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Hub MRC Biostatistics Unit	Host University University of Cambridge
Supervisor Sofia S. Villar sofia.villar@mrc-bsu.cam.ac.uk	Co-supervisors Adrian Mander
Is the project clinical or non clinical? Non clinical	
Title of PhD project Bayesian dose adaptive trials using non-myopic response-adaptive methods	

Background to the project

In dose finding studies the aim is to find the maximum tolerated dose of an agent or to find a dose which is closest to a target dose. In dose-ranging studies different doses of an agent are tested against each other to establish which dose works best and/or is least harmful by estimating a response-dose relationship. However, achieving either of these goals with a high precision can imply exposing a large number of patients to highly toxic doses, imposing a trade-off between learning about the doses and dosing patients at the `right' dose. Despite extensive recent work has been done in using decision theory for optimally addressing such a trade-off in the context of phase II or phase III clinical trials, little work has been done to extend such a framework for dose-finding/dose-ranging studies. The main limitation to using such a decision-theoretic approach has been computational. However, recent methods to achieve approximate solutions to these type of dynamic optimisation problems can be deployed to produce computationally tractable and near optimal patient allocation rules for dose finding studies.

What the studentship will encompass

This PhD project will look at developing novel decision-theoretic non-myopic response-adaptive dose-ranging methodology for dose-finding studies. The project will make use of recent advances in bandit theory to try and reduce the computational complexity of finding the optimal (or nearly optimal) solution derived from a set of relevant optimisation problems. The PhD will cover some of the following areas:

- Use and extend existing response-adaptive randomisation rules to be incorporated into the design of dose-escalation studies.
- Investigate novel optimal response-adaptive adaptive designs that can handle multivariate conflictive outcomes (efficacy-toxicity).
- Assess how these methods perform in terms of estimation purposes and patient gain decisions (administering doses nearest to the target toxicity level).
- Use of the dynamic optimisation (bandit) literature to develop suitable and practical non-myopic adaptive randomisation methods specifically designed for dose adaptive trials;
- Produce easy to use software in R and/or Stata to implement methods;
- Compare the resulting decision-based designs to the real trial.

Detail of supervision

The main supervisor will be Sofia S. Villar and Adrian Mander will co-supervise. The supervisors and student will have weekly or fortnightly meetings.

Planned field work/secondments

The project does not include any field work or industrial placement.

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Supplementary information

1. Describe the alignment of the project with the HTMR Network strategy
   The project will develop innovative methodology for the design of non-myopic adaptive trials for dose-finding studies. Both supervisors are part of the HTMR Adaptive designs working group (the primary supervisor SV is the co-lead of the group) and will promote collaboration to develop and implement the methodology within the HTMR Network and potentially translate it to a wider community. Further, implementing adaptive designs like the ones to be developed by this project can help to bring the health impacts of fundamental research to people more quickly.

2. Does this project align with the work of a HTMR Working Group; if so, which?
   The project aligns with the Adaptive Design Working Group, with the work aiming to investigate near-optimal adaptive dose finding schemes.

3. Describe how this project aligns with the host Hub strategy
   The BSU Hub is focused on developing novel statistical methodology, in particular adaptive designs, and so the project's aim to investigate optimal designs of adaptive dose finding aligns very well with the host Hub strategy.

4. Detail of any Project specific training offered in the studentship
   The BSU offers students free access to relevant training courses (e.g. WinBUGS and missing data methods). In addition, BSU students are required to attend the Academy for PhD Training in Statistics (APTS) course, which is a four week course that trains students in theoretical and computational statistical methods. PhD students at the BSU can attend any degree course at the University of Cambridge and the university also provides training in other skills e.g. scientific writing.

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: Either a first class undergraduate degree in mathematics with a demonstrable statistical component or an MSc in statistics or medical statistics.