes, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London UK SE5 9RJ
2. Digital Therapeutics, Scientific Modelling, Novo Nordisk A/S, Søborg, Denmark.
3. Department of Psychology, University of Southern Denmark, Odense, Denmark.
4. School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK.
5. Department of internal medicine, Radboud university medical centre, Nijmegen, the Netherlands
6. Department of internal medicine, division of Endocrinology, Maastricht University Medical Centre, Maastricht, The Netherlands
7. CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, the Netherlands
8. Department of Endocrinology and Nephrology, Nordsjællands Hospital Hillerød, Hillerød, Denmark
9. Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
10. Department of Endocrinology, Diabetes, Nutrition, Montpellier University Hospital,
11. Institute of Functional Genomics, University of Montpellier, CNRS, INSERM, Montpellier, France
12. Wellcome Trust-MRC Institute of Metabolic Science and Department of Medicine, University of Cambridge, UK
13. School of Psychology, Deakin University, Geelong, Australia
14. The Australian Centre for Behavioural Research in Diabetes, Diabetes Victoria, Melbourne, Australia
15. Systems Medicine, School of Medicine, University of Dundee, United Kingdom
16. Novo Nordisk A/S, Bagsvaerd, Denmark
17. University of Sheffield, Sheffield, UK
18. Abbott Diabetes Care, Wiesbaden, Germany
19. Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, Austria.
20. Division of Endocrinology and Diabetology, Medical University of Graz, Graz, Austria
21. Diabetes Research Centre, University of Leicester, Leicester, UK LE5 4PW

Corresponding Author: Patrick Divilly patrick.divilly@kcl.ac.uk

Manuscript word count 3000, abstract word count 249

Abstract

Introduction: Hypoglycaemia is a significant burden to people living with diabetes and an impediment to achieving optimal glycaemic outcomes. The use of continuous glucose monitoring (CGM) has improved capacity to assess duration and level of hypoglycaemia. The personal impact of sensor-detected hypoglycaemia (SDH) is unclear. Hypo-METRICS is an observational study designed to define the threshold and duration of sensor glucose that provides the optimal sensitivity and specificity for events that people living with diabetes experience as hypoglycaemia.

Methods:

We will recruit 600 participants: 350 with insulin-treated type 2 diabetes, 200 with type 1 diabetes and awareness of hypoglycaemia and 50 with type 1 diabetes and impaired awareness of hypoglycaemia who have recent experience of hypoglycaemia. Participants will wear a blinded CGM device and an actigraphy monitor to differentiate awake and sleep times for 10 weeks. Participants will be asked to complete three short surveys each day using a bespoke mobile phone app, a technique known as ecological momentary assessment. Participants will also record all episodes of self-detected hypoglycaemia on the mobile app. We will use particle Markov chain Monte Carlo optimization to identify the optimal threshold and duration of SDH that have optimum sensitivity and specificity for detecting patient reported hypoglycaemia. Key secondary objectives include measuring the impact of symptomatic and asymptomatic SDH on daily functioning and health economic outcomes.

Ethics and dissemination: The protocol was approved by local ethical boards in all participating centres. Study results will be shared with participants, in peer-reviewed journal publications and conference presentations.

Keywords: hypoglycaemia, continuous glucose monitoring, quality of life, patient reported hypoglycaemia, sensor-detected

Introduction

Hypoglycaemia has been a barrier to optimal glycaemic outcomes in people with diabetes since the discovery of insulin. The International Hypoglycaemia Study Group, defines three biochemical classifications of hypoglycaemia: level 1, below ≤3.9 mmol/l; level 2, below ≤3.0 mmol/l; and level 3, severe hypoglycaemia (requiring 3rd party assistance)[1,2]. These classifications are based on the current evidence for the biomedical and cognitive effects associated with the different levels. The varied impact of these levels of hypoglycaemia on different aspects of daily functioning and quality of life (QoL) in people living with diabetes is poorly understood.

In the past decade, continuous glucose monitoring (CGM) has become increasingly used in clinical practice and research. CGM devices measure interstitial glucose data every few minutes and reveal significantly more estimated episodes of hypoglycaemia than capillary blood glucose (CBG), with eight times more hypoglycaemic episodes recorded on CGM than reported by people with diabetes [3]. While the information provided by CGM has altered diabetes care and can help people with diabetes (e.g. to lower haemoglobin A1c (HbA1c), reduce hypoglycaemia, and potentially reduce the psychological burden) [4], there are concerns about whether all episodes of hypoglycaemia identified by sensors are clinically and personally meaningful.

There are differences when we measure hypoglycaemia using interstitial glucose as opposed to capillary or venous glucose. Interstitial glucose measurements lag behind blood glucose levels [5,6]. Operational issues (e.g. compression of the sensor during sleep) may create artefacts that are difficult to differentiate from true hypoglycaemia [6].“Noise” in the data can cause small fluctuations around any given threshold. Conversely, CGM provides data on the duration of episodes of hypoglycaemia, which now need to be included in the definition of sensor-detected hypoglycaemia (SDH). The limitations of SDH can be confusing for and frustrating to the person with diabetes, who is trying to make sense of both the data and the personal impact of the episode[7].

A consensus statement recently defined a hypoglycaemic event using CGM as an event with sensor glucose of ≤3.0 mmol/l for at least 15 mins [1]. This definition appears to have a high sensitivity for hypoglycaemia but a low specificity, leading to a high rate of asymptomatic episodes even in those with apparently well-preserved awareness of hypoglycaemia[8]. These details are important regarding the personal impact of hypoglycaemia and in the research environment, when duration below a threshold or number of episodes may be key outcomes.

Increasingly, time below target glucose range (TBR) has become a key metric for clinical and research outcomes. While TBR is useful for considering overall hypoglycaemia exposure, it is also likely that different durations and thresholds of hypoglycaemia will have different impacts. The personal impact of multiple short episodes versus a prolonged overnight event may be comparable even though the experiences are quite different. This granularity is lost with the overarching metric of TBR and when questionnaires with long recall periods are used to assess the personal impact. Given the high proportion of asymptomatic SDH events it is unclear whatimpact these have on daily functioning and what the implications are for QoL.

Increasing the precision and detection of symptomatic and asymptomatic hypoglycaemia and understanding the direct impact of these on daily functioning and QoL will enable a universal definition of SDH with known health economic outcomes. Such an evidence-based definition will help standardise hypoglycaemia outcome reporting and assist policymakers in their remuneration decisions.

The Hypo-RESOLVE programme is funded by the European Union Innovative Medicines Initiative to increase our understanding of hypoglycaemia and its personal, clinical and economic consequences [9]. Within Hypo-RESOLVE, the Hypo-METRICS trial will provide an evidence-based definition of SDH and further our understanding of the clinical, psychological and health economic impact of both symptomatic and asymptomatic hypoglycaemia. While we know that symptoms of hypoglycaemia, and glucose thresholds for those symptoms, vary between as well as within individuals, this study will identify the optimal parameters of SDH that offer the best trade-off between sensitivity and specificity across a population.

Methods and analysis

Study design

Hypo-METRICS is a multinational, observational study. It will use blinded CGM, actigraphy, validated questionnaires (Table 1), collection of routine clinical data and daily ecological momentary assessments (EMA) through a bespoke Hypo-METRICS app[10] over a period of ten weeks to collect data on sensor glucose levels, sleep, activity and person-reported outcomes. Recruitment commenced in October 2020 and is due to be completed by January 2022.

Study setting

The trial will take place in specialist diabetes centres at eight sites in five countries: the United Kingdom, Denmark, the Netherlands, Austria and France. Each site will recruit approximately 75 participants.

Participants

Six hundred participants will be recruited;

1. 200 adults with living with type 1 diabetes (T1DM) and normal awareness of hypoglycaemia (NAH) (Gold score[11] <4).
2. 50 adults with T1DM and impaired awareness of hypoglycaemia (IAH) (Gold score[11]≥4).
3. 350 adults with living type 2 diabetes (T2DM) taking ≥1 insulin injection/day (a minimum of 25% of participants will be over 60 years of age).

Awareness of hypoglycaemia will be measured by the Gold score (10). Key inclusion criteria for the study are being adult (aged 18-85 years) living with T1DM or T2DM, taking at least one insulin injection per day and recent experience of hypoglycaemia. Key exclusion criteria are an eGFR of < 30 mls/minute/1.73m^2 and the use of automated insulin delivery systems. A full list of inclusion and exclusion criteria is available in the supplemental 2 appendix.

Study procedures and follow-up

Baseline assessments

Informed written consent will be obtained, with time allowed for the participant to read the participant information sheet, consent form and ask questions. Baseline data will be recorded for each participant, including a brief medical history, documentation of healthcare resource use in the previous 12 months and experience of hypoglycaemia. The participant will complete a set of baseline questionnaires (see Table 1) via an online platform (Qualtrics) https://www.qualtrics.com.

Blood samples will be taken at baseline for HbA_{1c} and creatinine. Urine samples will be taken for albumin creatinine ratio. If data are available from routine care records within the last 4 weeks, these results can be used.

A 4-week download will be taken from each participant's routine glucose monitoring device, insulin pump and/or downloadable insulin pens. These will be anonymised, stored and recorded in the electronic CRF[12].

Participants will be trained to use the study devices and asked to record episodes of self-reported hypoglycaemia on the Hypo-METRICS app. For this study, we have defined self-reported hypoglycaemia as symptomatic episodes that resolved on ingestion of carbohydrate, or a measured glucose value <4 mmol/l.

	Questionnaire	Domain assessed
1.	Hypoglycaemic Fear Survey II (HFS-II) [13]	Fear of hypoglycaemia
2.	Modified Clarke [14], Gold Score [11], Hillerød method [15], and Hypo-AQ [16]	Awareness of hypoglycaemia
3.	Hypo Cues Questionnaire[16]*	Experiences with hypoglycaemia
4.	SF-36 Vitality subscale only [17]	Energy levels
5.	PAID-20 (Problem Areas In Diabetes) [18]	Diabetes distress
6.	DIDP (DAWN Impact of Diabetes Profile) [19]	Diabetes-specific quality of life
7.	PDQ-20 (Perceived Deficit Questionnaire)[20]	Perceived cognitive difficulties
8.	DS-14 (Type D Scale)[21]	Type D personality trait
9.	GAD-7 (General Anxiety Disorder-7)[22]	Anxiety symptoms
10.	PHQ-9 (Patient Health Questionnaire – 9)[23]	Depressive symptoms

Table 1: List of questionnaires

* UK sites only, to be validated

** Completed at visit 1 only

Study Devices

Continuous Glucose Monitoring

The Abbott Freestyle Libre 2 sensor and reader will be used for this study. This device measures interstitial glucose data every 5 minutes and sends the data via Bluetooth to a reader device. The reader will be blinded, using bespoke software provided by Abbott, and alarms will be disabled. If the reader is out of Bluetooth range of the sensor, up to 8 hours data can be retrieved from the sensor by scanning with the reader. Participants will be trained on insertion and removal of sensors and asked to scan at least 3 times a day to maintain data coverage if Bluetooth connection is lost. Data will be stored on the reader for the duration of the 10-week study and downloaded using bespoke software at visit 5.

The Hypo-METRICS app

Participants will complete a check-in on the app three times per day for 10 weeks. The design and development of the Hypo-METRICS app are detailed here[10]. Briefly, the app includes:

1. **"Check-ins":** Participants will be asked to complete three short sets of questions daily ("check-ins") in the morning, afternoon and evening. These will capture details about daily functioning across domains of sleep, mood, anxiety, fear of hypo- and hyperglycaemia, cognitive functioning, social functioning and productivity. The App will notify the participant when the check-ins are due. Participants will also self-report details of any hypoglycaemic episodes that have occurred since the last check-in, including detection and treatment.
2. **The "Motif":** this feature enables reporting of hypoglycaemic symptoms and severity in real time (Figure 1).
3. **Validated questionnaires**: Three validated questionnaires are also administered via the app. The first is a daily assessment of health status (EQ-5D-5L(22)). In addition, there are weekly validated assessments of sleep[24] and productivity[25].

The Hypo-METRICS app is delivered via the software platform provided by uMotif Limited (https://www.umotif.com/), which participants can download to their smartphone (Figure 1).

Study smartphones are provided for those without a compatible device.

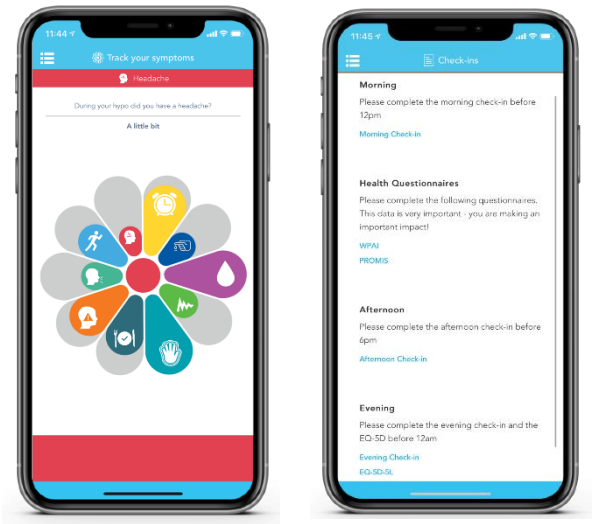

Figure 1. Motif and check-ins

Actigraphy

The FitBit Charge 4 will collect data on sleep duration[26], heart rate and step count. This will need to be worn continuously on the wrist, including through the night, to allow determination of when the participant was awake or asleep.

Subsequent Visits

Visits 2, 3, and 4. These will be brief virtual visits that will take place at weeks 2, 4 and 6. Issues with the devices will be addressed and confirmation of minimum data collection. Details of adverse events (including severe hypoglycaemic episodes) will be recorded on standardised forms.

Visit 5. This visit, occurring at week 10, will mark the end of the data recording on the study devices. At this visit the study team will:

- Download data from the Libre 2 reader and the participants' glucose meter, insulin pump and/or connected pen.
- Download data from the Hypo-METRICS app and FitBit
- Re-administer the questionnaires (see Table 1)
- Collect blood samples for HbA_{1c} and random C-peptide level
- Collect data on health care resource utilisation and severe hypoglycaemic episodes over past 10 weeks

Participants will have the option to provide additional blood samples at this visit for biobanking and peripheral blood mononuclear cell samples.

Visit 6. There will be one follow-up visit up to 52 weeks after beginning the study. Data will be collected, using standardised reporting forms, about episodes of severe hypoglycaemia since completing the study, healthcare resource utilisation since visit 5, major health issues that have occurred, a blood sample will be taken for HbA_{1c} and the questionnaires in Table 1 will be repeated.

Participant timeline

The participant timeline for the study is outlined in the supplemental appendix table 2. Due to the Covid 19 pandemic, participants can do all visits virtually.

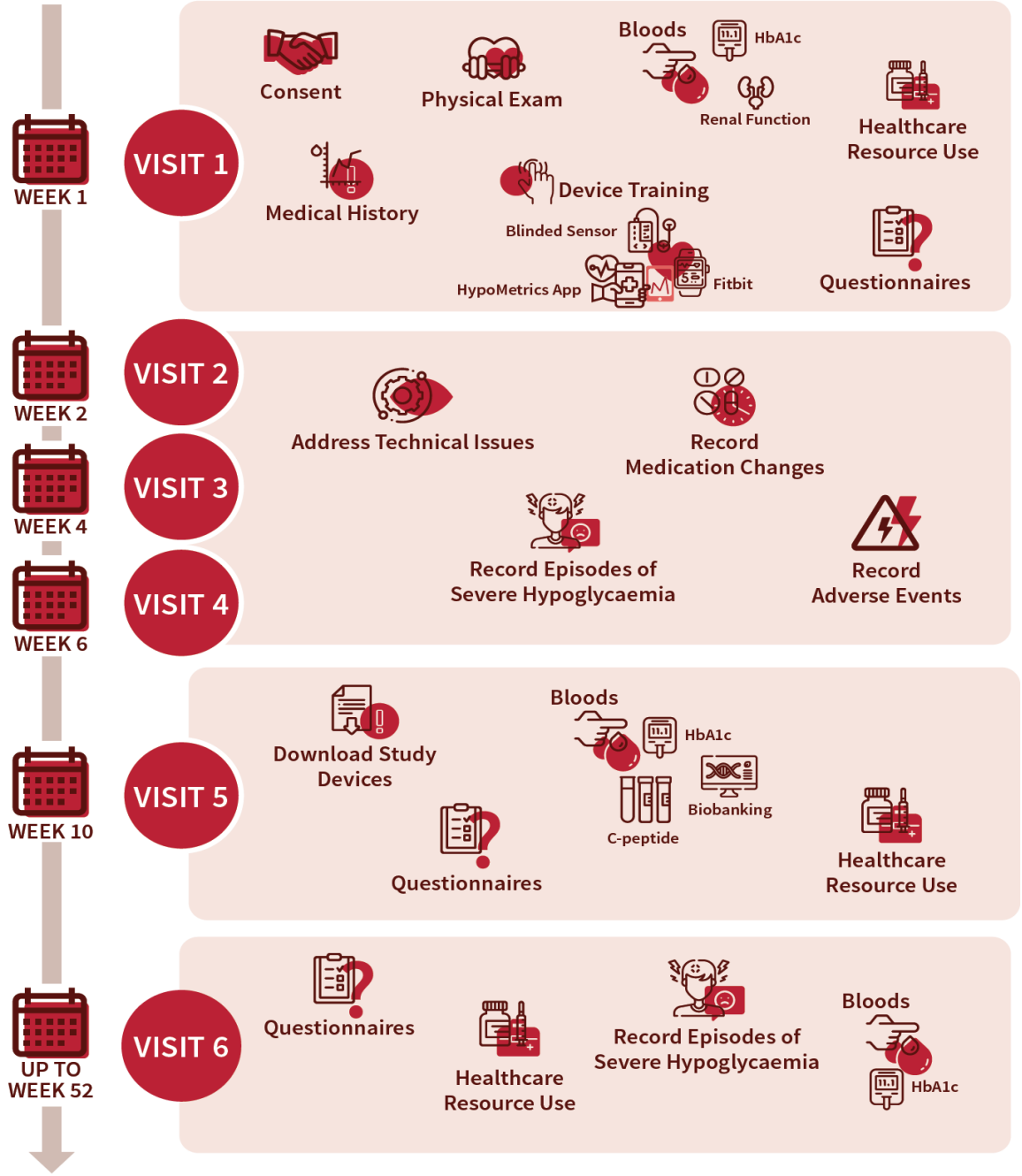

Figure 2. Participant timeline for the study

Patient and Public Involvement (PPI)

People living with diabetes have been involved throughout the development of the Hypo-METRICS study. The Hypo-RESOLVE Patient Advisory Committee has assisted us in the selection of the questionnaires and has provided feedback on the viability of study visits. Two specific PPI groups local to King's College London supported the development of the questions used for the Hypo-METRICS app.

Primary and Secondary Objectives

Primary Objectives

The primary objective of this study is to define the threshold and duration of sensor glucose that provides the optimal sensitivity and specificity for events that people living with diabetes experience as hypoglycaemia.

Secondary objectives

Secondary outcomes (table 2) are the evaluation of the impact of symptomatic and asymptomatic SDH using the definition from the primary objective, on 3 key domains (table 2)

Primary Objective
1. To define the threshold glucose value and duration of sensor glucose that provides the optimal sensitivity and specificity for events that people living with diabetes experience as hypoglycaemia.
Secondary Objectives
Biochemical
1.1 To assess the effect of the following factors on sensitivity and specificity of the newly defined SDH: 1.1.1 Type of diabetes (T1DM or T2DM) 1.1.2 Sleep status (asleep or awake) 1.1.3 Usual method of glucose monitoring (CBG vs Flash vs CGM) 1.1.4 Rate of SDH during the study 1.1.5 Glycaemic Variables (HbA_{1c}, Time in range, mean glucose) 1.2 Compare the rates of hypoglycaemia as defined by our new definition vs ATTD consensus definition in independent data sets. 1.3 To investigate the following baseline factors as predictors of SDH and PRH: 1.3.1 Biochemical factors 1.3.2 Psychological factors (see Table 1) 1.3.3 Socio-demographic factors 1.4 To compare the rates of SDH and PRH in those using CBG vs Flash/CGM 1.5 To assess the impact of the rate of SDH on rates of PRH and severe hypoglycaemia
Daily Functioning and Psychological Factors
2.1 To conduct psychometric analyses to explore reliability and validity of the Hypo-METRICS app. 2.2 To explore the impact of symptomatic and asymptomatic SDH on domains of daily functioning (measured with the Hypo-METRICS app). 2.3 To investigate if the impact (from 2.2) of changes depending on diabetes type, sleep status, hypoglycaemic awareness status and after adjustments for relevant variables. 2.4 To explore the cumulative effect and duration of effect of SDH on daily functioning.
Health Economic
3.1 To calculate the country-specific quality adjusted life year (QALY) associated with SDH. 3.2 To calculate the effect of SDH on work and productivity. 3.3 To explore the relationship of SDH with healthcare utilization. 3.4 To determine the parameters of SDH that best identify 1.5-hour loss of effective work/ activity and a reduction of 0.07 QALYs.

Table 2. Table of objectives

Sample size

Sample size calculations were performed for the primary objective for hypoglycaemia aware T1DM and T2DM participants separately, with the statistical power of ɣ=80% and the significance level of α = 0.05. The sample-size was calculated for the negative binomial regression, as this regression directly models the effect of SDH rate on the rate of PRH events which is the main response in the primary objective. Using published data, we estimated rates of SDH and PRH to be 4.8 and 1.3 events/patient-week respectively in T1DM [8] and 1.9 and 0.3 events/patient-week in T2DM [27,28]. Employing these parameters, the minimum required number of T1DM and T2DM participants was

calculated as 180 and 321 respectively. We adjusted for 10% dropout, aiming to recruit to 200 T1DM with NAH and 350 T2DM.Participants with IAH will not be included in the primary analysis.

Statistical methods

Primary objective: The primary objective of the study is to define the threshold and duration of sensor glucose that provides the optimal sensitivity and specificity for events that people living with diabetes experience as hypoglycaemia

The definition of SDH has two parameters: a glucose threshold (h) and a minimum duration (t) below that threshold, as illustrated in Figure 3.

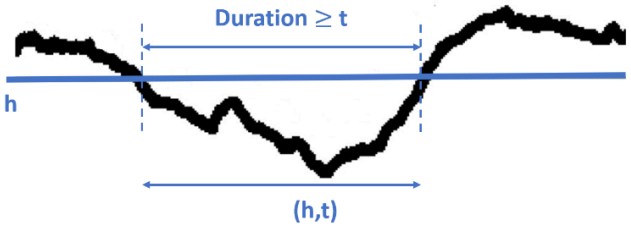

Figure 3. A SDH defined by a threshold, h, and a minimum duration, t, under the threshold.

PRH will be obtained from the Hypo-METRICS app. We will exclude events where the reported glucose was > 5.6 mmol/l or the participant reported that they "prevented" hypoglycaemia. We will apply ranges for threshold between 5.6 and 2.2 mmol/L and for duration between 5 – 300 minutes, values considered of potential clinical relevance. We will use the lowest glucose within ±1 hour of the reported time for the analysis, to allow for any inaccuracy of the time stamp reported by the participant on the app. We will use particle Markov chain Monte Carlo optimisation to identify the optimal threshold and duration of SDH that makes the best trade-off between the sensitivity and specificity for detecting PRH[29]. The sensitivity is calculated as the number of true positives over the total number of PRHs, where a true positive is a PRH which is matched to a SDH. A SDH which is not matched to a PRH, is a false positive. By dividing the number of false positives by the total number of SDH events, the precision is calculated by subtracting this fraction from one. This allows the calculation of the F_β score, measuring the effectiveness of the SDH to detect PRH, using the formula below;

F_β= (1 + β^2).((Precision . sensitivity)/ (β^2 Precision + Sensitivity))

When beta is > 1 sensitivity is prioritized and when beta is < 1 precision is prioritized. Thus, the optimal parameters for SDH are the threshold and duration that have the highest F_β score (or detection performance for PRH). The statistical analysis plan has been tested in various simulations reported in Mahmoudi et al[29]. Optimal parameters for each participant will be calculated, and then we will generate an overall optimal definition that combine data from all participants and weight for individual events of SDH and PRH.

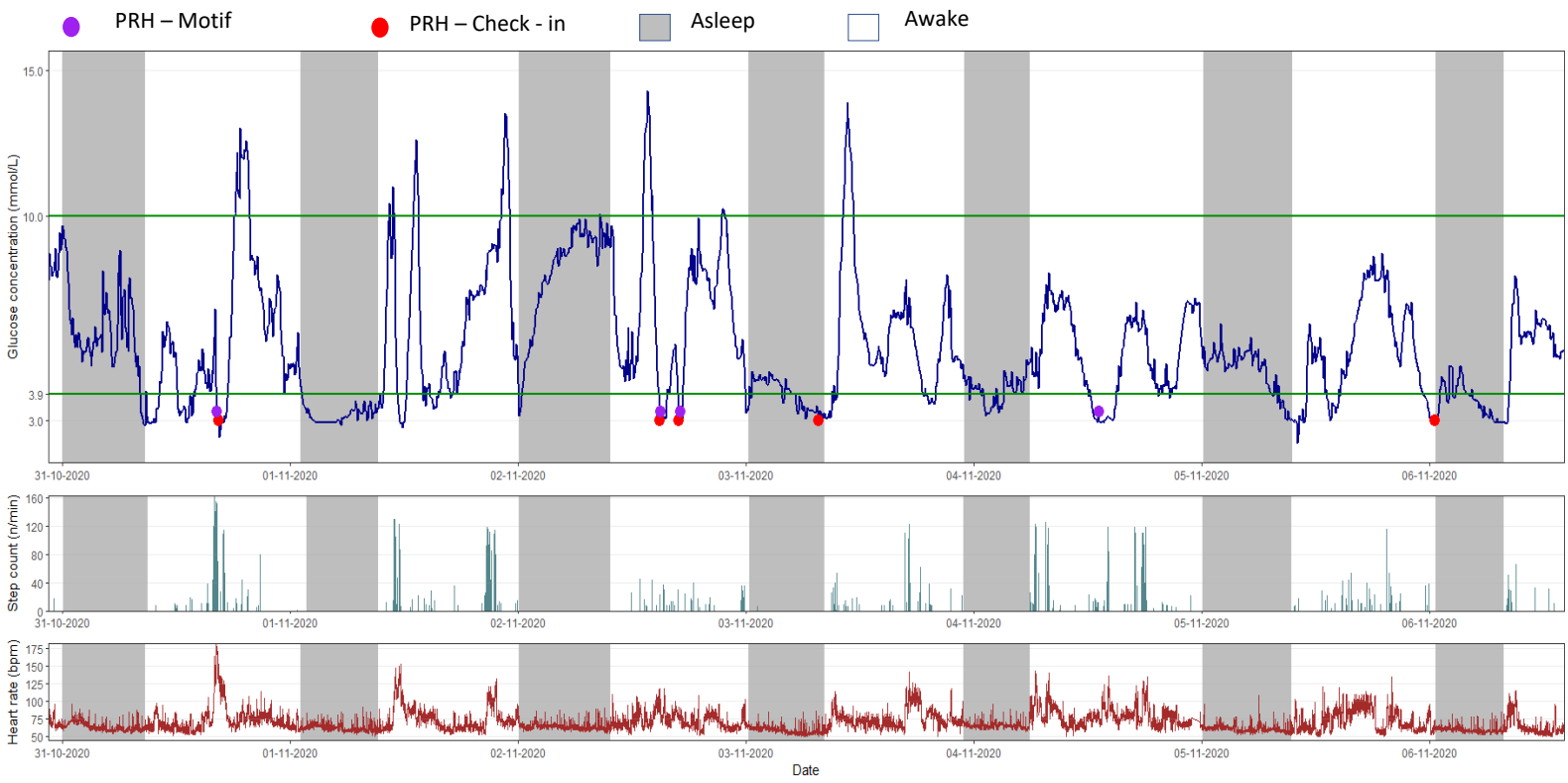

Figure 4. Data visualization; Sensor glucose with step count and heart rate over time

Secondary Analyses:

Once the primary objective is complete, the new definition will be used to analyse the secondary objectives. The secondary objectives in Table 3 will be examined in an independent fashion in each domain.

Biochemical outcome analysis

By dividing our data set into validation and test data we will test the sensitivity and specificity of our definition of SDH in T1DM and T2DM, by sleep status, by method of glucose monitoring and based on rate of SDH during the study. We will then use our new definition and compare the rate of SDH using our new definition to the consensus definition from the ATTD[2]. We will use independent data sets from the wider Hypo-RESOLVE group to measure the rate of SDH using both definitions. We will also analyse the rates of SDH and PRH in those using CGM vs those use CBG during the 10 weeks of the study and the impact of different bio-psychosocial variables on rates of SDH and PRH.

Daily Functioning and Psychological Factors analysis

Key amongst our secondary objectives is exploring the impact of symptomatic and asymptomatic SDH on domains of daily functioning (measured with the Hypo-METRICS app), which will have been validated, as described in Søholm et al [30]. Using the definition from our primary objective and data collected from the Hypo-METRICS app and the blinded CGM, a comparison of daily functioning between days with and without symptomatic and asymptomatic hypoglycaemia will be made. We will also explore if the impact changes depending on diabetes type, sleep status, baseline awareness-

level, and after adjustments for related variables. Finally, we will explore the cumulative effect and duration of effect of SDH on psychological factors (see Table 1) at follow-up.

Health Economic analysis

We will calculate utility scores from the EQ-5D-5L responses using country specific tariffs[31–36] using data recorded in the Hypo-METRICS app and our eCRF. For countries with no tariff, we will use the UK tariff. We will calculate QALYs from the utility scores using the area under the curve method. We will calculate the total number of working hours lost either due to absenteeism or low productivity using the WPAI. We will use panel data methods to estimate the effect of SDH on working hours lost and QALYs in each week. We will adjust for age, gender, severe hypoglycaemic episodes, diabetes-related complications and study site. We will conduct exploratory analyses on health care resource use to see if SDH over a 10-week period is associated with changes in mediation, visits to family doctors/general practitioners and hospital visits both over the 10-week period and in the longer term (52 weeks).

Data collection

We have created an electronic case report, created in REDCap, form that is GDPR and HIPPA compliant[12]. Data collected during all study visits will be entered directly into REDCap with source data, such as CGM and CBG downloads, uploaded as .csv files into this database. Questionnaires will be completed on Qualtrics and exported as .csv files into REDCap.

All data collected through uMotif, Qualtrics, REDCap and FitBit will be collected using a unique patient identifier.

Monitoring

Regular monitoring will be performed according to the trial specific Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the trial specific monitoring plan. The monitors will verify that the clinical trial is conducted, and data are generated, documented and reported in compliance with the protocol, UK good clinical practice guidelines, and the applicable regulatory requirements.

Ethics

Ethical approval to conduct the study has been granted in the UK by Oxford B Research Ethics Committee, in the Netherlands by CMO Region Arnhem-Nijmegen, in Austria by Ethikkommission der Medizinischen Universität Graz, in Denmark by Videnskabsetisk Komite for Region Hovedstaden and in France by the Comite Die Protection Des Personnes SUD Mediterranne IV.

The trial is registered at https://www.clinicaltrials.gov/ct2/show/NCT04304963.

Dissemination

We will report the results of the trial to the participants through written and verbal reports, at national and international conferences and in peer-reviewed scientific journals.

Bibliography

1. Amiel SA, Aschner P, Childs R N B, et al. Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the Europian Association for the Study of Diabetes. *Diabetologia*. 2017;60(1):3-6. doi:10.1007/s00125-016-4146-6

2. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care*. 2017;40(12). doi:10.2337/dc17-1600

3. Levy JC, Davies MJ, Holman RR. Continuous glucose monitoring detected hypoglycaemia in the Treating to Target in Type 2 Diabetes Trial (4-T). *Diabetes Research and Clinical Practice*. 2017;131:161-168. doi:10.1016/j.diabres.2017.01.022

4. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *The Lancet*. 2016;388(10057). doi:10.1016/S0140-6736(16)31535-5

5. Basu A, Dube S, Veettil S, et al. Time lag of glucose from intravascular to interstitial compartment in type 1 Diabetes. *Journal of Diabetes Science and Technology*. 2015;9(1):63-68. doi:10.1177/1932296814554797

6. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S. The Performance and Usability of a Factory-Calibrated Flash Glucose Monitoring System. *Diabetes Technology and Therapeutics*. 2015;17(11):787-794. doi:10.1089/dia.2014.0378

7. Kubiak T, Mann CG, Barnard KC, Heinemann L. Psychosocial Aspects of Continuous Glucose Monitoring: Connecting to the Patients' Experience. *Journal of Diabetes Science and Technology*. 2016;10(4):859. doi:10.1177/1932296816651450

8. Henriksen MM, Andersen HU, Thorsteinsson B, Pedersen-Bjergaard U. Hypoglycemic Exposure and Risk of Asymptomatic Hypoglycemia in Type 1 Diabetes Assessed by Continuous Glucose Monitoring. *Journal of Clinical Endocrinology and Metabolism*. 2018;103(6). doi:10.1210/jc.2018-00142

9. Galan BE, McCrimmon RJ, Ibberson M, et al. Reducing the burden of hypoglycaemia in people with diabetes through increased understanding: design of the Hypoglycaemia REdefining SOLutions for better liVEs (Hypo-RESOLVE) project. *Diabetic Medicine*. 2020;37(6). doi:10.1111/dme.14240

10. Uffe Søholm, Melanie Broadley, Natalie Zaremba, et al. Investigating the day-to-day impact of hypoglycaemia in adults with type 1 or type 2 diabetes: design and validation protocol of the Hypo-METRICS application. *BMJ open (in press)*. Published online 2021.

11. Gold AE, Macleod KM, Frier BM. Frequency of Severe Hypoglycemia in Patients With Type I Diabetes With Impaired Awareness of Hypoglycemia. *Diabetes Care*. 1994;17(7). doi:10.2337/diacare.17.7.697

12. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical Informatics*. 2019;95. doi:10.1016/j.jbi.2019.103208

13. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of Hypoglycemia: Quantification, Validation, and Utilization. *Diabetes Care*. 1987;10(5). doi:10.2337/diacare.10.5.617

14. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt MD, Polonsky W. *O R I G I N A L Reduced Awareness of Hypoglycemia in Adults With IPPM A Prospective Study of Hypoglycemic Frequency and Associated Symptoms*.

15. Pedersen-Bjergaard U, Agerholm-Larsen B, Pramming S, Hougaard P, Thorsteinsson B. Activity of angiotensin-converting enzyme and risk of severe hypoglycaemia in type 1 diabetes mellitus. *The Lancet*. 2001;357(9264). doi:10.1016/S0140-6736(00)04405-6

16. Speight J, Barendse SM, Singh H, et al. Characterizing problematic hypoglycaemia: iterative design and preliminary psychometric validation of the Hypoglycaemia Awareness Questionnaire (HypoA-Q). *Diabetic Medicine*. 2016;33(3). doi:10.1111/dme.12824

17. Ware JE Jr SC. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. Published online June 30, 1992:473-483.

18. Polonsky WH, Anderson BJ, Lohrer PA, et al. Assessment of Diabetes-Related Distress. *Diabetes Care*. 1995;18(6). doi:10.2337/diacare.18.6.754

19. Holmes-Truscott E, Skovlund SE, Hendrieckx C, Pouwer F, Peyrot M, Speight J. Assessing the perceived impact of diabetes on quality of life: Psychometric validation of the DAWN2 Impact of Diabetes Profile in the second Diabetes MILES – Australia (MILES-2) survey. *Diabetes Research and Clinical Practice*. 2019;150. doi:10.1016/j.diabres.2019.03.020

20. Sullivan MJ, EK, & DE. A survey of multiple sclerosis: I. Perceived cognitive problems and compensatory strategy use. *Canadian Journal of Rehabilitation*. Published online 1990:99-105.

21. Denollet J. DS14: Standard Assessment of Negative Affectivity, Social Inhibition, and Type D Personality. *Psychosomatic Medicine*. 2005;67(1). doi:10.1097/01.psy.0000149256.81953.49

22. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder. *Archives of Internal Medicine*. 2006;166(10). doi:10.1001/archinte.166.10.1092

23. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *Journal of General Internal Medicine*. 2001;16(9). doi:10.1046/j.1525-1497.2001.016009606.x

24. Buysse DJ, Yu L, Moul DE, et al. Development and Validation of Patient-Reported Outcome Measures for Sleep Disturbance and Sleep-Related Impairments. *Sleep*. 2010;33(6):781-792. doi:10.1093/SLEEP/33.6.781

25. MC R, AS Z, EM D. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics*. 1993;4(5):353-365. doi:10.2165/00019053-199304050-00006

26. de Zambotti M, Goldstone A, Claudatos S, Colrain IM, Baker FC. A validation study of Fitbit Charge 2™ compared with polysomnography in adults. *Chronobiology International*. 2018;35(4):465-476. doi:10.1080/07420528.2017.1413578

27. Levy JC, Davies MJ, Holman RR. Continuous glucose monitoring detected hypoglycaemia in the Treating to Target in Type 2 Diabetes Trial (4-T). *Diabetes Research and Clinical Practice*. 2017;131:161-168. doi:10.1016/j.diabres.2017.01.022

28. Pratik Choudhary. THE USE OF CONTINUOUS GLUCOSE MONITORING IN THE INVESTIGATION OF HYPOGLYCAEMIA IN PATIENTS WITH TYPE 2 DIABETES. Published online 2010.

29. Mahmoudi Z, del Favero S, Jacob P, Choudhary P. Toward an Optimal Definition of Hypoglycemia with Continuous Glucose Monitoring. *Computer Methods and Programs in Biomedicine*. 2021;209:106303. doi:10.1016/J.CMPB.2021.106303

30. Uffe Søholm, Melanie Broadley, Natalie Zaremba, Patrick Divilly, Pratik Choudhary, Frans Pouwer. Investigating the day-to-day impact of hypoglycaemia in adults with type 1 or type 2 diabetes: design and validation protocol of the Hypo-METRICS application. *Pending publication*. Published online 2021.

31. Rencz F, Gulácsi L, Drummond M, et al. EQ-5D in Central and Eastern Europe: 2000–2015. *Quality of Life Research*. 2016;25(11). doi:10.1007/s11136-016-1375-6

32. Dolan P. Modeling Valuations for EuroQol Health States. *Medical Care*. 1997;35(11). doi:10.1097/00005650-199711000-00002

33. van Hout B, Janssen MF, Feng YS, et al. Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. *Value in Health*. 2012;15(5). doi:10.1016/j.jval.2012.02.008

34. M. Versteegh M, M. Vermeulen K, M. A. A. Evers S, de Wit GA, Prenger R, A. Stolk E. Dutch Tariff for the Five-Level Version of EQ-5D. *Value in Health*. 2016;19(4). doi:10.1016/j.jval.2016.01.003

35. Andrade LF, Ludwig K, Goni JMR, Oppe M, de Pouvourville G. A French Value Set for the EQ-5D-5L. *PharmacoEconomics*. 2020;38(4). doi:10.1007/s40273-019-00876-4

36. Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. *Applied Health Economics and Health Policy*. Published online February 2, 2021. doi:10.1007/s40258-021-00639-3

Authors' contributions:

PD revised and adapted the protocol, is responsible for the operations of the study, wrote and revised the paper.

PC contributed to the design of the study and the development of the Hypo-METRICS app, led the PPI and PAC reviews of the protocol, supported the writing of the paper, reviewed drafts and is the trial PI.

NZ wrote the first draft of the protocol, contributed to the design of the study and the development of the Hypo-METRICS app, led the PPI and PAC reviews of the protocol, and is the trial manager.

UF was involved in development of the Hypo-METRICS app, contributed to writing of passages and reviewed the paper for content.

JS reviewed the draft protocol for critical content and approved the final version.

Conflicts of interest disclosures:

SAA has served on advisory boards for NovoNordisk and Medtronic and has spoken at an educational symposium sponsored by Sanofi

MLE has served on advisory boards and/or received lecture fees and/or research support from NovoNordisk, Eli Lilly, AstraZeneca, Medtronic, Dexcom, Ypsomed, Abbott Diabetes Care, Roche, NGM Pharma, Zucara, Pila Pharma

UPB has served on advisory boards and has received lecture fees from Sanofi and Novo Nordisk.

JKM is a member in the advisory board of Boehringer Ingelheim, Eli Lilly, Medtronic, NovoNordisk AS, Prediktor A/S, Roche Diabetes Care, Sanofi-Aventis and received speaker honoraria from Abbott Diabetes Care, Astra Zeneca, Dexcom, Eli Lilly, Medtronic, MSD, NovoNordisk AS, Roche Diabetes Care, Sanofi, Servier and Takeda.

ER has served as consultant/advisor for Abbott, Air Liquide SI, Astra-Zeneca, Boehringer-Ingelheim, Dexcom, Eli-Lilly, Hillo, Insulet, Medirio, Novo-Nordisk, Roche, Sanofi-Aventis, Tandem, and received research support from Dexcom and Tandem.

JS has served on advisory boards for Janssen, Medtronic, Roche Diabetes Care, and Sanofi Diabetes; her research group (Australian Centre for Behavioural Research in Diabetes [ACBRD]) has received honoraria for this advisory board participation and has also received unrestricted educational grants and in-kind support from Abbott Diabetes Care, AstraZeneca, Medtronic, Roche Diabetes Care, and Sanofi Diabetes. JS has also received sponsorship to attend educational meetings from Medtronic, Roche Diabetes Care, and Sanofi Diabetes, and consultancy income or speaker fees from Abbott Diabetes Care, AstraZeneca, Medtronic, Novo Nordisk, Roche Diabetes Care, and Sanofi Diabetes.

PC has received personal fees Abbott Diabetes Care, Insulet, Dexcom, Novo Nordisk, AstraZeneca, Medtronic, Roche Diabetes Care and Sanofi Diabetes. Research funding support form Abbott Diabetes Care, Medtronic and Novo Nordisk.

Acknowledgments

Hypo-RESOLVE has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 777460

Abbott Diabetes Care provided the continuous glucose monitors used in the study.