# R16

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| Hub: London | Host University: UCL |
| Supervisor: Ian White<br>rmjwiww@ucl.ac.uk | Co-supervisors: Matthew Sydes (CTU); Nick Latimer (University of Sheffield) |
| Is the project clinical or non clinical? Non-clinical | |
| Title of PhD project: Statistical methods for adjusting for treatment changes in randomised trials | |

**Background to the project**. The estimated effect of a randomised treatment in a trial is often impacted by later treatments to which patients are exposed. Participants often change treatment during the course of clinical trials, particularly long-term trials with survival-based outcome measures. These treatment changes may be specified by the protocol, may respond to unexpected clinical or personal events, or occasionally may follow a second randomisation. Sometimes the protocol specifies a treatment change at a first disease event, but subsequent treatments are at the investigator's discretion. In most cases, treatment changes affect the power of a trial, and they affect what quantity is estimated by a standard intention-to-treat analysis of the trial. In particular, in trials for patients with late-stage cancers, placebo arm patients may commonly be given the experimental treatment after their disease progresses. Many other forms of treatment changes occur in a wide range of trials.

The standard intention-to-treat analysis is of practical interest to many audiences in that it compares the effect of "treatment now" with "(possible) treatment on progression". However, many funders, notably cost-effectiveness bodies such as NICE, typically want to compare the effect of "treatment now" with "no treatment".

Complex statistical methods are needed to tackle this problem and provide the most useful estimates to each audience. The most commonly used are rank-preserving structural nested failure time models (RPSFTMs), inverse probability of censoring weighting, and a two-stage method. A weighted log-rank test was recently proposed to improve the power of the intention-to-treat analysis and the RPSFTM analysis.

**What the studentship will encompass**. The student will explore ways to improve and extend the statistical methods for analysing trials with treatment changes. Depending on the interests and skills of the student, this will involve some of:

1. Extending the weighted log-rank test to handle baseline covariates that predict outcome, treatment changes or both.
2. Exploring the suitability of the existing methods to a range of clinical trials drawn from across UCL's Institute of Clinical Trials and Methodology and hubs in the HTMR Network.
3. Applying the methods in depth to a specific (yet to be identified) clinical trial.
4. Building software for general application of the three methods.
5. Disseminating methods through tutorial-type articles.
6. Understanding the similarities and differences between the inverse probability of censoring weighting and the two-stage method, and hence improving the latter.
7. Understanding how the methods should be adapted to inform health economic and cost effectiveness analyses.
8. Extending methods to handle complexities such as changes to many different treatments and missing data about the treatment changes.

**Detail of supervision, including the roles of any named co-supervisors**. Ian White will be the primary supervisor. Ian has 20 years of experience in developing statistical methods for handling treatment changes in clinical trials. He is joining MRC CTU at UCL in Jan 2017 as Professor of Statistical Methods for Medicine. Co-supervisors will be Matthew Sydes who will provide a practical, questioning angle and help to identify trials; and Nick Latimer who will contribute from a health economic perspective.

**Detail of any planned field work / Secondments / industry placement**. None.

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## Supplementary information

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

The project will develop methods that are relevant to trials (strategy 1) and will disseminate them through software and tutorial-type articles (strategy 3). The methods being developed are relevant to NICE and we will explore suitable links (strategy 4).

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

There is some alignment with the Health Economics Working Group since treatment changes especially impact health economic evaluations.

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

The host hub performs methodology research "to find solutions to problems we face in the design, conduct and analysis of our trials and other studies". This project tackles important problems relevant to trials in CTU and the wider research community.

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

The student will attend courses given by Prof White and Dr Latimer - initially as a learner, later as a helper. An advisory board will give guidance in finding a wider range of trials where the methods may be developed and usefully applied.

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 student should have a master's degree in biostatistics or medical statistics. No prior knowledge of the specific statistical methods is required, but an ability to engage with new methods mathematically and conceptually is required.