R23

Hub: North West	Host University: The University of Manchester
Supervisor: Richard Emsley	Co-supervisors: Matthias Pierce, Andrea Jorgenson
Is the project clinical or non clinical? Non-clinical	
Title of PhD project: Trial designs integrating biomarker information for the evaluation of treatment-effect mechanisms in stratified medicine	

Background to the project: Developing novel trial designs incorporating efficacy and mechanisms evaluation (EME) is a vital component for obtaining robust inferences in stratified medicine. A key development that has advanced stratified medicine is the expansion in routinely collected biomarkers, which are defined as any measureable clinical trait, including genomic, proteomic, microbiomic and clinical variables. If a biomarker that is predictive of treatment response is identified, we should be able to test the mechanism underpinning the stratification. We have recently proposed a biomarker-stratified efficacy and mechanism evaluation (BS-EME) trial design for this purpose (Dunn et al, Clinical Trials, 2013). This assumes a single biomarker at a fixed point in time, but we need to extend this idea to combinations of multiple biomarkers which might be measured longitudinally.

What the studentship will encompass: The project will evaluate the properties of a BS-EME trial design, with reference to the precision and potential bias of parameter estimates, functional form of the clinical outcome, statistical power and sample size requirements, to ensure such a trial is feasible. It will consider extending the trial design to incorporate multiple biomarkers. Monte Carlo simulation studies will be used to extensively test the methodology, and applications to real datasets will be available through collaborators. The simulations will:

1. Consider a wider range of parameter values in reference to real-world clinical situations;
2. Vary the effect size of the treatment by predictive biomarker interaction on the mechanism;
3. Look at the effects of the relative sizes of the predictive biomarker strata on estimator performance;
4. Quantify the effects of misclassification/measurement error in the predictive and prognostic biomarkers;
5. Assess the performance of the study design under different data-generating scenarios, to include the situation where the functional form of the multiple biomarkers is misspecified;
6. Compare estimation methods for instrumental variable approaches, including Bayesian MCMC estimation, two-stage least squares, generalised method of moments and maximum likelihood, and whether different estimation approaches allow for relaxation of the identifying assumptions.

A key aspect is to consider how strong the evidence regarding a single, or more likely a set of, predictive biomarkers would be before preceding to a BS-EME trial. Extending the incorporation of mechanisms evaluation to alternative trial designs, such as adaptive trials, will also be encouraged.

The specific project aims are:
A1. Examine the statistical properties of the BS-EME trial design for a continuous outcome using extensive Monte Carlo simulation studies;
A2. Extend the instrumental variable analysis methods to binary and survival outcomes (including multivariate outcomes to allow for adverse side-effects) and test the BS-EME trial design for these outcomes using further Monte Carlo simulation;
A3. Produce guidelines for the design of BS-EME trials, including sample size recommendations and suggested analysis methods and limitations.

Detail of supervision: Prof Richard Emsley will be the primary supervisor, based at The University of Manchester. Co-Supervision will be provided by Dr Matthias Pierce (Manchester, expertise in personalised treatment rules and stratified medicine) and Dr Andrea Jorgenson (Liverpool, expertise in biomarker validation and stratified medicine). The student will link with clinical collaborators through the supervisors' existing programmes of work.

R23

Supplementary information

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

This project aligns with the HTMR strategy by: promoting high quality methodological research relevant to trials; encouraging the appropriate use of these methods in clinical trials,engaging with researchers beyond the Hubs through the developing of guidelines for its use; and contributing to the delivery of MRC strategy through applications of trial methodology and biomarker evaluation in stratified medicine.

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

The HTMR network Stratified Medicine Working Group is led by Dr Jorgenson and includes the other proposed supervisors; the student will also join the Working Group. The project meets the objectives of the Working Group by building capacity amongst trial methodologists and by developing suitable methods for stratified medicine. We will link with researchers in the MRC BSU Hub working on adaptive designs for stratified medicine.

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

The project is a key component of the Hub's Theme 4 (Efficacy and Mechanisms Evaluation in Targeted Therapies), in particular work package 1 ("Evaluating the BS-EME trial design"). The work will also feed into work package 4 ("Decisions for/against pursuing the BS-EME trial") and work package 5 on Hub training by developing guidelines for the design and implementation of stratified medicine trials. The student will be encouraged to link with other postgraduate students in the host Hub to develop a strong research student culture, as well as existing postgraduate students in the Centre for Biostatistics.

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

Depending on prior knowledge of the successful student, they will be encouraged to attend specialist courses on: randomised clinical trials, biomarker evaluation and validation, causal inference/mediation analysis and stratified medicine. Some of these courses are delivered by the host Hub, the North West Clinical Trials Collaboration or the Centre for Biostatistics in Manchester. If not provided locally, the most relevant course will be identified and the student will attend at another institution (for example, Bristol, London School of Hygiene and Tropical Medicine or King's College London).

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: Some experience of medical statistics and clinical trials would be an advantage, but is not essential as full training will be provided.