



Design of Experiments in Medicine (and AGM) - Chandler House (UCL)

Wednesday 23rd November 2016

This meeting, with the theme of Design of Experiments in Medicine, will include the Presidential Address by John Matthews and be preceded by the AGM.

Location: Chandler House (UCL), 2 Wakefield Street, London, WC1N 1PY

Closest Stations: Kings Cross Overground and Russell Square Underground (both within 10 minutes walk).

(Please note, the venue has been changed from Birkbeck College)

[Google Maps](#)

Programme

13:00 -
13:30 **2016 AGM for the IBS British & Irish Region**

John Matthews (Newcastle University)
Stepped Wedge - Cluster or Crossover?

13:30 -
14:10 Stepped wedge designs (SWDs) have received considerable attention recently, as they are potentially a useful way to assess new treatments in areas such as health services implementation. They have largely arisen from areas where cluster-randomized designs are usually necessary and are often discussed as special forms of such designs. While this is certainly true, they also have much in common with crossover trials: they follow a particular design, with periods and sequences; they also permit within-cluster comparisons, analogous to the within-patient contrasts that are central to crossover designs. This talk will explore what insights can be gained into stepped wedge designs by viewing them from the perspective of crossover trials and designed experiments more generally. The opportunity will also be taken to comment on the position of design of experiments in the various curricula which underpin the training of statisticians.

Rosemary Bailey (University of St Andrews),

Design of dose-escalation trials: Research spurred by a trial that went wrong

14:10 -
14:45 In March 2006 the topic of designed experiments briefly hit the British newspaper headlines when a clinical trial near London went badly wrong. When a working party of the Royal Statistical Society looked into this, my experience from designing experiments in other areas, such as agricultural field trials and microarray experiments, proved useful in improving the design of dose-escalation trials to obtain better information without compromising safety or using more volunteers. I shall say something about the recommendations of the RSS working party, something about the ethical constraints on Phase I clinical trials, and something about the new designs.

Lisa Hampson (AstraZeneca & Lancaster University)

Optimal data combination rules in seamless Phase II/III clinical trials

14:45 -
15:10

We consider seamless Phase II/III clinical trials which compare K treatments against a common control in stage 1 and select the most promising for further testing against control in stage 2. Such a trial requires careful upfront planning if it is to win regulatory acceptance as a pivotal study. For seamless trials to be attractive, this increased planning should be offset by efficiency gains made possible because data accumulated across the study are combined to make a final decision on the efficacy of the selected treatment.

We derive optimal versions of final decision rules maximising power. Rules with the correct familywise error rate maximising power for different configurations of means are found as solutions to Bayes decision problems. Different solutions are found as the shape of the mean vector changes but we find only small gains in power are possible by making strong assumptions about the structure of the mean vector. By studying procedures with optimal decision rules, we can assess the efficiency of alternative proposals, namely closed testing procedures based on p-value combination rules. For procedures with efficient decision rules, we find that Phase II observations on the selected treatment and control retain between 22-98% of their value as Phase III observations. Thus, efficient seamless designs can offer large savings in sample size which may have important implications, for example, for the feasibility of trials in rare diseases.

15:10 -
15:40

Tea & coffee

Steve Gilmour (Kings College London) & Rebecca Walwyn (University of Leeds)

Building on design of experiments methodology for clinical trials of complex interventions

15:40 -
16:15

Complex healthcare interventions, such as psychotherapy and surgery, are widely described as 'interventions that contain several interacting components'. This recognises them as multi-component but such interventions are often represented by a single treatment variable in the analysis, just as a drug would be in a conventional drug trial. More recently, it has been argued that intervention packages should be represented by multiple treatment variables, allowing these to interact, using factorial and response-surface experimental designs. This addressed the first feature of intervention complexity highlighted by the Medical Research Council, namely the number of interacting components, but it does not address all four features of intervention complexity. Building on design of experiments methodology, we will describe how the need to characterise delivery, the degree of tailoring and the potential levels at which interventions might work could also be addressed, illustrating these with examples. The required methods from design theory will be outlined. We will suggest that new experimental designs are needed that simultaneously handle all four of the complexities outlined by the MRC, discussing how these might be developed.

Tomas Jaki (Lancaster University)

Optimal Designs for Multi-arm Multi-stage Clinical Trials

16:15 -
16:40

In early stages of drug development there often is uncertainty about the most promising among a set of different treatments. These distinct treatments could be different doses of the same drug or different combinations of drugs. In order to ensure the best use of resources in such situations it is important to decide which, if any, of the treatments should be taken forward for further testing. There is a range of well established fixed sample methods for evaluating several treatments against control simultaneously. In the light of efficient decision making, however, it may be desirable to monitor the trial at a series of interim analyses in order to allow early stopping if efficacy is quickly established and similarly to eliminate ineffective treatments early.

In this talk we discuss optimal design of multi-arm, multi-stage (MAMS) designs whose advantage lies in the efficient evaluation of several treatments. By comparing several treatments within one trial the sample size and duration required tends to be markedly smaller than if each treatment would have been evaluated separately. Moreover a direct, head-to-head, comparison of treatments is undertaken that ensures that many potentially influential outside factors are eliminated.

The specification of such MAMS designs, however, involves many different tuning parameters, such efficacy/futility boundaries and allocation ratio, making it difficult to find the best among the many different designs available. In this talk we will introduce a method for identifying optimal designs based on stochastic search and show that triangular boundaries are quick to find and close to optimal. A more time-intensive procedure yields designs with somewhat better properties but becomes infeasible for a moderate number of stages.