Subject: PhD Studentship: Design, Trials and Statistics Group;

University of Sheffield

The Design, Trials and Statistics (DTS) group, at the School of Health and Related Research (ScHARR), University of Sheffield has a fully funded PhD studentship available, to start in September/October 2013, in ONE of the eight projects listed below. The deadline for applications is Friday 14th June 2013.

Design, Trials and Statistics (DTS) is a section within the School of Health and Related Research (ScHARR) and consists of three subgroups: the NIHR Research Design Service for Yorkshire and the Humber (RDS YH); the Clinical Trials Research Unit (CTRU); and the Medical Statistics Group (MSG). The section is involved with the design, conduct, data processing, statistical analysis and reporting of high quality randomised controlled trials (RCTs) and other studies to evaluate the clinical and cost-effectiveness of new services, therapies and health technologies. The Section has over 50 members of staff and attracts in excess of £3.2 million of research funding every year.

Project titles:

1. **Prediction of future trials** (Supervisor: Professor Steven A. Julious; s.a.julious@sheffield.ac.uk)
2. **Sample Sizes for Studies with an Accelerated Failure Time Endpoint** (Supervisor: Professor Steven A. Julious; s.a.julious@sheffield.ac.uk)
3. **Non-Inferiority Margin Setting from Indirect Comparisons** (Supervisor: Professor Steven A. Julious; s.a.julious@sheffield.ac.uk)
4. **Validation and updating lung cancer risk models.** (Supervisor: Dr Dawn Teare; m.d.teare@sheffield.ac.uk)
5. **Standardising institutions for case-mix** (Supervisor: Professor Michael Campbell; m.j.campbell@sheffield.ac.uk)
6. **Clustering by health professional in individually randomised controlled trials (iRCTs)** (Supervisor: Professor Stephen J Walters; s.j.walters@sheffield.ac.uk)
7. **Covariates to include in the imputation of missing outcome data (**(Supervisor: Professor Stephen J Walters; s.j.walters@sheffield.ac.uk)
8. **Predicting consent, recruitment and attrition rates for single and multi-centre RCTs** (Supervisor: Professor Stephen J Walters; s.j.walters@sheffield.ac.uk)

Further details about the projects are given below or at
http://sheffield.ac.uk/scharr/sections/dts/statistics

Applications:

Applicants should hold (or expect to obtain) a minimum upper-second honours degree (or equivalent) in mathematics, statistics or related area. A Masters degree in statistics or medical statistics would be an advantage.

This 3-year full-time studentship will provide full support for tuition fees, an annual tax-free stipend of £13,590. The project is available to UK/EU nationals only due to the nature of the funding and is due to start September/October 2013.

Enquiries

For general enquiries about the PhD studentship interested candidates should contact Professor Michael Campbell m.j.campbell@sheffield.ac.uk. For specific enquiries about individual projects interested candidates should contact the potential supervisor.

How to apply:

You can apply for postgraduate study, at the University of Sheffield, by using the Postgraduate Online Application Form. Please complete the online Postgraduate Research Application form and provide at least two references. To access the online application form please visit:

http://www.sheffield.ac.uk/postgraduate/research/apply/applying

Please clearly state the prospective main supervisor in the respective box.

Prediction of future trials

Supervisor: Professor Steven A. Julious s.a.julious@sheffield.ac.uk

Project:

Methods have been approached that allow you to predict the results of a trial based on the results in another study [Julious et al]. the issues with these proposals, however, is that they ignore the sequential nature of trials – the fact the second study may only take place if the first study is statistically significant. An additional complication is that the first study may be a pilot investigation (in a small number of subjects with tight inclusion criteria) while the second could be a definitive study (more representative of the patient population) which would only start depending on the results of the first study. This project will look at how to predict future trials and will investigate how the sequential nature of trials can influence their predictability. It will apply the results using publicly available retrospective data from regulatory submissions for a number of compounds

Julious SA, Walters SJ and Campbell MJ. Predicting where future means will lie based on the results of the current trial. Contemporary Clinical Trials 2007;28:352-7

Sample Sizes for Studies with an Accelerated Failure Time Endpoint

Supervisor: Professor Steven A. Julious s.a.julious@sheffield.ac.uk

Project:

Trials with a survival endpoint can be simply divided into two: trials where the wish is to slow the time to the event, in which case a proportional hazards approach is taken, and trials where the wish is to speed up time to the event, in which case an accelerated failure time approach is used. In the former case, a Log-Rank test would be the primary analysis, and in the latter case it would be a Generalized Wilcoxon Test. For the Log-Rank test the methods for sample size calculations are relatively straightforward, assuming proportional hazards and possibly exponential survival time [Julious, 2009]. For the Generalized Wilcoxon test the situation is relatively straightforward when individual patient data is in hand and not so straightforward when there is no individual patient data [Julious 2009]. With access to individual patient data, methods for calculating sample sizes include those of Whitehead(1993) and Noether(1987), both of which require the removal of censored data. If censored data are to be included a bootstrap method can be used.

This project will review the current methods for sample size calculations for the number of events in a trial and investigate approaches for the for the calculation sample sizes for accelerated failure time models in which individual patient data is not available. on.

Once the number of events have been calculate and estimate of the total sample size is required. For sample size calculations for the Log-Rank test methods that model the rate of patient accrual assuming uniform accrual or truncated exponential are used. It will be investigated if these can be extended to the situation with accelerated failure time.

Throughout the dissertation will be a number of case studies will be used to illustrate the calculations.

Julious SA, “Sample Sizes For Clinical Trials”, Chapman and Hall 2009.

Non-Inferiority Margin Setting from Indirect Comparisons

Supervisor: Professor Steven A. Julious s.a.julious@sheffield.ac.uk

Project:

In a non-inferiority trial to assess a new investigative treatment there may need to be consideration of an indirect comparison with placebo using the active control in the current trial. We can therefore use the fact that both there is a common active control make comparisons the investigative treatment and placebo. In analysing a non-inferiority trial, the ABC of: Assay sensitivity; Bias minimisation and Constancy assumption; needs to be considered. Often though there can be an effect called placebo creep – where the effect over placebo falls over time making the ABC assumptions implausible.

The proposed research plan would be to undertake a review of the statistical literature on various types of setting non-inferiority limits and to investigate the effect of placebo creep from publish systematic reviews with the view to develop new methods.

Validation and updating lung cancer risk models.

Supervisor: Dr Dawn Teare m.d.teare@sheffield.ac.uk

Project

Robust risk prediction models are important tools frequently used to support clinical decisions. Such models are already in use in lung cancer prevention to identify subjects who would benefit from screening[1, 2]. The continuing improvement of lung cancer risk models is important to ensure accurate and robust lung cancer risk stratification as a first step to screening activities leading to earlier detection and improved survival. Several lung cancer risk prediction models have been developed, however, each of these models has been formed within a specific study population making it potentially difficult to interpret results when applying to a new population. Recently researchers have examined the transferability of some risk models to new populations (3,4).

While it can be relatively straightforward to develop and propose a risk model, the recognized concern over lack of generalisability often leads to new teams of researchers building their own models from scratch. This in turn leads to the development of many prediction models and a new practitioner may have little real guidance on which model is best for the specific scenario she is considering [5].

The contributing studies which make up the ILCCO consortium present a powerful opportunity to evaluate the performance of existing risk prediction models in a wide variety of study populations. ILCCO was established in 2004 and now has membership representing over 60 international lung cancer studies (case-control and cohort) studies. From this total of 60 studies there are in excess of 60,000 lung cancer cases and controls.

The main aims of this project are: 1) To identify and systematically review all lung cancer risk prediction models; 2) To evaluate the performance of existing lung cancer models when applied to study populations similar and distinct to the model development study characteristics; 3) To identify and formulate a better lung cancer risk model and thereby offer a more powerful tool to stratify screening populations into risk groups for lung cancer.

References

1. Duffy, S.W., et al., Use of lung cancer risk models in planning research and service programs in CT screening for lung cancer. Expert Review of Anticancer Therapy, 2009. 9(10): p. 1467-1472.

2. Maisonneuve, P., et al., Lung Cancer Risk Prediction to Select Smokers for Screening CT-a Model Based on the Italian COSMOS Trial. Cancer Prevention Research, 2012. 4(11): p. 1778-1789.

3. D'Amelio, A.M., Jr., et al., Comparison of discriminatory power and accuracy of three lung cancer risk models. British Journal of Cancer, 2010. 103(3): p. 423-429.

4. Etzel, C.J., et al., Development and Validation of a Lung Cancer Risk Prediction Model for African-Americans. Cancer Prevention Research, 2008. 1(4): p. 255-265.

5. Moons, K.G.M., et al., Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart, 2012. 98(9): p. 683-690.

Standardising institutions for case-mix

Supervisor Professor Michael Campbell m.j.campbell@sheffield.ac.uk

Project

When the death rates from two institutions are compared, one has to allow for differing characteristics of the populations attending these institutions. For example to compare two hospitals, one needs to account for the age, sex and type of disease in the patients treated by the hospitals. One would not want to penalise one hospital simply because it admitted patients who were sicker. One issue is the constant risk fallacy, which means that a risk factor may have a different effect in one hospital compared with another. Thus in Sheffield the risk of dying for a particular age group is different in different parts of the city. We have data from over 30,000,000 admissions to hospital of whom about 4% died within 30 days of admission. The project would be to investigate how to standardise by different case mix, and whether the constant risk fallacy matters in practice. The project suitable for someone with a quantitative background, and familiar with data processing.

Reference: Campbell MJ, Jacques RM, Fotheringham J, Maheswaran R, Nicholl J (2012) Developing a summary hospital mortality index: retrospective analysis in English hospitals over five years. BMJ doi=10.1136/bmj.e1001

Clustering by health professional in individually randomised controlled trials (iRCTs)

Supervisor: Professor Stephen J Walters s.j.walters@sheffield.ac.uk

Project

In an individually randomised controlled trial (iRCT) where the intervention is delivered by a health professional it seems likely that the effectiveness of the intervention, independent of any treatment effect, could depend on the skill, training or even enthusiasm of the health professional delivering it. This may then lead to a potential clustering of the observations or outcomes for patients treated by the same health professional. If we believe that the observations may be clustered then the usual statistical methods for analysing an RCT, for example an independent two sample t-test, to compare the mean outcomes between the intervention and control groups, may not be appropriate as they assume that the observed outcomes on different patients are independent lack of independence among the outcomes can lead to inflated standard errors, P-values and wider confidence intervals and a reduction in the effective sample size, which leads to a reduction in the power of the study.

The proposed research plan would be to undertake a review of the statistical literature on adjusting for clustering by health professional in iRCTs; followed by an audit of recently published iRCT with health professional lead interventions to determine what analyses are commonly in used. This project would describe and estimate the cluster effect from a variety of iRCT datasets where the intervention is delivered by a health professional. The project would then involve some computer simulation and analysis to compare the power of standard methods (such as the t-test and linear regression), to detect a treatment effect, compared with alternative methods (such as random-effect and marginal general linear models) when there is clustering.

Walters S.J. Therapist effects in randomised controlled trials: what to do about them. Journal of Clinical Nursing 2010; 19(7-8): 1102-1112.

Lee KJ & Thompson SG. (2005) The use of random effect models to allow for clustering in individually randomized trials. Clinical Trials 2, 163–173

Roberts C. (1999) The implications of variation in outcome between health professionals for the design and analysis of randomized controlled trials. Statistics in Medicine 18, 2605–2615.

Covariates to include in the imputation of missing outcome data

Supervisor: Professor Stephen J Walters s.j.walters@sheffield.ac.uk

Project

Missing data exists in almost every clinical trial and are almost unavoidable in research. Missing data may bias the results of a study. Missing data presents statistical issues when estimating treatment effects. Patient Reported Outcome measures (PROMs) are becoming increasingly used in clinical research. PROMs typically have several dimensions and use multiple items to measure these dimensions. Missing items are more likely to occur with PROM data than with clinical data as most PROMs are self-completed and patients may refuse to answer some or all of the items. Missing PROM values may be imputed.

There are several different methods for imputing missing PROM data: Simple mean, Last Observation Carried Forward (LOCF), Horizontal mean, regression, Markov chain, hot deck, multiple linear regression imputation, predictive mean matching, multiple imputation, monotonic multiple imputation and multivariate Normal imputation. The regulators regard most imputation methods as imperfect. However, they recommend: specifying imputation methods in advance in the protocol/statistical analysis plan; imputing missing PROM items according to instrument developer's guidelines; using several imputation methods with a sensitivity analysis of the results. It is desirable to report analyses with and without imputation and to explore different imputations techniques in order that intention to treat analysis can be performed.

For some of the imputation methods such as LOCF the randomised treatment group is effectively included in the model. For other imputation methods such as: Markov Chain; hot deck; multiple linear regression imputation; predictive mean matching; multiple imputation; monotonic multiple imputation and multivariate normal imputation the statistician has to make a decision about whether or not to include the randomised treatment group as covariate in the imputation model/method.

The proposed research plan would be to undertake a review of the statistical literature on methods for imputing missing data in RCTs and in particular whether or not to include randomised treatment group as a covariate in the imputation; followed by an audit of recently published RCTs to determine what imputation methods are commonly in used and whether or not the treatment group is included as a covariate in the imputation process. The imputation methods and their effect on statistical analysis and conclusions will be compared using the data from several RCTs with PROMs. The project would then involve some computer simulation and analysis to compare the different methods of imputation (with and without the randomised treatment group as a covariate) with the view to developing guidance on whether or not to include the treatment group as a covariate in the imputation model.

Predicting consent, recruitment and attrition rates for single and multi-centre RCTs

Supervisor: Professor Stephen J Walters s.j.walters@sheffield.ac.uk

Project

In 2010/11, the National Institute for Health Research (NIHR) funded £210.5 million of research grants across a broad range of programmes and initiatives to ensure that patients and the public benefit from the most cost effective, up-to-date health interventions and treatments as quickly as possible (NIHR Annual Report). A substantial proportion of these research grants were for Randomised Controlled Trials (RCTs) to assess the clinical effectiveness and cost-effectiveness of new health technologies. RCTs are widely regarded as the most powerful research design for evaluating new health technologies and decision makers, such as NICE, are increasingly looking to the results of RCTs to guide practice and policy.

A frequently reported problem with publicly funded RCTs is that the recruitment of participants is often slower or more difficult than expected, with many trials falling to reach their planned sample size within the originally envisaged trial timescale and trial funding envelope. The National Institute for Health Research (NIHR) has funded studies that, at the design and application stage, have been overly optimistic about the number of eligible patients, consent rates, recruitment rates and retention/attrition rates. Consequently, these studies have failed to recruit on time and on target. The investigators have been forced to ask the NIHR programme for an extension in both time and extra money to successfully complete the study. A review of a cohort of 122 trials funded by the UK Medical Research Council and the NIHR Health Technology Assessment programme (HTA) found that less than a third (31%) of the trials achieved their original patient recruitment target; 55/122 (45.1%) achieved less than 80% of their original target and half (53%) were awarded an extension (McDonald et al 2006).

The CONSORT statement is a set of standards for publication of results of RCTS in medical journals. They are both for the article itself and the article abstract (Schulz et al 2010). The CONSORT statement includes details of the number of eligible patients; number of patients randomised; number of recruiting centres and recruitment time period (start and finish time of recruitment).

The proposed research plan would be to undertake a review of the literature on what factors influence consent, recruitment and attrition in RCTs; followed by an audit of articles in leading medical journals to assess the consent, recruitment and attrition rates for single and multi-centre RCTs using the CONSORT checklist. The audit will assess whether any factors influence the consent, recruitment and attrition rates for such trials such as: source of funding (industry or publicly funded); number of centres; population/disease; affiliation of authors; type of intervention (drug or non-drug). The project would try and develop a statistical model to predict consent and recruitment, and attrition rates for future RCTs; and compare this with the rates observed in several on-going RCTs at the Sheffield CTRU; with the view to developing guidance on realistic consent, recruitment and attrition rates to RCTs.

References

McDonald AM et al. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. Trials. 2006; 7: 9. Published online 2006 April 7. doi: 10.1186/1745-6215-7-9.

National Institute for Health Research Annual Report 2010/11.

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.