About the NIHR Doctoral Research Fellowship

Overarching aim

The main aim of this fellowship is to explore and describe forms of adaptive designs applicable in publicly funded confirmatory clinical trials and provide guidance on their implementation from a statistical and practical perspective. In routine practice when planning a trial, it is common to have sub-optimal information to inform its design which could later undermine its validity. Furthermore, the assumptions made are often overoptimistic. Adaptive designs, in which accumulating trial data may be used to modify key aspects of the trial, may be beneficial. More so, there may be other reasons to justify stopping an ongoing trial early either for efficacy or futility. Nonetheless, such designs have drawbacks: they are more complex, are considered controversial in some quarters and may not be amenable to the constraints of public funding bodies. At present, adaptive designs appear to be rarely applied in publicly funded trials.

The fellowship will investigate and address the issues raised by adaptive designs, specifically in publicly funded trials, and provide guidance on their implementation. It will employ a statistical literature review of potential adaptive designs, elicit views of experts and use both retrospective and prospective case studies of clinical trials to illustrate their implementation. The project is structured in three stages as follows;

Phases of the project

Stage 1:

An extensive statistical literature review will be undertaken to explore forms of adaptations that could be employed in publicly funded trials to provide statistical efficiency, economic and ethical advantages. Statistical issues will includes sample size re-estimations, futility assessment using conditional power, group sequential trials and their stopping rules, drop the loser/pick the winner in multiple arm trials and any other potential candidates to be adopted in publicly funded trials. Due consideration will be given to;

1. The motivation behind the adaptation and its potential benefits compared to a conventional fixed design approach.
2. Description of the adaptive methodology including technical details.
3. Statistical issues such as blinding and impact of the adaptive methodology on statistical inference with emphasis on control of type I and II error rates, and estimation procedures to obtain unbiased estimates of the treatment effect with its associated confidence intervals (CIs) and P – values.
4. Practical or operational challenges associated with the adaptive methodology with emphasis on the publicly funded setting.
5. Statistical issues which are not well understood or gaps in the literature which could constitute areas of further research. Important consideration are given to the distinction between established methodology where there is consensus and those which are not well-established or known with little or no consensus.

Stage 2:

The study will employ both qualitative and quantitative work to explore the views of experts in UK based clinical trial units (such as trial statisticians, investigators and independent DMC members), academia, public funding bodies (panel members) and pharmaceutical companies on the use of adaptive designs using a web based survey and interviews. It is important to understand barriers and opportunities to the use of adaptive designs in routine practice from the key stakeholders in medical research (both public and commercial). In addition, we will also explore the awareness and attitudes towards the routine application of adaptive designs. This is in recognition of the fact that the reasons for poor uptake of these designs in publicly funded trials are multifaceted across the hierarchy of research. The qualitative component will help to inform the quantitative component and also generate possible solutions to the barriers on the implementation of these designs. We will also undertake an audit of registered clinical trials to highlight the current state regarding the uptake of adaptive designs, shed some light on some of the claims in the literature by advocates and critics of adaptive designs, and explore whether the routine uptake in clinical trials practice is improving.

Stage 3:

The main goal of this final stage is to illustrate the practical implementation in order to increase their uptake. Hence we will utilise both retrospective and prospective case studies from public funded trials conducted by the University of Sheffield CTRU and other collaborators, and results from statistical literature review to illustrate how these designs are statistically implemented in real practice. Key questions will be on whether;

1. These trials could have been stopped earlier than planned either for efficacy or futility and what are the potential quantifiable benefits (patients, time and economic).
2. Some of the inferior treatment arms could have been dropped earlier during the course of the trial.
3. The decision making regarding the clinical effectiveness of an intervention under investigation is biased given that the fixed sample size final results of the trials are already known in retrospect. Thus, we intend to investigate the impact and extend of bias in point estimates with associated CIs and P – values following a group sequential trial and what would the results and decision on interpretation would have been if adjusted estimates were used? This is aimed to illustrate how to conduct statistical inference following such an adaptive design.

Other issues will be informed by the stage 1. For generalisability of our results, we will utilise simulation for sensitivity analysis on these case studies to explore whether decisions are consistent under different scenarios.