R17

Hub London	Host University UCL
Supervisor Tim Morris tim.morris@ucl.ac.uk	Co-supervisors Mahesh Parmar, Babak Choodari-Oskooei
Is the project clinical or non clinical? Non clinical	
Title of PhD project Improving power and power calculations in randomised trials with non-proportional hazards	

Background
Randomised trials with time to event outcome measures are typically designed using the log-rank test for the primary analysis. However, non-proportionality of hazards is increasingly being observed (Trinquart *et al*. estimate that non-PH occurred in 1 in 4 trials in oncology; also see Royston and Parmar 2014). Non-PH thus presents a pressing issue that should not be ignored in design or analysis: if it is a potential issue then the sample size and statistical analysis plan, which must be unambiguously pre-specified, should take this into account. Under non-proportional hazards (non-PH) the log-rank test retains its size but loses power. The loss in power relates not only to the presence of non-PH, but the form that non-PH takes.

How then should we approach trial design? Some trialists plan to use a weighted log-rank test, but this is not reflected in the sample size calculations. Two recent proposals (Royston and Parmar 2014, Royston and Parmar 2016) involve calculating sample size based on extended tests that have two components, both of which include the log-rank. This project aims to further improve methods and provide guidance for the design and analysis of trials in which non-PH may be anticipated.

What the studentship will encompass
The studentship will begin with

- Familiarisation with survival analysis and the standard design of trials with time to event outcomes
- Exploration of *how* the unweighted log-rank test loses power in certain situations
- A review of available methods for handling non-PH and exploration of properties

The student will apply suitable methods to real trial datasets held by the MRC CTU at UCL and digitise published Kaplan–Meier curves and apply methods to some of these.

The student will then consider which tests are amenable to inclusion in sample size calculations, and compare their power and flexibility using simulation studies: do some lend themselves to certain forms of non-PH? Are others more generic? Further, an exploration of whether tests correspond to particular estimation procedures – or how they could do – will be undertaken. The aim would be to develop a proposal and guidance for a robust approach to design (and analysis) of trials with a time-to-event outcome, which does not involve too-large an increase in sample size compared with the currently traditional approach of designing trials using the proportional hazards assumption.

Given the development of suitable methods, the student will be expected to advise on the design of real trials in which non-PH may be possible. Further development of software in Stata (or R) will be implemented for methods which are not currently available.

Detail of supervision, including the roles of any named co-supervisors
The student will be primarily supervised by Tim Morris, with input from Mahesh Parmar and Babak Choodari-Oskooei at regular intervals. Patrick Royston will be involved in an advisory capacity. This project is flexible as to its applied / theoretical leaning; there is scope for both.

There is no planned field work, secondment or industry placement.

L Trinquart, J Jacot, SC Conner, R Porcher. *J Clin Oncol*. 2016; **34**(15):1813–19
P Royston, MKB Parmar. *Trials* 2014; **15**:314
P Royston, MKB Parmar. *BMC Medical Research Methodology* 2016; **16**:16

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Supplementary information

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

The project aligns well with the HTMR Networks strategic objectives 3 (*encourage the implementation of the most effective and appropriate methods in clinical trials*), 5 (*strengthen research training and capacity in the UK*) and 6 (*contribution to MRC strategy of picking research that delivers – the project will directly impact on the way some of our randomised trials are designed and analysed*)

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

No

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

The London hub has a particular interest in developing better methods for the design and analysis of trials. This would be another important strand to this activity. The Hub has developed user friendly software for the design of trials, meta-analyses and observational studies. This project relates design and analysis, with implications for our randomised trials which methods will feed through to.

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

The student would attend courses on analysis of survival data and on simulation studies.

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: A postgraduate qualification in statistics (ideally medical statistics) is a necessary prerequisite (or equivalent practical experience).