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Hub: North West	Host University: University of Liverpool
Supervisor: Andrea Jorgensen a.l.jorgensen@liverpool.ac.uk	Co-supervisors: Munir Pirmohamed, Dyfrig Hughes (Bangor) Industrial collaborator: Matt Nelson, Director of Statistical Genetics, GSK Academic collaborator: Richard Emsley (Manchester)
Is the project clinical or non clinical? Clinical or non-clinical	
Title of PhD project: Evidence synthesis for biomarker validity to inform biomarker-stratified trials	

Background

A biomarker stratified ('BM-stratified') trial is the gold standard for testing clinical utility of a biomarker-guided approach to treatment. Lack of such trials is one of the main obstacles delaying translation of pharmacogenetic (PGx) discoveries into clinic. However, prior to committing to a trial, there must first be robust evidence of the biomarker's validity. However, the extent of evidence required and how it should be compiled is unclear. The first part of this project will explore how robust evidence of biomarker validity must be to proceed to a BM-stratified trial. Related to this is the fact that once compiled, the evidence of biomarker validity from observational studies may rule out a BM-stratified trial on ethical grounds, e.g. it may be unethical to conduct a trial when compelling evidence shows some subgroups would not benefit from treatment, or are at increased risk of adverse events. Further, where outcome is rare, for example an adverse event, undertaking a BM-stratified trial is not feasible due to the large sample size required. In such situations, evidence for translation into clinic can come only from observational data. Examples of integrating patient characteristics to guide treatment choice into clinical practice based on observational data only already exist (e.g. a drug's summary of product characteristics (SmPC) advising reduced doses for those with impaired liver or renal function). The second part of this project will explore how observational data may be used as evidence for translation of a biomarker-guided approach into clinic.

What the studentship will encompass

For the first part, a systematic review of previous genetic BM-stratified trials will be undertaken to assess and critically evaluate how evidence of biomarker validity was compiled, and the extent of evidence that led to the trial, and whether this impacted on the use of the medicine. Methodologies that could help in ascertaining a biomarker's validity, including systematic reviews, meta-analyses and quality assessment tools will be explored and guidelines on how the evidence should be compiled will be developed for those embarking on stratified trials in the future. For the second part, a systematic review will be undertaken of PGx studies where outcome is an adverse event. Evidence from the studies will be synthesized by way of a meta-analysis, and the precision of the effect size compared to that which would be achieved in a BM-stratified trial. Consideration will also be given to how healthcare practitioners and regulatory bodies will view such evidence in the absence of a supporting randomized controlled trial. Patients' perspective will also be explored with patients identified via resources such as Genetic Alliance UK. To complement the second part of the project, an economic framework will be developed to undertake value of information analyses for quantifying the potential benefit of additional information regarding patient stratification in the face of uncertainty.

Details of supervision

Primary supervision will be provided by Dr Andrea Jorgensen, Senior Lecturer in Biostatistics with expertise in statistical PGx, systematic reviews and meta-analyses of PGx studies. Andrea co-leads the MRC HTMR Network's Stratified Medicine Working Group. Co-supervision will be provided by Professor Sir Munir Pirmohamed, the NHS Chair in PGx, as well as a Member of the Commission on Human Medicines and Chair of its Pharmacovigilance Expert Advisory Group and Professor Dyfrig Hughes, Professor of Pharmacoeconomics and co-director of the Centre for Health Economics and Medicines Evaluation, University of Bangor. Matt Nelson, Head of Genetics, Glaxo Smithkline has also agreed to be collaborator on the project, as he has an interest in how observational data can be utilised to demonstrate clinical utility in stratified medicine and has agreed to regular meetings via teleconference to support and help progress the project. Professor Richard Emsley, University of Manchester, who co-leads theme 4 of the North West Hub with Andrea Jorgensen has also agreed to be collaborator.

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Supplementary information

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

The project aligns with the Network's strategy with respect to the following objectives: i) promoting high quality collaborative methodological research relevant to trials; ii) to contribute to the delivery of MRC strategy, in particular it focuses on developing methodology to support novel challenges in stratified medicine (namely what is considered to be sufficient evidence of biomarker validity prior to embarking on a trial, and the level of evidence required from observational data in the absence of a randomised controlled trial), an area of strategic importance for the MRC. This will be strengthened via our links with the stratified medicines working group; iii) strengthen research training and capacity in methodology in the UK; iv) encourage implementation of the most effective and appropriate methods in clinical trials – in this case the most effective and appropriate methods for demonstrating the biomarker's validity prior to embarking on a stratified trial.

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

The project aligns with the work of the HTMR Stratified Medicine Working group, and the successful candidate would be a member of this group. Through discussion with the MRC, evidence on biomarker validation and how it informs trials has been identified as one of the key priorities for the working group. There are also aspects in common with the Evidence Synthesis Working Group (in terms of value of information analysis), and the Economics Working Group.

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

The project aligns with Theme 4 of the North West Hub: 'Efficacy and Mechanisms Evaluation of Targeted Therapies'. One of the theme's aims is to become a national focal point in trials methodology for stratified medicine and to support methodology to ensure robust inferences in translational medicine. It also aligns with the cross-cutting economic theme of the Hub and represents added value to the (a) MRC Centre for Drug Safety Science, where stratified medicine is a key cross-cutting theme; (b) the Wolfson Centre for Personalised Medicine, a multi-disciplinary group of researchers investigating the omic basis of personalized drug prescribing; (c) the personalized health theme in the North West Coast CLAHRC (Pirmohamed theme lead).

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

The student would be mentored by the supervisory team. Relevant training opportunities e.g. in clinical trial design, methods of systematic reviewing and introductory medical statistics would be identified as and when appropriate.

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: First degree and/or Masters degree with a substantial statistical component, or a medical degree. Experience of conducting systematic reviews and/or meta-analyses would also be desirable.