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Hub MRC Biostatistics Unit	Host University of Cambridge
Supervisor Adrian Mander Adrian.Mander@mrc-bsu.cam.ac.uk	Co-supervisors Graham Wheeler
Is the project clinical or non-clinical? Non-clinical	
Title of PhD project Bayesian dose adaptive trials with multiple outcomes	

Background to the project

A recently completed dose-ranging trial (Todd *et al.*, PLOS Medicine, 2016) was designed to find two targeted doses of the biological agent Proleukin that resulted in a 10% or 20% immune response (as measured by the change in the amount of regulatory T-cells) in newly diagnosed diabetes patients. Proleukin is administered by injection and any dose can be administered within the safe therapeutic range. Dose decisions were made by using optimal design theory of minimising the variance of the doses that gave the targeted responses. A follow-up study is planned to identify the best dose and frequency of repeat administration of dose. The primary outcomes are laboratory measurements of three blood-based markers and dose-changing decisions are made using a multivariate regression model.

What the studentship will encompass

This PhD project will look at extending existing dose-ranging methodology by designing and investigating novel optimal adaptive designs that can handle multivariate outcomes. These new approaches will be closer to the real world situations faced in the decision-making process early on in dose-ranging clinical trials. This may include aims such as:

1) Quantify the information loss by using dimension reduction techniques, such as principle components analysis and using univariate outcomes;
2) Investigate model-robust methods such as Bayesian model averaging techniques and likelihood-based information methods (previous BSU PhD work);
3) Using historical data to inform dose-changing decisions, e.g. using data from the single Proleukin dose study in the second study via techniques such as commensurate and power priors (Hobbs *et al.*, Biometrics 2011);
4) Exploring fully Bayesian approaches to handle uncertainty in parameter estimates;
5) Using penalised D-optimality methods (Pronzato, J. Stat. Planning 2010) when safety endpoints are in the multivariate outcome;
6) Produce easy to use software in R and/or Stata to implement methods.

Detail of supervision

The main supervisors will be Dr Adrian Mander and Dr Graham Wheeler, who will meet with the student weekly.

Secondments/industry placement

There are no planned industry placements, but the methods developed will be very relevant to the pharmaceutical industry. Dr Mander has collaborations with GSK, Roche and AZ in the area of adaptive dose designs and Dr Wheeler works on implementing novel trial designs at the Cancer Research UK and UCL Cancer Trials Centre at University College London.

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Supplementary information

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

This project gives a methodological framework for early dose-ranging studies incorporating multiple endpoints. Its aim to identify the best dose early within a clinical development plan fits in well with the aims of the network.

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

This project extends methods already developed within two previous BSU Hub PhD studentships from within the adaptive designs working group and does not overlap with other PhD projects being proposed from the working group.

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

The BSU Hub aims to develop and disseminate novel statistical methods for improving the efficiency of clinical trials, with one research programme specifically focused on adaptive trial designs. This project will closely fit within this 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 APTS course, which is a four week course that trains students in theoretical and computational statistical methods. BSU members 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 or master's degree in statistics, or mathematics with a demonstrable statistical component or a master's degree in statistics or medical statistics.

Prerequisite knowledge of clinical trials is not required.