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Hub: North West	Host University: Liverpool University PhD, with student based in Edinburgh, Liverpool or Aberdeen
Supervisor: Carrol Gamble (Liverpool) c.gamble@liverpool.ac.uk	Co-supervisors: Steff Lewis, Marion Campbell, Jonathan Cook
Is the project clinical or non clinical? Non-clinical	
Title of PhD project Extensions of the fragility index to non-binary data	

Background to the project: The fragility index [Walsh 2014] calculates how many events would be required to change a statistically significant trial result into a non-significant result for binary data. A smaller fragility index indicates a more "fragile" trial. The index has recently gained prominence as a practical way of demonstrating how vulnerable a trial result is. In a recent study [Ridgeon 2016], the median fragility index for multicentre randomised controlled trials in critical care medicine reporting mortality was 2, and 40% (of 56 trials) had a fragility index of less than or equal to 1. This result suggests that much of the evidence we rely on is weak. The fragility index is currently not considered at the planning and design stage of a clinical trial. Furthermore it is currently only applicable to trials with a binary outcome looking to detect superiority. Developing the fragility index to allow its use within non-inferiority and equivalence trials as well as trials with ordinal or continuous outcomes would greatly help our understanding of the robustness of these trial results. Additionally the fragility index may lead to a stronger evidence base if it can be incorporated at the design stage for example adjusting the trial sample size to achieve a minimal index for results to be considered convincing to clinicians.

What the studentship will encompass: This PhD will develop methodology to allow the use of the fragility index to be extended. The student will consider how the fragility index could be incorporated at the design phase of a clinical trial and allow for its use in alternative frameworks. They will propose new indices, based on the ideas underlying the fragility index, which can be applied to ordinal scales, continuous scales and survival data, including a review of the relevant literature. They will investigate which of the new indices are more easily understood by clinicians, policy makers and patients, and make recommendations on where they should be used in the future, e.g. in Data Monitoring Committee reports. They will investigate how vulnerable a selection of recently published trials are, across a range of outcome data types.

Detail of supervision, including the roles of any named co-supervisors: Lead supervisor: Carrol Gamble (Liverpool) is Professor of Medical Statistics at the University of Liverpool, Deputy Director and Head of Statistics of the Clinical Trials Research Centre, and co-theme lead for later phase trials in the North West Hub for Trials Methodology Research. She is also Chair of the UKCRC registered CTU Statistics Operational Group.

2nd supervisor: Steff Lewis (Edinburgh) is Professor of Medical Statistics at Edinburgh University and leads the Edinburgh Clinical Trials Unit (ECTU) statistics team. She has access to a wealth of example trial datasets relevant to the project, across many clinical specialties. She has been working in trials methodology for 25 years and is an experienced PhD supervisor (including through the HTMR programme).

3rd supervisor: Marion Campbell (Aberdeen) is Professor of Health Services Research, and medical statistician, at the University of Aberdeen and an experienced trialist. She has been investigating the fragility index and its use in a cohort of UK trials. She is an experienced PhD supervisor

4th supervisor: Jonathan Cook, is Associate Professor and Fellow of St Hugh's College Centre for Statistics in Medicine University of Oxford and a member of the Bristol HTMR.

Detail of any planned field work / secondments / industry placement: This PhD topic could be undertake full or part-time. It would work well alongside systematic review experience and clinical trials. The successful candidate would be encouraged to gain experience within each of these areas across the Liverpool, Edinburgh, and Aberdeen. Travel to the three sites will be required.

References

Walsh et al. The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index. J Clin Epidemiol. 2014;67(6):622-8

Ridgeon EE, et al. The Fragility Index in Multicenter Randomized Controlled Critical Care Trials. Critical care medicine. 2016;44(7):1278-84.

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Supplementary information

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

The HTMR Network strategy requires demonstration of increased engagement with methodological researchers and clinical trialists beyond the Hubs themselves. This is a strength of this PhD project which strengthens links with Scottish collaborators where there are no Hubs but strong methodological experience.
Network engagement within this project is strong and aligns with the UKCRC registered CTU Statistics Operational Group for which Carrol Gamble is Chair, and Steff Lewis is Deputy-Chair. The membership of this Network is a senior statisticians from every UKCRC registered trials unit in the UK. The project will utilise experience from this group, and feedback results to it.
The primary aim of this PhD is to create indices that can be easily understood by anyone, and they could become very widely used in the clinical trial community. It is expected that they will be used by statisticians in sample size discussions at the design stage of clinical trials as well as in interpreting final results.
The PhD aims to develop new indices, which are extensions of an existing method used in the clinical trials community.

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

The results of this project will be useful to those involved in trial design, Data Monitoring Committees, trial analysis, and disseminating results. The project will align with the evidence synthesis working group and adaptive designs.

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

This projects fits within the NWHTMR later phase trials theme. It will impact design and interpretation of later phase trials.

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

The student will have the opportunity to gain training at three different institutions, both at the level of a standard PhD student, and to join training undertaken within the various trials units. They will have opportunities to present work, run workshops, and gain feedback through the UK-CRC Statistics Operational Group, which meets twice a year.

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: Degree in medical statistics or other discipline with large statistical component. Experience in communicating statistical concepts with clinicians and in analysing and drawing conclusions from randomised controlled trials (or systematic reviews) would be beneficial.