

Applications for 2012/13 entry welcome!

**PhD Project in Statistics
in co-operation with the pharmaceutical company Novartis in Basel, Switzerland.**

Supervisors: Dr Barbara Bogacka (QMUL), Prof. Byron Jones (Novartis, QMUL)

"Optimum Design for Pharmacokinetic Sampling and Dose-level Allocation in Phase II/III Clinical Trials"

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 development (Phase III).

The Phase III trials are meant to provide convincing evidence to regulatory agencies that the drug is safe and effective at the chosen doses. However, despite advances in the development of statistical methodology that help increase the success of drug development programmes, there are still important areas where better methodology is needed. One such area, which this PhD project will address, is the improved selection of doses. 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. Although the application of mathematical models is a growing trend in the field, it is pursued more in academic institutions than in industry. A collaboration between academia and industry is needed to cross-learn about the usage and development of such statistical methods and the practical requirements and constraints for their application.

One of these methods, and an important one, is the theory of optimum design of experiments. Although the application of this theory is not widely used within the pharmaceutical industry generally, there is a growing trend for its use and an appreciation of its utility for the design and analysis of clinical trials. Although much has been done for trials where doses are increased in a formal, staggered manner, not all possible information is utilized to determine the next dose in the escalation pattern. 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. The goal of such approaches is often multi-purpose: parameter estimation, population PK modelling and PK/PD modelling. Pharmacodynamic (PD) models aim to explain the effect a drug has on a patient in terms of the response observed, e.g., pain relief in migraine or lowering of blood pressure in hypertension. In most trials, the collection of PK data is generally quite routine. However, in oncology trials, intensive PK sampling, particularly multiple samples within a day, is often considered too much of a burden on a patient. Therefore, multiple blood samples are often taken from a small sub-population of patients and for all the remaining patients, the trough concentration samples at selected visits are collected. 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). This is a topic where the application of optimum design theory has so far been quite limited.

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