R4

Hub MRC Biostatistics Unit	Host University University of Cambridge
Supervisor James Wason james.wason@mrc-bsu.cam.ac.uk	Co-supervisors: Paul Newcombe
Is the project clinical or non clinical? Non-clinical	
Title of PhD project Methods for using high-dimensional biomarker information prospectively in clinical trials	

Background

With advances in high-throughput biological techniques, huge numbers of potentially predictive biomarkers are becoming routinely collected in modern clinical trials. However, current designs do not make best use of these data, and there is potential for better approaches that will provide more information on which subgroups of patients benefit and which don't.

The adaptive signature design (ASD) of Freidlin and Simon[1] is a trial design that was developed to make better use of biomarker data. It aims to: 1) develop a predictive biomarker signature that classifies patients as 'sensitive' or 'non-sensitive' to the treatment; 2) test the treatment effect in sensitive patients; and 3) test the treatment effect in all patients. An alternative approach is the adaptive enrichment design (AED), in which the eligibility criteria of patients are adapted within the trial according to observed efficacy in biomarker subgroups. Proposed methodology for AEDs is limited to the use of one pre-specified biomarker.

What the studentship will encompass

During this project, the student will learn about state-of-the-art statistical techniques from the fields of adaptive clinical trials and high-dimensional statistical analysis. They will then work on combining these fields in order to propose designs that can improve on the ASD and AED.

The ASD method, as currently proposed, develops the predictive biomarker signature by testing for interaction between treatment assignment and each biomarker separately. This technique is known to have sub-optimal properties when there are many correlated biomarkers to choose from. Biomarkers that are associated with the same underlying causal effect are likely to be incorrectly included. This leads to lower predictive ability of the signature and over-confident predictions. We will seek to modernise the ASD with state of the art variable selection methods such as Bayesian sparse regression[2], so that the ASD has good performance for correlated high-dimensional biomarker data.

We will then work on applying similar methodology to extend the AED so that it can also be used with high-dimensional biomarker information. Such a trial design would develop a biomarker classifier at an interim analysis that can be used to determine whether future patients would benefit or be harmed by treatment. This opens up possibilities such as not recruiting patients who would likely be harmed, or allocating patients to treatments that are more likely to benefit them (when there are multiple experimental treatments available). The benefits of this are that patients are more ethically treated and the trial will be more efficient (as the recruited patients will likely have a higher treatment effect). However we will also investigate potential drawbacks of this approach.

Detail of supervision

The student will be supervised by James Wason, who has expertise in adaptive clinical trial design methodology including trials that use biomarkers prospectively. The student will also be supervised by Paul Newcombe from the statistical genomics group, who has expertise in statistical methods for analysing high-dimensional data. Both supervisors will meet with the student on a weekly basis. An advisory group of two other BSU statisticians will be appointed who will meet on a termly basis with the student.

The student will have access to James and Paul's clinical collaborators who work in clinical trials of Stroke, pulmonary arterial hypertension and alcoholic hepatitis. These clinicians have expressed strong interest in these proposed designs and have provided real trial data

References

1 Freidlin B, Simon R. Clinical Cancer Research 2005;11(21):7872-8.
2 Newcombe PJ, et al. Statistical methods in medical research.

R4

Supplementary information

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

This project will develop innovative methods in areas that align well with MRC and HTMR network strategy. In particular methods developed in this project cover one of the MRC's priority areas – stratified medicine.

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

Yes, this project aligns with the stratified medicine working group (co-chaired by James Wason), and the adaptive designs working group (of which James is a member). The student would be encouraged to join and contribute to both working groups.

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

The MRC BSU hub aims to develop and disseminate novel statistical methods for improving the efficiency of clinical trials. One research programme in the BSU specifically focuses on adaptive trial designs. Another research programme in the BSU develops methods for analysing genomic data. This project brings together expertise in adaptive trials and genomic analysis from across the BSU in a manner that would be difficult to do elsewhere in the UK. Thus this project closely fits within the strategy of the BSU and the BSU hub.

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: A master's degree in a quantitative subject with a considerable statistical component. Prior knowledge of clinical trials would not be required but would be advantageous.