

Hub Clinical Trial Service Unit	Host University University of Oxford
Supervisor William Stevens will.stevens@ctsu.ox.ac.uk	Co-supervisors Michael Lay, Jim Davies, Martin Landray
Is the project clinical or non clinical? Non clinical	
Title of PhD project: Modelling adverse event processing in clinical trials	

Background to the project: In clinical trials, an adverse event (AE) is defined as an untoward medical occurrence in a trial participant. This may range from symptoms (e.g. nausea, headache) that do not require any medical attention through to hospital admissions or death. Some AEs may be related to the trial intervention, others may be incidental. Efficient ascertainment, review and analysis of relevant AE data is critical to the safety of study participants and the reliability of the results – key outcomes may be defined in terms of AEs. Regulatory requirements for rapid reporting may be demanding. E.g. in our HPS2-THRIVE trial of niacin vs. placebo in 25000 participants with cardiovascular disease over 64000 AEs were recorded over an average of 4 years' follow-up. Definition and interpretation may be challenging: a single report may correspond to multiple AEs, the same AE may be reported several times. Many AE reports are altered as a consequence of coding (e.g. using MedDRA, ICD), or clinical adjudication as new information becomes available. Furthermore, an AE may be linked to other clinical trial data, e.g. as a reason for withdrawal from a trial, or for stopping treatment. Any subsequent changes to the event must retain the meaning of these references. The status of an AE report may only be finalised at the end of the trial when the database is locked. A full audit of all changes must be maintained to allow reconstruction of the process. Producing standardised guidance (for example via the Clinical Data Interchange Standards Consortium (CDISC)) on AE processing that contains a well-defined model of the process would result in more streamlined AE data processing pathways, yielding substantial savings in time and cost, as well as enhancing data quality and the oversight of participant safety.

What the studentship will encompass: The student will review current AE processing practices, then apply analysis methodologies from computer science in order to produce a published model of the process that will be applicable to a wide range of clinical trial designs. The model will take into account regulatory expectations about describing the effect of AE processing. There is currently very little published in this area; there is an opportunity to make a significant contribution to clinical trials methodology. The focus will be on getting the logic of the model right (methodology) rather than on implementation. The model will be used to design future AE processing software systems. The correctness and usefulness of the model will be assessed against recently completed and active trials. The student will work on communicating relevant parts of the model to all types of users: programmers who write software implementations, clinicians who will help design the model, statisticians who need to understand the data output by an AE processing system, trial managers who use software to help carry out some processing tasks.

Detail of supervision, including the roles of any named co-supervisors: Dr William Stevens, statistical analyst programmer, CTSU (lead supervisor, using CDISC standards in large-scale clinical trials, co-lead CDISC UK Network), Dr Michael Lay, Head of Project Information Science, Nuffield Department of Population Health (supervisor, clinical trials design and compliance, data governance, analysis, and QA), Professor Jim Davies, Professor of Software Engineering, Department of Computer Science, and Director of Clinical Informatics, Oxford NIHR Biomedical Research Centre (domain-specific modelling, model-driven transformation). Professor Martin Landray, Professor of Medicine and Epidemiology; Deputy Director, Big Data Institute (AE processing aspects of large-scale clinical trials).

Detail of any planned field work/ Secondments/industry placement: The University of Oxford is a platinum member of CDISC, who have expressed an interest in this project. This project could potentially lead to CDISC-published guidance on adverse event processing. CDISC have a Fellows program that the student could become involved with. CTSU's membership of the FDA Clinical Trials Transformation Initiative will provide opportunities to explore the needs of regulators, pharma and other stakeholders and will ensure the relevance of the project outcomes for future users.

Supplementary information

1. Describe the alignment of the project with the HTMR Network strategy

This PhD project has the potential to have a major effect on the efficiency of future trials. It seeks to tackle the methodological challenge of capturing, processing, analysing and reporting AE information at the scale, volume and speed required for the future generation of clinical trials. This work aims to improve trial conduct, efficiency and cost-effectiveness and so fits well with the HTMR Network strategy. It will particularly focus on the development of novel, streamlined and highly cost-effective methods for use in clinical trials.

2. Does this project align with the work of a HTMR Working Group; if so, which?

This PhD aligns most closely with the work of the Health Informatics group (of which Dr Lay is a member). The Trial Conduct group will also find the results of interest as the main aim of this project is to make substantial improvements in efficiency and data quality of future trials. Potential for cross-hub collaboration exists in particular with the North West Hub who have a shared interest in Health Informatics.

3. Describe how this project aligns with the host Hub strategy

This fits well into the CTSU Hub strategy to achieve reliable results through supporting streamlined approaches to conducting large cost-effective randomized trials of relevance to public health. The successful candidate will be able to draw on CTSU's expertise in large-scale clinical trials, experience of using routine healthcare data (hospital admissions, death, cancer) for other trials and for UK Biobank, and integral role in data analytics capacity of the Big Data Institute. Prof Davies, who will be located in the Big Data Institute when it opens in January 2017, provides additional expertise in software engineering and the extraction, annotation and analysis of electronic healthcare records gained through his work for the 100,000 Genome Project and the NIHR Health Informatics Collaborative.

4. Detail of any Project specific training offered in the studentship

The project will provide the opportunity to be involved in collaborations across the MRC HTMR network and wider, learn to write project proposals, to attend relevant training courses and to present research findings at relevant meetings. The project will be based in the Clinical Trial Service Unit and Epidemiological Studies Unit which has excellent facilities, and a world-class community of scientists and statisticians. The student will spend at least some of their time located in the adjacent Big Data Institute, providing access to data analysts and software engineers with experience of developing data models for clinical workflows.

5. Are there any prerequisite qualifications or experience for this studentship?

Candidates for an MRC-funded studentship must meet residence eligibility and hold qualifications in a relevant subject at the level of, or equivalent to, a good honours degree from a UK academic institution (see methodology website for more details- www.methodologyhubs.mrc.ac.uk).

For this project: The successful applicant is expected to have a good grounding in computer science, and will work closely with experienced clinicians, statisticians, data analysts and software engineers.

A PhD candidate at the Nuffield Department of Population Health needs to demonstrate:

1. Proven academic excellence (i.e., 1st class or upper second-class undergraduate degree; or international equivalent)
2. Proficiency in English
3. Research or employment experience relevant to population health