Joint DSBS/FMS Meeting

October 2, 2014

Hilton Copenhagen Airport

Programme

08.00 – 09.00	**Registration and Breakfast**
09.00 – 09.05	**Welcome and Opening of Meeting** *Charlotte Hindsberger, President of DSBS* *Marcus Thuresson, President of FMS*
09.05 – 10.00	**Open data and closed minds? The pharmaceutical industry and its critics in the coming era of data-sharing** *Professor Stephen Senn, Centre de Recherche Public de la Santé, Luxembourg*
10.00 – 10.30	**Coffee**
10.30 – 11.30	**Mediation analysis – a tool to move from estimating treatment effect to understanding treatment mechanism** *Associate Professor Theis Lange, Section of Biostatistics, Department of Public Health, University of Copenhagen*
11.30 – 12.30	**Bayesian methods for the design and interpretation of clinical trials in very rare diseases** *Dr Lisa Hampson, Lancaster University*
12.30 – 13.30	**Lunch**
13.30 – 14.00	**A systematic application of good statistical practice in In-vivo studies** *Janeli Sarv and Sofia Tapani, Discovery Statistics AstraZeneca, Mölndal*
14.00 – 14.30	**Using modern statistical methodology for validating and reporting Patient Reported Outcomes** *Karl Bang Christensen Department of Biostatistics University of Copenhagen*
14.30 – 15.00	**Coffee**
15.00 – 15.30	**Evaluating dose-response under model uncertainty using several nested models** *Corine Baayen, Lundbeck, Copenhagen*
15.30 – 16.00	**Challenges in design and analysis of large register-based epidemiological studies** Caroline E. Weibull, Anna L.V. Johansson, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm
16.00 – 16.05	**Closing remarks** *Charlotte Hindsberger, President of DSBS* *Marcus Thuresson, President of FMS*
16.05	**End of Meeting**

Abstracts

Open data and closed minds? The pharmaceutical industry and its critics in the coming era of data-sharing

Stephen Senn, CRP-Santé, Luxembourg

The old era of private data and public analyses is being replaced by an era of public data and private analyses. I consider what the implications of this are for decision-making in drug regulation.

The results of many trials are unpublished and although one could argue that the results of trials, published or not, will have helped inform decisions that led to rejecting or selecting pharmaceuticals for further study or eventual use, it is clear that this is wasteful. There is a growing realisation that there is an ethical obligation on trial sponsors to make sure that results are published.

Unfortunately, if the traditional route for publication, the medical journal, is chosen, there is no guarantee that the results of a trial will be published. As I shall show, and contrary to what has been claimed elsewhere, journal editors are almost certainly biased against negative studies. In any case the only way to ensure that trials are published in a timely manner is to make those who run them also the publisher. My proposal is that every regulatory submission should have a publication plan as part of it and fulfilment of this plan should be a pre-requisite for getting a marketing license.

This still leaves open the question of what should be published. Should summaries of analyses be enough or should the original data be open to all? If so, what guarantees for analysis should we have? Should one insist on pre-specified analysis plans and a firm commitment to publish each and every pre-specified analysis? Will the problem of missing publications be replaced by one of missing analyses?

I discuss these and related issues with the help of some examples and come to the conclusion that public data-sharing is unstoppable and will bring many benefits but also some unwanted side-effects.

Mediation analysis – a tool to move from estimating treatment effect to understanding treatment mechanism

Theis Lange, Section of Biostatistics, Department of Public Health, University of Copenhagen

Mediation analysis aims at quantifying the different causal pathways, which transports/mediates the effect of a given treatment to a clinical outcome. The talk will initially introduce the intuition behind mediation analysis and explain how mediation analysis can be used as a stepping stone from "merely" establishing that a given treatment works to a deeper understanding of how and why the treatment works. Next, the talk will present practical solutions for conducting mediation analyses in R based on the results in Lange et al. 2012. All methods and concepts will be illustrated by a pharmacological study. Ref: T. Lange, S. Vansteelandt, and M. Bekaert, "A simple unified procedure for assessing mediation by marginal structural models", American Journal of Epidemiology, Vol. 176(3), p. 190-195, (2012).

Bayesian methods for the design and interpretation of clinical trials in very rare diseases

Lisa Hampson, Lancaster University

In this presentation, we consider the design and interpretation of clinical trials comparing treatments for conditions so rare that worldwide recruitment efforts are likely to yield total sample sizes of 50 or fewer, even when patients are recruited over several years. For studies in such rare diseases, the sample size needed to meet a conventional frequentist power requirement is clearly infeasible. Rather, the expectation of any such trial has to be limited to the generation of an improved understanding of treatment options. We propose a Bayesian approach for the conduct of rare disease trials comparing an experimental treatment with a control where patient responses are classified as success or failure. A systematic elicitation from clinicians of their beliefs concerning treatment efficacy is used to establish Bayesian priors for unknown model parameters; the possibility of formally incorporating results from related trials into priors is also considered. As sample sizes are to be small it is possible to compute all possible posterior distributions of the two success rates and to summarise the range of outcomes. Consideration of the extent to which opinion can be changed, even by the best feasible design, can help to determine whether such a trial is worthwhile. We illustrate the proposed methodology by describing the process used to elicit expert prior opinion for a future Bayesian randomised trial for a rare inflammatory paediatric disease, childhood polyarteritis nodosa.

A systematic application of good statistical practice in In-vivo studies

Janeli Sarv and Sofia Tapani, Discovery Statistics, AstraZeneca, Mölndal

Recent articles highlighted concerns about the robustness of research in pre-clinical in-vivo studies. At AstraZeneca (AZ) we adopt a systematic approach to the integration of statisticians into in-vivo work at the design stage to assure good science. The drivers for this strategy are three-fold: i) it helps to support AZ's external reputation, ii) it ensures that the data we generate internally are of good quality leading to confident decisions and iii) it helps to make sure that our use of animals in research is both ethical and appropriate. The principles for this approach are enshrined in the corporate Bioethics Policy.
The process for implementation involves the statistician working closely with the scientist prior to study start, to address 10 key areas of experimental design to ensure that the study is in line with AZ demands of validity and scientific rigour. The agreed outcome of these discussions is documented in a statistical health check and the study is deemed compliant with good statistical practice. By applying the practice in our decision making process we gain enhanced external reputation for integrity and transparency. We become confident that we have the right design at the first time conducting experiments. By these measures we improve the confidence in decisions from quality data design and generation in line with good science and ethics. In the long run this systematic approach serves as a stepping stone for information translated to clinical stage.
To be able to gain the improvement of quality by good statistical practice, the key to success is to get all the scientists on board. The value of extra input and spending more time for planning needs to be visible and understandable to all.

Using modern statistical methodology for validating and reporting Patient Reported Outcomes

Karl Bang Christensen, Department of Biostatistics, University of Copenhagen

Purpose: Patient Reported Outcomes (PRO's) describe aspects of a patient's health status that are reported directly by the patient. Based on standardized questionnaires, they are used to measure the health status and also the impact of interventions on aspects of health status. They are typically reported as standardized (e.g. zero to 100) mean scores, but are in fact derived ordinal data.
Methods: We evaluate whether ordinal regression models with random effects can be used to describe level and change in self-reported health. This is done for comparison of (treatment) groups and at the individual patient level.
Results: Ordinal regression models are shown to provide better statistical power and furthermore have the ability to quantify the uncertainty on change scores estimated for individual patients. Ordinal regression models appear to be especially promising for PRO's where the observed score distribution is skewed.
Conclusion: The use of ordinal regression models should be encouraged when designing studies that measure the effect of interventions using PRO's.

Evaluating dose-response under model uncertainty using several nested models

Corine Baayen, Lundbeck, Copenhagen. Co-authors: P. Hougaard, C.B. Pipper

During development of a drug, typically the choice of dose is based on a Phase II dose-finding trial, where selected doses are included with placebo. Two common methods to analyze such trials are separate comparisons of each dose to placebo using multiple testing procedures, or fitting a dose-response model to the data. The first approach does not provide information on doses that have not been evaluated in the trial, whereas the second approach does, but its validity depends on the correctness of the assumed dose-response model. Bretz et al. (2005; Biometrics 61, 738-748) suggested an alternative approach, named MCP-Mod, which selects one or more suitable models from a set of candidate models using a multiple comparison procedure. The method was recently qualified by EMA as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. The method requires a priori estimates of any non-linear parameters of the candidate models, such that a degree of model misspecification is still possible. Also, when the model selection is based on p-values for the hypothesis of no effect, it does not provide a way to control the type I error when comparing the candidate models with each other. We propose an alternative multiple testing procedure, which evaluates a candidate set of nested dose-response models against each other to select one final model. The method does not require any a priori parameter estimates and controls the Type I error rate of selecting a too complex model.

Challenges in design and analysis of large register-based epidemiological studies

Anna L.V. Johansson, Caroline E. Weibull, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm

Within epidemiological research, observational data from population-based health registers are frequently used. Examples of such registers are the National Patient Register, the Cancer Register and the Prescribed Drug Register. Large population registers in the Nordic countries are a goldmine for epidemiologists, and the recent development of clinical quality registers with detailed diagnosis and treatment information will boost epidemiology research even further in the future. By using the personal identification number (PIN) it is possible to enrich data by combining multiple sources in a way that is not possible in many other countries. This makes it possible to address new and more detailed research questions. The downside of the data availability is however the delicate problem of “too much” data. Design issues are of special importance with respect to selection of informative study participants and computing resources.

We will give a short introduction to epidemiological designs in register-based research, e.g., different case-control and cohort sampling strategies, as well as various family designs. We will illustrate these using some recent studies from our department.