EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ISBS

INTERNATIONAL BIOMETRIC SOCIETY DEUTSCHE REGION

The Second International Symposium on Biopharmaceutical Statistics

"Bridging Drug Development from Research to Marketing"
March 1 – 3, 2011 • Berlin • Germany

Joint conference of the European Medicines Agency, the International Society for Biopharmaceutical Statistics, and the German Region of the International Biometric Society

With pre-conference short courses on February 27th and 28th, 2011

Organization

Executive Committee
• Frank Bretz (Cochair, Novartis) • Jie Chen (Cochair, Merck-Serono) • Richardus Vonk (Cochair, local organization) • Norbert Benda (BfArM) • Carl-Fredrik Burman (AstraZeneca) • Robert Hemmings (MHRA) • Franz König (EMA) • Spiros Vamvakas (EMA)

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Website
Wenjin Wang (Pfizer)

Local Organization
Richardus Vonk (Bayer Schering Pharma AG, President of the German Region of the International Biometric Society)

Special Conference Issue in Statistics in Medicine
Papers based on the presentations at the Second International Symposium on Biopharmaceutical Statistics may be submitted for a special conference issue of Statistics in Medicine. We invite all speakers to submit high-quality manuscripts. Submitted manuscripts will go through the usual review process. The deadline for submission is June 1, 2011.

General Information

Conference Venue
Hotel Palace Berlin
Budapester Straße 45
10787 Berlin
Germany
Tel. +49 30 2502-0
Fax: +49 30 2502-1119
www.palace.de

Conference Rooms

Short Course 1: Burgund III, 2nd floor
Short Course 2: Burgund II, 2nd floor
Short Course 3: Burgund I, 2nd floor
Short Course 4: Provence I-III, 4th floor
Short Course 5: Burgund I, 2nd floor
Short Course 6: Provence I-III, 4th floor

For participants who registered for course 1 and 2, the registration fee includes lunch. Participants who registered in two consecutive courses on Monday, February 28, the registration fee also includes lunch. Lunch vouchers for Monday, February 28, are in the conference package.

Plenary: Bordeaux I-II + Burgund III, 2nd floor
Track 1: Bordeaux I, 2nd floor
Track 2: Bordeaux II, 2nd floor
Track 3: Burgund III, 2nd floor
Track 4: Provence I-III, 4th floor
Track 5: Romanée/Petrus, 1st floor
Track 6: Montrachet, 1st floor

Lunch is served in the restaurant “Bon Dia”, on the 2nd floor, and in Burgund I + II, also on the 2nd floor.

Short Courses

Sunday, February 27, 2011

Course Number 1: 10:00 – 17:00
Recent Advances and Emerging Challenges of Clinical Trial Methodologies
• H.M. James Hung (FDA) • Sue-Jane Wang (FDA)

Monday, February 28, 2011

Course Number 2: 09:00 – 17:00
Introduction to Statistical Issues in Drug Development
• Simon Day (Roche) • Armin Koch (Medizinische Hochschule Hannover)
• Thomas Lang (AGES)

Course Number 3: 09:00 – 12:30
Statistical Approaches to Biopharmaceutical Product Safety Surveillance
• Jie Chen (Merck Serono R&D Beijing Hub) • Yi Tsong (FDA)

Course Number 4: 09:00 – 12:30
Dose Finding Studies: Methods and Implementation
• José Pinheiro (Janssen Pharmaceuticals, J&J) • Frank Bretz (Novartis)

Course Number 5: 14:00 – 17.30
Statistics in Research and Non-Clinical Safety Development
• Richardus Vonk (Global Drug Discovery Statistics, Bayer Schering Pharma AG)
• Ludwig Hothorn (Leibniz University Hannover)

Course Number 6: 14:00 – 17.30
Multiple Testing
• Willi Maurer (Novartis) • Martin Posch (Med. Universität Wien) • Franz König (Med. Universität Wien)

Program at a Glance

Tuesday, March 1, 2011

08:00 – 10:00	Registration
10:00 – 11:00	Opening Session Dr. Richardus Vonk (IBS-DR) Dr. Jie Chen (ISBS) Dr. Rob Hemmings (HMRA)
11:00 – 12:00	Keynote Presentation Christy Chuang-Stein, Statistical Research and Consulting Center, Pfizer Inc “Looking Back and Moving Forward”
13:00 – 18:10	Parallel Sessions
18:10 – 20:10	Welcome Reception

Wednesday, March 2, 2011

08:30 – 18:10	Parallel Sessions

Thursday, March 3, 2011

09:00 – 12:45	Parallel Sessions
14:00 – 16:00	Keynote Presentations Andy Grieve “Pharmaceutical Statisticians: A Profession or Technicians Under Threat” Kent Woods “The evaluation of medicines throughout the product life cycle: looking to the future”
16:00 – 16:30	Closing Session Martin Posch (European Medicines Agency) Jie Chen (ISBS) Richardus Vonk (IBS-DR)

Session Overview

Tuesday, March 1, 2011					
08:00 – 10:00	Registration				
10:00 – 11:00	Welcome: Richardus Vonk (IBS-DR), Jie Chen (ISBS), Rob Hemmings (HMRA)				
11:00 – 12:00	Plenary Session – Keynote Speaker: Christy Chuang-Stein “Looking Back and Moving Forward”				
12:00 – 13:00 Lunchbreak					
	TRACK 1	**TRACK 2**	**TRACK 3**	**TRACK 4**	**TRACK 5**
13:00 – 14:30	Adaptive Designs: 4 years CHMP Reflection Paper, 1 Year Draft FDA Guidance (Session 1 of 2) ID 9 on page 14	Drug Development in Harmony ID 13 on page 24	Best Practices in Meta-Analysis of Randomized Controlled Trials for Product Safety Regulation ID 8 on page 34	Regulatory Statistics in Europe ID 44 on page 44	Modeling Exposure-Response Data to Support Drug Development ID 16 on page 54
14:30 – 14:40 Short break					
14:40 – 16:10	Adaptive Designs: 4 years CHMP Reflection Paper, 1 Year Draft FDA Guidance (Session 2 of 2) ID 10 on page 15	Statistical Issues of Bridging and Multi-Regional Clinical Trials ID 48 on page 25	Creating Effective Visual Tools for the Assessment and Characterization of Pharmaceutical Product Safety: General Principles, Illustrations, and Public Access ID 41 on page 35	Subgroup Analyses in Randomised Controlled Trials ID 45 on page 45	Innovative Methods for Dose-Response Estimation ID 46 on page 55
16:10 – 16:40 Coffee					
16:40 – 18:10	Adaptive Designs in Clinical Trials – Where are we Today? ID 21 on page 16	Issues and Considerations in Multi-Regional Clinical Trial Design and Data Interpretation ID 22 on page 26	Statistical Challenges on Assessment of Drug Abuse Potential in Human ID 11 on page 36	Optimal Methodological Approaches to Progression Free Survival –Ffindings from a PhRMA Expert Group ID 6 on page 46	Experimental Designs in Pharmaceutical Industry ID 19 on page 56
18:10 – 20:10	Welcome Reception				

Wednesday, March 2, 2011						
	TRACK 1	**TRACK 2**	**TRACK 3**	**TRACK 4**	**TRACK 5**	**TRACK 6**
08:30 – 10:00	Applications of Adaptive Designs in Early to Mid-Phase Clinical Trials in Drug Development ID 12 on page 17	The Impact of Globalization on the Statistical Services ID 26 on page 27	Maximizing Information in Early Development Trials ID 3 on page 37	Drug Development in Children ID 43 on page 47	DMC Models and Interim Decision Making ID 37 on page 57	Consideration of Design of Experiments for Dynamic Processes in Supporting the ICH Q8 Definition of Design Space with Applications ID 33 on page 64
10:00 – 10:30 Coffee						
10:30 – 12:00	Adaptive Drug Development Programs ID 14 on page 18	The Future of Biostatistics and Statistical Programming in the Pharmaceutical Industry in an Ever Increasing Outsourced / Offshored Environment (Panel Discussion) ID 31 on page 28	Model-Based Drug Development ID 7 on page 38	Bayesian Methods for Evaluating Clinical Safety Data ID 34 on page 49	Applying Decision Analysis Methods to Drug Development ID 108 on page 58	Advanced Statistical Methods in Early Drug Development ID 103 on page 65
12:00 – 13:00 Lunchbreak						
13:00 – 14:30	To Adapt or not to Adapt? How Adaptive Designs have Reshaped the Clinical Trial Paradigm. ID 4 on page 19	Responder Analysis ID 38 on page 29	Missing Data in Clinical Trials with Discrete Endpoints ID 23 on page 39	Discounting and Pooling in Non-Inferiority Trials ID 20 on page 48	Role of Statistics in Valuation and Optimization of Drug Development Portfolios ID 25 on page 59	Non-Clinical Statistics by Simultaneous Inference Approaches ID 102 on page 66

Wednesday, March 2, 2011 (Continued)						
	TRACK 1	**TRACK 2**	**TRACK 3**	**TRACK 4**	**TRACK 5**	**TRACK 6**
14:30 – 14:40 Short break						
14:40 – 16:10	Adaptive Clinical Trial Designs: New Paradigm in Clinical Development ID 5 on page 20	Statistical Issues in Comparative Effectiveness Research ID 24 on page 30	The National Academy of Science' & EMA Report on Missing Data ID 28 on page 40	Statistical Computing for High Dimensional Data ID 109 on page 50	Using modeling and simulation in getting treatments to market ID 36 on page 60	
16:10 – 16:40 Coffee						
16:40 – 18:10	Innovative study designs for multiple sclerosis ID 2 on page 21	Decisions in the Context of Reimbursement and Drug Approval - Differences and Similarities ID 40 on page 31	Missing Data and the Role of Mixed Models ID 105 on page 41	Bayesian Designs in Pharma: pros and cons ID 29 on page 51	p-values, treatment effect estimation and bias in clinical trials with multiple endpoints – what needs to be adjusted? ID 1 on page 61	

Thursday, March 3, 2011					
	TRACK 1	**TRACK 2**	**TRACK 3**	**TRACK 4**	**TRACK 5**
09:00 – 10:30	Simultaneous Confidence Intervals in Clinical Trials ID 101 on page 22	Distribution Characteristics and Modeling of Some Commonly Used Measurements in Pharmacoeconomics and Outcome Research ID 42 on page 32	Statistical methods in pharmacovigilance – where do we go from here? ID 35 on page 42	Recent Development of Bayesian Methodologies in Clinical Trials ID 32 on page 52	Expanding the scope of development decisions to commercial impact ID 39 on page 62
10:30 – 11:15 Coffee					
11:15 – 12:45	Multiplicity Issues in Clinical Trials ID 18 on page 23	Confronting Statistical Challenges in Vaccine Trials ID 17 on page 33	Statistical Issues on Thorough QT Clinical Trials ID 47 on page 43	Novel Bayesian Decision Procedures in Clinical Trials ID 106 on page 53	Biomarker in the Pharmaceutical Industry ID 30 on page 63
12:45 – 14:00 Lunchbreak					
14:00 – 15:00	Plenary Session – Keynote Speaker: Andy Grieve “Pharmaceutical Statisticians: A Profession or Technicians Under Threat”				
15:00 – 16:00	Plenary Session – Keynote Speaker: Kent Woods “The evaluation of medicines throughout the product life cycle: looking to the future”				
16:00 – 16:30	Conference End: Richardus Vonk (IBS-DR), Jie Chen (ISBS), Martin Posch (EMA)				
16:30 – 17:00 Coffee					

Keynote Presentations

Looking Back and Moving Forward

Christy Chuang-Stein
Statistical Research and Consulting Center
Pfizer Inc

Abstract

Vaccination, control of infectious diseases and decline in deaths from coronary heart disease and stroke were touted as 3 of the top 10 greatest public health achievements of the 20th century. Better glucose control and management of major CNS disorders have brought quality of life to countless suffers. Pharmaceutical industry, with its innovations and scientific focus, contributed greatly to these advancements. The 21st century brings new opportunities in the areas of genetic disease and geriatric medicine. Yet, an industry, once respected and productive, found itself face demanding expectations from the public, close government scrutiny and a less-promising pipeline. The public is expecting the industry to develop breakthrough life-saving medicines that are safe and affordable. Government officials question the ethics of industry's marketing practice. Pharmaceutical companies increasingly rely on mergers and acquisitions to increase the pipeline prospect. Yet, despite all these, pharmaceutical industry continues to be an exciting place to work. Cutting edge technology has helped fuel information explosion in biology and immunology. Efforts to transform information to useful knowledge have led quantitative scientists to look for new decision-making paradigms. The new business and operating model, with a focus on agility, has challenged the traditionally long drawn-out product development process. In this presentation, we will examine the environment we are in from the business, regulatory and personal perspective. We will discuss the core competencies of statisticians in the 21st century and how statisticians can help further shape drug development in this fast-moving environment. The latter includes moving towards a highly quantitative drug development process, better articulation of the benefit and risk balance and closer industry-academia-government collaborations. Statisticians need to promote statistical excellence and champion statistical influence. Most importantly, statisticians need to advocate transparent decisions to help bring integrity, trust and pride back to an industry that had made substantial contributions to the medical evolutions in the 20th century.

The evaluation of medicines throughout the product life cycle: looking to the future.

Kent Woods MD SM FMedSci
Chief executive
Medicines and Healthcare products Regulatory Agency, UK

Abstract

Despite great advances in the basic biomedical sciences, the development of new medicines to meet unmet health needs faces increasing difficulties. The information requirements of developers, regulators and payers have increased to support their key decisions. The time and cost imposed in gathering that information is an important factor in determining the economic feasibility of pharmaceutical innovation. What efficiencies are possible in the acquisition and analysis of data throughout the product life cycle? How can quantitative sciences be better used to generate and synthesise data so that key decisions from proof of concept through to licensing, re-imbursement and post-marketing safety are properly informed? This presentation will give an overview of options in the design of clinical trials, the integration of epidemiological data gained from population exposure and the progressive refinement of knowledge of efficacy, safety, effectiveness and cost-effectiveness over time. Industry, regulators, HTA bodies and payers will be helped to make timely and appropriate decisions by optimum study designs and the full utilisation of data generated within the healthcare system.

Pharmaceutical Statisticians: A Profession or Technicians Under Threat

Andy Grieve
Senior Vice President Clinical Trial Methodology
ClinResearch GmbH, Cologne

Abstract

The position of statisticians in pharmaceutical companies has improved greatly since the first moves to establish their own organisations in the 1970's. The introduction of GCP requiring statisticians to be involved; the development of statistical guidelines, for example ICH E9 and the recognition by governments and regulatory agencies of the importance of statisticians and statistical thinking as witnessed by the FDA's Critical Path Initiative and the EU's Innovative Medicines Initiative. Nonetheless, there are threats to pharmaceutical statisticians, not least from academic medical journals requiring independent statistical analysis by "academic statisticians". In this talk I look at the causes of these threats and suggest that the solution is partially in the hands of pharmaceutical statisticians themselves.

Session Details

Topic		Adaptive Designs: 5 years CHMP Reflection Paper, 1 year draft FDA Guidance - Where are we now?	
Track	1	**Time**	Tuesday, March 1, 13:00 – 14:30
ID		9	
Title		Adaptive Designs: 4 years CHMP Reflection Paper, 1 year draft FDA Guidance (Session 1 of 2)	
Organizer		Joint IBS-DR and -ROeS Working Group on Adaptive Designs and Multiple Testing Procedures (Marc Vandemeulebroecke, Novartis)	
Chair		Martin Posch	Medical University of Vienna

Abstract

Adaptive designs continue to attract great attention from academia, industry and regulatory agencies. Methodological research has been prolific, and a number of practical applications have followed. From the regulators' side, two position papers have recently been issued: the CHMP Reflection Paper on "Methodological Issues in Confirmatory Clinical Trials with Flexible Design and Analysis Plan" (2007), and the draft FDA guidance on "Adaptive Design Clinical Trials for Drugs and Biologics" (2010). In the present session, we comment on these position papers and discuss their reception and impact.

Speakers

Sue-Jane Wang	FDA	US FDA draft guidance - a year later
Armin Koch	University of Hannover	European reflection paper: Need for revision?
Brenda Gaydos	Eli Lilly / PhRMA LDKIT	An Industry Perspective on the EMA and FDA Adaptive Design Guidances
Marc Vandemeulebroecke	Novartis / IBS-DR and IBS-ROeS WG on AD+MCP	Some comments on recent guidances for adaptive design clinical trials

Topic	Adaptive Designs: 5 years CHMP Reflection Paper, 1 year draft FDA Guidance - Where are we now?		
Track	1	**Time**	Tuesday, March 1, 14:40 – 16:10
ID	10		
Title	Adaptive Designs: 4 years CHMP Reflection Paper, 1 year draft FDA Guidance (Session 2 of 2)		
Organizer	Joint IBS-DR and -ROeS Working Group on Adaptive Designs and Multiple Testing Procedures (Marc Vandemeulebroecke, Novartis)		
Chair	Michael Branson	Novartis	

Abstract

Adaptive designs continue to attract great attention from academia, industry and regulatory agencies. Methodological research has been prolific, and a number of practical applications have followed. From the regulators' side, two position papers have recently been issued: the CHMP Reflection Paper on "Methodological Issues in Confirmatory Clinical Trials with Flexible Design and Analysis Plan" (2007), and the draft FDA guidance on "Adaptive Design Clinical Trials for Drugs and Biologics" (2010). This is the second of two sessions discussing this topic, including a case study, some points of controversy and a panel discussion.

Speakers

Frank Miller	Astra Zeneca	Adaptive dose-finding in Phase IIa/b: Approaches for design and type I error control
Michael Proschan	NIH/NIAID	Adaptations made before unblinding
Previous speakers	--	Panel discussion on adaptive designs and emerging regulatory positions

Topic		Adaptive Designs: 5 years CHMP Reflection Paper, 1 year draft FDA Guidance - Where are we now?	
Track	1	**Time**	Tuesday, March 1, 16:40 – 18:10
ID		21	
Title		Adaptive Designs in Clinical Trials – Where are we today?	
Organizer		Olga Marchenko	I3 Statprobe
Chair		Olga Marchenko	I3 Statprobe

Abstract

The release of EMA reflection paper on Adaptive Designs in 2007 followed by the release of the FDA draft guidance on Adaptive Design Clinical Trials in 2010 considerably helped advance definition and application of adaptive and well-controlled trials. Both documents recognized an importance of adaptive designs in clinical trials and outlined expectations, prerequisites, problems and pitfalls. Adaptive designs provide new ways to improve quality, speed, and efficiency of drug development when appropriately implemented. During the last decade, adaptive designs proved to be highly beneficial in clinical development although their novelty and distinctions raise a number of challenges. New approaches impact all stages of business from packaging to reporting and bring new challenges to the existing structure. In this session, presenters will share their experience with adaptive designs through case studies, discuss logistical and operational challenges that adaptive designs bring and ways to handle them. Good practices for the planning and implementation of adaptive designs from experiences gained in industry will be discussed during this session.

Speakers

Brenda Gaydos	Lilly	A Sample of Adaptive Dose-Finding Case Studies
Olga Marchenko	I3 Statprobe	Adaptive Designs in Confirmatory Clinical Trials: Case Studies
Jose Pinheiro	Johnson&Johnson	Discussant: Adaptive designs beyond the fad: Advantages, hurdles, and limitations

Topic	Adaptive Designs: 5 years CHMP Reflection Paper, 1 year draft FDA Guidance - Where are we now?		
Track	1	**Time**	Wednesday, March 2, 08:30 – 10:00
ID	12		
Title	Applications of Adaptive Designs in early to mid-phase clinical trials in drug development		
Organizer	Amit Bhattacharyya	GSK	
Chair	Amit Bhattacharyya	GSK	

Abstract

In recent years, the use of adaptive designs is more and more being considered as an efficient and optimal way of designing clinical trials. Most of the applications are prevalent in early to mid-phase trials, primarily in phase IIa and IIb trials. In view of this becoming popular in today's environment, this session would focus on examples of the successful application in studies across the pharmaceutical industry so that the pros and cons are discussed and debated from the industry and regulatory aspects.

Speakers

Sergei Leonov	GlaxoSmithKline	Application of adaptive model-based designs in early development
Jose Pinheiro	Johnson & Johnson Pharmaceutical R&D	Adaptive Designs in the Learning Phase of Clinical Development
Vladimir Dragalin	Quintiles	Adaptive Designs for Trials of Cognitive Impairment Associated with Schizophrenia
Sue-Jane Wang	US FDA	Discussant

Topic		Statistics in Decision Analysis / Go – No Go Decisions	
Track	1	**Time**	Wednesday, March 2, 10:30 – 12:00
ID		14	
Title		Adaptive Drug Development Programs	
Organizer		Carl-Fredrik Burman	AstraZeneca
Chair		José Pinheiro	Johnson & Johnson

Abstract

The design of clinical trial programmes is much more challenging than the design of separate clinical trials.
While lot of research has gone into areas of experimental design, optimal designs, adaptive designs, etc., very little work has been done on optimizing entire development programs. Important aspects to study in the program problem are go / no go decisions, and the quantification of the value of early phase information for these decisions. Adaptive features between and within studies also deserve attention. Bayesian decision analysis is used for internal optimization, while the regulatory response is modeled based on frequentist analysis of efficacy and of benefit/risk.

The presentations in this session are built on the work in the PhRMA/DIA workstream on adaptive programmes. The goal of this workstream, with representatives from a number of companies and universities, is to define a generic model for clinical programs and to optimize application examples from a number of therapeutic areas.

Speakers

Carl-Fredrik Burman	AstraZeneca	A model for drug development
Christopher Jennison	Bath University	Optimising the Phase IIB, Phase III process
Nitin Patel and James Bolognese	Cytel	Designing Adaptive Programs for Phases 2b and 3 in Neuropathic Pain
David Wright	MHRA	Discussant

Topic	Adaptive Designs: 5 years CHMP Reflection Paper, 1 year draft FDA Guidance - Where are we now?		
Track	1	**Time**	Wednesday, March 2, 13:00 – 14:30
ID	4		
Title	To adapt or not to adapt? How adaptive designs have reshaped the clinical trial paradigm.		
Organizer	Frank Fan	Vertex Pharmaceuticals	
Chair	Willi Maurer	Novartis	

Abstract

During the past years, adaptive design (AD) clinical trials have gradually evolved from a novel ideal to more like a standard norm in pharmaceutical industry. In light of this new clinical trial paradigm, regulatory agencies have also expanded their attention and issued (draft) guidance on this topic. In this session, experts and opinion leaders from both industry and regulatory as well as U.S. and EU side will discuss their own experience and perspectives of AD. Topics include the growing popularity of AD within companies and its growing 'concerns' within agencies on the other hand. Some industry feedback to the recent FDA draft guidance on the AD will also be discussed.

Speakers

Jeff Maca	Novartis	Designing an adaptive study, which allows both the duration of the study and the sample size to be modified, based on interim results for key secondary variables
Keaven Anderson	Merck	The Merck ADAPT Initiative, 2008-2010
Loïc Darchy	Sanofi-Aventis	Interim dose selection in phase III - The TAO study with Otamixaban in unstable angina / Non ST segment elevation myocardial infarction
Martin Posch	Medical University of Vienna	Discussant
Sue-Jane Wang	FDA	Discussant

Topic	Adaptive Designs: 5 years CHMP Reflection Paper, 1 year draft FDA Guidance - Where are we now?		
Track	1	**Time**	Wednesday, March 2, 14:40 – 16:10
ID	5		
Title	Adaptive Clinical Trial Designs: New Paradigm in Clinical Development		
Organizer	Ivan Chan	Merck	
Chair	Ivan Chan	Merck	

Abstract

In an effort to improve the global clinical development of new medicine, adaptive designs have been gaining popularity in all phases of clinical development. In general, adaptive designs are developed to increase the flexibility of clinical trials, such as modification of sample size, dropping ineffective treatment arms, enriching study populations, or early stopping for either futility or efficacy. Such designs are useful in both the “learning” and “confirming” phases of clinical development. In this session, speakers will introduce the concept of adaptive clinical trial designs and highlight the related statistical issues, challenges in operation and implementation, and regulatory experiences. Then speakers will offer some practical guidance on how to manage these challenges from different perspectives.

Speakers

Jerald Schindler	Merck	The Next Wave of Adaptive Trials: Broad Implementation and Efficient Clinical Development
Frank Bretz	Novartis	On the Efficiency of Adaptive Designs
Cyrus Mehta	Cytel	Combining Design and Execution of Adaptive Clinical Trials: Case Studies and Software
Sue-Jane Wang	US FDA	Discussant

Topic	Adaptive Design for Clinical trials		
Track	1	**Time**	Wednesday, March 2, 16:40 – 18:10
ID	2		
Title	Innovative study designs for multiple sclerosis		
Organizer	Tim Friede	University Medical Center Göttingen, Germany	
Chair	Tim Friede	University Medical Center Göttingen, Germany	

Abstract

Multiple sclerosis (MS) is a chronic neurological disease associated with irreversible progression of physical disability. It is the most common neurological disorder in younger adults affecting up to 2.5 million people worldwide. In this session various approaches to study design will be explored that have the potential to speed up clinical development in MS. These will include adaptive designs for clinical trials (e.g. adaptive seamless Phase II/III designs) and innovative choices of endpoints (e.g. MRI).

Speakers

Heinz Schmidli	Novartis Pharma AG, Basel, Switzerland	Blinded Sample Size Re-estimation with Negative Binomial Counts in Superiority and Non-inferiority Trials
Sue Todd	University of Reading	A novel adaptive design strategy increases the efficiency of clinical trials in secondary progressive multiple sclerosis
Maria Pia Sormani	University of Genoa, Italy	Magnetic Resonance Imaging as a Potential Surrogate for Relapses in Multiple Sclerosis: A Meta-analytic Approach
Jose Pinheiro	Johnson & Johnson Pharmaceuticals R&D	Discussant

Topic		Multiplicity Issues in Clinical Trials	
Track	1	**Time**	Thursday, March 3, 09:00 – 10:30
ID		101	
Title		Simultaneous Confidence Intervals in Clinical Trials	
Organizer			
Chair		Frank Bretz	Novartis
Abstract			
Speakers			
Mario Hasler		Christian-Albrechts-University of Kiel, Germany	Multiple Contrasts Tests for Multiple Endpoints
Ludwig Hothorn		Leibniz Universität Hannover	Demonstrating non-inferiority for multiple endpoints in multi-armed studies
Frank Schaarschmidt		Leibniz Universität Hannover	Simultaneous confidence limits for ratios of fixed effects parameters in linear mixed models
Björn Bornkamp		Novartis	Optimally tuning multiple comparison procedures

Topic		Multiplicity Issues in Clinical Trials	
Track	1	**Time**	Thursday, March 3, 11:15 – 12:45
ID		18	
Title		Multiplicity Issues in Clinical Trials	
Organizer		Frank Bretz	Novartis
Chair		Frank Bretz	Novartis

Abstract

Methods for addressing multiplicity issues have attracted much attention in the statistical literature over the past twenty years. Recent developments in this area include new approaches to defining false-positive error rates and new classes of multiple comparison procedures. The goal of this session is to highlight important aspects in the fast growing area of multiple comparison research that are relevant to pharmaceutical applications. The session will focus on multiplicity induced by multiple endpoints as well as other multiple comparison problems. This will be discussed from the regulatory, academic and industry viewpoint.

Speakers

Franz König	Medical University of Vienna	To p or not to p strict - what should be questioned?
David Li	Pfizer	Testing individual hypothesis marginally at 0.05: when and how
Willi Maurer	Novartis	Extended sequentially rejective graphical multiple test procedures for clinical trials
Mohammad Huque	FDA	Discussant

Topic		Globalization and its Impact on Drug Development in the Different Regions	
Track	2	**Time**	Tuesday, March 1, 13:00 – 14:30
ID		13	
Title		Drug Development in Harmony	
Organizer		Jorgen Seldrup	Quintiles
Chair		Jorgen Seldrup	Quintiles

Abstract

The need for a common set of 'rules' for the development of new medicinal product has long been high on the agenda for all stakeholders – patients, caregivers, society/regulators and the pharmaceutical industry. Recent regulatory initiatives have once again reminded us of the relevance of speeding up the drug development process in order to make new medicines available to patients faster and more efficiently. This session plans to hear from regulators what efforts continue to be made to shorten the road to marketing authorization and how this is being pursued in the common interest of one submission being acceptable in the global world. An industry perspective will supplement these efforts. In part at a high level, the session will also explore how individual disciplines within the regulatory agencies, academia and the pharmaceutical industry strive to work together to create better access to better medicines.

Speakers

Jorgen Seldrup	Quintiles	Whatever happened to harmonisation?
Yuki Ando	Pharmaceuticals and Medical Devices Agency, Japan	Global drug development – How much data should we obtain, when and from which regions?
Robert Hemmings	MHRA, Biostatistics Working Party	The A to E of global development
All speakers plus James Hung (FDA)		Panel Discussion

Topic		Globalization and its Impact on Drug Development in the Different Regions	
Track	2	**Time**	Tuesday, March 1, 14:40 – 16:10
ID		48	
Title		Statistical issues of bridging and multi-regional clinical trials	
Organizer		Yi Tsong	FDA
Chair		Joanne Zhang	FDA

Abstract

In 1998, the International Conference on Harmonization (ICH) published a guidance to facilitate the registration of medicines among ICH regions including European Union, the United States of America, and Japan by recommending a framework for evaluating the impact of ethnic factors on a medicine's effect such as its efficacy and safety at a particular dosage and dose regimen (ICH E5, 1998). The purpose of ICH E5 is not only to evaluate the ethnic factor influence on safety, efficacy, dosage and dose regimen, but also more importantly to minimize duplication of clinical data allow extrapolation of foreign clinical data to a new region. The eleventh question and answer (Q&A) to ICH E5 (1998) was published in 2006. This Q&A describes points to consider for evaluating the possibility of bridging among regions by a multiregional trial. The primary objective of a multiregional bridging trial is to show the overall efficacy of a drug in all participating regions while also evaluating the possibility of applying the overall trial results to each region. This session consists of two presentations on the statistical considerations of designing and analyzing a bridging trial. The other two presentations will cover the statistical considerations in the designing and assessing the efficacy in the local regions in a multi-regional trial.

Speakers

Chin-Fu Hsiao	National Health Research Institutes, Taiwan	Statistical Methods for Bridging Studies
Yoko Tanaka	Lilly Company	Multiregional Drug Development: Asking the Right Questions and Getting the Right Answers
Hsiao-Hui Tsou	NHRI-Taiwan	Weighted evidence approach of bridging study
Yi Tsong	FDA	Discussant: Evaluation of Regional Treatment Effect in a Multi-Regional Clinical Trial

Topic		Globalization and its Impact on Drug Development in the Different Regions	
Track	2	**Time**	Tuesday, March 1, 16:40 – 18:10
ID		22	
Title		Issues and considerations in multi-regional clinical trial design and data interpretation	
Organizer		Hui Quan	sanofi-aventis
Chair		Loic Darchy	sanofi-aventis

Abstract

Multi-regional clinical trials (MRCTs) have been widely used for efficient global new drug developments. These trials present us tremendous opportunities but also significant challenges. We need to separate issues for trial design and data interpretation. For trial design, many factors have to be taken into consideration including trial objective and setting. Assumptions are usually made regarding homogeneity to slight heterogeneity of treatment effects for sample size and power calculations for both the overall treatment effect assessment and consistency assessment of treatment effects across regions. We also have to be cautious when interpreting trial results due to potential lack of power for consistency assessment and impact of intrinsic and extrinsic factors. In this session, issues and considerations in MRCT design and data interpretation will be discussed.

Speakers

Hui Quan	sanofi-aventis	Methods for assessing consistency of treatment effects in multi-regional trials
James Hung	FDA	A Regulatory Perspective on Emerging Challenges in Planning and Analyzing Multi-regional Clinical Trials
Hiroyuki Uesaka	Osaka University	Statistical considerations for a multiregional bridging trial
Kevin Carroll	Astrazeneca	Discussant

Topic		Globalization and its Impact on Drug Development in the Different Regions	
Track	2	**Time**	Wednesday, March 2, 08:30 – 10:00
ID		26	
Title		The Impact of Globalization on the Statistical Services	
Organizer		Tzy-Jyun Yao	University of Hong Kong
Chair		Tzy-Jyun Yao	University of Hong Kong

Abstract

The globalization of drug development has shifted about a quarter of study sites of all clinical trials registered in ClinTrials.gov to regions outside of North America and Western Europe. This session plans to present how this phenomenon has impacted on drug development, from the aspect in hardware: the development in infrastructure, the establishment of bio-statistical units, to the aspect in software: statistical designs and specific analyses of the global trials.

Speakers

Philip Hougaard	H. Lundbeck A/S	Experience from working in a biostatistics department, integrated over three continents
Masahiko Ohishi	MSD, Japan	Some considerations on regional/Ethic differences in multiregional clinical trials
Paul Gallo	Novartis	Issues in implementing statistical evaluations of regional consistency
Jorgen Seldrup	Quintiles	Discussant

Topic		Globalization and its Impact on Drug Development in the Different Regions	
Track	2	**Time**	Wednesday, March 2, 10:30 – 12:00
ID		31	
Title		The future of Biostatistics and Statistical Programming in the pharmaceutical industry in an ever increasing outsourced / offshored environment (Panel Discussion)	
Organizer		Dave Laha	Cognizant
Chair		Dave Laha	Cognizant

Abstract

The global pharmaceutical and biotechnology industry is in the midst of challenging times. In the past two years, this market has grown at the slowest rate in the last decade, and is expected to slow down further. This has forced the industry to look at three key areas for creating and sustaining profitable growth – new technology, emerging markets and efficiency enhancement. With strong focus on implementing cost containment - restructuring within as well as outsourcing both core and non-core functions to emerging markets is no more an option but a strategic imperative for pharmaceutical companies. Under this backdrop, biostatistical and statistical programming services are one of many functional areas that are increasingly sourced from emerging markets such as India or China. With the availability of a qualified resource pool in these countries, it provides a cost arbitrage to sponsor companies that addresses their cost containment measures. It would be a “win-win” solution if not for its challenges:

• What challenges exist in quality and timeliness of delivery, how do we address and ensure this become a viable model with little pain

• What training can be provided to offshore resources to better meet expectations and industry challenges

• What is the role of next generation biostatisticians or statistical programmers at pharma companies

• Share some offshore challenges faced in your organization, and whether there has been acceptable resolution and how it was achieved

Speakers

Kannan Natarajan	Sr. VP. Biometrics and Data Mgmt., Novartis
Amit Bhattacharyya	Sr. Director, Quantitative Sciences, GSK
Michael Ostland	Global Head Metabolism Biostatistics and Statistical Methods & Research, Roche
William Malbecq	Sr. Director Late Development Statistics, ex-US Subsidiaries, Merck MSD
Jie Chen	Director, Biostatistics and Statistical Programming, Merck Serono (Beijing)
Dr. Chitra Lele	Chief Scientific Officer, Sciformix Corp., India

Topic			
Track	2	**Time**	Wednesday, March 2, 13:00 – 14:30
ID		38	
Title		Responder Analysis	
Organizer		Christoph Gerlinger	Bayer
		Michael Kunz	Bayer
Chair		Franz Koenig	Medical University of Vienna

Abstract

Responder Analyses have been present in the statistical literature for a long time and research continues until today. These analyses also play a role in many regulatory guidance documents, both disease specific, but also methodological ones. Responder analyses are often mentioned in connection with the assessment of clinical relevance. Despite the presence of responder analyses in regulatory guidance documents its use is for several reasons seen rather critical by statisticians. In the presentations the different aspects of responder analyses will be discussed including both theoretical, but also practical aspects of responder analyses.

Speakers

Michael Kunz	Bayer	Responder Analyses in the Drug Development Process - Some Critical Aspects
Christoph Gerlinger	Bayer	A practical method to define responders for patient reported outcomes
Meinhard Kieser	University of Heidelberg	In response to responders – some considerations on planning and analysis
Norbert Benda	BfArM	Discussant

Topic		Comparative Effectiveness Research	
Track	2	**Time**	Wednesday, March 2, 14:40 – 16:10
ID		24	
Title		Statistical Issues in Comparative Effectiveness Research	
Organizer		Demissie Alemayehu and Joe Cappelleri	Pfizer
Chair		Demissie Alemayehu	Pfizer

Abstract

Comparative effectiveness research (CER) has received sizeable attention in recent years, thanks in part to its incorporation in the American Recovery and Reinvestment Act of 2009. Given the considerable implication of the topic on healthcare delivery, much methodological work is needed for its proper implementation and eventual success. In this session, current approaches in CER will be reviewed, with special emphasis on the statistical issues associated with commonly used methods and on potential areas for further research. Particular attention will be paid to mixed and indirect treatment comparisons, Bayesian approaches, and observational data analysis in the context of CER.

Speakers

Joe Cappelleri and Demissie Alemayehu	Pfizer	Good Research Practices for Nonrandomized Studies of Treatment Effects Using Secondary Data Sources
Anirban Basu	U of Washington	Estimating decision-relevant comparative effects using instrumental variables
Jeroen Jansen	MAPI Values	Network meta-analysis of time-to-event data
Jesse Berlin	Johnson & Johnson	Discussant

Topic		Incorporating Payer Perspectives in Drug Development – The (statistical) needs of regulators, reimbursers (e.g. Nice, IQWIG) and Industry	
Track	2	**Time**	Wednesday, March 2, 16:40 – 18:10
ID		40	
Title		Decisions in the Context of Reimbursement and Drug Approval - Differences and Similarities	
Organizer		Ralf Bender	Institute for Quality and Efficiency in Health Care (IQWiG)
Chair		Bruno Flamion	SAWP, EMA/CHMP

Abstract

A frequent misconception is the assumption that drug approval automatically demonstrates additional benefit justifying reimbursement. However, although the available data and the general principles of drug approval and reimbursement decisions may be similar, the specific assessment goals and conclusions may be different. This session will discuss similarities and differences in the context of drug approval and reimbursement with a special focus on heterogeneity and subgroup analyses.

Speakers

Ralf Bender, Armin Koch	IQWiG, Cologne, University of Hanover	Different assessment goals may lead to different conclusions regarding subgroup analyses
Guido Skipka	IQWiG, Cologne	Intervention effects in the case of heterogeneity between three subgroups
Theodor Framke, Anika Großhennig, Armin Koch	Institute for Biometry, Hanover Medical School	Cochran's Q for the assessment of heterogeneity
Christoph Gerlinger	Bayer Schering Pharma	Biometrical project planning to address drug approval and reimbursement simultaneously

Topic		Pharmacoeconomics and Outcome Research	
Track	2	**Time**	Thursday, March 3, 09:00 – 10:30
ID		42	
Title		Distribution Characteristics and Modeling of Some Commonly Used Measurements in Pharmacoeconomics and Outcome Research (Health Utility Index, Quality of Life, Medication Compliance)	
Organizer		Ying Zhang	Acadia University, Canada
Chair		Ralf Bender	IQWiG, Germany

Abstract

This session focuses on the methodology discussion about some commonly used measurements in
Pharmacoeconomics and Outcome Research such as health utility index, quality of life and medication compliance. The analysis for these so-called patient reported outcomes is often challenging due to its complex measurement system and the human natures. The special methodology research is needed (Austin & Escobar, 2003; Zhang, Cabilio, Grubisic and Gwadry-Sridhar, 2010). The proposed talks will discuss the problems often arising in the literature in the case that the outcome measure is considered either as a response or as an explanatory variable. This session will cover the topics of the distribution characteristics of those measurements, and the corresponding issues associated with modeling.

Speakers

Dyfrig Hughes	Bangor University, UK	Distributional properties of costs and QALYs in pharmacoeconomics research
Femida Gwadry-Sridhar	University of Western Ontario, Canada	Applying an evidence base in medication compliance-weighing the costs and outcomes in chronic disease from a provider, payer and patient perspective
Ying Zhang	Acadia University, Canada	What are the issues from the distributional perspective when using HUI and other patient-reported outcomes in the data analysis?

Topic		Statistics in Vaccine Trials	
Track	2	**Time**	Thursday, March 3, 11:15 – 12:45
ID		17	
Title		Confronting Statistical Challenges in Vaccine Trials	
Organizer		G. Frank Liu	Merck & Co. Inc
		Jingyee Kou	US FDA/CBER
Chair		G. Frank Liu	Merck & Co. Inc

Abstract

Vaccines are biological products and many of them are developed for disease protection and prevention. Because of biological nature, there are many unique statistical issues and challenges in vaccine clinical trials. Some examples are: the rigorous safety requirement because vaccines are to be administrated to millions of healthy individuals; large studies needed to demonstrate efficacy due to low incidence rate of disease and strict requirement on a positive lower bound to show adequate efficacy; identifying and using biomarkers based on correlates of protection; using acceptability criteria to evaluate vaccine responses; and application of innovative methods such as adaptive designs in vaccine trials. In this session, speakers from the regulatory agency and pharmaceutical industries will talk about some of those unique features and challenges in design and analysis of vaccine trials, and discussing the perspectives from trial sponsors and from regulatory point of view

Speakers

Jos Nauta	Abbott	A generalized worst-case sensitivity analysis for a single seroresponse rate
Ivan Chan	Merck & Co. Inc.	Use of adaptive designs in vaccine studies
Andrew Dunning	Sanofi-pasteur	Post-licensure Immunological Correlates of Protection: Experimental Designs and Statistical Methods

Topic		Use of Meta-analysis in Regulatory Safety Assessments	
Track	3	**Time**	Tuesday, March 1, 13:00 – 14:30
ID		8	
Title		Best Practices in Meta-analysis of Randomized controlled Trials for Product Safety Regulation	
Organizer		George Rochester	FDA
Chair		Juergen Kuebler	Novartis

Abstract

Regulation of drugs and biologics require monitoring of the safety profile throughout the lifecycle of a product. FDA is working on guidance for industry, and policy and procedures for reviewers, on best practices in meta-analysis of randomized controlled trials (RCTs) for medical product safety evaluation. The typical pre-market dossier is limited to characterize the safety of products with respect to the serious and uncommon (rare) adverse events. While it is desirable to conduct large simple safety studies to study certain adverse events of special interest it is not always feasible and the information needed for regulatory actions may not be available in real time. Among the tools for regulatory actions is to synthesis the available data, retrospective review of what has been done; or prospectively plan the assessment of an anticipated safety issue over a product development program. This session will discuss the unique features of meta-analysis for safety for regulatory purposes for both the prospective and retrospective cases. Specifically, we will discuss principles and best practices in protocol development, conduct, reporting, weight of evidence, and interpretation, and regulatory implications of the use meta-analyses as a tool for safety signal evaluation of rare events. Case studies will be presented.

Speakers

George Rochester	FDA	Overview of best practices and principles from the regulatory perspective
Jesse Berlin	Johnson & Johnson Co.	Perspectives from a Regulated Industry Statistician
Ekkehard Glimm	Novartis	Meta-Analysis of Safety Data with Rare Events
All speakers, Thomas Lang, Jürgen Kübler		Panel Discussion

Topic		Safety Graphics	
Track	3	**Time**	Tuesday, March 1, 14:40 – 16:10
ID		41	
Title		Creating Effective Visual Tools for the Assessment and Characterization of Pharmaceutical Product Safety: General Principles, Illustrations, and Public Access	
Organizer		Andreas Brueckner	Bayer Schering Pharma
Chair		Andreas Brueckner	Bayer Schering Pharma

Abstract

General principles for creating effective visualization tools will be reviewed, and examples which illustrate the effective and efficient communication of safety information based on clinical trial data obtained during the product development program will presented and discussed. The use of the CTSpedia website will also be described. This site allows public access to all of the visualization tools developed by the FDA/Industry/Academia Safety Graphics Working Group, and it provides an opportunity for users to contribute new graphics or suggest modifications for existing graphics.

Speakers

Fabrice Bancken	Novartis	General visualization principles - concepts and examples
Anziano, Richard	Pfizer	QTc Clinical Questions and Example Graphs
George Rochester	FDA	Discussant

Topic		Drug Safety	
Track	3	**Time**	Tuesday, March 1, 16:40 – 18:10
ID		11	
Title		Statistical Challenges on Assessment of Drug Abuse Potential in Human	
Organizer		Ling Chen	U.S. FDA
		Alan Y. Chiang	Eli Lilly
Chair		Yi Tsong	U.S. FDA

Abstract

The human abuse potential study for new drugs plays a critical role in understanding whether a drug produces positive subjective responses indicative of abuse potential. This type of study is very different from drug efficacy and general drug safety studies. The study is typically designed as randomized, double-blind, double-dummy, placebo- and positive-controlled, crossover designed investigation with multiple treatments, multiple comparisons, and multiple abuse potential measures. Study subjects are healthy recreational drug users who have a preference for the drug class associated with the test drug. Most outcome measures in these studies are based on self-reported responses. In this session, we will discuss statistical issues and challenges in assessing drug abuse potential in human. We will also give some suggestions, and propose some new methodologies for improving the assessment.

Speakers

Kerri A. Schoedel	Kendle Early Stage – Toronto	Defining Abuse Potential in Clinical Studies: Practical Approaches to a Complex Analytical Problem
Michael Klein	U.S. FDA	Abuse Potential Evaluation: Regulatory Perspective
Ling Chen	U.S. FDA	Abuse Potential Evaluation on Subjective Responses to Drug Liking VAS - Issues and Strategies
Yi Tsong, Alan Y, Chiang, all speakers		Panel Discussion

Topic		Translational Medicine	
Track	3	**Time**	Wednesday, March 2, 08:30 – 10:00
ID		3	
Title		Maximizing Information in Early Development Trials	
Organizer		Laurence Colin	Novartis
Chair		Christoph Gerlinger	Bayer Schering Pharma

Abstract

The early position of Translational Studies in a development program implies a high degree of uncertainty around central questions (e.g. the target indication) and planning assumptions (e.g. the anticipated treatment effect), and the financial investment is limited. In this situation, it is crucial to use statistical approaches that are tailored to this setting. In the first presentation, a Bayesian study design in the respiratory therapeutic area will be discussed, where the knowledge generated from historical data on the active control is incorporated into the planning and analysis of the study. Building on the first talk, the second presenter will show a case study in dental pain where proof of concept is assessed with a Bayesian criterion using historical controls. This part is then seamlessly extended into a response-adaptive dose-ranging study, allocating the patients such that the information generated about the dose-response is maximized. The third presenter will discuss the translatability of biomarkers to predict outcomes of later project phases. Finally, a regulator's point of view on Translational Studies will be given.

Speakers

Lilla di Scala	Novartis	Synthesis of historical and current evidence – a case study in COPD
Marc Vandemeulebroecke	Novartis	Dealing with uncertainty and maximizing information in Translational Science - a Case Study in Dental Pain
Arne Ring	Boehringer-Ingelheim & University of Ulm	Translatability of biomarkers to predict outcomes of later project phases
David Wright	MHRA	Discussant

Topic		Predictive Medicine / Translational Medicine	
Track	3	**Time**	Wednesday, March 2, 10:30 – 12:00
ID		7	
Title		Model-based Drug Development	
Organizer		Harry Yang	MedImmune
Chair		Harry Yang	MedImmune

Abstract

To meet the increasing challenges of high attrition rates and cost in drug development, biotech and pharmaceutical industries are adopting the new paradigm of model-based drug development. Model-based drug development is at the center of the Critical Path Initiative published by the FDA, and it serves as a powerful tool to accumulate knowledge gained during drug development and provide quantitative justification for many key decisions along the drug development process. For instance, PK/PD models bridge data from animals, healthy subjects and patients through mechanism-based models, and biomarker modeling leads to identification of patients that are more likely to the drug under development and thus improves the efficiency of clinical trials. In this session, case studies will be presented to demonstrate the opportunities and challenges of utilizing various PK/PD and statistical models to (1) predict first-time-in-man dose based on preclinical data; (2) identify biomarker to improve clinical trial design and interpretation; and (3) dose and schedule optimization in phase I-III trials. The session is targeted towards the general audience of the preclinical and clinical statisticians and PK/PD modelers involved in the decision making at any stage of clinical development of the drug.

Speakers

Athula Herath	MedImmune	Model-based drug development, “People, have you seen the elephant?”
Liang Zhao	FDA	Dose and dosing regimen determination using modeling and simulation for Phase I/II/III studies
Parviz Ghahramani	Forest Research Institute	Challenges in developing a drug with biliary excretion - a case example
Juan Jose Perez Ruixoi	Amgen	Discussant: Applications of PKPD modeling and simulation in drug development

Topic		Missing Data and the Role of Mixed Models	
Track	3	**Time**	Wednesday, March 2, 13:00 – 14:30
ID		23	
Title		Missing Data in Clinical Trials with Discrete Endpoints	
Organizer		Heinz Schmidli	Novartis
Chair		Heinz Schmidli	Novartis

Abstract

In randomized controlled clinical trials, the primary endpoint is often missing for some of the patients. A statistical analysis ignoring those patients with missing endpoint generally leads to invalid conclusions. Considerable progress has been made in the last decades on how to obtain valid statistical inference with missing data, and the European Medicines Agency recently released a draft guideline on missing data in confirmatory trials. When the primary endpoint is discrete, for example a binary endpoint (e.g. responder/non-responder) or a count endpoint (e.g. number of relapses), mixed effect models for analyzing clinical trials with missing data are more complex than for continuous endpoints. This may be the reason why in many clinical trials with discrete endpoints simple ad-hoc procedures for handling missing values are common. The speakers will discuss the different approaches for dealing with missing discrete data, and discuss their validity, from a regulatory, academic and industry perspective.

Speakers

Mike Kenward	London School of Hygiene & Tropical Medicine	Handling dropout in longitudinal trials with discrete outcomes
Mouna Akacha	University of Warwick / Novartis	The Impact of Dropout on the Analysis of Dose-Finding Studies with Recurrent Event Data
Gerd Rosenkranz	Novartis	How are incomplete discrete data handled in practice?
David Wright	MHRA	Issues with missing data in regulatory submissions using discrete endpoints

Topic		Missing Data	
Track	3	**Time**	Wednesday, March 2, 14:40 – 16:10
ID		28	
Title		The National Academy of Science' & EMA Report on Missing Data	
Organizer		Richard Kotz	FDA, ISBS
Chair		Michael O'Kelly	Quintiles

Abstract

The problem of missing data in clinical trials can pose significant problems in the interpretation of trial results. Therefore the US National Academy of Sciences' Committee on National Statistics was commissioned by the FDA to hold a Panel on Handling Missing Data which resulted in the July 19, 2010 publication of "The Prevention and Treatment of Missing Data in Clinical Trials." Also this summer the European Medicines Agency also addressed this issue with the release of their "Guideline on Missing Data in Confirmatory Clinical Trials." This session will present, discuss, and contrast these 2 documents on preventing and addressing missing data in clinical trials from industry, regulatory, and academic perspectives.

Speakers

Geert Molenberghs	Leuven Biostatistics and statistical Bioinformatics Centre	Analysis and sensitivity analysis for incomplete clinical trial data
James Hung	CDER, FDA	What to Expect for Handling Missing Data in Regulatory Applications
James Rogers	GSK, UK	"What-if" sensitivity analyses for early withdrawal in longitudinal studies
David Wright	MHRA	Discussant

Topic		Missing Data and the Role of Mixed Models	
Track	3	**Time**	Wednesday, March 2, 16:40 – 18:10
ID		105	
Title		Missing Data and the Role of Mixed Models	
Organizer			
Chair		Gerd Rosenkranz	Novartis
Abstract			
Speakers			
Michael O'Kelly		Quintiles	Mixed models and missing data in practice
Dorothee Ball		BfArM	Comparison of recurrent events analysis methods in the presence of event-related dropout
Bianca Teodorescu		Arlenda, Belgium	Modeling Pain score in clinical trials using a joint survival-longitudinal mixed model with a Beta distribution in presence of missing values not occurring at random
Guanghan (FRANK) Liu		Merck	On adjustment of baseline values in mixed models for analysis of clinical trials with missing data

Topic		Meta-Analyses, Safety and Pharmacovigilance	
Track	3	**Time**	Thursday, March 3, 09:00 – 10:30
ID		35	
Title		Statistical methods in pharmacovigilance – where do we go from here?	
Organizer		Jim Slattery	EMA
Chair		Michael Kayser	Bayer

Abstract

Post-marketing surveillance for suspected adverse drug reactions is required to characterise the full safety profile of new medicines. Individual case safety reports are the primary source of information to detect potential risks to patients from medicines in regular clinical practice. Such reports are anecdotal in nature and do not represent a random sample; they are not suitable as a basis for statistical inference, but statistical methods provide real value in identifying outstanding reporting patterns for clinical review, and in flagging reporting artefacts that may otherwise mislead the analyst. This session will bring together speakers from the pharmaceutical industry, regulatory agencies, and non-government organisations participating in the public-private partnership Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) to discuss current challenges and future directions in statistical methods for pharmacovigilance. It will cover challenges in the empirical evaluation of statistical methodology, drug-drug interaction surveillance, risk group identification, and the use of alternative data sources such as longitudinal patient records.

Speakers

Jim Slattery	EMA	Comparison of methods for identification of adverse drug reactions from spontaneous report datasets
Bharat Thakrar	Hoffmann-La Roche	Detecting drug-drug interactions in spontaneous report datasets
Suzie Seabroke	MHRA	Stratification and subgrouping in spontaneous report datasets
Niklas Norén	Uppsala Monitoring Centre	Statistical pattern discovery for medical outcomes in electronic patient records

Topic		Drug Safety	
Track	3	**Time**	Thursday, March 3, 11:15 – 12:45
ID		47	
Title		Statistical Issues on Thorough QT Clinical Trials	
Organizer		Yi Tsong	FDA
Chair		Yi Tsong	FDA

Abstract

ICH region regulatory agencies request all sponsors of new non-arrhythmic drugs to conduct thorough QT/QTc studies to determine whether the drugs have potential effects to delay cardiac repolarization measured by QT/QTc interval. Although the ICH E14 (2005) guidance provides useful recommendations to the industry, there are still multiple remaining challenging statistical issues related to efficient QTc trial design and data analysis. They include (1) sample size considerations for different types of thorough QT/QTc study designs; (2) conservativeness of the conventional primary intersection-union test for assessing active treatment effect; (3) multiplicity adjustments for demonstrating assay sensitivity or known effect of the active control; and (4) PK/PD modeling for connecting drug-exposure and QTc response. In this session, presenters from the FDA, academia, and industry will have the opportunity to share their thoughts on addressing these issues based on their research and trial experience in the area.

Speakers

Joanne Zhang	FDA	Optimal Sample Size Allocation in a Thorough QTc Study
Robert Schall	University of Free State, South Africa	Mixed models for data from thorough QT studies. Part 1. Assessment of marginal QT prolongation.
Arne Ring	Boehringer-Ingelheim Pharma GmbH & Co.	Mixed models for data from thorough QT studies. Part 2. Assessment of conditional QT prolongation
Doulao Wang	London School of Hygiene and Tropical Medicine	Discussant

Topic		Regulatory Statistics	
Track	4	**Time**	Tuesday, March 1, 13:00 – 14:30
ID		44	
Title		Regulatory Statistics in Europe	
Organizer		EMA&BWSP and EFSPI	
		Franz König	Medical University of Vienna
Chair		Kit C.B. Roes and Francesco Pignatti	University of Utrecht, EMA

Abstract

This session will focus on regulatory statistics in Europe. This will include an overview about the current situation and recent developments such as the constitution of the Biostatistics Working Party (BS WP) of CHMP and the European Medicines Agency (EMA) in 2010.

Speakers

Eva Skovlund	Vice-Chair Biostatistics Working Party, CHMP member	Increasing focus on regulatory statistics: a new working party is born.
Joachim Roehmel	Former BfArM	Biostatistical Regulatory Guidance in the Past and Future Challenges
Spiros Vamvakas	EMA	ICH: The long journey of 20 years of harmonisation
Kit C.B. Roes	Julius Center for Health Sciences and Primary Care	Discussant

Topic		Regulatory Statistics	
Track	4	**Time**	Tuesday, March 1, 14:40 – 16:10
ID		45	
Title		Subgroup Analyses in Randomised Controlled Trials	
Organizer		Franz König	Medical University of Vienna
Chair		James Matcham	Amgen

Abstract

In this session the plan for a specific CHMP guidance document on assessment of subgroup analyses will be discussed. Analysis of subgroups is important in every confirmatory trial. Subgroup analyses are used for assessment of internal consistency, to try to rescue trials that 'fail' based on the full analysis set or to try to identify patient groups with the most favourable benefit-risk profile. Subgroups may be pre-specified in the trial protocol, based on demographic, genomic or disease characteristics (e.g. sub-entities of a disease that are widely recognized within the medical community) or may materialize based on a need or desire to further explore study results. Formal statistical methods for investigating the homogeneity of the treatment effect across subgroups do exist and these are sometimes used to provide re-assurance or to challenge the applicability of overall findings to subgroups. In some dossiers, the investigation of results in subgroups is minimal, perhaps in fear of (possibly false) negative findings that may complicate assessment.

Speakers

Rob Hemmings	MHRA	'Subgroup analyses - why guidance? what guidance?
Kit C.B. Roes	Julius Center for Health Sciences and Primary Care	Perspectives on assessing effects in subgroups in randomized clinical trials and their meta-analyses
Gerd Rosenkranz	Novartis	Is there a need for subgroup analyses?
Kit C.B. Roes, Rob Hemmings, Armin Koch, Gerd Rosenkranz		Discussants

Topic		Progression Free Survival	
Track	4	**Time**	Tuesday, March 1, 16:40 – 18:10
ID		6	
Title		Optimal methodological approaches to Progression Free Survival – findings from a PhRMA Expert Group	
Organizer		Andrew Stone	AstraZeneca
Chair		Andrew Stone	AstraZeneca

Abstract

Progression Free survival (PFS) has increasingly been used for approval of drugs in oncology and has been the subject of recent detailed methodological guidance by FDA and EMA. Despite the existence of these guidance documents, there are a number of controversies surrounding the use of PFS. The Pharmaceutical Research and Manufacturers of America (PhRMA) formed an Expert Group, in January 2008, on the use of Progression Free Survival (PFS) endpoints in oncology clinical trials. This session will debate findings of the group, covering the following topics

• The role of independent reviews and the proposal for the review to be based on a random sample of scans

• Alternative interval censored analysis techniques that may be much more robust to departures from protocolled assessment frequency

• When and if patients' data should be censored

Speakers

Jonathan Denne	Eli-Lilly, PhRMA team member	The role of an independent review in the analysis of PFS data – Results from the PhRMA PFS working group
Hans-Ulrich Burger	Roche, PhRMA team member	Recommendations for handling censoring & missing data in the analysis of Progression Free Survival
Marc Buyse	IDDI	Beyond PFS: survival post progression
Robert Hemmings	MHRA	Discussant

Topic		Regulatory Statistics	
Track	4	**Time**	Wednesday, March 2, 08:30 – 10:00
ID		43	
Title		Drug Development in Children	
Organizer		Julia Saperia	EMA
Chair		Ralf Herold	EMA

Abstract

In the light of the relatively new European paediatric regulation that requires the use of medicinal products in children and young people to be explored, there is a continued need to address the practical and ethical problems of conducting clinical trials in this population. This session looks at the need for innovative approaches and how current knowledge about a drug can influence future trials. There will also be a discussion of the interaction between clinicians and statisticians in the planning of trials in children and young people.

Speakers

Daniel Brasseur	Chair of EMA's Paediatric Committee	How statisticians can help meet children's needs
Paula Williamson	University of Liverpool	Methodological challenges in trials of medicines for children
Julia Saperia	European Medicines Agency	Finding new ways to predict the future

Topic		Non-inferiority Guidances	
Track	4	**Time**	Wednesday, March 2, 10:30 – 12:00
ID		20	
Title		Discounting and Pooling in Non-inferiority Trials	
Organizer		Tie-Hua Ng	US FDA
Chair		Tie-Hua Ng	US FDA

Abstract

European Medicines Agency (EMEA) issued a guideline on non-inferiority trials entitled "Guideline on the Choice of the Non-Inferiority Margin" in January of 2006. With the issue of the draft guidance on non-inferiority (NI) trials by the US Food and Drug Administration (FDA) in March of 2010, two of the three ICH regions now provide guidance on the design, conduct and analysis of non-inferiority trials. All be it that at the time of this submission the FDA guideline is in draft, this session will first give a brief overview of the guidance in the two guidelines. Next, several concepts in the FDA guidance will be discussed in details: The NI margin notion of M1 and M2, the methods of determination of the margin, and the two approaches for testing NI hypothesis, that is, fixed margin and the synthesis method. The session will then be completed with an illustration of discounting and pooling in the determination of the NI margin

Speakers

Jorgen Seldrup	Quintiles	Regional Regulatory Non-inferiority Guidances and Beyond
Tie-Hua Ng	US FDA	Non-inferiority Margins (M1 and M2) and Two Statistical Approaches in the FDA Draft Guidance
James Hung and Thamban Valappil	US FDA	Historical Evidence of Treatment effect: Discounting and Pooling

Topic		Bayesian Statistics in Research and Drug Development	
Track	4	**Time**	Wednesday, March 2, 13:00 – 14:30
ID		34	
Title		Bayesian Methods for Evaluating Clinical Safety Data	
Organizer		Jouni Kerman	Novartis Pharma AG
Chair		Jouni Kerman	Novartis Pharma AG

Abstract

Interpretation of clinical safety outcomes is a challenging and a critical issue for all stakeholders involved in drug development. Bayesian methods provide a suitable statistical framework for both complex modeling and incorporating information from past trials. Bayesian signal detection procedures may use prior information to make more accurate predictions, while at the same time they can be used to evaluate different clinical scenarios using skeptical priors. Also, data from past clinical trials provides an opportunity for modeling the outcomes so that information can be synthesized to obtain a more complete picture of the safety profile of a drug. We present examples of the use of Bayesian methodology in safety data analysis and signal detection from both regulatory and industry perspective, and discuss their advantages and limitations.

Speakers

Alun Bedding	GlaxoSmithKline	Bayesian methods for signal detection accounting for multiplicity in a vaccines program
Beat Neuenschwander	Novartis Pharma	"Rare Events: Assumptions and Analyses"
Jim Slattery	EMA	Comprehensive synthesis of safety data. Just a dream?
Mauro Gasparini	Politecnico di Torino	Discussant

Topic	Statistical Computing		
Track	4	**Time**	Wednesday, March 2, 14:40 – 16:10
ID	109		
Title	Statistical Computing for High Dimensional Data		
Organizer	Richardus Vonk Tuomas Eerola	Bayer Schering Pharma AG Techila	
Chair	Tuomas Eerola	Techila	

Abstract

In the quest to understand biological background to diseases, and linking it to clinical endpoints, new and challenging statistical techniques are developed. The search, however, is often hindered by the high dimension of the underlying data. Examples are searches for pathways in biochemical networks, and statistical techniques that take interactions into account.

Under the umbrella of computational statistics, this session addresses the challenges of analyzing high dimensional data using real life examples.

Speakers

Tarmo Äijö, Kirsti Rautajoki, Harri Lähdesmäi	Tampere University of Technology, Aalto University School of Science and Technology	Unraveling cell-type specific signaling pathway models using a dynamical model with a nonparametric and probabilistic extensions using high-performance computing
Harald Binder	University of Freiburg	Computational challenges when fitting multivariable regression models with a huge number of molecular covariates
Juho Rousu	University of Helsinki	Kernel methods for predicting complex biological data

Topic		Bayesian Statistics	
Track	4	**Time**	Wednesday, March 2, 16:40 – 18:10
ID		29	
Title		Bayesian Designs in Pharma: pros and cons	
Organizer		Prof. Valerii Fedorov	GSK
Chair		Prof. James Roger	GSK

Abstract

Recently there has been increasing interest in the use of Bayesian designs in Pharmaceutical R&D. All participating speakers contributed either to the development of Bayesian methodology or its implementation in the clinical trial design setting. However the deeper understanding the major mathematical ideas of Bayesian methodology and its applicability is still on the research agenda of many scientists and practitioners. The session is another step in this pursuit.

Speakers

Andy Grieve	Kings College, London	Issues in implementing Bayesian Designs in Pharmaceutical R&D
Sue-Jane Wang	FDA	Utility of Bayesian approaches in design and analysis of a therapeutic clinical development
Jouni Kerman	Novartis	Default prior information in models estimating rates and proportions: the case for neutral priors
Robert Cuffe	GSK	Adding historical control data to a trial's primary analysis leads can reduce the trial's power.

Topic		Bayesian Statistics	
Track	4	**Time**	Thursday, March 3, 09:00 – 10:30
ID		32	
Title		Recent Development of Bayesian Methodologies in Clinical Trials	
Organizer		Soumi Lahiri	GSK
Chair		Soumi Lahiri	GSK

Abstract

Application of Bayesian methodologies is becoming more and more popular in clinical trial. In this session recent development and application of Bayesian methodologies in clinical trial will be explored. Bayesian model based approaches will be discussed for combination dose finding in oncology. The computational aspect traditionally limited the implementation of Bayesian methods. Some of the recent development of Bayesian software will be illustrated. A Bayesian joint modeling approach will be discussed to improve the parameter estimation by sharing information between two different endpoints. Finally, a robust Bayesian model will be presented for longitudinal clinical trial data with missing values.

Speakers

Stuart Bailey	Oncology, Novartis Pharma AG, Switzerland	Bayesian model-based approaches for combination dose finding in oncology
Gang Li	UCLA	Joint Modeling of Longitudinal and Competing Risks Survival Data
James Roger	Director, Statistics & Programming, GSK, UK	Practicalities of MCMC in an adaptive trial
Satrajit Roychoudhury	Oncology, Novartis, US	Semi-parametric Bayesian model for longitudinal ordinal outcomes with missing values in clinical trial

Topic		Bayesian Statistics in Research and Drug Development	
Track	4	**Time**	Thursday, March 3, 11:15 – 12:45
ID		106	
Title		Novel Bayesian Decision Procedures in Clinical Trials	
Organizer			
Chair		Soumi Lahiri	GSK
Abstract			
Speakers			
Wilbert (W.G.F.) van Duijnhoven		Business & Decision	Bayesian methodology for an adaptive dose-finding trial with a bivariate binary response
Roland Fisch		Novartis Pharma AG	Trial Simulation to Optimize Bayesian Oncology Phase 1 Trials
Joanna in ‘t Hout		Merck	Prediction of the target dose of a novel compound using the Bayesian inverse estimator on the joint biomarker responses
David Ohlssen		Novartis	An overview of evidence synthesis in drug development

Topic		Exposure-Response (=PK/PD) nonlinear mixed effects modeling of clinical trial data to support Drug Development	
Track	5	**Time**	Tuesday, March 1, 13:00 – 14:30
ID		16	
Title		Modeling Exposure-Response data to support Drug Development	
Organizer		Roland Fisch	Novartis Pharma AG
Chair		Roland Fisch	Novartis Pharma AG

Abstract

In Pharmaceutical Drug Development, it is of the utmost importance to quantitatively model the relationship between exposure to the drug and its clinically relevant responses (PKPD models), with respect to efficacy and safety. In combination with a dose-exposure (PK) model, this allows to support important decisions, e.g. on doses and dose regimens, or target populations. Many responses are measured repeatedly over time. Therefore the typical PKPD model structure will be a mixed effects model, where the random effects account for between-patient variability. Many useful models are nonlinear (nlme's), where the deterministic model structure is given by ordinary differential equations (ODE). The speakers will present examples of current research, illustrated with relevant examples: Firstly, on the use of Bayesian approaches to models with stochastic differential equations (SDE's); secondly, on Bayesian ways of integrating the PK and the PKPD models; thirdly, on methods to develop optimal PKPD designs. This will be discussed from the regulatory, academic and industry viewpoint.

Speakers

France Mentre	INSERM - Université Paris Diderot	Optimal design for nonlinear mixed effect modeling of dose-exposure -response
Marina Savelieva Praz	Novartis Pharma AG	Accounting for inter-patient variability in a hierarchical PKPD model
Julien Cornebise	Univ. of British Columbia, Vancouver	Stochastic Mixed Effects Models with Particle Markov Chain Monte Carlo in Pharmacokinetics/Pharmacodynamics
Efthymios Manolis	European Medicines Agency	Discussant

Topic		Innovative Methods for Dose-Response	
Track	5	**Time**	Tuesday, March 1, 14:40 – 16:10
ID		46	
Title		Innovative Methods for Dose-Response Estimation	
Organizer		Björn Bornkamp	Novartis
Chair		Björn Bornkamp	Novartis

Abstract

Estimating the dose-response profile is one of the most important tasks during the development of a pharmaceutical compound. Understanding well the relationship between dose and an efficacy/safety parameter is critical for internal go/no go decisions and provides important information for an adequate planning of confirmatory Phase III trials. ANOVA approaches have been used for many decades in the drug development arena. More recently, modeling approaches have been discussed that provide an estimate of the whole dose-response profile and additionally lead to more efficient estimates of the response at the observed doses. In this session we will investigate and discuss innovative approaches for estimating the dose response in clinical Phase II studies.

Speakers

Georgina Bermann	Novartis	Using covariances for improved dose response estimation
José Pinheiro	Johnson & Johnson	Generalizing the MCP-Mod approach beyond normal, independent data: Concepts, implementation, and software
Andy Grieve	King's College	Multi-Stage Dose Response Studies: How much adaption is good for you?
Efthymios Manolis	EMA	

Topic		Experimental Designs in Pharmaceutical Industry	
Track	5	**Time**	Tuesday, March 1, 16:40 – 18:10
ID		19	
Title		Experimental Designs in Pharmaceutical Industry	
Organizer		Frank Bretz	Novartis
Chair		Björn Bornkamp	Novartis

Abstract

Under the current environment in the Pharmaceutical Industry to implement more efficient clinical trial designs, experimental design theory has much to offer. Efficient drug development is demanded by all major stakeholders. The speakers will present examples of current research, illustrated with relevant examples, to cover the use of optimal design theory in pharmacokinetic and dose finding studies together with an overview of web-based software solutions useful for the pharmaceutical industry. This will be discussed from the regulatory, academic and industry viewpoint.

Speakers

Tim Holland-Letz	Univ Bochum	Multiplicative algorithms in population pharmacokinetics
Vladimir Dragalin	Quintiles	Experimental Designs for Dose-Ranging Studies
Weng Kee Wong	UCLA	A web based approach to finding optimal dose response designs
Norbert Benda	BfArM	Discussant

Topic		Statistics in Decision Analyses / Go- No Go Investment Decisions	
Track	5	**Time**	Wednesday, March 2, 08:30 – 10:00
ID		37	
Title		DMC models and interim decision making	
Organizer		Dr. Norbert Benda	BfArM
Chair		Dr. Norbert Benda	BfArM

Abstract

A data monitoring committee (DMC) reviews accumulating data from an ongoing clinical study. The DMC advises the sponsor regarding the continuing safety of the trial patients as well as the continuing validity and scientific merit of the trial. The DMC may also apply predefined rules to interim data related to the efficacy outcome of the study either to stop, to modify, or to continue the trial. Many different models have been proposed and used for the operation of DMCs. Some models may be appropriate in situations where other models would fail. The session will discuss different models with their potential risks and advantages in particular situations. Different views, from sponsors as well as regulators, are included in the discussion including both, theoretical and practical aspects of the different DMC models.

Speakers

David Lawrence	Novartis, Horsham	The road less travelled: using a DMC for treatment selection in an adaptive phase III trial
Karola Beckmann	Bayer Schering Pharma AG, Berlin	DMC Models - Experiences from a Sponsor's Perspective
Tim Friede	University of Göttingen	DMCs and interim decision making: The perspective of an DMC member
Peter Volkers	Paul-Ehrlich-Institut, Langen	Discussant

Topic		Statistics in Decision Analyses / Go- No Go Investment Decisions	
Track	5	**Time**	Wednesday, March 2, 10:30 – 12:00
ID		108	
Title		Applying Decision Analysis methods to drug development	
Organizer			
Chair		Richard Nixon	Novartis
Abstract			
Speakers			
Robert Cuffe		GSK	Decision analytic selection of a go-no go threshold for a futility interim analysis.
Lev Sverdlov		Merck Research Laboratory	Use of the Exploratory Discriminant Analysis in Separating Study Population by Treatment Subgroups in Phase 2 Clinical Trial
Pierre Lebrun		Arlenda & Université de Liège	Trial predictions vs. trial simulations in Model-based Drug Development: integrating uncertainties to evaluate the predictive probability of success.
Jullion Astrid		Arlenda, Belgium	A prediction-based Clinical Utility Index (p-CUI) for decision making in drug development

Topic		Statistics in Decision Analysis/Go No-Go Investment Decisions	
Track	5	**Time**	Wednesday, March 2, 13:00 – 14:30
ID		25	
Title		Role of Statistics in Valuation and Optimization of Drug Development Portfolios	
Organizer		Zoran Antonijevic	Quintiles, Inc.
Chair		Jose Pinheiro	Johnson & Johnson Pharm. R&D

Abstract

There are three key components in assessing the value of Pharmaceutical development portfolios: cost, expected revenues, and risk. It is a common practice among portfolio strategists and analysts to rely on deterministic models and industry averages when assessing these components. Clinical trial statisticians can contribute to assessing the value of a portfolio by using the available data, or by providing scenario analysis. Statistical methods have also been developed to support go/no go decision making, portfolio size optimization, and project prioritization. First presentation in this session will give an overview of statistical input at portfolio valuation stage, and statistical methods applicable to assessment at various stages of development. Second presentation will address methods that maximize portfolio's NPV subject to budget constraints and constraints that reflect downside risk. Third presentation will describe cost effectiveness based go/no go decision criteria. Forth speaker will give an overview of an increasing role of statisticians in portfolio optimization.

Speakers

Zoran Antonijevic	Quintiles, Inc.	Value Based Drug Development
Nitin Patel	Cytel, Inc.	Maximizing NPV of a portfolio subject to budget and risk constraints
Larry Gould	Merck	Practical Application of a Decision Science Method to Project Evaluation Decisions
Alun Bedding	GSK	Discussant

Topic		Modeling and Simulation	
Track	5	**Time**	Wednesday, March 2, 14:40 – 16:10
ID		36	
Title		Using modeling and simulation in getting treatments to market	
Organizer		PSI Modelling and Simulation special interest group (SIG)	
		Michael O'Kelly	Quintiles
Chair		Brenda Gaydos	Eli Lilly / PhRMA LDKIT

Abstract

Modelling and simulation can help the development process in very many ways, but is just a tool that must be used responsibly and is only as good as the data and assumptions that go into it. Speakers will propose principles that can be adopt in planning, conducting and reporting on simulations; how modeling and simulation has been used by pharmaceutical companies to improve dose-finding; and an example of how modeling and simulation helped as a communication tool for a multifunction drug development team.

Speakers

Joachim Grevel	BAST Inc.	The process of MBDD
Alun Bedding	GSK	Efficient Modelling and Simulation of Adaptive Dose Finding Trials in Phase II
Michael O'Kelly	Quintiles	Examples of using modelling and simulation in getting treatments to market

Topic		Multiplicity Issues in Clinical Trials	
Track	5	**Time**	Wednesday, March 2, 16:40 – 18:10
ID		1	
Title		p-values, treatment effect estimation and bias in clinical trials with multiple endpoints – what needs to be adjusted?	
Organizer		Ekkehard Glimm	Novartis Pharma
Chair		Ekkehard Glimm	Novartis Pharma

Abstract

The intention of the session is to shed some light on the question if and if yes, how we have to adjust results from clinical trials with simultaneous inference of any kind (e.g. multiple endpoints, multiple treatment groups, interim analyses). It seems widely accepted that p-values of multiple statistical tests require adjustment. For interval and point estimation, there appears to be more of a controversy. Werner Brannath will report on his recent research regarding bias correction of treatment effect estimates. Adeniyi Adewale will present his recent work on multiplicity adjustment in the context of clinical safety analysis. Georg Gutjahr will give a talk on how to assess cost versus effect. Jörg Zinserling will give a regulatory perspective of the impact of bias from multiplicity on the interpretation of clinical trial results.

Speakers

Werner Brannath	University of Bremen	Bias correction of treatment effect estimates
Adeniyi Adewale	Merck Pharma	Multiplicity adjustment in the context of clinical safety analysis
Georg Gutjahr	University of Bremen	Simultaneous Inference in CostEffectiveness Analysis
Jörg Zinserling	BfArM	Discussant: Regulatory perspective of the impact of bias from multiplicity on the interpretation of clinical trial results

Topic		Statistics in Decision Analyses / Go- No Go Investment Decisions	
Track	5	**Time**	Thursday, March 3, 09:00 – 10:30
ID		39	
Title		Expanding the scope of development decisions to commercial impact	
Organizer		Richard Nixon	Novartis AG
Chair		David Ohlssen	Novartis AG

Abstract

Drug-disease models are commonly used within the Pharmaceutical industry for informing clinical decisions. Commercial models, typically assuming a given clinical effect, are then used to make predictions about market value and ultimately eNPV. In this session we explore holistic modeling frameworks where the effect of clinical decisions during drug development is carried through to commercial impact. Four presentations are given. (1) A hybrid health economics/actuarial model which demonstrates the quality-adjusted life year and financial effects of case management for major depression. (2) An analysis of whether to continue development of an existing formulation of Censirone for anxiety, or wait for a new formulation for both anxiety and depression, based on the forecast commercial potential of the efficacy and tolerability profiles (3) An analysis of a blinded interim adaptation, linking a drug-disease model for event rate with a market model which predicts revenue given the treatment effect to estimate the eNPV of an adaptation strategy. (4) A framework for analyzing commercial rationale for early Phase III vs amended Phase II.

Speakers

Joanne Buckle	Milliman	Applying a hybrid health economic and actuarial decision model to assess case management for major depression
Vassilis Lefkaditis / Philip Geerts	IMS health	Modelling patient flow and treatment dynamics for early stage decision making
Richard Nixon	Novartis AG	Using Decision Analysis to choose a strategy for a trial interim adaptation

Topic		Nonclinical Statistics/Biomarkers	
Track	5	**Time**	Thursday, March 3, 11:15 – 12:45
ID		30	
Title		Biomarker in the Pharmaceutical Industry	
Organizer		Katja Remlinger	GSK
		Steve Fox	GSK
Chair		David M. Shera	Merck

Abstract

Biomarkers play an important role in all stages of the drug discovery process. They are often being used for target identification, screening drug candidates in early development for likely efficacy, or to predict safety problems by identifying toxicity markers that give early warnings. In clinical trials, biomarkers can help to forecast the likely course of a disease or a future outcome.

We will start the session with an introductory talk to biomarkers in the pharmaceutical industry, followed by two talks that will provide specific case studies from different therapeutic areas, namely liver fibrosis and COPD. The session will close with a presentation on planning of a prospective clinical study for the validation of prognostic biomarkers.

Speakers

Viswanath Devanarayan	Abbott	Overview of biomarkers for drug development and some important statistical considerations
Katja Remlinger	GSK	Assessing Stages of Liver Fibrosis in a Non-Invasive Manner
Steve Fox	GSK	The search for COPD biomarkers of the future
Vivian Lanius	Bayer Schering Pharma AG	Study planning for the validation of a prognostic marker

Topic		Non-Clinical Statistics – Improvements to Research and Preclinical Development	
Track	6	**Time**	Wednesday, March 2, 08:30 – 10:00
ID		33	
Title		Consideration of Design of Experiments for Dynamic Processes in supporting the ICH Q8 definition of Design Space with Applications	
Organizer		Mohammad Yahyah	GSK
Chair		Gillian Amphlett	GSK

Abstract

Abstract (1st talk): Manufacturers of pharmaceuticals and biopharmaceuticals are facing increased regulatory pressure to (i) better understand how their manufacturing processes work and to (ii) be able to quantify the reliability and robustness of their manufacturing processes. In particular, the ICH Q8 Guidance has introduced the key concept of Design Space. The ICH Q8 defines “Design Space" as “The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." It further states that “Working within the Design Space is not considered as a change - Movement out of the Design Space is considered to be a change and would normally initiate a regulatory post-approval change process”. As the concepts of Design Space in the QbD framework move on from their inception to implementation, the ambiguity of definition has led to considerable discussion, diversity of opinions and uncertainty around how best to define these ideas. This presentation provides an in-depth discussion on two unit operations from the pharmaceutical industry (chemical kinetic reaction & crystallization of API manufacture) focusing attention on the design of experiments conducted, the modeling undertaken and the subsequent determination of Design Spaces derived.
Abstract (2nd talk):This is joint work with Stefanie Biedermann, Susan Lewis and David Woods (Southampton Statistical Sciences Research Institute). Models to describe dynamic processes which are derived from differential equations occur frequently in the pharmaceutical industry. Experiments are needed to estimate the model parameters accurately so that these processes can be better understood and optimised. Developing methods to obtain efficient and effective designs for these experiments can be problematic: the models are usually non-linear in the unknown parameters, making the optimal choice of design dependent on the parameter values, and the observations made within a run of the process may be correlated to an unknown degree. The work presented uses an example in chemical kinetics from GlaxoSmithKline, which illustrates a key step in the process of implementing the concept of Design Space, as presented by Mohammad Yahyah (Applications of the ICH Q8 Definition of Design Space). The example is used to motivate, develop and evaluate designs using Bayesian D-optimality techniques which allow chemists' knowledge to inform the choice of design. We show, using simulation studies, that the approach we recommend gives designs that are insensitive or robust to misspecification of the unknown parameter values and to the strength of correlations between the observations.

Speakers

Mohammad Yahyah	GSK	Applications of the ICH Q8 Definition of Design Space
Kieran Martin	University of Southampton	Design of Experiments for a Dynamic Model with Correlated Observations
Pierre Lebrun	Arlenda & Université de Liège	Design Space and desirability index. A Bayesian predictive risk-based approach to flexibly achieve multi-criteria decision methods.

Topic		Non-Clinical Statistics – Improvements to Research and Preclinical Development?	
Track	6	**Time**	Wednesday, March 2, 10:30 – 12:00
ID		103	
Title		Advanced statistical methods in early drug development	
Organizer		Richardus Vonk	Bayer Schering Pharma AG
Chair		Bernd-Wolfgang Igl	Bayer Schering Pharma AG
Abstract			
Speakers			
Thomas Jaki		Lancaster University, UK	A flexible non-compartmental method for estimation of PK parameters
Tina Müller		Bayer Schering Pharma AG	Analyzing tumor sizes
Hannes-Friedrich Ulbrich		Bayer Schering Pharma AG	Metastases: modeling right censored count data
Songthip Ounpraseuth		University of Arkansas for Medical Sciences	Estimating misclassification error: bootstrap cross-validation versus k-fold cross-validation

Topic		Non-Clinical Statistics – Improvements to Research and Preclinical Development?	
Track	6	**Time**	Wednesday, March 2, 13:00 – 14:30
ID		102	
Title		Non-Clinical Statistics by Simultaneous Inference Approaches	
Organizer		Ludwig Hothorn	Leibniz University Hannover
Chair		Ludwig Hothorn	Leibniz University Hannover

Abstract

US-NTP propose Dunnett- and Williams-type procedures for the evaluation of continuous endpoints. In this session the related evaluation of mortality, arbitrarily distributed endpoints and counts will be discussed. Related software (R libraries) will be provided and the usefulness will be demonstrated by the analysis of real assays data.

Speakers

Daniel Gerhard	Leibniz Universität Hannover	Estimating simultaneous confidence limits with focus on small sample sized count data in toxicological studies
Esther Herberich	Ludwig-Maximilians-Universität München	A Williams-type Procedure for the Evaluation of Mortality in Long-Term Carcinogenicity Studies
Dr. Frank Konietschke	Universitätsmedizin Göttingen / Abt Medizinische Statistik	Evaluation of toxicological studies using a non-parametric Shirley-type trend test
David M. Shera	Merck	In-Silico Evaluation of Screening Strategies

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