Abstracts
Joint FMS/DSBS Meeting
Statistical analysis of risks and safety data
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Radisson Blu Hotel, Malmö

Application of extreme value modelling to safety data from clinical trials
Harry Southworth, Data Clarity Consulting Ltd., UK

Extreme value modelling of clinical trial safety data was introduced by Southworth & Heffernan in 2012 and appears to have gained some momentum since. This presentation briefly describes the current status of the approach, motivates the issues through examples and provides an introduction to the underlying theory. Practical issues around performing inference are discussed and some real life examples are treated in some detail.

Use of survival analysis methods in the assessment of safety
Per Kragh Andersen, Biostatistics, University of Copenhagen

In clinical trials, the primary end-point is often a time-to-event such as disease-free survival or relapse of disease, and state-of-the-art methods from the area of survival analysis are then used when assessing the treatment effect.

When it comes to safety data, however, methods of analysis often tend to be more simplistic using, e.g. simple counts of adverse events in spite of the fact that adverse event data are also time-to-event data and that follow-up time may vary among patients. Furthermore, adverse event data are often complicated by their recurrent nature and by the presence of competing risks.

In this talk, I will review how quite simple methods for the analysis of time-to-event data may be used when assessing safety, even when competing risks and recurrent events need to be taken into account. Inspiration and examples will be taken from a recent special issue of "Pharmaceutical Statistics" (vol. 15, 4; July-August 2016) specially devoted to the analysis of adverse event data.

Recent regulatory considerations on summarising safety data from clinical trials
Andrew Thomson, European Medicines Agency, UK

In this talk I will present two issues with respect to the reporting and interpretation of safety data from a regulatory perspective.
In August 2016 CIOMS published the report "Evidence Synthesis and Meta-Analysis for Drug Safety". I will highlight they key areas from this extensive piece of work where there is the potential to further clarify regulatory thinking and expectations.
In the second part of the talk, I will highlight regulatory challenges with interpreting mortality data in the presence of competing risks, motivated by a recent case study. I will discuss how an appropriate estimand may be defined, and consider the challenges in estimating this.

Drug safety during pregnancies – Evaluation with register based pharmacoepidemiology

Pär Karlsson, Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm

It is important to discover potential drug effects on the baby during pregnancy. There are ethical concerns regarding performing dedicated clinical trials to evaluate potential effects. During a typical clinical development program a few women might have been pregnant, and they are followed up carefully. But as there are only a few pregnancies in the program, so only very strong effects can be discovered. Thus, the only way is to evaluate pregnancies when the drug is out in the market.
One way of assessing potential effects is to combine information that is gathered in the administrative registers. In Sweden pregnancies are registered in a birth register. This register contains a lot of information, for example the length of pregnancy, weight, congenital malformations. There is no one registering when a patient takes a drug (luckily). What we have in Sweden is a register of the dispensing of a prescription at the pharmacy. Thus, there are great uncertainties in the drug exposures. Of course there are other issues and limitations of the registers.
In this talk I'll describe strengths and weaknesses in the registers and how I have used these registers in order to evaluate potential drug effects.

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Søren Rasmussen, Novo Nordisk, Copenhagen

Results from the randomised trial the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) will be presented.
LEADER is a cardiovascular safety study where 9340 patients with T2DM at high risk for cardiovascular disease were randomised to either liraglutide or placebo combined with standard of care. Follow-up was up till 5 years and the primary endpoint was time to first major cardiovascular event (MACE).

Modelling duration of diabetes in a design with matched controls

Stefan Franzén, Centre of Registers Västra Götaland, Gothenburg

I will discuss a "problem" when analysing a trial with diabetes patients together with matched (age and gender) non-diabetic persons. The aim of the study is to compare different subgroups of diabetes patients with respect to their excess mortality defined as the hazard ratio comparing the group of diabetes patients to the controls. An important variable that might confound of such an analysis is the duration of the diabetes disease (at baseline). However duration of diabetes is not defined for the controls and can therefore not easily be included in an analysis model such as a Cox regression. Previous studies have taken different approaches to this problem by for example setting the duration to zero for the controls or stratifying the analysis based on the duration for the diabetics and letting the matched controls follow their diabetes patient. The intension of this presentation is to clarify the statistical consequences of these approaches.

Statistical analysis of recurrent events, based on simple frailty models, and extensions

Philip Hougaard, Lundbeck, Denmark

Recurrent events refer to multiple occurrences of some event, for example, epileptic seizures, hypoglycemic episodes in diabetes or heart attacks. The actual data may refer to a count of events during an interval, or to data of times when the event occurs. Studying only the time to the first event is possible by means of standard survival data methods, which is quite simple but in many cases also unsatisfactory. Studying all occurrences gives a more complete picture of the disease burden. At the same time, it gives a more precise picture but at the price of using more complex statistical methods that adequately account for the relevant sources of random variation. Typically, there is subject variation, that is, the event rate differs between subjects, for example, due to unobserved risk factors. Such overdispersion may be modelled by a frailty model, where the frailty is a random term describing the effect of individual unobserved risk factors and the events then occur according to a Poisson process conditional on the frailty. The simplest case is when the frailty is constant and follows a gamma distribution, in which case, the number of events in an interval follows the negative binomial distribution. Three potential extensions of this classical model will be discussed. First, one can use other distributions than the gamma. Second, one can allow for observation periods that differ between individuals. Third, one can release the assumption of the frailty being constant. This extension is relevant for a cross-over type experiment as well as for a deeper study of the dependence over time that could apply for a clinical study with several phases, such as titration and maintenance.

Latent class analysis for more effective exploration of suspected adverse drug reactions

Niklas Norén, Uppsala Monitoring Centre
WHO Collaborating Centre for International Drug Monitoring, Uppsala

Most side effects of drugs that are identified after approval are found through reports of suspected adverse reactions submitted by patients and health professionals.
One of many challenges in the analysis of adverse event data is that descriptions of complex medical conditions must be projected onto standard terminologies, by which different reports may use different terms to describe similar conditions, and any analysis based on individual terms may fail to capture disease resulting in multiple symptoms.
As an alternative to univariate analyses, we have explored the use of latent class cluster analysis to identify natural subgroups based on the spectra of reported adverse events. Specifically, we assume a mixture model with independent binomial distributions for adverse events, and use Expectation-Maximization iteration to fit the model by seeking local optima to the penalized likelihood. As a final step, we apply a consensus clustering algorithm, in order to increase the stability of the overall solution and to use more of the information entailed in the family of local optima found.
Evaluation of the methodology in VigiBase, the World Health Organisation's international database of 12 million suspected adverse drug reactions, indicate that it can yield valuable insights, qualitatively different from those of univariate analyses.