School of Mathematical Sciences,
Queen Mary, University of London
PHD STUDENTSHIPS

Project title:
Optimum Design of Experiments for Pharmacokinetic Sampling and Dose-level Allocation in Clinical Trials

Project area:
Statistics; in particular optimum design of experiments, mixed effects non-linear regression, clinical trials

Supervisor(s):
Dr Barbara Bogacka (QMUL) and Prof Byron Jones (Novartis and QMUL)

Start date:
September 2012 or earlier

Project details:
The development of a new therapeutic drug can take up to 10 years and is very costly and ethically sensitive. In the early phase of development (Phase I) the safety and tolerability of a candidate drug are assessed. In the following phase (Phase II) its potential efficacy and therapeutic doses are determined. Finding an appropriate dose to prescribe to patients is one of the main purposes of the clinical trials run in Phase II. This is a complex task and is made more difficult by the inherent heterogeneity of the population of patients that take part. Much work has been done in this phase to assist the evaluation of the relationship between the drug's dose and the effect it produces. This aids the selection of the dose or doses to take forward to the last confirmatory phase of drug development (Phase III).

The aim of this PhD project is to determine improved methods for dose selection, using information that is often routinely collected in the early phases of the development programme. Current methods for dose selection are often based on simple to follow rules. However, knowledge of the human physiological process makes it possible to mathematically model the effect a given dose of a drug will produce. An important source of additional information can be obtained from pharmacokinetic (PK) data obtained from repeated blood samples. From these the time-course of the concentration of the drug in plasma can be calculated. Use of this PK information has the potential to speed up the dose selection experiments and make them more accurate and less costly. This PhD project will extend the theory of optimum design and its application to take account of the additional information provided by the PK data.

Despite the potential of using this extra information, not much work has been done in this direction. One of the difficulties is the heterogeneity of the patient population which leads to models with random parameters; the so called population models. In a dose selection process we want to learn about the best dose level, but the process is constrained by possible toxic outcomes at unacceptable levels. Relating the exposure of the drug in the body to the dosing regimen seems natural, but has not been given as much consideration as it deserves. Other aspects of the diversity of the population also need to be taken into account. Currently, the two main ways of achieving this are to develop statistical models that include covariates (such as gender, age, kidney function, etc.) and to apply Bayesian methodology in model building and inference. The optimum choice of the PK sampling times in the learning and confirmatory trials, that take place in Phases II and III of drug development, can be determined by a mixture of practical and theoretical approaches.

In most trials, the collection of PK data is generally quite routine. However, in oncology or in trials involving very young children intensive PK sampling is often considered too much of a burden on a patient. These trials will be a particular focus of the PhD research. A challenging topic to be considered in this PhD project will be the development of clinical trial designs that optimize multiple success criteria (e.g., for efficacy and safety) under practical constraints (e.g., no more than 4 samples per day) as well as constraints coming from the specificity of the population of very young children. This is a topic where the application of optimum design theory has so far been quite limited.

Suitable candidates:
The successful candidate should have excellent knowledge in mathematics and statistics and very good computer programming skills. First or a very good upper second BSc (preferably also MSc) degree in Mathematics and Statistics.

Funding details:
The studentship is jointly funded by QMUL and by the pharmaceutical company Novartis (Basel, Switzerland) and will cover student fees and a tax-free stipend starting at £15,590 per annum and is available to candidates of all nationalities.

The student will be expected to visit Novartis (for up to three months over the three year period). The visits will be financially supported by Novartis.

Information about the School of Mathematical Sciences:
The School of Mathematical Sciences is one of the largest UK mathematical science departments and is one of five Schools in the Faculty of Science and Engineering at Queen Mary. The School offers energetic and diverse postgraduate activity across the spectrum of mathematical sciences from pure and applied mathematics to statistics. Our staff includes international leaders in many areas of mathematical research, and the School is a hive of activity, providing a vibrant postgraduate life. For more information about the School please see http://www.maths.qmul.ac.uk/

Contact:
Informal enquiries can be made by email to Barbara Bogacka, B.Bogacka@qmul.ac.uk

How to apply:
To apply for this studentship and for entry on to the mathematics research programme please fill in online application form at http://www.qmul.ac.uk/postgraduate/applyresearchdegrees/index.html

If you have any queries regarding the application process please contact the postgraduate administrative officer (maths-pg@qmul.ac.uk / +44 (0)20 7882 5454).

Application deadline:
Deadline for applications is 31st January 2012.