PSI - EFSPI Conference | 08

PSI - EFSPI Joint Conference

18–21 May 2008

Hilton Hotel, Brussels

Call for Registration

INVITATION

From 18-21 May 2008, PSI and EFSPI will hold their first joint conference, at the Hilton Hotel in Brussels. For the organisation of this year's conference, the PSI scientific committee has been joined by representatives from several of the other EFSPI member organisations around Europe, and we hope that you will see this reflected in the agenda and list of speakers.

The enclosed call for registration provides the up to date details of our conference agenda, which we hope will be sufficient to whet your appetite for the meeting to come. Further details will be added as they are finalised, and will be accessible at the PSI website, www.psiweb.org. You can also register to attend the conference online at this website.

We hope you'll be able to join us for the conference, but why not take part as well? The deadline for Contributed Papers has now passed but it is not too late to consider submitting a poster – submissions can be sent to Nancy Barker – BarkerNancy@PRAIntl.com.

Whether you're planning to speak, or sit back and learn, we hope to see you in May.

John Davies
Chair, Conference Programme Committee

LOCATION & FACILTIES

The Brussels Hilton Hotel is located in the Boulevard de Waterloo, in the heart of this historic European capital city, approximately 30 minutes drive from Brussels Zaventem airport. The hotel is less than one mile away from the Midi International train station. There are regular scheduled flights to Brussels from many U.K. and European airports and this year you can also travel in style on Eurostar from London St. Pancras direct to Brussels-Midi, in a dedicated PSI carriage. A return ticket costs £55 per delegate. More details can be found on the Registration form.

CONFERENCE REGISTRATION

The Conference fees are detailed on the enclosed registration form. **Please note that a penalty is payable for late registration**. The fee includes accommodation on the Sunday, Monday and Tuesday nights and all meals taken at the hotel, plus entertainment. Registration forms should be returned to the Executive Office. You can also register for the conference online at www.psiweb.org. Please note that completed registration forms need to be returned / submitted by **5pm on Friday 7th March 2008 to avoid paying the penalty for late registration.**

Refund policy: All delegates who cancel their booking before 5pm on 7th March 2008 will receive a refund less the cost of the hotel charges and an administration charge of £50.00. No refunds will be given for cancellations made after 5pm on 7th March 2008, although substitutions may be made. All changes/cancellations must be made in writing to Dan Hollingshurst.

PROMOTIONAL OPPORTUNITIES

For information on sponsoring or exhibiting at the conference please contact Jenny Butterworth at the Executive Office.

CONTACT POINT

Any queries about the conference should be directed to Dan Hollingshurst or Jenny Butterworth at the PSI Executive Office, Association House, South Park Road, Macclesfield, Cheshire, SK11 6SH, UK. Tel: +44 (0)1625 267882 Fax: +44 (0)1625 267879 Email: psiconference@resourcesforassociations.co.uk.

SUNDAY 18th MAY

14.30 – 18.00
½ DAY WORKSHOP: SAFETY DATA METHODS
Speakers: A. Lawrence Gould (Merck); Michael O'Connell (Insightful)

If you wish to register for this ½ day workshop please ensure you complete the relevant section of the registration form.

The analysis of safety data from clinical trials is as important as the analysis of efficacy data. The most appropriate analysis strategy for an adverse event depends on whether it was identified a priori, not identified a priori but not 'rare', or not identified a priori and 'rare'. This presentation describes some general considerations in planning for safety evaluation, presents some ways to summarize data using confidence or credible intervals, describes a Bayesian approach to interpreting the outcomes, and suggests a simple graphical way to address multiplicity.

Once a drug has been approved for release to the marketplace, surveillance continues to identify rare potential toxicities that are unlikely to have been observed in the clinical trials carried out before approval. This surveillance process accumulates databases containing large numbers of spontaneous adverse event reports.

Bayesian screening techniques are useful in both the pre-marketing and post-marketing contexts for identifying potential drug-event associations needing confirmation or refutation.

The first part of the course, conducted by A. Lawrence Gould (Merck) will provide an overview of the methods available with examples of their application.

The second part of the course, conducted by Michael O'Connell (Insightful), will provide practical examples of basic analytical and graphical presentations, emerging safety graphic standards, and Bayesian and frequentist statistical approaches for signal detection using S-PLUS. Recent updates from interactions with regulatory authorities, particularly FDA, will be discussed.

16.00 – 21.00
Registration

18.00 – 20.00
Welcome Drinks Reception

20.00 – 21.30
Buffet Dinner

MONDAY 19th MAY

08.00 – 09.00
Registration

08.45
SARA HUGHES – Chair, PSI
Opening Remarks

09.00 – 11.00
PLENARY 1

DOES THIS HOUSE BELIEVE THAT ALL EU MEMBER STATES REVIEWING SUBMISSIONS, AND GIVING ADVICE ON DRUG DEVELOPMENT, SHOULD RECRUIT PERMANENT STATISTICIANS?

Chair – Professor John Lewis (Visiting Professor of Medical Statistics, Newcastle University)

Thousands of statisticians are employed by the pharmaceutical industry and contract research organisations. In the majority of companies, designing a drug development programme without expert statistical input would not be contemplated.

To PSI's knowledge, four national regulatory agencies in Europe employ multiple full-time statisticians, while a few others employ a single statistician. A number of agencies which play a major role in the European regulatory process do not employ any full-time statisticians instead relying on external consultants. PSI and EFSPI are concerned that this situation needs to change. The aim of this session is to raise awareness of:

(i) the history of statistical input to drug regulation
(ii) the contrast between statistical input to regulatory decision making in US and Europe
(iii) the lack of statistical support in some EU agencies,
(iv) PSI's initiative to promote recruitment of permanent statisticians in more European agencies
(v) different models for increasing involvement of statisticians in the European regulatory network for the future.

After an opening statement on PSI's continuing activities in this area by Sara Hughes (GSK, PSI Chair), speakers will include John Lewis, University of Newcastle and formerly MHRA (the UK regulatory agency), Bernard Asselain, who provides expert statistical input for AFSSAPS (the French regulatory agency), Eva Skovlund, a CHMP member from Norway and Hans-Georg Eichler the Senior Medical Officer at EMEA. The chair of CHMP, Eric Abadie, has also been invited to participate. The session will end with a debate involving both the speakers and the attendees on the optimal model for future statistical input in European drug regulation.

11.00 – 11.30
Coffee Break

11.30 – 13.00
PARALLEL SESSIONS:

SESSION 1A **REGULATORY TOPICS PART I**
Chair: Rob Hemmings (MHRA).
Speakers: Prof. Deborah Ashby (Wolfson Institute of Preventive Medicine); Dr Tim Friede (University of Warwick); Dr. Ian Hirsch (Pfizer); Alan Philips (Icon); Rob Hemmings (MHRA).

The first session will consist of talks covering contemporary and controversial issues in regulatory submissions and raise awareness of ongoing regulatory discussions together with industry perceptions of recent initiatives. Professor Deborah Ashby (CHM member and Professor of Medical Statistics, Wolfson Institute of Preventive Medicine), a long-standing member of MHRA's advisory committee, will talk about 'Common Issues in Submissions'. Dr Tim Friede (University of Warwick) will offer description and opinion of the recently released CHMP Reflection Paper on adaptive designs. Dr Ian Hirsch from Pfizer (and previously of MHRA) will discuss regulatory requirements for dose-finding, contrasting experiences in Europe and US. Alan Philips (Icon) will give an overview of the conditional approval legislation and of the thoughts from PSI's Expert Group on Conditional Approval. Rob Hemmings (Statistics Unit Manager, MHRA and member of CHMP's Scientific Advice Working Party) will provide a commentary on European regulatory experience with adaptive designs and conditional approval.

SESSION 1B **EDITORS' CHOICE**
Chair: Mike Smith (Editor, Pharmaceutical Statistics)

The editors of two of our industry's leading journals (Pharmaceutical Statistics and Statistics in Medicine) have been asked to nominate their favourite papers of 2007. The authors of those papers will each give a short talk on their paper.

SESSION 1C **NEW STARTERS**
Speakers: Andrew Thomson (MHRA); Carly Donovan (GSK)

This session is aimed at PSI members (statisticians and programmers) with up to three years experience in industry/government, academia or the NHS. This session offers a good opportunity to meet other, new, delegates working in many different areas, to learn from their experience. In addition, this year, we have a presentation on an overview of the regulatory process in the UK and in Europe.

Carly Donovan (GSK) will give a talk on: Working in Neurosciences - Experiences of a Phase II-IV Statistician (2 years on)

Andrew Thomson's (MHRA) talk is entitled: Life as a statistician within a regulatory agency. Andrew says:

"This talk is aimed at statisticians new to the industry, with little exposure to the work of the MHRA. In this talk, I will briefly talk about the role of the Agency in regulating medicines in the UK and across Europe. I will discuss the different roles that statisticians have within the Agency and the statistical input at the different stages of a product's lifecycle. I will consider how regulatory standards and requirements might affect your life as a statistician, and how you can optimise regulatory interactions. I will then talk in more detail about the kind of work I do, focusing in particular on assessment work and scientific advice. I will describe some of my experiences to date: how I, as a new starter to the pharmaceutical industry, am finding life as a regulatory statistician."

Sarah Kirk (Roche) will give a talk on: Working as a statistician in oncology – experiences of academic and pharmaceutical clinical trials.

David Bock (AstraZeneca): Title to be confirmed.

SESSION 1D **CARDIOVASCULAR RISK ASSESSMENT IN SAFETY PHARMACOLOGY**
Chaired by: Toxicology Special Interest Group

Cardiovascular (CVS) toxicity, including QT prolongation, is one of the main reasons for drug withdrawals over the last decade. CVS side-effects are diverse and can be life-threatening. In most cases they are not even related to the primary pharmacological target, the therapeutic class or the chemical class.

A generic CVS / QT testing strategy, accommodating both ICHS7A and ICHS7B guidances, should test a drug on different assays of varying complexity, including the assessment of the recording of K+ current from hERG transfected cell line; the recording of the action potential from cardiac tissue; and the recording of the ECG in a relevant in vivo model, for example the dog.

This session will review several areas, including the sensitivity of existing pre-clinical CVS models; defining a pharmacologically significant effect (e.g. does QT-shortening have greater risk than QT-prolongation, or whether is ST more informative than QT); the link between ecg-based parameters and Torsades de Pointes; consistency in correcting ecg data (e.g. QT) for heart rate; joint parameter versus single parameter modelling; TK/PK modelling.

13.00 – 14.00
Lunch

14.00 – 15.30
PARALLEL SESSIONS

SESSION 2A **REGULATORY TOPICS PART II**
Chair: Ian Hirsch
Speakers: All from Session 1B, plus Prof. John Lewis; Dr. Armin Koch (BfARM) and others to be confirmed.

This second session will support an open discussion between all parties interested in the statistician's role in drug development and registration. In this interactive session, there will be the opportunity to discuss issues with current and former regulators plus leading statisticians from industry. Some "hot topics" will be identified in advance, in part based on problems arising from the first session. However, the session is primarily aimed at providing attendees with the opportunity to raise issues and your input will be sought prior to conference! So if you have any burning questions or want to question, challenge, or simply to further understand regulatory guidance then this is the session for you! Topics will be sought from attendees, who will be asked to prepare a (very) short presentation highlighting an issue for discussion. Some examples of potential topics could include latest developments in missing data, experiences with the new European 'paediatric' legislation, how many primary endpoints to define, when is it mandatory to have two pivotal trials? … But it really is up to you! So why wait, propose a topic for discussion by sending an e-mail to Ian.Hirsch@pfizer.com.

The panel will comprise speakers from the first session plus additional regulatory experience from Prof John Lewis (University of Newcastle and, formerly, MCA / MHRA) and Dr Armin Koch from the German regulatory agency, BfARM, plus additional industry experience (to be confirmed).

SESSION 2B **CONTRIBUTED PAPERS – Early Clinical Development**

Birgit Gaschler-Markefski (Boehringer-Ingelheim)
A practical evaluation of two different two stage designs for use in a first-in-human oncology study

In cancer drug development, phase I studies are usually conducted in late stage cancer patients and designed as dose-finding studies with the primary objective to estimate the maximum dose without unacceptable toxicity (maximum tolerated dose, MTD). One underlying assumption is that efficacy increases as the dose increases.

There are different constraints on the design of a phase I oncology trial. One is the ethical requirement to approach the MTD level from below and to minimize the number of patients treated above the MTD. Other constraints refer to the limited overall number of patients (usually 15-30) in such phase I studies.

The statistical literature evaluates various potential designs. The most widely used design is the traditional 3+3 dose escalation design or an adaptations like Storer's two stage design. Recently, continual reassessment method (CRM) designs were introduced in phase I oncology studies.

To plan a first-in-human study with an oncology drug, we conducted a simulation study to evaluate the performance of an adapted Storer's two stage design compared to a likelihood-based CRM design. Under a variety of dose–response settings, we examined bias and precision of estimates, and the fraction of estimates that were extremely high or low. We also studied in detail the influence of small sample sizes. As one conclusion of our simulation studies, a careful study specific evaluation of the CRM design for use in a first-in-human study should always be taken into consideration prior conduct such a design.

Alun Bedding, GlaxoSmithKline
Adaptive Within Subject Dose-Escalation with an Application to Dose Titration

First time in human studies employ a within subject dose-escalation, starting from the lowest available dose. These studies, however, will tend to have a fixed dosing scheme, and will step slowly through the doses to reach the maximum tolerated dose. Data are reviewed after each cohort of subjects, however, statistical methods are rarely used.

Whitehead et al (2001) and Zhou et al (2006) have suggested methods for use in dose escalation studies, however, the implementation has been slow. Tibaldi et al (2008) implemented a Bayesian adaptive design in a diabetes study, and a number of studies with GlaxoSmithKline are planning on utilising the methods.

This presentation will outline the main methodology illustrated by case studies. It will be shown how the methodology can be expanded to dose titration in phase II studies, with the overall aim of improving the probability of success in phase III.

Peter Treasure (Independent Consultant)
Using Empirical Likelihood to Determine Maximum Tolerated Dose

Although widely discredited, the 'three-up three-down' method is still widely used. The natural alternative - fitting a model for the probability of a dose-limiting toxicity as a function of dose - is not always straightforward to implement. Using a non-parametric method such as empirical likelihood may provide a middle way. The speaker willl discuss and demonstrate the use of empirical likelihood in determining maximum tolerated dose.

SESSION 2C **CONTRIBUTED PAPERS – SAS / Stat**

Kevin Kane, Anna Passera, Pinal Patel (Phastar)
Non-Parametric estimates and confidence intervals adjusting for confounding factors

Non-parametric statistics are commonly used in clinical trials when comparing two groups of patients to estimate a treatment effect. However, methods that generate estimates and confidence intervals as well as adjust for possible confounding factors are not in common use, probably due to the fact that they are not available directly in SAS. Some options that are used include the Van-Elteren extension to the Wilcoxon Rank Sum Test, a method proposed by Gary Koch's team and applying GLM techniques on ranked data. The talk will present a comparison of these methods using simulations in a variety of situations, such as skewed data, data with outliers etc. In addition to the comparison of these methods, a proposal for a conceptually simple method for generating point and interval estimates using either the Van-Elteren or the ranked GLM method will be presented.

Paul Talsma (Syne Qua Non)
Some special applications of Kaplan-Meier survival analysis and the log-rank test

In this talk some recent experiences with reporting survival analysis results will be shared. Presenting a table and graph indicating when events are happening over time will be discussed. A “naïve” method of presenting this is depicting the number of events per time period (say every 3 months), but such a graph or table does not take censoring into account. Therefore a way is proposed to directly obtain this information from the Kaplan-meier results. SAS® code will be provided.

In the second part of the talk, the log-rank test will be discussed. The log-rank test has a close relationship with Cox regression, but this relationship is not described very clearly in several textbooks and in SAS® documentation, and can be confusing when one analyses survival data. This relationship is therefore explained. In addition, different ways of calculating the log-rank test are described, and a way of partitioning the log-rank test into its treatment group components, similar to the χ^2 test, is provided, together with the corresponding SAS® code.

Eddie Channon (Chirostat Statistical Consulting)
Fitting Straight Lines to Scatter Graphs When Both Variables are Subject to Error

It is easy to plot a scatter graph for two repeated measurements (x and y) of an assay variable and to add a line using simple linear regression. Many packages do not caution the user that any error in x has been ignored.

Linear regression with errors in both variables may be appropriate. There is a lot of literature in this area but none of the methods is available in SAS®. A pragmatic approach is to fit regression lines for y on x and x on y and then to choose the bisector of the lines.

When correlation between the variables is high, there is no practical advantage of allowing for any error in x. In other cases, the most appropriate method depends on the interpretation to be made from the fitted line.

SESSION 2D **BIOLOGICALS – STRATEGY FOR REPRODUCTIVE TOXICOLOGICAL ASSESSMENT?**
Chaired by: Toxicology Special Interest Group

The assessment and evaluation of reproductive toxicity for small molecules (i..e new chemical entities) and Biologicals (e.g. monoclonal antibodies) differ in two key respects: 1) the choice of pharmacologically relevant species is non-human primate (e.g. cynomolgus monkey) and humans only and 2) Biological exposure time is much longer (half lives are typically several hundred hours).

This session will outline the statistical issues; consider potential study designs; review measurable endpoints and their sensitivity. The progress made by ILSI (International Life Sciences institute) on this matter will also be reviewed.

SESSION 2E **CONTRIBUTED PAPERS – Pharma/CRO relationships**

Natalie Fforde (Fforde Management)
Integrating Functional Service Provision within the European Outsourcing Model

Functional Service Provision (FSP) has become a common feature in outsourcing in the United States it is seen less often in Europe.

Cultural differences mean that European outsourcers are having to identify and implement new genres incorporating aspects of Functional Service Provision but ultimately re-modelled to best fit the market.

Stephanie Noller (Quintiles)
Are you Guilty? – The Crimes and Punishments of the CRO-Pharma Relationship

Are you a Pharmaceutical Company Statistician/Programmer who regularly works with a CRO Statistician/Programmer or vice versa? If so, what type of Pharma-CRO relationship do you think you currently have? Are you guilty of late requests for additional work or agreeing to deadlines that you subsequently don't meet? Do you think there is room for improvement and would you benefit from some tips on how to get the most out of your Pharma-CRO relationship?

In this presentation, we shall consider various Pharma-CRO relationship styles ranging from the completely "hands-off" approach to the "micro-managers". We will look at each style in turn discussing what works well, what not so well (the "Crimes") and the resulting consequences of each style (the "Punishments"). We will also share our own experiences of working with different types of Pharmaceutical Companies (we call them "Customers"), providing some practical tips on how to build and maintain a good working relationship with different styles. It is important in a fast-pace, ever-changing clinical trials environment that Statisticians and Programmers "stick-together" and get the most out of their Pharma-CRO relationships. Well, we are all on the same side after all aren't we?

15.30 – 16.00
Coffee Break

16.00 – 17.30
PSI ANNUAL GENERAL MEETING

18.30 – 19.30
POSTER SESSION and Drinks Reception

If you would like to submit a poster please email Nancy Barker, **BarkerNancy@PRAIntl.com**.

19.30
Dinner

TUESDAY 20th MAY

09.00 – 11.00

PLENARY 2 **KNOCKING DOWN THE PILLARS OF NON-INFERIORITY TRIALS**
Chair: John Lewis (Newcastle University)
Speakers: Steve Snapinn (Amgen); Armin Koch (BfArM); John Lewis

Non-inferiority trials in drug development have been widely discussed over a decade or more but remain controversial. Two concepts are central to their design: setting a margin, and preservation of effect. Each provides what at first sight appears to be an attractive means to construct a framework for establishing non-inferiority. Setting a non-inferiority margin is routinely used and is recommended in various regulatory guidance documents; however, it is extremely inefficient relative to an approach which pools data from the non-inferiority trial with historical data comparing the active control with placebo. On the other hand, approaches that seek to preserve a fraction of the active drug effect compared to placebo can be shown to lead to serious logical inconsistencies. In this session, three leading contributors to the theory and practice of non-inferiority designs discuss current thinking on the subject and possible ways forward.

SESSION SC I **STATISTICAL COMPUTING SESSION 1**
Standardisation of Efficacy reporting at Roche (SHARE macros)
Speaker: Denise Guimaraes (Roche Products Ltd)

A couple of years ago, Roche identified the opportunity to make efficacy reporting more efficient, by standardizing some aspects of it. In my presentation I will cover the process we used to make the best out of this idea: creation of a global group, selection of 'what' and 'how' to standardize. I will also talk about some aspects of the suite of macros behind those standards (i.e. key features, pilots run prior to roll-out, validation methods, regression testing and maintenance).

Print Driver – An alternative to Proc Report
Speaker: Jason Reucassel (i3 Statprobe)

Driven by a requirement from our Medical Writing department to have Tables and Listings stored in Word Tables rather than standard text, I was asked to investigate an alternative reporting process to our current one.

I discovered and implemented a solution used in our US offices known as “Print Driver”, it is an alternative to Proc Report and is a suite of macros which essentially coverts user/data definitions into a RTF output file.

After an initial learning curve the flexibility of Print Driver became apparent with problems such as difficult page breaking, sub-grouping and conditional footnotes being easily overcome.

In my presentation I will give some background into Print Driver’s history as well it’s architecture. I will also demonstrate a live example showing how it works.

11.00 – 11.30
Coffee Break

11.30 – 13.00
PARALLELSESSIONS:

SESSION 3A **CLINICAL TRIALS IN RHEUMATOID ARTHRITIS: CASE STUDIES**
Chair: Rebecca Sudlow (Roche Products Ltd, UK)
Speakers: Hayley Pocock (GSK Greenford, UK); Rebecca Blackburn (Study Statistician, Roche Products Ltd, UK); Francisco Ramirez (Statistician, Roche Products Ltd, UK)

This session will focus on the current practical and statistical challenges faced by statisticians working on clinical trials in Rheumatoid Arthritis. There will be three presentations addressing the following areas:

- Practical issues in RA study design and analysis (e.g. blinding, challenges of composite endpoints, multiplicity)
- Swollen and tender joint counts. Do joint counts based on the 66/68 joint counts provide different responses to those based on 28?
- Composite endpoints for assessment of efficacy. Is the ACR20 (American College of Rheumatology) the most appropriate endpoint?

SESSION 3B **NEUROLOGICAL DISEASES**

This session will focus on the current practical and statistical challenges faced by statisticians working on clinical trials in Alzheimer's Disease. It is planned that the presentations in this session will provide examples of issues faced by practitioners in the design and analysis of trials in Alzheimer's disease and a critical review of the recent CHMP Points to Consider guidance on the design, conduct, analysis and interpretation of clinical trial in this disease.

SESSION 3C **CARDIOVASCULAR**
Speakers: Stuart Pocock (London School of Hygiene & Tropical Medicine); Georgina Bermann (Novartis, Switzerland); Karin Nelander (AstraZeneca, Sweden)

This session aims to demonstrate how statisticians act to help design, conduct, analyse and interpret clinical trials to obtain evidence of efficacy and safety in the cardio-vascular disease area. It is planned that three presentations will be followed by a short panel discussion.

The session will include a talk by Stuart Pocock outlining perspectives for cardio-vascular trials. Issues regarding the design of trials, such as choice of comparator, patient population, endpoints and trial size will be discussed, as well as appropriate analysis and data monitoring strategies, all illustrated by recent trial experiences.

Georgina Bermann will focus on the dialogue with regulatory agencies. Starting out from the recently issued draft guidance document on "Cardio-Vascular Disease Prevention". Her presentation will also consider ways in which statisticians can contribute to the dialogue with regulators regarding cardiovascular trial design.

The final presentation by Karin Nelander will look at biomarkers in the cardio-vascular disease area. Examples of some prominent biomarkers are discussed, with a specific focus on imaging techniques. Statistical challenges in analysing these markers are examined, and the value of the markers in supporting efficacy claims, either as a primary or as a secondary endpoint, will be considered.

SESSION 3D **CONTRIBUTED PAPERS – Clinical Data I**

Simon Kirby, Christy Chuang-Stein, and Mark Morris (Pfizer)
Determining a Clinically Important Difference for a Patient Reported Outcome from a Within Subject Clinically Important Change

It can be difficult to know what difference between treatment groups for a patient reported outcome represents a clinically important difference. Some authors have concentrated on trying to derive a within-patient clinically important change and have then proposed using this as a guide to the within-patient change required for a new treatment. By comparison, in this talk we consider an approach which explicitly relates a desired difference in the proportion of subjects achieving a clinically important change on comparator and a new treatment to the difference in means for the patient reported outcome between the two treatments. We illustrate the method by application to data on neuropathic pain.

Alun Bedding (GlaxoSmithKline)
The Bayesian Analysis of Safety Data
In clinical trials safety data are always collected, however, much of these data go without formal analyses, and where they do, these analyses are wholly underpowered. This is an ideal opportunity for Bayesian methodology to be used, and indeed it has been said that the use of Bayesian methods in safety analyses can overcome some of the problems around multiplicity which could be associated with such analyses. Moreover, there is much safety information that can be taken from study to study within a clinical development plan. In the past there has been a suggestion to utilize Bayesian methods be used for examining rare events, using data from many sources, and indeed frequentist methods have difficulty in dealing with these analyses of rare events.

Berry and Berry (2005), have described a method of using hierarchical models to analyse safety data, overcoming the multiplicity aspect and in effect borrowing strength from within a body system, and whilst their methods have some shortcomings, such as an adverse event could be more than one body system, with work this could be a way of identifying safety signals, without having to resort to a large number of hypothesis test, and resultant p-values. Interpreting a p-value in this context I believe has its problems anyway, and any adjustment cannot be seen as conservative.

This presentation will give case study examples of these methods in clinical trials in the infectious disease and vaccine areas. It will examine the use that can be made of prior information along with predictions around the prevalence of safety concerns. In addition, the Berry and Berry methods will be expanded to look at safety signals across an integrated database, rather than an individual study.

Adam Jacobs (Dianthus)
Effects of opioid rescue medication in chronic pain: use of meta-regression in the absence of direct comparative data.

The use of short-acting opioids for breakthrough pain is controversial in the management of chronic non-malignant pain. There are no data from randomised studies directly comparing the long-term efficacy and safety of long-acting opioid therapy in chronic non-malignant pain patients with access to short-acting opioids for breakthrough pain and those without. We therefore used meta-regression to make indirect comparisons between long-acting opioid clinical studies that allowed short-acting opioid rescue medication with those that did not.

SESSION SC II **STATISTICAL COMPUTING SESSION II**

Challenges and Benefits of CDISC ADaM datasets
Speaker: Zoe Williams (LEO Pharma)

LEO Pharma has recently submitted datasets in CDISC ADaM format to the FDA. The ADaM format was introduced partway through the project, which added to the challenges of an already busy programme. However, the project timelines were still able to be met.
The study data were provided to the statistical team in CDISC SDTM format and ADaM datasets were then created using the Analysis Data Model Version 2.0. ADaM dataset specifications were developed to ensure datasets were consistent across studies within the project and to provide programmers and statisticians with the detailed naming of variables and formats.
As the use of ADaM datasets occurred part way through the project, earlier studies had already been reported using a different data format. Conversion of datasets to ADaM format was required for pooling and submission to the FDA,. This introduced additional work and quality control to ensure that the results presented in the clinical study reports were able to be reproduced from the new datasets.

Later studies were reported directly from ADaM datasets. After the initial overhead of personnel becoming familiar with the new format, there were few issues at the reporting stage. This demonstrated that reporting using ADaM format was possible and preferable to conversion of datasets after a study had been reported. The use of the standard ADaM format also facilitated pooling of data for reporting the Clinical Summaries of Efficacy and Safety. Thus, the datasets used in reporting have been submitted to the FDA without further modification.

It has been demonstrated that with good planning, documentation and processes it is possible to change to the CDISC ADaM format part way through a project, to enable analysis data to be submitted to the FDA according to the CDISC guidelines.
Based on experiences from this project, the ADaM format is now the standard for statistical reporting at LEO Pharma and the lessons learned and work done has formed the basis for developing standard working practices.

A further paper and speaker are to be confirmed for this session.

13.00 – 14.00
Lunch

14.00 – 15.30
PARALLEL SESSIONS:

SESSION 4A **FREE TUTORIAL: ADAPTIVE DESIGNS FOR CONFIRMATORY CLINICAL TRIALS**
Speakers: Frank Bretz and Heinz Schmidli (Novartis Pharma AG)

This short course will give an introduction to the theory and practice of adaptive designs for pivotal clinical trials. Adaptive designs allow mid-course design modifications such as the adjustment of sample size, the dropping of treatment arms or the selection of a subpopulation.

We will review and discuss statistical methodology that allows such adaptations, without compromising the overall type I error rate. All methods will be illustrated by examples. Several case studies will be presented, explaining in detail both methodological and practical issues which arise in designing and analysing an adaptive clinical trial.

Special attention will be given to adaptive seamless phase 2/3 trials, which can lead to substantial savings in both cost and time.

This session continues after the coffee break (session 5A).

SESSION 4B **CONTRIBUTED PAPERS – Use of historic controls**

Rob Cuffe (GlaxoSmithKline)
Using historical data to reduce the sample size of a phase IV trial

By phase IV, there is a large amount of data available on a compound's efficacy. Bayesian methods offer a natural way to incorporate this information into the design of a trial. GSK recently initiated a non-inferiority study comparing the licensed dosing regimen of one of our HIV drugs (BID) to a less burdensome one (QD). A prior distribution for the BID response could represent the existing data on the licensed dose.

This would reduce the number of patients needed to characterise control response in the trial, reducing the sample size. The talk discusses the benefits of such a design, the dangers of poor prior data and the simulations carried out to assess the type I error rate.

Nuala Peter (Boehringer-Ingelheim)
Determination of Sample Size for Prospective Putative Placebo Analysis using Binary and Survival Endpoints

Where it is no longer ethical to treat patients with placebo, there is a high unmet medical need, and one needs to be as efficient as possible with the number of patients treated, one can consider analysing a randomised controlled trial (RCT) using putative placebo (PP) techniques. In such a case, only the constancy assumption should remain as the PP comparison is based on within trial relative effects.

Generally, such a PP superiority analysis is a back-up for the main non-inferiority analysis, and most often such analyses are performed retrospectively and without any prior consideration for the sample size. However, it is intuitive to prospectively design the study, considering power for both analyses. Perhaps one can accept slightly lower power for the non-inferiority comparison whilst overpowering for the PP comparison, in an early Phase RCT.

Throughout this paper, we make use of the methodology by Hasselblad to simulate confidence intervals (CI) in SAS and thereby estimate the sample size. We consider cases where the endpoint can be either binary, using odds ratio (OR), relative risk (RR) or risk difference (RD), or survival data using the hazard ratio (HR). In the case of survival data, one needs to carefully consider censoring. The random uniform distribution is used for the binary measures, and the exponential distribution with exponential censoring for the hazard ratio. The simulated sample sizes for the binary data are then compared to those obtained by using the method outlined by Lloyd Fisher. Case studies are provided using all four endpoints, based upon an example in Oncology. Within one SAS program all of these sample sizes can be estimated for study design and planning.

Steven Julious (University of Sheffield) and Sue-Jane Wang (Food and Drug Administration)
How Biased Are Indirect Comparisons Particularly When Comparisons Are Made Over Time In Controlled Trials?

Indirect comparisons are undertaken when a comparison is made between two regimens where the regimens have usually never been given concurrently in any controlled trial investigating the same general patient population. This talk highlights the issues of making indirect comparisons when there has been a period of time between the studies particularly when indirect comparison is being made to placebo. The talk discusses the impact of any bias in indirectly estimating any effect over placebo in context with non-inferiority trials .

SESSION 4C **CONTRIBUTED PAPERS – Analysis of event-based endpoints**

Oliver Keene (GlaxoSmithKline)
Analysis of Recurrent Events in Clinical Trials: Example from a study in COPD

Recurrent events in clinical trials have been analysed using a variety of methods, including multiple time-to-event methods and direct approaches based on the distribution of the number of events. The different approaches to the analysis and the issues involved will be illustrated for the endpoint of exacerbation rate from a large trial in Chronic Obstructive Pulmonary Disease (COPD).

For exacerbation rate, clinical interest centres on a direct comparison of rates for each treatment which favours the distribution-based analysis, rather than a time-to-event approach. Poisson regression has been recommended as the appropriate method but the model does not satisfactorily account for variability between patients. By contrast use of a negative binomial model which corresponds to assuming a separate Poisson parameter for each subject offers a more appealing approach.

Issues remain about appropriate sensitivity analysis to explore the impact of missing data and some ideas in this area will be examined.

Peter Lane (GlaxoSmithKiline)
Fixed-effects meta-analysis with rare events

Meta-analyses are increasingly being used to summarize information across trials, often to publicize good or bad news. Public access to trial results on the Internet has made it especially easy to generate such meta-analyses, particularly of safety issues. Once the hurdles of acquiring and selecting data have been cleared, the task of analysis with some given technique is only too easy. The results can be strongly influenced, however, by the choice of technique and the approach to combining information when the operating details vary across individual trials. The analysis of rare events, particularly safety events, is prone to disagreement and misunderstanding. We will look specifically at the fixed-effects meta-analysis of a binary response, illustrated by publicly available data from last year's high-profile analysis of Avandia with respect to cardiovascular safety. This raised issues including the choice of summary statistic to employ, the combination of trials with different control treatments, and the handling of trials with no events. And lurking in the background was the ever-present danger of being misled by Simpson's Paradox.

Gerd Rosenkrantz (Novartis)
Issues with composite endpoints

Composite endpoints are fairly common in different disease areas like cardiovascular/metabolism and transplantation. Often they are composed by death and some non-fatal endpoints that are predictive for the fatal outcome. The reason for that is that in many indications death has become a rare event due to the progress of medicine. As a consequence, studies would become too large or take too long to be practical to prove an improvement of survival.

Issues with composite endpoints arise when the relevance of the components is different and differences can be proven only in terms of the less relevant components. This raises the question about how the individual components can be assessed in the presence of the correlated censoring by death (or loss to follow up). In the presentation we will first give an idea of the impact of dependent censoring on the results when classical survival analysis methods are used and discuss analyses that provide more consistent results.

SESSION 4D **CONTRIBUTED PAPERS – Clinical Data II**

Jürgen Hummel (PPD), Scott Wiseman (Eli Lilly - Elanco)
Non-inferiority studies with binary endpoint: Analysis with adjustment for covariates

Studies which intend to show non-inferiority of the investigational compound compared to an active comparator typically define the non-inferiority margin based on a difference between two treatments. If the primary endpoint is binary, interest will centre on a difference in proportions. The most popular approach for a binary endpoint analysis is often logistic regression. This parametric approach allows adjustment for other model terms and provides estimate and confidence interval of a treatment effect. However, the resulting treatment effect is presented as an odds ratio, not a difference in proportions.

Using the delta method it is possible to calculate the confidence interval for the difference in proportions based on the estimate and standard error of the parameter estimates obtained from the logistic regression model. Based on our experience this approach is not widely used. We believe that conversion of this ratio to a difference aids interpretation, both for the statistician and clinician alike, especially in the context of using a clinically meaningful difference to define a non-inferiority margin.

The presentation provides an overview of the mathematics behind the approach and then illustrates its use in a currently ongoing Phase III study. The robustness of the approach is investigated, comparing it to the confidence interval for the (unadjusted) difference in proportions obtained either using the normal approximation to the binomial or exact methods (STATXACT).

James Roger (Research Statistics Unit, GlaxoSmithKline)
Sensitivity analysis for longitudinal studies with withdrawal

Repeated measures analysis assuming a missing at random (MAR) withdrawal process allows a well-formulated modelling approach to handling withdrawal in late phase longitudinal studies. The approach is often known as MMRM. It allows an analysis that under the MAR assumption does not involve those biases that often come with complete cases (OC) and last observation carried forward (LOCF) approaches.

There needs to be more discussion in the industry to clarify best practice. Models need to be specified so that they do not misrepresent the data. For instance if parameters such as residual variances or baseline regression parameters are estimated as a single parameter across visits, then these will distort a final visit analysis. Standard errors will generally be too small and baseline corrections will over-compensate. Similarly Statisticians need to become more experienced in the addition of components to the model that will improve the MAR assumption, either through joint modelling or by including additional covariates.

In spite of this, MMRM is becoming increasingly accepted by regulatory authorities for confirmatory trials. However those regulators are indicating that they require some form of sensitivity analysis to go alongside the MMRM approach. Indeed MMRM is a useful first stage in a systematic approach to investigating the possible influence of the withdrawal mechanism on the resulting analysis. However sensitivity analysis should not simply be a collection of wrong analyses. It should be an attempt to explore the possible influence of differential withdrawal models on conclusions from the study.

It is argued here that MMRM forms a robust starting point for exploring the sensitivity to more complex withdrawal mechanisms. There are two main approaches. Firstly there is the joint modelling of outcome and withdrawal mechanism, which is most easily done in a Bayesian context. Here we use the alternative pattern-mixture approach. Under the MAR assumption a very similar analysis to the MMRM analysis can be carried out using Multiple Imputation. Assuming the same multivariate Normal repeated measures model for the outcomes, one draws parameter estimates form their Bayesian posterior based on MAR assumption, separately for each treatment arm. Then values are sampled from the multivariate Normal distribution of the missing values conditional upon the observed values and covariates for that subject. Then the complete data are analysed, usually at the end of trial separately for each imputed data set. Then the results for each imputation are combined using Rubin's formula. There are two advantages over MMRM of separating the

imputation model from the analysis model. Firstly it allows one to include covariates which predict withdrawal without predicting outcome. Second, and more important here, it allows one to have a separate model for the outcome following withdrawal. So we can make alternative assumptions about the distribution following withdrawal. In the MAR approach subjects are assumed to have the same distribution following withdrawal to those who remain in the study. Here we make alternative assumptions such as switching the pattern of means from that in the active arm to that in the placebo arm following withdrawal. Then there is a separate distribution for each pattern of withdrawal, based on potential extrapolation from the observed pattern for patients remaining in the study. This follows the approach of Little & Yau (1996) for what they call intent-to-treat analysis, answering the question "what happens if those who withdraw would have gone on to do something different".

We will show how this approach is relatively easy to implement in SAS and highlight some of the current limitations in our approach.

George Quartey (GlaxoSmithKline)
The Utilisation of Sample Selection Models to Account for Unobserved Confounding in Epidemiology

Confounding is a major problem in observational research. Although several statistical methods (e.g. multivariable (adjusted) analyses or propensity scores) would help to account for known confounders, unobserved confounding is unlikely to be corrected for by any of the above-mentioned standard methodologies. One potential method for accounting for unknown confounders is the use of sample selection models (also known as Heckman models). These models, initially described in the econometrics and health economics literature can be applied to account for unknown and unmeasured confounders in a medical setting.

This paper describes the basic concepts of Heckman's Sample Selection Models (HSSM) and presents a case study of the application of sample selection modelling approach to evaluate the effects of Cox-2/NSAID therapies in osteoarthritis patients. This case study presents empirical comparisons of methods such as propensity scores and standard logistic regression and discusses practical issues in the evaluation of sample selection models. Further, the performance of the HSSM method was evaluated using simulated data, i.e. under known conditions.

Analysis of simulated data suggests that, under our chosen scenarios, HSSM with Probit links are successful at reducing the impact of bias from a single unknown confounder. In the particular case of Cox-2/NSAIDs therapies in osteoarthritis patients, HSSM yielded similar conclusions regarding treatment effects compared to traditional logistic regression and propensity scores adjusted regression methods, but with the added benefit of IMR statistics indicating presence of unmeasured confounders. So, in observational research, assessing the sensitivity of the study conclusion to likely unmeasured confounders is essential and, we believe the use of HSSM could be a good option.

SESSION SC III

STATISTICAL COMPUTING SESSION III
A Two-stage Screening Approach to Pharmacovigilance
Speaker: Dave Smith (SAS UK)

A wide variety of techniques are used in the pharmacovigilance area to detect and confirm safety issues, ranging in sophistication from simple visualisation through signal detection algorithms (confusingly referred to as data mining by the FDA) to true data and text mining. This paper will examine these techniques, giving consideration to the personas that are appropriate to different types of data presentation. As these are commonly used in combination, the benefits and risks of such a combined approach will be examined. Finally a two stage screening approach will be proposed that should increase detection of true signals while optimising the use of clinician resources.

How integrating SAS Tools can improve Global Working in Biometrics: Vision vs Reality
Speaker: Margaret Jones (Takeda) Dave Smith (SAS)

Many companies are now adopting SAS Drug Development as part of their SAS solution. Additional SAS products can be used to allow simple statistical analysis (Enterprise Guide), self documenting Data Transformations (Data Integration Studio) and simple access to Web based reports (Business Intelligence).
This presentation will talk through the vision of how these products could work together to improve efficiency, and the reality as we roll-out the system across UK, US and Japan.

15.30 – 16.00
Coffee Break

16.00 – 17.30
PARALLEL SESSIONS:

SESSION 5A

FREE TUTORIAL: SEQUENTIAL AND ADAPTIVE DESIGNS
Speakers: Frank Bretz and Heinz Schmidli (Novartis Pharma AG)
Details under Session 4A above.

SESSION 5B

TRIAL DESIGN
Speakers: Prof Andy Grieve (King's College London);
Sara Hughes, (GSK and PSI Chair)

This session will use the example of designing a trial for pharmacogenetic (PGx) screening. Each presenter will be provided with the same background and objective: to design a trial that shows that PGx screening can reduce the incidence of side-effects associated with a particular drug. One speaker will introduce the area of PGx screening and the brief and each of the speakers will suggest trial designs and identify design issues for triallists faced with similar problems. Pharmacogenetic research is likely to become increasingly common and this session will provide an introduction to the main issues faced in its conduct and hopefully stimulate interesting discussion with the audience. To get more out of the session, why not come up with a trial design yourself? The briefing materials will be available on the PSI website prior to the conference.

SESSION 5C **META-ANALYSIS IN THE PHARMACEUTICAL INDUSTRY – ISSUES THAT ARISE**
Chairperson: Stephen Senn
Speakers: Anne Whitehead (University of Lancaster, UK); Theo Stijnen (Leiden University Medical Centre, Netherlands)

Meta-analysis methods can be usefully employed to provide a more precise estimate of the overall treatment effect, to evaluate the treatment effect in subgroups of patients, to evaluate an additional efficacy outcome that requires more power than individual trials provide, to evaluate safety in a subgroup of patients, or a rare adverse event in all patients and to improve the estimation of dose-response relationships. Issues that arise in the conduct of meta-analyses include heterogeneity in the results across studies, bias in the estimation of the treatment effect, comparisons between more than two treatment groups, and cumulative meta-analysis. These issues will be discussed and illustrated by examples.

Theo Stijnen will speak on 'Random effect meta-analysis with rare events':

Traditionally random effects meta-analysis of proportions (e.g. adverse event rates) or treatment effects (e.g. odds ratios) is based on the hierarchical normal-normal model. This model assumes a normal distribution for the random effect and a normal within study distribution of the effect estimate. If events are rare, the latter assumption might not be reasonable anymore. If the target parameter is a proportion, the normal within study distribution of the proportion might then be replaced by a binomial distribution for the number of events, leading to a hierarchical binomial-normal model. If the target parameter is an odds ratio, the inference could be based on the conditional hypergeometric-normal model. Alternatively one could use the bivariate binomial–normal model, which was recently introduced to meta-analyse simultaneously sensitivities and specificities of a diagnostic test. For meta-analysis of an incidence rate a Poisson-normal model could be used, and for an incidence density ratio a bivariate Poisson – normal model or a conditional binomial-normal model. These models seem not to be used in practice yet, although they can easily fitted nowadays using generalised linear mixed model programs, such as NLMIXED in SAS. In this talk I will compare by simulation studies the performance of these models in the situation of rare events relative to the traditional normal-normal model.

SESSION 5D **CONTRIBUTED PAPERS – Surrogate Endpoints**

Michael O'Kelly (Quintiles)
Quantifying sources of variability in readings of QT intervals

The QT interval is measured between 2 specific points in an ECG by expert cardiologists to assess cardiac safety of new drugs. ECGs from a single study may in practice be read by a team of 10 or more readers. Given the relatively subjective nature of the measurement, variability in QT interval measurements is a concern for regulatory authorities.

An experiment was used to examine variability stemming from

- the individual reader ('intra-reader' variability)
- differences between readers ('inter-reader' variability)
- the reader's choice of ECG lead

In the experiment, 29 trained readers were each asked to estimate the length of the QT interval for 100 ECGs presented in random order, and asked to repeat this estimate for the same ECGs, again presented in random order. Analysis of variance was used to estimate the above sources of variability, with variability expressed in terms of the standard deviation (SD). Among other things, the experiment also showed that the readability of individual ECGs varied considerably, so that homogeneity of variance cannot be assumed in the reading of ECGs.

Tomasz Burzykowski (MSOURCE)
Meta-analytic validation of surrogate endpoints – how many trials are needed?

Recent advances in the understanding of the biological mechanisms of disease development have resulted in the emergence of a large number of potentially effective new agents for each specific disease. In addition, there is increasing public pressure for new promising drugs to receive marketing approval as rapidly as possible. For these reasons, there is an urgent need to find ways of speeding up the new drug development process.

One possibility to achieve that is to use endpoints that could be measured earlier, more conveniently, or more frequently than the traditional ("true") endpoints like, e.g., overall survival. Such replacement endpoints are termed "surrogate" endpoints.

Methods for formal validation of candidate surrogate endpoints have been a topic of intensive research. In this paper, we focus on the so-called "meta-analytic" validation approach, that uses data from multiple randomized clinical trials and aims at measuring directly the association between the treatment effects on the surrogate and the true endpoint. In particular, we address the question: how many trials and patients are required to perform a reliable validation of a continuous surrogate for a binary true endpoint? To answer the question, we perform a simulation study. We also demonstrate the problems related to the use of a simple linear regression to estimate the correlation coefficient between the treatment effects on the surrogate and the true endpoint.

Frank Fleischer (Boehringer-Ingelheim)
A Statistical Model for the Dependence between Progression Free Survival and Overall Survival

Among the surrogate endpoints for overall survival (OS) in oncology trials, progression free survival (PFS) is more and more taking the leading role with an increasing acceptance by regulatory authorities. In general, OS is defined as the time from randomisation until death and PFS is given by the time between randomisation and progression or death, whichever occurs earlier. There have been several empirical investigations on the dependence structure between OS and PFS (in particular between the median OS and the median PFS) showing large correlations between them. Statistical models that are able to describe these dependence structures are up-to-now almost non-existing. This paper aims at filling this gap by introducing an easy-to-handle model based on exponential time-to-event distributions that describes the dependence structure between OS and PFS in mathematical terms. Based on this model explicit formulae for individual correlations are derived together with a lower bound for the individual correlation coefficient of OS and PFS which is given by the fraction of the two medians for OS and PFS. Methods for estimating the parameters of the model from real data are discussed and illustrated by case studies in non-small cell lung cancer. Furthermore, an algorithm is provided in order to predict differences in median OS based on observed differences in median PFS under some additional assumptions. The theoretical results are compared to literature data thereby showing good agreement.

SESSION SC IV STATISTICAL COMPUTING SESSION IV

Bayesian modelling with S-PLUS and the S+flexBayes library

Speaker: Andrew Jack (Insightful)
Bayesian methods are used increasingly across all phases of the pharmaceutical research and development cycle. Examples include early-phase adaptive clinical trial design, population-pk modelling and analysis of safety data in all phases. These applications are driving the need for robust, flexible and novel Bayesian analytics, graphics and reporting software.

This article and presentation reviews Insightful Corporation's approach to providing Bayes analysis software tools and solutions to support the needs of pharmaceutical development. In particular, the Insightful S-PLUS® flexBayes library (S+flexBayes), in conjunction with the collaborative S-PLUS framework, provide statisticians and statistical programmers with a flexible and productive solution for Bayes modelling. Results from these analyses are readily deployed as interactive clinical review graphics or publication reports as part of the Insightful Clinical Review and Reporting Solutions. We illustrate the S-PLUS Bayes modelling and collaborative Clinical Review Solutions with an application of the Berry and Berry (2004) model for analysis of adverse events.

What's new in SAS 9.2?
Speaker: Ian Sedgewick (SAS UK)
Featuring support for numerous new platforms, phase 1 of the SAS 9.2 release opens a new world of deployment opportunities on well known and established hardware and operating systems as well as delivering a great deal of new capabilities aimed at organizations utilizing SAS in the more traditional manner. From new SAS BASE and ODS capabilities through to numerous new statistical methods, analytical capabilities and graphing capabilities, the SAS 9.2 phase 1 release will deliver benefits that should be immediately visible to the SAS user community. This paper will give an overview of the new features that should appeal to SAS programmers and statisticians in the pharmaceutical sector.

19.30 – Gala Dinner

WEDNESDAY 21st MAY

09.00 – 10.30
PLENARY 3

LIES, DAMN LIES AND SAFETY SIGNALS: THE ANALYSIS OF EMERGING SAFETY DATA IN A LARGE, DOUBLE-BLIND PLACEBO CONTROLLED TRIAL
Chairperson: Kevin J Carroll (Chief Statistical Expert, AstraZeneca)

In an increasingly risk conscious environment for both new and established medicines, this session will explore the evaluation of a potential safety issue arising in a large, double-blind, placebo controlled clinical trial in Oncology, where randomized treatment has been provided as an adjunct to surgery of curative intent. For reasons of confidentiality, certain details will be suitably masked, though the essential issue and data will remain unchanged. Speakers will evaluate the scenario and present their analysis of the actual data. The size of the trial, the nature of the potential safety issue, its time to onset and prognosis, together with the multitude of other AEs reported by patients and epidemiological considerations serve to make for a complex problem.

Speakers will be invited to provide their expert opinion as to whether the emerging safety signal is, on balance of the available evidence, (i) most likely due to drug (ii) most likely not due to drug or (iii) indeterminate. Speakers will share their reasoning and will offer their recommendations, if any, for next steps in terms of further analysis and/or further data. Finally, the actual course of events will be revealed and general learnings shared with the audience.

10.30 – 11.15
Coffee Break

11.15 – 12.45
PLENARY 4

COMMUNICATING RISK
Speakers: Stuart Pocock (GSK) and others to be confirmed

The communication of risk is becoming more and more important, with both the public and the press needing understandable ways of communicating levels of risk about the latest disease or adverse effect of an established treatment. Recent examples include communicating the level of the risk of Avian Flu and the risks associated with the combined MMR injection.

Within the pharmaceutical industry the communication of risk is similarly important. Our colleagues in the industry, doctors, patients, regulatory bodies and reimbursement agencies also need to be able to readily understand levels of risk and to be able to interpret them.

This session will provide a review of how risk is currently communicated in the public domain and within the drug development community and will discuss advances that have been suggested to improve the communication and understanding of risk."

12.45
Closing Remarks

13.00
Lunch and Close

EXHIBITION SPACE

This year's exhibition will be held in a spacious area alongside the main conference rooms at the Hilton Hotel. This year we are offering single day and two-day stand rates – available for the Monday or Tuesday of the conference.

The cost of a stand for one of these two days is £750 (€1125). The cost for a stand on BOTH days is £1350 (€2000). These prices include day-exhibitor passes for up to two stand members – stand space costs are VAT exempt. Dinner, bed and breakfast costs are additional. Companies must provide their own public liability insurance.

SPONSORSHIP

The 2008 annual conference is a joint event, with EFSPI, the European Federation of Statisticians in the Pharmaceutical Industry. Both organisations are highly regarded within the industry, bringing together a wealth of expertise, ideas and research.

By sponsoring or exhibiting at the conference, you will have the opportunity to promote your product or service to around 200 delegates from industry representatives from across the UK and Europe. Regular attendees at our conference include senior managers and influential decision-makers from all major pharmaceutical companies and CROs in the UK and Europe. As ever, we anticipate attracting a good cross-section of younger statisticians, keen to learn and progress within the industry.

There are a number of ways in which you can become involved. The various options have been split into four price-banded tiers. If you're looking for broad exposure, platinum sponsorship is the ideal way to ensure delegates are constantly aware of your brand. Social event and meal sponsorship options provide the ideal opportunity to be associated with enjoyable events and remembered long afterwards – whilst spaces in the busy exhibition area are always keenly sought-after. This year, thanks to our European destination, you can even sponsor the 'PSI train' – a Eurostar carriage reserved for PSI delegates.

For all sponsorship and exhibition enquiries, contact Jenny Butterworth at the PSI Executive Office.

ADVERTISING

PSI provides a monthly mailing to all its members and a quarterly magazine, in both of which advertising space is also available. In addition, advertising is available on the PSI website, www.psiweb.org. For further information about advertising please email admin@psiweb.org.

PSI - EFSPI Conference 08