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Hub North West	Host University Bangor University
Supervisor Dyfrig Hughes d.a.hughes@bangor.ac.uk	Co-supervisors Bernard Vrijens (University of Liège, WestRock Healthcare), Ian White (MRC CTU, UCL)
Is the project clinical or non clinical? Non clinical	
Title of PhD project Defining outcome measures for medication adherence in clinical trials	

Background to the project
Deviations from protocol-defined dosing regimens, in the form of variable adherence to trial medication, are prevalent and problematic. An analysis of 95 clinical studies, reported that the number of patients taking prescribed oral medication(s) decreased progressively over time [Annu Rev Pharmacol Toxicol 2012;52:275-301]. By day 100, about 20% of patients had discontinued treatment, and 12% of those still engaged with the dosing regimen were omitting a proportion of the prescribed doses. Thus, less than 70% of patients were fully adhering to the protocol-specified dosing regimen. This can lead to incorrect interpretation of a medicine's efficacy, confound the selection of an appropriate dosing regimen and may mislead the attribution of safety concerns to trial medication. Under the auspices of the European Society of Patient Adherence, Compliance and Persistence (ESPACOMP), we have published a consensus taxonomy for medication adherence [Br J Clin Pharmacol 2012;73(5):691-705], and developed Medication Adherence Reporting Guidelines (EMERGE) to be adopted by the EQUATOR network. This PhD project will aim to further advance the methodology of medication adherence measurement and reporting in clinical trials.

What the studentship will encompass
As an explanatory variable, adherence to trial medication is conventionally measured as the proportion of doses taken (or some variation on this); and, as an outcome variable, as the proportion of patients achieving some arbitrary threshold (usually 80%) of doses taken over a defined period of observation. Both measures conceal differences in the nature of patients' adherence. Specifically, non-adherence includes non-initiation (which is a dichotomous outcome); poor implementation of the dosing regimen (patients who take the drug, but not according to the prescribed dosing regimen); and premature discontinuation (when they are fail to persist with treatment). The student will: (i) review the literature for measures and models of medication adherence; (ii) develop appropriate statistical models that more effectively represents the three phases of adherence, utilising data from 17,625 trial participants in whom adherence was measured electronically using the Medication Event Monitoring System (iAdherence Pharmionic Knowledge Centre database: http://www.iadherence.org); (iii) define a parsimonious model that characterises patients' adherence behaviour; (iv) assess the statistical properties of the model parameters, considering inter- and intra-individual variability; (v) develop a core outcome set of adherence measures for drug trials; (vi) make comparisons with conventional measures to highlight discrepancies in the measurement of electronically-compiled dosing histories. The findings will be extended to other forms of adherence measurement, depending on data availability.

Detail of supervision, including the roles of any named co-supervisors
The student will be part of a vibrant postgraduate research community within Bangor University's Institute of Health and Medical Research, recently established as a hub for interdisciplinary research and postgraduate research support. The lead supervisor will provide overall direction to the student, and mentorship with respect to the concepts and clinical / pharmacological context. Professors Bernard Vrijens and Ian White, and mathematical modellers within the Centre for Health Economics and Medicines Evaluation (Dr Rikesh Bhatt, Dr Catrin Plumpton) will contribute statistical and modelling expertise.

Detail of any planned field work/ Secondments/industry placement etc.
The student will engage with the ESPACOMP network for wider buy-in and will have an opportunity to spend periods of time at WestRock to gain first-hand experience of adherence measurement.

Supplementary information

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

The project specifically meets the Network's strategies of: (i) promoting high quality collaborative methodological research. The interdisciplinary nature of the research, engagement with external stakeholders and the applicants' track record of research publications, support the project's methodological rigour and effective collaboration. (ii) Working with external stakeholders, in particular to agree on shared priorities for research. Endorsement by our industry collaborator and by the ESPACOMP community is evidence of research priority within clinical drug development programmes. (iii) Encouraging the implementation of the most effective and appropriate methods in clinical trials. We will promote successful methods to be adopted and implemented in clinical drug development programmes through publication in peer-reviewed journals and direct involvement with ESPACOMP. (iv) Strengthening research training and capacity in methodology in the UK.

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

The project aligns most closely with the Outcomes Working Group. Among the working group's main areas of focus are core outcome sets and the reporting of outcomes. The proposed project will learn from the working group's methodological approaches in developing core outcome sets. The project will link directly with the MRC CTU Hub.

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

The project meets the NWHTMR's aims of conducting methodological research that will improve the design and analysis of trials, and working in partnership with others to maximise potential gains. The project fits in with existing research themes of the Hub, namely later phase trial analysis (theme 2), and builds on an a previous PhD project on non-adherence to treatment protocol in randomised controlled trials (Dr Susanna Dodd, supervised by Professor Ian White) as well as a the programme of research activity concerning medication adherence led by Professor Dyfrig Hughes.

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

The student will be supported for their learning needs by their supervisors and postdoctoral staff at the Centre for Health Economics and Medicines Evaluation. Additional training will be provided where appropriate, including specialist short courses on statistics (including those available via the Network of Hubs for Trials Methodology Research), and specialist workshops on adherence research delivered by ESPACOMP. There will also be opportunities for the student to undertake taught modules at postgraduate level to provide the extra skills and knowledge needed to undertake postgraduate research, as well as attend workshops and courses provided for postgraduate research students by Bangor University's Centre for the Enhancement of Learning (CELT).

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 degree in a mathematical or statistical discipline would be required. A Master's degree in a quantitative discipline would also be desirable.