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Hub MRC Biostatistics Unit	Host University University of Cambridge
Supervisor Adrian Mander Adrian.Mander@mrc-bsu.cam.ac.uk	Co-supervisors James Wason, Michael Grayling
Is the project clinical or non-clinical? Non-clinical	
Title of PhD project Investigating the role of single-arm trials in drug development plans	

Background to the project

Phase II oncology trials have classically been single-arm in design. However, the lack of randomisation in such trials means it is easy for a selection bias to be introduced, whilst their results can also be heavily influenced by variability in the historical control rate, or by temporal drift in patient response. It is thus not surprising that there has been much interest recently in whether it would be preferable to utilise a randomised design in phase II; with studies attempting to resolve this debate proposing that when possible randomised designs should be preferred.[1] Accordingly, it is logical to question the role single-arm trials should play in modern drug development. Attempting to explore this, a recent publication provided the first discussions on the efficiency of a phase II drug development plan consisting of a single-arm followed by a randomised two-arm trial.[2] It was demonstrated that in some circumstances such a development plan would be the optimal one to minimise the expected sample size.

What the studentship will encompass

Whilst results indicated that a single-arm to randomised two-arm development plan could be highly efficient, it remains unclear how precisely such a development plan should be designed and analysed. In what way should the results of the single-arm trial inform the design of the following randomised trial? Can the data gathered from both the single-arm and randomised trials be combined to better estimate the experimental regimens treatment effect? How would such considerations be affected if the single-arm trial were to assess a binary endpoint, as is typical in oncology, but the longer in duration randomised trial were to utilise a normal or survival endpoint? In this project, we propose to begin by investigating these questions. Specifically, we will look to develop a complete framework for the design and analysis of seamless single-arm to randomised two-arm trials.

Furthermore, conventional single-arm and randomised trials have indeed now been extensively compared. But, the suitability of multiple single-arm trials, versus a single adaptive enrichment trial design, at identifying efficacious treatment regimens in subgroups of interest has to date not been examined. Such considerations are particularly important given the former design has been used in practice, for example by the National Lung Matrix Trial. It may be that the efficiency gains made from sharing a control group mean that a randomised design could be almost universally preferable to multiple single-arm trials when a large number of drugs, and/or subgroups, are present in a trial. We will look to answer this by exploring the efficiency of multiple single-arm trials at enriching for subgroup-treatment interactions of interest.

It is hoped that the results of the project will be able to more adequately address the still present concerns over the appropriate design of phase II trials.

Detail of supervision

This project will be supervised by Adrian Mander, James Wason and Michael Grayling at the MRC Biostatistics Unit. It will build upon their previous work on the design and analysis of single-arm and multi-arm clinical trials.

References

1. Tang H, Foster NR, Grothey et al. Comparison of error rates in single-arm versus randomized phase II cancer clinical trials. J Clin Oncol 2010; 28:1936-41.
2. Grayling MJ, Mander AP. Do single-arm trials have a role in drug development plans incorporating randomised trials? Pharm Stat 2016; 15:143-51.

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Supplementary information

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

The project supports several aspects of the HTMR Network strategy. It will develop novel adaptive design methodology for use by the trials community; helping tackle important open problems related to preferred phase II trial design, and trials with many subgroups of interest. It will consequently, through publications and conference presentations, encourage the use of the most appropriate design for phase II trials. Finally, it will substantially enhance the knowledge of methodology related to single-arm trial designs held within the UK. Whilst such trials have historically been an integral part of the drug development pipeline, we are unaware of any UK based project that has explored the design or analysis of development plans that incorporate single-arm trials.

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

This project, given its focus upon the design and analysis of a type of sequential trial design, aligns well with the Adaptive Designs Working Group. It will also have relevance to the Stratified Medicine Working Group, and its goal of determining efficient designs for biomarker-stratified trials.

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

The MRC Biostatistics Unit Hub remains focused on developing novel statistical methods for trial design and analysis, in order to improve the efficiency of the drug development process. This project aligns clearly with this objective; exploring how to more efficiently design phase II drug development plans, which are carried out in their thousands each year. The MRC Biostatistics Unit Hub is also committed to ensuring novel designs are utilised in practice. The conference talks, publications, and software associated with this project will help further this goal.

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

The *adaptive methods in clinical research* course offered by the North-West Hub would provide significant enhanced training in some of the techniques to be extended as part of the project. Moreover, there is scope if a student is interested to explore the previous design and analysis procedures utilised for phase II trials through a systematic review. For this, the course *systematic reviews and meta-analyses of health research* offered at LSHTM would be particularly relevant. An advisory group of two other BSU statisticians would be appointed to provide input to the project from other areas of biostatistics (e.g. meta-analysis, genomics).

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 Masters level degree in Mathematics, Statistics, or a similar discipline would be required.