R11

Hub: ConDuCT-II	Host University: University of Bristol
Supervisor: Nicky Welton Nicky.Welton@bristol.ac.uk	Co-supervisors: Sofia Dias, Tony Ades
Is the project clinical or non clinical? Non-Clinical	
Title of PhD project: Powering trials on effectiveness and efficacy outcomes	

Background to the project

RCTs are typically designed to detect differences in a condition specific outcome, and yet decisions on whether to adopt a new treatment are based on broader assessments of its impact on patients lives. NICE, for example, uses quality adjusted life-years (QALY) on which to base reimbursement decisions. Because measures such as the EQ-5D (used to derive QALYs) are usually considerably less sensitive to treatment effects than disease specific measures used as trial end-points, trials are almost invariably under-powered to detect QALY effects. As a result, the practice has developed of "mapping" treatment effects from disease-specific measures into QALYs, using an externally derived mapping coefficient. This practice assumes there is a functional relation between the disease-specific and QALY scales. The objective of this PhD is to develop methods to map between *multiple* disease-specific and quality of life outcomes, and explore the impact that this has on statistical power for quality of life outcomes. This has implications for trial design, because greater power to detect difference in quality of life outcomes can potentially be achieved for a given sample size, if the functional relationships between multiple outcomes are captured through mappings.

What the studentship will encompass

The purpose of the PhD project is to develop new ways of powering trials when there are multiple outcomes that are functionally related. This PhD project develops methods of "mapping" treatment effects from condition-specific measures into QALYs, using an externally derived mapping coefficient. These methods can improve the design of RCTs to answer cost-effectiveness questions most relevant to policy makers. This will lead, potentially, to more efficient trials providing *more* information on economically significant outcomes such as QALYs.

The PhD research will include a review of current approaches to the role of economic outcomes in powering trials, and current practices among manufacturers in choosing whether to power on efficacy or on economic outcomes. The core work will involve mathematical analysis of how trial size (power) depends on: relative responsiveness of different test instruments to treatment differences; uncertainty in the mappings; correlations between responses to test instruments; and the functional relationships between treatment effects on different test instruments. The methods will be applied in fully worked-up examples, where the sample sizes required to reach a given power under standard and multiple outcomes with mapping methods, will be contrasted. The work will take as a starting point the work of Ades and Lu (2013), and will develop this further to consider multiple disease-specific and/or Quality of Life outcomes. Value of Information methods will be developed to determine whether it is efficient to collect further information on mappings prior to trial design.

Ades AE,Lu G,Madan JJ. Which Health-Related Quality-of-Life Outcome When Planning Randomized Trials: Disease-Specific or Generic, or Both? A Common Factor Model. Value in Health 2013:185-194.

Detail of supervision, including the roles of any named co-supervisors

Dr. Welton is the primary supervisor, with co-supervision from Dr. Dias and Prof. Ades. All supervisors are experienced statisticians working in advanced methods for evidence synthesis. Prof. Ades has recently developed methods for mapping between different outcome measures, which will be a starting point for this project. Dr. Dias leads an MRC project on methods for synthesis of studies reporting different, but related outcome measures, and will provide methodological and programming expertise. Dr. Welton jointly leads the ConDuCT-II hub theme on research prioritisation, and has expertise in the use of evidence synthesis to design new trials using value of information methods.

Detail of any planned field work/ Secondments/industry placement etc.

None planned.

R11

Supplementary information

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

The project cuts across many of the key priority topics of the network: using existing evidence in the design of trials; improving the design and efficiency of trials; choosing appropriate outcome measures for trials; finding effective and efficient ways to conduct trials; and improving economic evaluations. The PhD will offer a unique training opportunity in multivariate statistical methods, evidence synthesis, value of information analysis, Bayesian methods, and sample size / power calculations.

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

This project is aligned to the work of the Network Working Group on Evidence Synthesis in Trial Design, Conduct and Analysis, of which Dr. Welton is a member.

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

This work fits within the *Prioritisation and Design of Trials* theme and links to the *Outcomes* theme of ConDuCT-II, building on work undertaken by ConDuCT-I.

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

The student will be expected to attend regular team meetings of the Multi-Parameter Evidence Synthesis research group, where they will learn about the full range of research in the group, and also be able to present early work and be given positive feedback. The student will be expected to attend our 3-day course on Indirect and Mixed Treatment Comparisons, as well as having the opportunity to attend courses within the Schools short course programme.

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: This is a technical statistical project, and would be suitable for a student with a good background in mathematical statistics. Knowledge of multivariate statistical methods and evidence synthesis methods would be an advantage, as would an MSc in a quantitative subject.