Speaker Abstracts

CANNeCTIN Cutting Edge Symposium on Advanced Biostatistics and Methodological Issues in Clinical Trials

April 28-29, 2011

Summary of Talks

Role	April 28, 2011 Early Morning Session: 8:00 - 10:00 am	April 28, 2011 Late Morning Session: 10:20 - 12:20 am	April 29, 2011 Early Morning Session: 8:00 - 10:00 am
Chairs	Anne Holbrook	Stuart Connolly	Stan Shapiro
Speakers	1. Gordon Guyatt (Overview[1]) 2. Richard Cook 3. Nick Freemantle	1. Ralph B. D'Agostino (Overview) 2. George Wells 3. Victor De Gruttola	1. Hsien-Ming James Hung (Overview) 2. Robert Noble 3. Theodore G Karrison
Topic	Composite Outcomes	Surrogate Outcomes	Adaptive Designs
Objectives	• To discuss the methodological issues in using composite outcomes in trials • To discuss the knowledge gaps in using composite outcomes • To discuss the cautions to be heeded in using composite outcomes in trials	• To discuss the methodological issues in using surrogate outcomes in trials • To discuss the knowledge gaps in using surrogate outcomes • To discuss the cautions to be heeded in using surrogate outcomes in trials	• To discuss the pros and cos of adaptive designs vs traditional diesigns; • Discuss the necessary operational infrastructure for using adaptive designs • To discuss knowledge gaps in applications of adaptive designs;

[1] *The first presentation (by first speaker) will provide an overview of the key issues on the topic*

COMPOSITE OUTCOMES: April 28th 8:00 – 10:00 am

"Issues in Measurement of Composite Endpoints"

Speaker: Dr Gordon Guyatt (McMaster University)
Professor of Department of Clinical Epidemiology & Biostatistics
Joint Member of Department of Medicine

Abstract: When a trial specifies an outcome with a number of components (e.g. death, myocardial infarction, and stroke) and the occurrence of any one component counts as an event, we refer to the outcome as a composite. Reasons for use of composite outcomes in clinical trials include dealing with competing risks, capturing both the desirable and undesirable consequences of an intervention in a single measure, and reducing sample size requirements. The last is by far the most common reason for use of a composite endpoint.

The reason the composite endpoints issue is important is first because their use is epidemic, particularly in cardiology trials, and second because the interpretation of composite outcomes can be problematic. Interpreting the results of a composite outcome becomes increasingly problematic as the component outcomes vary in importance, as the most important components become less frequent in relation to the less important components, and as the apparent effect differs across components. Interpretation of results of individual trials and meta-analyses should often focus on component outcomes even when individual trials have specified composites as their "primary outcome".

"The Challenge in Interpreting Treatment Effects Based on Composite Endpoints"

Speaker: Dr Richard Cook (University of Waterloo)
Canada Research Chair in Statistical Methods for Health Research
Department of Statistics and Actuarial Science
Collaborators: Longyang Wu (University of Waterloo)

Abstract: Despite the widespread use of composite endpoints in large clinical trials, there has been relatively little attention paid to the statistical properties of associated estimators of treatment effect and the difficulties in interpreting them. Guidelines on the use of composite endpoints suggest that the components endpoints should be of comparable importance and the treatment effect across the components should be comparable in size. We formulate bivariate survival models using copula functions to link marginal distributions in which each marginal distribution features a proportional hazards regression model. A Cox regression model for the time to the first of these two events is adopted in composite endpoint analysis, and we examine the properties of the estimator arising from the corresponding Cox regression model.We point out that even when the treatment effect is the same for the two component events, under the current guidelines, what is being estimated with a composite endpoint analysis is inconsistent for this common value. Marginal methods for the analysis of multivariate failure time data yield consistent estimators of treatment effect and may therefore be preferred.

"Composite Outcome Measures – Does the devil hath power to assume a pleasing shape?"

Speaker: Dr Nick Freemantle (University College London)
Professor of Clinical Epidemiology & Biostatistics
Department of Primary Care and Population Sciences

Abstract: Composite outcome measures have been used commonly in regulatory trials for many years, although they continue to attract criticism. Properly defined, composite outcomes may have some advantages, particularly in improving the efficiency of trials in achieving their main objective, and in avoiding arbitrary decisions between different candidate component outcomes of potential interest. Composite outcomes certainly can also have some disadvantages, particularly in interpretation, as the results of an analysis of a composite apply to the cluster of events included and not to the individual components.

In the regulatory setting there have been many examples where composite outcomes were 'gamed' for the benefit of industry, and regulators may have been slow to develop a sensible approach to their interpretation (which could be an example of regulatory capture?). However this appears no longer the case and a recent example of judicious process will be discussed.

Some illusory properties of composite outcomes will be addressed, in particular relating to the extent to which we may interpret them. These will include: the erroneous suggestion that component outcomes should be of similar patient importance; the fallacious assertion that tests for heterogeneity in response among components of composite outcomes should in some way inform us on their interpretation.

Although regulators do seem to have developed thoughtful approaches to the appropriate use of composite outcomes, journals have been generally much less adept at addressing this methodological question (although this may be a more generalised problem). In order to assist journal editors in addressing this task there may be a case for some kind of CONSORT statement for composite outcomes. However to achieve and implement such a statement will require broad consensus on how to proceed, and it is not clear that we have reached that point.

SURROGATE OUTCOMES: April 28th 10:20 am – 12:20 pm

"Surrogate Variables: Background to the Major Issues on the Role of Surrogate Variables in Clinical Trials"

Speaker: Dr Ralph D'Agostino Sr. (Boston University)
Senior Statistician, Co-Principal Investigator, Framingham Heart Study
Professor of Mathematics

Abstract: A surrogate variable (or biomarker as it is also called) in clinical trials is a laboratory measurement or physical measurement that is used as a substitute for a clinically meaningful endpoint. For example, the use of blood pressure or total cholesterol level as surrogates for the development of myocardial infarction (MI). Ideally changes in a surrogate should relate to changes in the clinically meaningful endpoint (thus the reduction in blood pressure should be a direct indication of a reduction in MI development). In this talk we will review briefly why one would use surrogate variables and some of the history of their uses in clinical trials. Further, we will also discuss criteria for a valid surrogate. Along the way, we will give examples where surrogates have been used in clinical trials – some successfully and others not.

"Meta-analytic Methods for Surrogate Outcome Evaluation Using Trial Level Data"

Speaker: Dr George Wells (University of Ottawa Heart Institute)
Professor of the Department of Epidemiology and Community Medicine
Professor in the Department of Medicine
Senior Scientist at the Ottawa Health Research Institute
Director of the Cardiovascular Research Methods Centre

Abstract: A review of the meta-analytic, statistical methods for surrogate outcome evaluation that can be applied to summary level data without requiring the availability of data from individual patients was conducted. From the 608 potentially relevant articles identified, 31 met the selection criteria for the review. Methods identified included significance testing for study-wise agreement (percent concordance), rank correlation (Spearman's rank correlation coefficient), graphical analysis, regression analysis (weighted R2, surrogate threshold effect), and mixed models (beta, delta). The methods vary in complexity and data requirements, with the weighted R2 being a good balance between data availability and statistical information.

"The Role of Network Analyses in Research on Prevention of HIV Infection"

Speaker: Dr Victor DeGruttola (Harvard School of Public Health)
Professor of Biostatistics
Chair of the Department of Biostatistics
Collaborators: Ravi Goyal (Department of Biostatistics), Joseph Blitzstein (Department of Statistics, Harvard University)

Abstract: Efforts at prevention of HIV or other infectious diseases can be aided by an understanding of the transmission networks along which infection spreads. This understanding can aid in several ways: (1) characterization of the conditions under which interventions such as treatment, chemo-prophylaxis or vaccine can succeed in controlling the HIV epidemic, (2) identification of appropriate means of tailoring implementation strategies to local conditions, and (3) determination of the level of adherence with community-wide interventions needed for successful control. However it can be challenging to identify the most valuable network features to estimate, and to obtain sufficiently reliable estimates of them, particularly in the setting of sexually transmitted infections. Currently most efforts to understand sexual networks make use of only egocentric (individual level data), which allow estimation of certain quantities of interest like degree distribution (for sexual networks, this would be distribution of number of partners) but does not allow for estimation of other relevant quantities, like assortativity (the tendency of people with many partners to have partners who do as well). This presentation will start with a discussion of how network features can improve prediction of epidemic characteristics and therefore of impact of prevention strategies, compared to egocentric data alone. We will address the question: Given all relevant ego-centric data does additional information about the underlying sexual network still improve understanding of the spread of the disease? In particular, we will investigate the impact of graphical properties on the spread of infection. We then consider estimation of network features from a sample of a network; our focus will be on estimating the degree-degree mixing matrix—a matrix that quantifies assortativity. In addition we will discuss the use of the estimated degree mixing matrix for network construction. Such construction is valuable in the development of epidemic models that can be used for testing potential value of intervention strategies though simulation. The methods will be investigated using a data set characterizing the sexual network in Likoma Island, Malawi. We also consider ways in which network-level information can be incorporated into cluster randomized trials to improve efficiency, and interpretability of results.

DINNER PRESENTATION: April 28th 5 pm

"More Transparent Decision-Making for Drug Regulation: What do Bayes and other Formal Statistical Approaches have to Offer?"

Speaker: Dr Deborah Ashby (Imperial College London)
Professor of Medical Statistics and Clinical Trials and Co-Director
Imperial Clinical Trials Unit, School of Public Health

Abstract: The regulation of medicine requires evidence of the efficacy and safety of medicines, and methods are well-developed to deal with the latter and to a lesser extent the former. However, until recently, assessment of risk- benefit especially in relation to alternatives has been entirely informal. There is now growing interest in the possibilities of more formal approaches to risk-benefit decision-making. In this talk, we review the basis of drug regulation, the statistical basis for decision-making under uncertainty, current initiatives in the area, and discuss possible approaches that could enhance the quality and transparency of regulatory decision-making.

ADAPTIVE DESIGNS: April 29th 8:00 – 10:00 am

"An Overview on Essentials of Design Adaptation in Clinical Trial"

Speaker: Dr. H. M. James Hung (US Food and Drug Administration)
Director, Division of Biometrics I, OB/OTS/CDER

Abstract: As the costs increase dramatically, a typical clinical trial is highly expected to have capability of answering many study questions and subsequently the level of difficulty in conducting the trial rises significantly. Conventional non-adaptive fixed design methodology is therefore often deemed insufficient to achieve the many goals of the trial. In recent two decades adaptive design methodology has been extensively researched for the purpose of evaluation of an experimental treatment more flexibly and meeting the many goals of a clinical trial. By adaptation, it essentially means modification of design features during the course of the trial. Many adaptation methods have been developed for re-assessment of trial size and selection of doses or patient subpopulations for study in a subsequent stage of the trial. In this presentation I shall give an overview of adaptive design methodology and the key methodological issues that are heavily involved. Logistics issues are also to be discussed. A great many of recommendations and advices by U.S. Food and Drug Administration adaptive design guidance document will be articulated.

"Points to Consider when Opting for an Adaptive Clinical Trial"

Speaker: Dr. Robert Noble (GlaxoSmithKline Pharmaceutical)
Manager of Statistics

Abstract: Adaptive clinical trials allow the flexibility to modify clinical trials at interim stages. This flexibility can provide greater efficiency in drug development and decision making. Despite this promise, commonly, there is hesitation to implement such designs. We explore three possible reasons for the hesitation: (i) confusion with respect to the definition of an 'adaptive design' and when it is appropriate; (ii) controversy surrounding the use of sample size re-estimation methods; and (iii) logistical barriers that must be addressed for compatibility of adaptive designs within existing trial frameworks.

"Response-Adaptive Randomization in Clinical Trials: Bayesian and Group-Sequential Approaches"

Speaker: Dr. Theodore Karrison (University of Chicago)
Research Associate (Assoc. Prof.) & Director Biostat Lab
Department of Health Sciences

Abstract: There has been considerable methodological research on adaptive designs for clinical trials. Berry (SIM 1993;12:1377-93, Clin Adv Hematol Oncol 2007;5(7):522-24) has been a strong advocate for the use of these designs, particularly within a Bayesian framework. However, *response*-adaptive designs, in which accumulating information on outcomes are used in order to tilt the randomization probabilities to the better performing treatment arm, have seldom been used in practice. Two main reasons for this are logistical difficulties and the potential for bias due to "drift" in patient characteristics or risk factors over time. Cheung et al. (SIM 2006;25:55-70) and Thall and Wathen (EJC 2007;43(5)859-66) have proposed continuous, Bayesian adaptive randomization (BAR) designs in which treatment assignments are based on the posterior probability that one treatment is superior to the other given the current data. Recently, Lee et al. (Clin Trials 2010;7:584-96) have proposed BAR designs for evaluating targeted agents. While promising, these designs do not explicitly deal with the problem of drift.

In this presentation I will first review BAR designs and the advantages they offer. I will then discuss some of the logistical difficulties they present as well as the bias issue. This will be followed by description of a frequentist, group-sequential approach that addresses the bias concern, as well as being easier to implement in practice (Karrison, Huo, and Chappell, Cont Clin Trials 2003;24:506-22). The main advantage of the group-sequential approach is that a stratified analysis will eliminate bias due to drift. Patients in the first sequential group are allocated in a 1:1 ratio. For subsequent groups the allocation ratio is altered depending on the magnitude of the z-statistic comparing outcomes in the two treatment arms. An O'Brien-Fleming monitoring boundary is also incorporated and if the boundary is exceeded the trial is terminated.

Simulation studies and theoretical calculations indicate that the group-sequential method maintains the nominal type I error rate even when there is substantial drift in the patient population. When a true treatment difference exists, a modest reduction in the number of patients assigned to the inferior treatment arm can be achieved relative to a non-adaptive (equal allocation) design. We conclude that responsive-adaptive randomization designs may be advantageous in certain situations, but the randomization and analysis should be stratified in order to avoid potential bias due to time trends.