

SMi presents its 6th annual conference on...

Adaptive Designs in Clinical Trials

Holiday Inn Regents Park, London, UK

24TH - 25TH
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WHY ATTEND THIS EVENT:

- **Learn** from Michael Krams how to create an environment where adaptive designs can become the norm
- The only conference in Europe to **focus** specifically on adaptive designs in clinical trials
- **Benefit** from the first-hand experiences of speakers whose organisations have recently made breakthroughs in adaptive designs
- **Hear** from Vladimir Anisimov the very latest on predictive analytical techniques for increasing efficiency of drug development
- **Discover** at our post conference workshop how FACT software that supports the ever-increasing complexity of adaptive clinical trials works, hosted by Tom Parke of Tessella

KEY SPEAKERS INCLUDE:

- **Michael Krams**, MD, Global Head, Quantitative Sciences, Janssen Pharmaceutical Companies of Johnson & Johnson
- **Vladimir Anisimov**, Senior Strategic Biostatistics Director, Quintiles
- **Roger Lewis**, MD, PhD, Senior Medical Scientist, Berry Consultants
- **Loic Darchy**, Head of Statistical Methodology Group, Sanofi R&D
- **Lilla Di Scala**, Senior Statistical Scientist, Roche
- **Pantelis Vlachos**, Principle Biostatistician, Strategic Consulting, Cytel Corporation
- **Sue Todd**, Professor of Medical Statistics, University of Reading
- **Frank Fleisher**, Principal Statistician, Boehringer-Ingelheim
- **Christopher Jennison**, Professor of Statistics, University of Bath
- **Graeme Archer**, Statistics Director, GlaxoSmithKline

PLUS TWO INTERACTIVE POST-CONFERENCE WORKSHOPS

Wednesday 26th March 2014 | Holiday Inn Regents Park, London, UK

Workshop A:

Simulating Clinical Trials using the FACTS software package: Why simulate clinical trials, how to simulate clinical trials and the difference it will make

8.30am – 1.00pm

Workshop Leader: **Tom Parke**, Head of Clinical Trial Solutions, Tessella Ltd

Workshop B:

Identifying and Exploiting Opportunities for Efficiency in Clinical Trial Design: An Interactive Adaptive Design Workshop

1.00pm – 5.00pm

Workshop Leader: **Professor Roger J. Lewis**, MD, PhD, Senior Medical Scientist, Berry Consultants

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08.30 Registration & Coffee

09.00 Chairman's Opening Remarks

Michael Krams, MD, Global Head, Quantitative Sciences,
Janssen Pharmaceutical Companies of Johnson & Johnson

09.10 Application of Adaptive Design in PPP's

- Building infrastructure to apply broadly in a scalable fashion
- Creating an environment where adaptive designs can become the norm
- The execution and how to ensure this happens

Michael Krams, MD, Global Head, Quantitative Sciences,
Janssen Pharmaceutical Companies of Johnson & Johnson

09.50 Designing a trial to find the minimum inhibitory concentration of an anti-infective drug

- Use of adaptive design to characterize exposure-response relationship
- Addressing the challenge of adaptive dose-allocation under several constraints
- Simulation of operating characteristics to inform design choice

Baldur Magnusson, Senior Principal Statistical Scientist, Novartis International AG

10.30 Morning Coffee

10.50 Simulations: Barriers for routine use and how to overcome them

- Benefits of simulations are well known and often referenced; however, many companies still do not perform them
- With the main advocates of simulations in statistics departments, how can we engage people from other departments in the process?
- Case studies to show what has and has not worked well

Jurgen Hummel, Associate Statistical Science Director, PPD

11.30 The Collaborative Adaptive Clinical Trial Design Process: Teamwork Informed by Simulation

- Adaptive trial designs leverage the incoming stream of new information that arises during clinical trial conduct to improve the statistical efficiency, validity, and safety of a clinical investigation;
- Identifying the most powerful ways to use this incoming information stream is the "art" of adaptive design and requires, in each case, a detailed and quantitative understanding of the threats to trial validity and success
- The best adaptive clinical trial designs are created in a collaborative, interactive process involving statisticians, clinical domain experts, and trial implementers that are informed by detailed trial simulations.

Roger Lewis, MD, PhD, Senior Medical Scientist, Berry Consultants

12.10 Networking Lunch

13.30 Advances in Methodology for Phase II/III Clinical Trials

- Recent developments in design
- Methods of analysis for phase II/III trials
- Examples of implementation

Sue Todd, Professor of Medical Statistics, University of Reading

14.10 Using simulation and Biomarkers to speed phase I - II development: A case study

- The Development Scenario
- Bayesian Modelling Overview
- Simulation Cases
- Selected Results
- Conclusions

Pantelis Vlachos, Principle Biostatistician, Strategic Consulting, Cytel Corporation

14.50 Afternoon Tea

15.10 Case Study: Re-engineering Phase 2

- Phase 2 - the critical pivot point between discovery and full development
- Phase 2 studies designed for their true purpose: as gate-keepers to Phase 3 investment decision-making
- Introduction to the GSK R&D wide initiative called Re-engineering Phase 2 (RP2)
- Dose-response modelling, the formal incorporation of historical data into trial designs; making futility analyses routine within P2 studies and using those P2 data to make formal (Bayesian) predictions of potential Phase 3 outcomes; department-wide quantitative peer review
- The experience of trying to shift an organisation - both within Clinical Statistics and beyond
- Examples from GSK studies where the RP2 principles have been embedded ("before" and "after" examples), and descriptions of the educational material developed and used inside GSK

Graeme Archer, ADD Statistics Director, GlaxoSmithKline

15.50 Biomarker-adaptive designs in oncology: can confirmatory studies tackle sub-population finding?

- Bio/immune-markers potentially predictive of treatment benefits
- Examples of threshold identification as well as an example of an already dichotomized marker and the subsequent decision on the testing hierarchy
- Strategic concerns and implications of including a biomarker-defined sub-population in a confirmatory study

Lilla Di Scala, Senior Statistical Scientist, Roche

16.30 Cytel sponsored panel discussion Adaptive Designs: Barriers and the Future

- Critical appraisal of adaptive designs: where are the real gains?
- Is wider acceptance linked to how the methods fare in the public sector? To become common practice more people need to be using the approach - not just the pharmaceutical industry
- Has there been a collective "undue advocacy" of adaptive trials by proponents? Have we unintentionally created unrealistic expectations of improving outcomes and/or efficiencies?
- Will the adjective "adaptive" be dropped some day, as all trials will be adaptable (in one form or another)?
- How will trends toward modeled patients (physically and virtual) change the future of trials? Will we see trials without humans in our lifetime?

Discussion Moderator:

Michael Krams, MD, Global Head, Quantitative Sciences,
Janssen Pharmaceutical Companies of Johnson & Johnson

Panelists:
Loic Darchy, Head of Statistical Methodology Group, Sanofi R&D
Sue Todd, Professor of Medical Statistics, University of Reading
Christopher Jennison, Professor of Statistics, University of Bath
Pantelis Vlachos, Principle Biostatistician, Strategic Consulting, Cytel Corporation

17.10 Chairman's Closing Remarks and Close of Day One

Register online at: www.adaptivedesigns.co.uk • Alternatively fax

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We are leaders in adaptive trial planning and implementation. Every adaptive design reviewed by regulators has been deemed acceptable and all 25 leading global biopharma companies rely on our technology in their clinical studies. www.cytel.com



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08.30 Registration & Coffee

09.00 Chairman's Opening Remarks
Vladimir Anisimov, Senior Strategic Biostatistics Director, Quintiles

09.10 Revisiting the Biomarker Adaptive Threshold Design (BATD) - Is there a need for a study extension?

- The BATD design was recently proposed and assessed by the US National Cancer Institute
- The present work used as a starting point their landmark publication in Journal National Cancer Institute, 2007
- The limitations of the design will be discussed and naturally led us to consider an extension to the BATD design; that extension consists of an extension phase focusing on the particular subset of interest as identified by the testing procedure underlying their approach (if any) when the initial study is statistically inconclusive
- Go/no go criteria for such an extension are discussed

Loic Darchy, Head of Statistical Methodology Group, Sanofi R&D

09.50 Designing an Adaptive Trial using a Combination Test for a Survival Endpoint

- A clinical trial with a survival endpoint and treatment selection
- Protecting the type I error rate in an adaptive design
- Problems in applying a combination test to survival data
- A new combination test for an adaptive design with survival data

Christopher Jennison, Professor of Statistics, University of Bath

10.30 Morning Coffee

10.50 Predictive analytical techniques for modelling operational characteristics in clinical trials

- Main uncertainties and interactions between adaptive trial design, patient enrolment, randomization
- Modelling and adaptive adjustment of patient enrolment
- Predictive modelling operational characteristics (visits, events and associated costs)
- Optimization of different stages of drug development

Prof. Dr. Vladimir Anisimov, Senior Strategic Biostatistics Director, Quintiles

11.30 Designing multi-arm multi-stage trials with a safety and an efficacy endpoint

- Multi-arm clinical trials that compare several active treatments to a common control as an efficient means of making an informed decision about which treatment should be evaluated further in a confirmatory study
- The constraint that selection and formal testing should be based on a single efficacy endpoint, despite the fact that in practice, safety considerations will often play a central role in determining selection decisions
- Multi-arm, multi-stage design for a trial with an efficacy and a safety endpoint considering the situation where a minimal safety requirement is to be fulfilled and the treatment yielding the best combined safety and efficacy trade-off satisfying this constraint is selected for further testing
- Selections made at the first interim analysis while the whole trial is allowed to comprise of J analyses

Lisa Hampson, MRC Career Development Award Fellow in Biostatistics, University of Lancaster

12.10 Networking Lunch

13.30 Cost-effectiveness of alternative designs in CV outcome studies

- Fundamentals of sequential and adaptive design
- Robust design of clinical trials
- Decision support using a monetary utility function
- A case-study will illustrate the ideas using simulated data

Mats Kvarnström, Principal Statistician, AstraZeneca

14.10 Optimum Adaptive Design for Dose Finding in Early Clinical Trials Incorporating PK Information

- Efficient and ethical dose allocation
- Population variability accounted for in optimum PK sampling times
- Dose finding targeted at desirable drug exposure

Barbara Bogacka, Reader in Statistics, Queen Mary, University of London

14.50 Afternoon Tea

15.10 Flexible Designs in Phase I Pharmacokinetic Trials

- Basic concepts of Phase I PK trials
- Adaptive and flexible approaches to Phase I bioequivalence trials
- An evaluation of flexible designs vs pilot/main study approaches
- Case studies of group sequential designs in Phase I bioequivalence trials

Frank Fleisher, Principal Statistician, Boehringer-Ingelheim

15.50 Adaptive elements in clinical pharmacology trials

- Adaptations in first in human trials
- Efficient planning of bioavailability and bioequivalence trials
- The role of pilot and feasibility trials in particular in academic research

Arne Ring, Principal Statistician, University of Leicester

16.30 Chairman's Closing Remarks and Close of Day Two

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**Workshop A: Simulating Clinical Trials using the
FACTS software package: Why simulate
clinical trials, how to simulate clinical trials
and the difference it will make**

Workshop Leader:

Tom Parke, Head of Clinical Trial Solutions,
Tessella Ltd

Overview of workshop:

The purpose of the workshop is twofold, firstly to introduce the art of simulating clinical trials, and illustrating the many advantages of doing it. Secondly simulation will be demonstrated using the FACTS software (as this will allow us to specify and run simulations very quickly and visibly) and thus the workshop will show some of the capabilities of the FACTS software and how it can be used in trial design.

Workshop Agenda:

8.30 Coffee & Registration

9.00 Introduction to trial simulation

- The simulation process
- The design using simulation process – art and science
- Simulation and interaction with the project team

10.00 Worked example – phase 1 dose escalation using the New CRM method

- Specifying scenarios
- Conveying the design
- Optimising the design

10.45 Coffee Break

11.00 Worked example – phase 2 dose finding design

- Incremental design
- Dose response modelling
- Longitudinal modelling
- Adaptive design

12.00 Extending the example and the simulation process

- Using data from pharmacometrics
- Optimising the design in the light of the whole development program

12.45 Final Discussion/Q&A

13.00 Close of workshop

About the workshop host

Tom has been working at Tessella for over fifteen years. In 1998 he had the great good fortune to work on Pfizer's ASTIN Stroke trial managed by Dr Michael Krams and designed by Prof Don Berry and Dr Peter Mueller. This was a landmark trial that used Bayesian modelling to optimize the allocation of subjects to doses and decide when to stop the trial.

Tom has now helped implement numerous Bayesian, response adaptive, phase 2 dose finding trials, for a range of pharmaceutical companies across a range of indications. Building systems to support the running of the trials and integrate the adaptive algorithms with existing IVRS and EDC systems.

He is currently leading projects within Tessella to develop tools for the modelling and simulation of drug development including 'FACTS' the Fixed and Adaptive Clinical Trial Simulator, that is developed in partnership with Berry Consultants.

Workshop B: Identifying and Exploiting Opportunities for Efficiency in Clinical Trial Design: An Interactive Adaptive Design Workshop

Workshop Leader:

Professor Roger J. Lewis, MD, PhD, Senior Medical Scientist, **Berry Consultants**

Overview of workshop:

Using trial examples provided by the workshop participants, the instructor will demonstrate the process of identifying opportunities for increasing clinical trial efficiency and minimizing the risk of a failed trial, by applying adaptive design principles. By using actual examples, modified to whatever extent is required by considerations of confidentiality, the focus will be on solving real challenges facing those working on the development of innovative pharmaceuticals, biologics, or medical devices. Logistical and implementation challenges associated with the proposed designs, and their solutions, will be discussed as well.

Workshop Agenda:

1.00 Coffee & Registration

1.30 Opening

- Review of the “toolbox” of adaptive techniques that can commonly be applied
- Advantages, challenges, and regulatory considerations in the choice of adaptive techniques to be considered
- Evaluation and “stress testing” of proposed adaptive designs

2.00 Identification and Evaluation of Opportunities for Increasing Clinical Trial Efficiency

- Interactive discussion of clinical trial examples provided by workshop participants
- Identification of opportunities for increased statistical and operational efficiency
- Discussion of simulation and other evaluation methods for determining the operating characteristics of proposed designs

3.00 Networking break

3.30 Logistical and Implementation Considerations

- Discussion of logistical challenges and implementation methods for multicentre trials incorporating the adaptive approaches discussed in the workshop
- Discussion of experiences (both successful experiences and adverse experiences) associated with the implementation of adaptive clinical trials

4.30 Oversight and Monitoring of an Adaptive Trial

- Approaches to the oversight and monitoring of adaptive clinical trials
- Considerations in the formation of Data and Safety Monitoring Boards (DSMBs) and their operation
- Methods to ensure ongoing trial integrity and the acceptability of final trial results to regulators

5.00 End of workshop

About the workshop host

Roger J. Lewis, MD, PhD received his PhD in Biophysics in 1986 and his MD in 1987 from Stanford University. He completed clinical training in emergency medicine in 1990 and is currently a Professor at the David Geffen School of Medicine at UCLA and Chair of the Department of Emergency Medicine at Harbor-UCLA Medical Center. Dr. Lewis is a member of the Board of Directors for the Society for Clinical Trials. He is also the Senior Medical Scientist at Berry Consultants, LLC, a statistical consulting group that specializes in the design and implementation of adaptive clinical trials.

ADAPTIVE DESIGNS IN CLINICAL TRIALS

Conference: Monday 24th and Tuesday 25th March 2014, Holiday Inn Regents Park, London, UK Workshops: Wednesday 26th March 2014, London

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Workshop A B

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