

Summary: *Clostridium difficile* Life Table Study

1. Purpose and summary

To determine if *Clostridium difficile* (*C. difficile*) infection is associated with excess all cause mortality.

Survival of individuals with an episode of *C. difficile* infection at Addenbrooke's Hospital will be compared with a population of patients who had no episode of *C. difficile* infection admitted to the same medical specialities, using record linkage of clinical records and UK national death registration and the statistical methods of survival analysis.

2. Background

C. difficile Associated Disease (CDAD) ranges from apparently uncomplicated diarrhoea to shock, pseudo membranous colitis, toxic megacolon and death. Although the less frequent and severe complications of CDAD - pseudo membranous colitis and toxic megacolon, are easily recognised, there remains concern that overall mortality from all levels of severity of CDAD may be increased, and that the seriousness of this infection may continue to be under-estimated.

Between 44,563 and 55,658 episodes of *C. difficile* infection were reported in each of the years 2004 to 2007 declining to 40,704 in 2008, by Hospitals in England in compliance with the government's mandatory reporting scheme. Over 8,000 death certificates mentioned *C. difficile* in 2007 in residents of England and Wales (Office for National Statistics 28 Aug 2008).

Although the NHS has experienced substantial *C. difficile* infection, *C. difficile* is probably largely preventable by high quality nursing, infection control and by avoidance of unnecessary broad spectrum antibiotics.

The risk that *C. difficile* infection poses to patient survival remains uncertain because published research so far is deficient in one or more of the following ways:

- difficulty in assigning a clear causative role for *C. difficile* infection in the complex chain of events leading to individual deaths
- absence of suitable reference populations for determining relative risk of death in infected compared to non-infected individuals
- Failure to accurately measure and adjust for co-morbidities, risk factors and treatment.

Therefore, there is an urgent need to reliably measure the association between *C. difficile* infection and patient survival in a hospital population representative of the UK National Health Service, so that correct priority is given to the prevention and control of this common and severe health care associated infection.

In a pilot study conducted at a Hospital in the East of England in 2007, 45 of 79 (57%) of *C. difficile* cases died over one year following infection compared to 68 of 287 (24%) in a sample of non-case patients drawn from similar clinical specialties (Relative Risk 2.4). That is, *C. difficile* infected patients appeared to have had an almost two and half times greater risk of dying in the year following *C. difficile* infection than patients who were not infected. These observations are not however reliable because no adjustment was made for the complexity of the medical conditions, age and sex and because biases may have operated in the selection of cases and non-cases for study.

We therefore intend to conduct an historic cohort study in a representative sample of patients who had an episode of *C. difficile* infection compared to a representative sample of non- *C. difficile* infected patients admitted to the same clinical specialties at Addenbrooke's Hospital in 2005, 2006 and 2007. We will compare the relative probability of survival in each group by linkage of clinical records and national death registration data bases, calculation of exact time from index admission to death, and use of survival analysis, including Kaplan Meier plots and Cox proportional hazards models, to make full adjustment of all cause mortality for patients' risk factors, co-morbidities, treatments, smoking, alcohol consumption and Multiple Deprivation Score derived from post code of address of residence at index admission.

The study will use clinical data which already exist and vital registration data which has been or will be generated routinely by the National Death Registration system as members of the cohort die. The study does not require contact with subjects, their relatives or medical attendants. The process of enrolment will not compromise the medical confidentiality of subjects nor adversely affect their medical or social care at this or any future time.

The study requires the use of patients' Personal Identifying Information (PII). The study design ensures that PII and clinical data are handled in strict medical confidence at all times and are kept separated in paper and electronic form and can only be linked by the investigators for the purpose of data entry and data cleaning within secure Caldicott compliant sites.

Briefly, the cover page of the clinical notes review questionnaire, which contains the PII of each subject, will be separated from the clinical information section of the questionnaire as soon as the questionnaire has been completed and the unique study reference number added to each page. The two parts of the questionnaire will be filed in separate locked cabinets. PII and clinical information will be entered into separate password protected data bases held on the study coordinating centre secure local area network. Linkage of the PII data base and clinical information and deaths data base will only be possible in computer Random Access Memory. Linkage in computer Random Access Memory will only be possible for the lead investigator and approved data entry and data cleaning officers, because knowledge of the passwords of the two data bases will be required and known only to them.

The National Health Service Information Centre (NHS-IC) Medical Research Information Service (MRIS) is the organisation which undertakes record linkage in the national Death Register. Application to NHS-IC to link data and provide mortality

records for individuals requires approval by the National Information Governance Board (NIGB).

A search for registered deaths of study subjects and a copy of the Death Certificate will be requested for study subjects from the NHS-IC in accordance with NHS-IC standing procedures.

Officers of the NHS IC MRIS have read, commented on and approved the study protocol, with respect to feasibility and the protection of confidentiality of PII.

The Investigators involved in patient data abstraction at the Addenbrooke's Hospital Department of Microbiology and nurses working in the Addenbrooke's Hospital Infection Control team, deal with data of the type to be collected for this study, as a matter of routine as part of their regular work. All clinician data abstraction will be undertaken by these staff and all will have contracts with the Cambridge University Hospitals NHS Foundation Trust.

The design of the protocol has also been undertaken in consultation with, and approved by, of each of the departments involved at Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust.

3. Ethical Approvals

3.1 Cambridgeshire Research Ethics Committee

The study was approved by the Cambridgeshire Research Ethics Committee in 2009.

3.2 National Information Governance Board

Demonstration of Addenbrooke's Hospital User Involvement is required by the National Information Governance Board before its ethical committee can reach a final decision on approving linkage between hospital records and death certificates required in this study.

Hospital User Involvement

A survey of users of Addenbrooke's Hospital will be undertaken to elicit their view of the acceptability of the study. The users will be recruited from a panel administered by the Cambridge University Hospitals NHS Foundation Trust Research and Development office. Service Users will be sent a covering letter, a copy of this summary and a structured questionnaire to elicit their opinion on the acceptability of the study.

The questionnaire contains structured and free text responses, a question on whether the respondent will be willing to attend an open meeting on the study with the Principal Investigator, and an invitation to be sent the full study protocol and questionnaires, if the respondent requests this. An open meeting will be held comprising a further presentation on the project and a questions and answers session, the results of which will be recorded and summarised. The analysis of the

questionnaires and open meeting will be submitted to the Ethics and Confidentiality Committee of the National Information Governance Board so that it may reach its final decision as to whether this research project can be approved by the Board.