Lancaster University, UK

Senior Research Associate or Research Associate within the Medical and Pharmaceutical Statistics Research Unit

Reference: A429
Department: Mathematics and Statistics
Closing Date: Monday 25 June 2012
Interview Date: Tuesday 10 July 2012
Salary: £25,251 to £35,938

The Medical and Pharmaceutical Statistics Research Unit (MPS) (www.mps-research.com) is directed by Professor Anne Whitehead and undertakes collaborative research with the pharmaceutical industry and medical research institutes. The post is offered for a two year period in the first instance. MPS is funded by grants from the MRC North West Hub for Trials Methodology Research (NWHTMR), the US National Institutes of Health (NIH) and various pharmaceutical companies. The NWHTMR is a collaboration between the Universities of Liverpool, Lancaster and Bangor in which the Unit leads the theme on the design and analysis of early phase clinical trials. You will work on the NWHTMR project concerning the use of statistical methods to improve the design of early phase paediatric trials and input to other MPS research projects. You will also become involved in professional development courses associated with your expertise.
The Medical and Pharmaceutical Statistics Research Unit

MPS is part of the Department of Mathematics and Statistics which includes one of the largest and strongest statistics research groups in the UK comprising 18 academic staff, 7 research associates and 32 FTE research students. Research interests in the Department include the development of statistical methodology such as Markov chain Monte Carlo, particle filtering, extreme value theory, wavelets and the analysis of longitudinal and spatial data. Application interests include medicine, industry and the social sciences. The Department provides an MSc in Statistics which prepares students for professional and research careers in statistics, particularly in medical applications. The person appointed will thus join a thriving statistics research community in which they will be able to widen and deepen their statistical skills.

The objectives of MPS are to develop and evaluate novel methods of study design and data analysis relevant to pharmaceutical companies and medical research institutes. MPS is funded by grants from the public sector and various pharmaceutical companies, and earnings from the provision of consultancy and professional development courses related to our research.

Further information about the NWHTMR, which is led from the University of Liverpool, may be found at http://www.liv.ac.uk/nwhtmr/.

Current research interests of MPS include

- Bayesian procedures for phase I/II dose-finding trials
- Design strategies for phase II clinical trials
- Dynamic approaches for the detection and exploitation of drug by genome interactions
- Meta-analysis of Clinical Trials

The Research Associate post

You will work on the NWHTMR project concerning the use of statistical methods to improve the design of early phase paediatric trials and input to other MPS research projects. Details of the NWHTMR project and the current research interests of MPS are provided below.
NWHTMR Project: Using Bayesian methods to improve the design of early phase studies in epilepsy

Recent regulatory changes place greater emphasis on ensuring that medicines used to treat children have undergone rigorous examination and are appropriately authorised for use in this patient group. Clinical trials are predominantly carried out in adults. With few paediatric trials being conducted it is estimated that over 50% of medicines prescribed in the EU to children are unauthorised for paediatric use. To encourage more high quality industry-sponsored trials in children, the EU Regulation on Medicines for Paediatric Use made testing new products in children mandatory from 2008 onwards if regulatory approval was to be granted for the product in adults. The optimal dose of a new medicine in children will often differ from that used in adults because the ways in which the body breaks down and reacts to a drug may change subtly as it matures. Therefore using adult data to infer the optimal dose in children can lead to medicines being prescribed at ineffective or toxic doses. It is imperative that prescribing decisions in children are supported by evidence from well-designed clinical trials in this patient group.

The project will start with a literature review of current approaches used in practice (in any indication) to justify the extrapolation (or ‘bridging’) of clinical efficacy data from adults to children. The second part of the project will focus on epilepsy trials and will explore and develop methods for identifying the number of subgroups in the paediatric population with different drug concentration-response curves. The aim is that such methods would form part of a formal strategy for optimising the future research strategy in children. Methods based on the concentration-response models presented in Girgis et al. (2010) and Nedelman et al. (2007), which support bridging arguments for two adjunctive therapies in epilepsy, will be developed and evaluated.

References

Current research interests of MPS

Bayesian procedures for phase I/II dose-finding trials

The development of statistical procedures for phase I dose-finding studies has long been a research interest of MPS. Early work [1] concerned methods for evaluating a single novel agent available at a number of doses administered to subjects participating in a single treatment period and returning a single binary indicator of toxicity. Such a structure is common when evaluating cytotoxic drugs for cancer. Unlike the Continual Reassessment Method, doses are chosen on the basis of a two-parameter logistic regression model. An informative prior is imposed that ensures that the lowest dose is tried first and that there is an appropriate reaction to observed toxicities. A similar approach was then taken to healthy volunteer studies in which subjects participate in several treatment periods, receive different doses, and provide a continuous pharmacokinetic response [2]. The approach was successfully implemented in a trial conducted in Scandinavia [3]. More recently, we have been exploring procedures in which no functional form is given to the relationship between responses and dose, only monotonicity is assumed. This approach has applied to the situation originally explored, in which patients return a single binary response [4]. It has also been generalised to studies of combinations of two agents in which both toxicity and benefit are observed as correlated binary outcomes [5]. This last case allows the objectives of phase I and early phase II studies to be addressed in a single trial.

References

Design strategies for phase II clinical trials

There is a growing awareness of the need for careful evaluation of novel medical therapies prior to the conduct of a major, definitive clinical trial. The former stage comprises phase II studies intended to determine whether the treatment shows sufficient promise to justify the resources needed for phase III and studies to select which treatment and which dose to take forward to large scale trials. Often, the definitive clinical assessment of a treatment is not possible until the end of a lengthy follow up period, and phase II decisions have to be based on observation of intermediate endpoints that are indicative of benefit. In cancer studies the conventional approach is to treat all trial patients with the experimental compound and to observe whether the tumour responds by shrinking in size. Two-stage designs have long been used for such studies, and recent MPS research [1] has focussed on exact approaches to the subsequent trial analysis, allowing for the small sample size and the interim look at the data. In other therapeutic areas, phase II trials randomise between the experimental treatment and a control, and responses are often continuous. Two-stage designs allowing for early stopping and sample size revision have been developed [2] and simple SAS programs for two-stage and multi-stage designs have been created [3]. Other research has investigated how databases of clinical outcome data can be used to relate intermediate outcomes to longer-term clinical responses to help in setting the sample size for phase II [4], and designs for the selection of treatments for phase III amongst several candidates [5].

References

Dynamic approaches for the detection and exploitation of drug by genome interactions

The incidence of adverse drug reactions during a clinical drug development programme can lead to abandoning treatments that have the potential for benefitting many patients. Sometimes it is only a minority of patients who are at risk of such reactions, and sometimes these patients can be identified through genetic features present in the genome. This strand of MPS research started with the challenge of finding a sequential procedure to detect the presence of an interaction between a drug and the genome which meant that a certain genetic subgroup of patients were at an elevated risk of suffering an adverse reaction. A procedure which could quickly lead to a signal during the course of a clinical trial or series of trials, and which and a controlled risk of giving a false signal was developed [1]. Once such an interaction has been established, attention turns to the identification of which SNP or set of SNPs within the genome is associated with elevated risk [2, 3]. The practical question of which patients to exclude if the trial programme is to continue, and how to update the exclusion rule as further reactions are observed was also considered [4]. A related problem that has been investigated is that of identifying genetic subgroups which respond positively to drug treatment, with the potential for recommending the treatment only for that subgroup [5].

References

Meta-analysis of Clinical Trials

Over the last thirty years, the numbers of published health-related meta-analyses has grown tremendously. This has been mainly due to greater emphasis on evidence-based medicine and the need for reliable summaries of the vast and expanding volume of clinical research. MPS has had a long-term interest in developing methodology for meta-analysis and in the conduct of such analyses. Methods for conducting meta-analyses based either on summary statistics extracted from publications or on individual patient data are presented within a general framework in [1]. Examples of applications include a meta-analysis of individual patient data from randomised controlled trials of Donepezil for the treatment of Alzheimer’s disease [2] and a systematic review on injury prevention programmes and strategies for older people with cognitive impairment and dementia in hospital and care home settings [3]. Recent research has addressed the issue of meta-analyses of studies in which repeated observations have been made on subjects at different time points across studies [4]. Problems arise when only summary data from published papers are available, and consideration needs to be given to the handling of correlation between time points and missing observations. Another research area concerns cumulative meta-analysis, where the meta-analysis is updated after new studies are completed. The updating of meta-analyses needs to account for the possibility of false-positive findings due to repeated significance tests. Sequential methods incorporating random effects to allow for heterogeneity across studies, using an approximate semi-Bayes procedure to update evidence on the heterogeneity, have been proposed [5].

Qualifications: Candidates should hold a PhD in statistics and/or have research experience in statistics relevant to clinical trials.

Experience of teaching and programming skills using software such as SAS and R are desirable, but training on these aspects of the job can be provided.

Starting date: 1 September 2012 or as soon as possible thereafter.

For further information about the post, please call Professor Anne Whitehead on 01524 594282, e-mail p.a.whitehead@lancaster.ac.uk

Further details on how to apply for the post can be found at

http://hr-jobs.lancs.ac.uk/Vacancy.aspx?ref=A429

This appointment will be to either a Senior Research Associate (Grade 7) or a Research Associate (Grade 6).

Closing date for applications 25 June 2012 and interviews are planned for 10 July 2012.