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Hub MRC Biostatistics Unit	Host University University of Cambridge
Supervisor Simon White simon.white@mrc-bsu.cam.ac.uk	Co-supervisors Adrian Mander
Is the project clinical or non clinical? Non-clinical	
Title of PhD project Adaptive designs for longitudinal trials to efficiently estimate biomarker change-point outcomes and time-to-change-point	

Background to the project
Within a clinical trial it is common to make longitudinal observations of biomarkers (and other covariates). If the primary outcome is concerned with a change in the longitudinal biomarker we could consider assessing the time until a change-point occurs in the longitudinal process, that is, when the long-term behaviour of the biomarker changes abruptly. A change-point is an identifiable shift in the long-run biomarker level at an individual level, only some individuals may have a change-point and the time when this occurs will vary by person. This is a non-linear longitudinal model of the biomarker and is appropriate when the trajectory of the biomarker over time is of interest as a clinical outcome, rather than simply the overall change.

For example, monitoring cognition in older individuals, there is a distinct rapid decline in cognitive ability linked with dementia and other cognitive impairments, beyond the normal age-related decline. Rather than assessing a treatment's effect on preventing a change in cognition, another outcome would be to delay the change to so-called rapid decline. A treatment might fail to prevent rapid decline, but could delay the time until onset of rapid decline; to test this involves analysing the time to the change-point (between normal and rapid decline of cognition). The estimation of the change-point in cognitive decline is well established in the cognition literature, using the Mini-Mental State Exam (MMSE), but there is little research on designs with the time to a change-point as the outcome.

What the studentship will encompass
The ultimate aim of the project is to create a novel adaptive design that adapts the number and interval of observations for each individual and to demonstrate whether this leads to an increased power to detect a treatment affect, within a biomarker with change-point(s), which could lead to changes in clinical practice.

The MRC Biostatistics Unit is a partner in the European Prevention of Alzheimer's Dementia (EPAD) Consortium, this study includes a longitudinal cohort from which participants will be recruited into trials. The EPAD study, as well as historical cognition studies (using, for example the MMSE), will be used to assess novel designs developed during the project. The project will investigate alternate methods for analysing time to change-point type trials, such as assessing the proportion that have changed after a fixed interval or inferring the time of the change-point using regularly timed observations, and compare the power and efficiency of these designs to the adaptive design. Within the context of EPAD, there is the additional issue of designing trials within longitudinal cohort studies, that will need to be incorporated into the trial design. The focus of the project is to investigate adaptive sampling of individuals. Adapting the observation interval and number will minimise the number of observations on each individual, thus leading to a more efficient design for each participant and overall reducing the number of observations required. The project will investigate the power, efficiency and bias of the adaptive design compared to the alternate methods.

Detail of supervision
The main supervisor will be Simon White and Adrian Mander will co-supervise. The supervisors and student will have weekly or fortnightly meetings.

Planned field work/secondments
The project does not include any field work or industrial placement.

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Supplementary information

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

The project will develop innovative methodology for the analysis of adaptive trials for studies with a time-to-change-point outcome. The primary supervisor's (SW) links with the field of cognition will promote collaboration beyond the HTMR Network and potentially translate the methodology to a wider community. Further, the link with cognition and ageing outcomes align with the wider MRC Strategic Objective "to advance knowledge in the biology of ageing and degeneration of human tissue and to progress research tackling dementia".

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

The project aligns with the Adaptive Design Working Group, with the work aiming to investigate optimal adaptive sampling schemes.

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

The BSU Hub is focused on developing novel statistical methodology, in particular adaptive designs, and so the project's aim to investigate optimal designs of adaptive sampling aligns very well with the host Hub strategy.

The BSU is involved in several grants for the design of trials in prevention of dementia including the MRC UK dementia platform grants and the existing MRC CFAS grants.

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

The BSU offers students free access to relevant training courses (e.g. WinBUGS and missing data methods). In addition, BSU students are required to attend the Academy for PhD Training in Statistics (APTS) course, which is a four week course that trains students in theoretical and computational statistical methods. PhD students at the BSU can attend any degree course at the University of Cambridge and the university also provides training in other skills e.g. scientific writing.

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: Either a first class undergraduate degree in mathematics with a demonstrable statistical component or an MSc in statistics or medical statistics.