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SMi Presents the 10th Annual...

Adaptive Designs in Clinical Trials

Copthorne Tara Hotel, Kensington, London, UK

CONFERENCE:
9TH - 10TH
WORKSHOPS: 11TH

APRIL 2018

Exploring experimental and novel approaches to improve the flexibility, efficiency, and ethical aspects of your clinical trials

HIGHLIGHTS IN 2018:

- **Hear** exciting case studies on enrichment designs and group sequential trials from **Boehringer-Ingelheim, Sanofi Aventis** and **H.Lundbeck**
- **Explore** the current industry outlook and evaluate the promises and challenges of digital technology use with **Amgen** and **Novartis**
- **Discover** how **AstraZeneca** and **UCB Pharma** are using Platform Trials and self adapting priors to advance their adaptive clinical trials
- **Examine** how **Roche** and **Merck KGaA** are using adaptive clinical trials to produce targeted therapies

CHAIRS FOR 2018:

- **Alex Sverdlov,** Director, Statistical Scientist, **Novartis**
- **James Matcham,** Head of Biometrics, Early Clinical Development, **AstraZeneca**

FEATURED SPEAKERS 2018:

- **Christine Fletcher,** Executive Director Biostatistics, **Amgen**
- **Chris Harbron,** Principal Statistical Scientist, **Roche**
- **Frank Fleischer,** Expert Statistician Methodology, **Boehringer-Ingelheim**
- **Olivier Collignon,** Biostatistician, **European Medicines Agency**
- **Corine Baayen,** Senior Biostatistician, **H.Lundbeck**
- **Loic Darchy,** Senior Statistician, **Sanofi Aventis**
- **Ros Walley,** Statistician, **UCB Pharma**
- **Daniela Casula,** Lead Statistician, **GlaxoSmithKline**
- **Heiko Goette,** Biostatistician, **Merck KGaA**
- **Beatrice Panico,** Medical Assessor, **MHRA**

PLUS TWO INTERACTIVE HALF-DAY POST-CONFERENCE WORKSHOPS
WEDNESDAY 11TH APRIL 2018, COPTHORNE TARA HOTEL, LONDON, UK

A: Multiple Hypothesis Testing in Group Sequential and Adaptive Clinical Trials

Workshop Leader: **Christopher Jennison,**
Professor of Statistics, **University of Bath**
08.30 - 12.30

B: Unlocking the potential of platform trials

Workshop Leader: **Tom Parke,**
Director of Software Solutions, **Berry Consulting**
13.30 - 17.30

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LETTER FROM THE CHAIRS:

Dear participants,

With recent continuous developments in biotechnology, genomics and medicine, there is a high demand for more innovative and adaptive ways to design drug development programs. Adaptive designs, when properly implemented, can improve flexibility, efficiency, and ethical aspects of both exploratory and confirmatory clinical trials. Over the past two decades, there has been an increasing interest among stakeholders in academia, industry, and health authorities in applying these designs in practice.

The 10th SMi conference Adaptive Designs in Clinical Trials is a continuation of the discussion series on recent developments and applications of state-of-the-art adaptive design techniques in clinical research. The invited speakers have substantial experience in designing, conducting, and analysing adaptive clinical trials. In the spotlight are recent real-life applications of group sequential and adaptive enrichment designs, confirmatory designs with treatment selection, use of basket, umbrella and platform studies in personalised medicine, evaluation of digital technologies in randomised clinical trials, updates on regulatory perspectives on adaptive trials, and many other important topics. The panel discussion will bring together experts from regulatory, academia and industry to highlight and elaborate on current issues and emerging areas of interest for adaptive designs in clinical development. I look forward to meeting with you at this exciting event in London in April 2018!

Alex Sverdlov,
Director,
Statistical Scientist,
Novartis

James Matcham,
Head of Biometrics,
Early Clinical Development,
AstraZeneca

08.30 **REGISTRATION & COFFEE**

09.00 **CHAIRMAN'S OPENING REMARKS**
Alex Sverdlov, Director, Statistical Scientist, **Novartis**

CURRENT INDUSTRY OUTLOOK

09.10 **KEYNOTE ADDRESS**
INNOVATIONS IN CLINICAL TRIAL DESIGN: LESSONS LEARNED FROM ADAPTIVE DESIGNS
- Why are adaptive designs used in clinical trials?
- What have we learned from adaptive designs?
- What does the future of adaptive deigns look like?
- Other innovations in clinical trial design

Christine Fletcher, Executive Director Biostatistics, **Amgen**

09.50 **MHRA: REGULATORY PERSPECTIVE ON ADAPTIVE DESIGN TRIALS**
- Points to consider for initial Clinical Trial Authorisation (CTA) applications
- Points to consider when submitting substantial amendments
- Safety considerations

Beatrice Panico, Medical Assessor, **MHRA**

10.30 **MORNING COFFEE**

11.00 **REAL-LIFE EXAMPLES FROM AN INDUSTRY PERSPECTIVE**
- A confirmatory enrichment design using group-sequential and interleaving techniques
- Comparing different adaptive enrichment designs
- A selection design for determining the most equivalent drug formulation
- Adaptive randomisation for cut-off determination in the early phase
- Future areas of interest for adaptive designs in clinical development

Frank Fleischer, Expert Statistician Methodology, **Boehringer-Ingelheim**

THE INFORMATION AGE – THE INCREASING USE OF TECHNOLOGY IN ADAPTIVE DESIGNS

11.40 **EVALUATING DIGITAL TECHNOLOGY IN ADAPTIVE CLINICAL TRIALS: PROMISES AND CHALLENGES**
- Use of digital devices (including wearables) in clinical research
- How to make sense of the data collected from digital devices
- What experimental designs are appropriate for evaluating digital therapeutics
- Examples of adaptive trials

Alex Sverdlov, Director, Statistical Scientist, **Novartis**

12.20 **NETWORKING LUNCH**

13.20 **HOW DOES THE INCREASED USE OF TECHNOLOGY AND NOVEL CLINICAL TRIAL DESIGN IMPACT REGULATORY ADVICE AND SHAPE DEVELOPMENT OF NEW MEDICINES**
- How does the increased use of technology in adaptive trials impact regulatory guidance?
- What are the regulatory bodies' attitudes to novel adaptive clinical trials?
- What are the challenges and opportunities with novel adaptive designs
- How will in vitro diagnostic regulations impact the application of adaptive trials?
- What does the future for adaptive designs, in the context of other approaches to obtaining evidence on the safety, efficacy and effectiveness look like?

Bob Clay, Managing Director, **Highbury Regulatory Sciences**

EXPERIMENTAL APPROACHES PART 1

14.00 **CONFIRMATORY ADAPTIVE DESIGNS INVOLVING SELECTION**
- Summary of options for trials with treatment selection
- Consideration of trials with subpopulation selection
- Overview of examples of trials in practice

Sue Todd, Reader of Medical Statistics, **University of Reading**

14.40 **ADAPTIVE DESIGNS FOR COPD VACCINE**
- What adaptive approaches were used in the development of the COPD vaccine?
- How was this useful?
- What challenges were faced and how were they overcome?

Daniela Casula, Lead Statistician, **GlaxoSmithKline**

15.20 **AFTERNOON TEA**

15.50 **LATEST DEVELOPMENTS IN ADAPTIVE DESIGNS, A COMPANY PERSPECTIVE**
- Overview of the latest research at Sanofi
- Examples of how Sanofi is currently using adaptive designs in their clinical trials
- Current issues being faced and challenges ahead

Loic Darchy, Senior Statistician, **Sanofi Aventis**

16.30 **SEQUENTIAL TRIALS IN THE CONTEXT OF COMPETING RISKS – A CASE STUDY**
- How can we evaluate competing risk data in group sequential trials?
- A case study illustrating the state of the art, typical challenges and open issues
- A discussion of remaining open questions

Corine Baayen, Senior Biostatistician, **H.Lundbeck**

17.10 **CHAIRMAN'S CLOSING REMARKS AND CLOSE OF DAY ONE**

08.30 REGISTRATION & COFFEE

09.00 CHAIRMAN'S OPENING REMARKS
James Matcham, Head of Biometrics, Early Clinical Development, **AstraZeneca**

EVALUATING MULTIPLE TREATMENTS WITH ADAPTIVE DESIGNS

OPENING ADDRESS

09.10 PLATFORM STUDIES IN DRUG DEVELOPMENT
- The Use of Basket and Umbrella Studies
- Benefits of a Platform Study approach in oncology
- Practical challenges with Platform Studies
- Applications in other therapeutic areas

James Matcham, Head of Biometrics, Early Clinical Development, **AstraZeneca**

09.50 REGULATORY PERSPECTIVES FOR THE PLANNING AND ASSESSMENT OF UMBRELLA AND BASKET TRIALS
- Evaluation of the consistency of response across several sub-studies based on different conditions, pooling of the sub-studies and impact on regulatory assessment
- The debatable necessity to control for multiplicity
- Additional issues relating to biomarker development and integration of historical controls

Olivier Collignon. Biostatistician, **European Medicines Agency**

10.30 MORNING COFFEE

11.00 DESIGN AND ANALYSIS OF PLATFORM CLINICAL TRIALS ASSESSING MULTIPLE TREATMENTS AND BIOMARKERS
- How traditional trial design could be improved when treatments are expected to have different efficacy in different groups
- A review and comparison of designs available for testing multiple treatments in multiple subgroups
- An overview of methodology work done to address statistical issues arising when new treatments and biomarkers can be added in, including error rates, use of non-concurrent controls, planning confirmatory studies
- A description of future research directions in this area.

James Wason, Group Leader, **MRC Biostatistics Unit**

11.40 PANEL DISCUSION: EXPERIMENTAL AND NOVEL APPROACHES IN ADAPTIVE DESIGNS
- What experimental and novel approaches are being used by pharmaceutical companies?
- Why are novel approaches used and what benefits do they bring?
- Challenges associated with the use of novel adaptions
- Future outlook for new experimental adaptions and novel approaches

Olivier Collignon, Biostatistician, **European Medicines Agency**
James Matcham, Head of Biometrics, Early Clinical Development, **AstraZeneca**
Ros Walley, Statistician, **UCB Pharma**

12.20 NETWORKING LUNCH

EXPERIMENTAL APPROACHES PART 2

13.20 SELF ADAPTING PRIORS
- Incorporating relevant historical information though a Bayesian informative prior is increasingly used in Early Clinical Development
- Concern about potential prior-data conflict can lead to heavy discounting of this information
- Instead "self-adapting priors" can be used which alter the down-weighting depending on the discrepancy between the prior and the data

Ros Walley, Statistician, **UCB Pharma**

14.00 THE ROLE OF RE-RANDOMIZATION TESTS IN ADAPTIVE METHODS WITH PLANNED OR UNPLANNED CHANGES
- Unplanned changes can still be analysed in a valid way
- The real null hypothesis being tested with covariate- and response-adaptive randomization
- Temporal trends? Re-randomization tests to the rescue!
- Are re-randomization tests always valid?

Michael Proschan, Mathematical Statistician, **National Institute of Allergy and Infectious Diseases, USA**

14.40 AFTERNOON TEA

ADAPTIVE DESIGNS FOR TARGETED THERAPIES

15.10 RIGHT PATIENT, RIGHT DESIGN: FACILITATING PERSONALISED HEALTHCARE WITH ADAPTIVE DESIGNS
- Personalised HealthCare (PHC), targeting therapies to those patients most likely to benefit is becoming increasingly important
- During development there can be uncertainty on the optimal PHC strategy, both on the need for a biomarker and the exact definition of a biomarker
- Adaptive designs provide an efficient way of mitigating this uncertainty whilst still maintaining the overall rigour and operating characteristics of the trial

Chris Harbron, Principal Statistical Scientist, **Roche**

15.50 SIMULATION-BASED ADJUSTMENT AFTER EXPLORATORY BIOMARKER SUBGROUP SELECTION IN PHASE II
- When investigating targeted therapies subgroups are typically defined by biomarkers
- Promising results may lead to the decision to select the respective subgroup as the target population for a subsequent phase III trial
- We describe how Approximate Bayesian Computation techniques can be used to derive a simulation-based bias adjustment method in this situation
- Recommendations for the implementation of the approach are given

Heiko Goette, Biostatistician, **Merck KGaA**

16.30 CHAIRMAN'S CLOSING REMARKS AND CLOSE OF DAY TWO

HALF-DAY POST-CONFERENCE WORKSHOP A
Wednesday 11th April 2018
08.30 – 12.30
Copthorne Tara Hotel, London, UK

Multiple Hypothesis Testing in Group Sequential and Adaptive Clinical Trials

Workshop Leader: **Christopher Jennison,**
Professor of Statistics, **University of Bath**

Overview of the workshop

The workshop will introduce group sequential designs and their applications. We shall consider designs that combine multiple testing with group sequential monitoring, in particular, testing a secondary endpoint on termination of a group sequential trial.

Adaptive designs include: enrichment designs, seamless Phase II/III designs, and multi-arm, multi-stage Phase III trials. We shall describe the general methodology for creating such designs and illustrate this in a case study of a Phase III trial with treatment selection and a survival endpoint.

Why you should attend?

Sequential and adaptive designs are used increasingly to study new treatments and establish their effectiveness. The workshop will equip participants to understand when such methods are appropriate and how to go about implementing these designs.

Programme

08.30 **Registration and Coffee**

09.00 **Opening remarks and introductions**

09.10 **Group sequential tests (GSTs)**
- Motivation for sequential testing
- Error spending tests
- Example: A GST with a survival endpoint
- Inference on termination of a GST

09.50 **Multiple testing procedures**
- Introduction to multiple testing
- Graphical representations
- Combining multiple testing and GSTs
- Testing a secondary endpoint after a GST

10.30 **Morning Coffee**

11.00 **Adaptive clinical trial designs**
- Combination tests
- Sample size re-estimation
- Testing multiple hypotheses
- Closed testing procedures

11.40 **Example: A survival trial with treatment selection**
- An adaptive design
- Avoiding type I error inflation
- Assessing the benefits of the adaptive design

12.20 **Closing remarks**

12.30 **End of workshop**

About the workshop leader

Christopher Jennison is Professor of Statistics at the University of Bath, UK. His PhD research at Cornell University concerned the sequential analysis of clinical trials and he has continued to work in this area for the past 35 years. His book with Professor Bruce Turnbull, "Group Sequential Methods with Applications to Clinical Trials", is a standard text on this topic and is widely used by practising statisticians.

Professor Jennison's research is informed by experience of clinical trial analysis at the Dana Farber Cancer Institute, Boston and a broad range of consultancy with Medical Research institutes and Pharmaceutical companies.

University of Bath

The University of Bath received its royal charter in 1966. The University's traditional strengths in science and technology are now complemented by activity in management and the social sciences. We place a strong emphasis on vocational education with many students taking a one-year industry placement during their degree courses.

In 2017, Bath was ranked 12th in the Good University Guide. Its many notable graduates include the medical statistician Doug Altman and the skeleton bobsleigh gold medallist Amy Williams.

HALF-DAY POST-CONFERENCE WORKSHOP B
Wednesday 11th April 2018
13.30 – 17.30
Copthorne Tara Hotel, London, UK

Unlocking the potential of platform trials

Workshop Leader: **Tom Parke,**
Director of Software Solutions, **Berry Consulting**

Overview of the workshop

The "Platform Clinical Trial" is a very powerful new idea that not only allows us to test new treatments more efficiently than ever before but also makes practical trials in indications that heretofore have been very hard to study successfully such as (for very different reasons) Ebola, Alzheimer's and Pneumonia.

The workshop will look at the efficiencies Platform trials can bring and some case studies, along with the statistical, political, regulatory and operational difficulties specific to Platform Trials.

Why you should attend?

This workshop will show why, and in what circumstances platform trials are attractive as a clinical testing method both in abstract and in specific case studies. However platform trials a considerably more complex to set up and the workshop will explore the key hurdles specific to platform trials that will need to be overcome.

Learning Objectives

The aim of this workshop is firstly to explain what a platform trial is and how it differs from a conventional trial. Attendees will gain an understanding of the incredible opportunities of "Platform Trials" to revolutionise the clinical testing of new medical treatments, and also to gain an appreciation of the necessary complexities of these trials – both statistically and practically.

Programme

13.30 **Registration and Coffee**

14.00 **Opening remarks and introductions**

14.10 **Session Introduction: Basket Trials, Umbrella trials and Platform trials. What's the big attraction?**
- What are Basket, Umbrella and Platform Trials?
- If we consider the time taken, and the number of subjects tested to develop a successful treatment, how do these trials compare to conventional development strategies?

14.50 **Case Studies**
- We will look as the similarities and differences in the designs of the platform trials for:
  - Ebola
  - Brain cancer (Glioblastoma – "GBM").
  - Cystic Fibrosis
  - Alzheimer's

15.30 **Afternoon Tea**

16.00 **Statistical issues**
- What are the key statistical issues for a platform trial?
- The use of adaptation
- The use of longitudinal modelling
- Who are the control subjects?
- What is the required degree of type -1 error control?

16.40 **Political, Operational and Regulatory issues.**
- Setting up a platform trial – where's the money coming from?
- Where are the treatments coming from?
- Who is more important, the subject or the provider of the novel treatment?
- How do we consent patients
- How do we manage: updates, limiting un-blinding, adding treatments, frequent and complex statistical analyses?
- What do the regulators think of all this?

17.20 **Closing Remarks**

17.30 **End of Workshop**

About the workshop leaders

Tom Parke is Director of Software Solutions for Berry Consultants. Tom joined Berry Consultants in 2016 and previously worked at Tessella, a UK scientific software company where he first met Don Berry in 1998 when he managed the development and running of a software system to support Pfizer's ASTIN Stroke trial – a ground breaking response adaptive randomization dose ranging trial designed by Don and Peter Mueller.

Berry Consultants

Berry Consultants
Statistical Innovation

Berry Consultants is a statistical consulting company specializing in the Bayesian approach to medical statistics, and strives to set the standard for innovative clinical trial design and analysis in the statistical and medical communities.

ADAPTIVE DESIGNS IN CLINICAL TRIALS

Conference: Monday 9th & Tuesday 10th April 2018, Copthorne Tara Hotel, Kensington, London, UK
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