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Adaptive Designs in Clinical Drug Development

2nd - 3rd February 2011
Crowne Plaza - The City, London, United Kingdom

Day One - 2nd February 2011

8.30 Registration and coffee

9.00 Chairman's opening remarks
Jennifer Dudinak, Global Head, Inflammation, Regulatory Affairs, **Roche**

9.10 Implementing an adaptive design: the investigative site perspective
- Patient access with complex design studies and maintaining patient trust
- Organisation and structures - study schedule, data entry, queries, volume of supplies
- Taking advantage of the challenges

Pierre Gervais, President and Executive Director, **Q&T Research**

9.50 Adaptive design and operational impact
- Need to understand the operational perspective of an adaptive design
- Issues with operational aspects of adaptive clinical trials
- Case study example

Melissa Mitchener, Global Study Manager, **Roche**

10.30 Morning coffee

11.00 Co-ordination and trial planning: maximising the benefits of an adaptive design through effective management
- Critical insight into the breakdown of people involved in an adaptive rather than a traditional trial: preparing for a more flexible operation
- Co-ordinating more people under increased time pressure: maximising your efficiency in order to take best advantage of the potential benefits
- Ensuring that your study managers are equipped to deal with adaptive trials: establishing the training implications
- Adapting communication strategy to ensure that with increased numbers of investigators involved, protocol amendments can be made quickly in order to save time and resources

Catarina Mattsson, Project Lead, **AstraZeneca**

11.40 The question of ethics
- Adaptive designs pose a difficult problem for ethics review boards
- Ethical review during a trial - for each change?
- Keeping lines of communication open

Jack Corman, President, **IRB Services**

12.20 Networking lunch

1.50 Developing internal regulatory guidance for adaptive trials
- Current Health Authority guidance
- Points to consider: Partnering with internal stakeholders; engaging with Health Authorities
- Strategic internal planning

Jennifer Dudinak, Global Head, Inflammation, Regulatory Affairs, **Roche**

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2.30 A perspective on the draft FDA adaptive designs guidance

- Emerging FDA position on the implementation of adaptive designs in adequate and well-controlled studies
- In what situations can adaptive designs be considered; what features make an adaptive design more or less controversial; what requirements are to be fulfilled by an adaptive design
- Comments and perspectives from the IBS German and AustroSwiss working group

Marc Vandemeulebroecke, Expert Statistician, **Novartis**

3.10 Afternoon tea

3.40 Statistical inference after an adaptive trial

- Gaining a better and fuller analysis after an adaptive clinical trial
- Confidence intervals
- Point estimation

Chris Jennison, Professor of Statistics, **University of Bath**

4.20 Detecting real treatment effects - an example from oncology

- Traditional designs fail where patients can switch between treatments
- Conventional intention-to-treat analysis vs. adaptive designs
- Avoiding unnecessary termination of investigation of a promising candidate

Pavel Pisa, Translational Medicine Leader, **Roche**

5.00 Chairman's closing remarks and close of day one

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8.30 Re-registration and coffee

9.00 Chairman's opening remarks

Robert Cuffe, Statistician, Infectious Diseases, Medicine Development Centre, **GlaxoSmithKline**

9.10 New designs — merging phase IIb and III

- Reducing the time required for clinical studies
- When is merging the right choice?
- Challenges of getting it right

Robert Cuffe, Statistician, Infectious Diseases, Medicine Development Centre, **GlaxoSmithKline**

9.50 Majesty and misery of interim dose selection
As conjectured from a 3-doses configuration

- In inferential phase II/III seamless designs, an interim analysis allows selection of doses to be kept until the end of the trial
- By sequentially using the information, this adaptive design is expected to be more efficient than ordinary fixed designs. This design can also be used for a full phase II study devoted to the choice of 1 or 2 doses in a future phase III study
- After discretising and constraining the usual case of three doses candidates, the research articulates in two stages:
- (1) Identifying the best multiple comparison procedures to be used in fixed design analyses
- (2) Combining these chosen procedures for adaptive designs and comparing their performance with that obtained for fixed designs
- There is a particular focus on the comparative effect of unbalancing treatment groups in fixed and adaptive designs - the problem of the latency period is also considered

Eric Derobert, Statistician, **Sanofi-Aventis**
Fanny Windenberger, Statistician, **Sanofi-Aventis**

10.30 Morning coffee

11.00 Developing a simulation plan and simulation report

- When designing a clinical trial, one needs to understand the performance metrics for a given design
- This is of particular importance for adaptive trials where one needs to consider many factors and how the results will depend on certain design choices
- Simulations are a key tool in evaluating the performance metrics of these choices in adaptive designs
- A simulation plan is extremely helpful in deciding on which design factors will vary and which will remain fixed
- Additionally one can describe how several competing designs will be assessed and compared with one another
- The Simulation Report summarised the performance metrics of the simulations and provides rationale as to why the design was chosen

David Manner, Group Leader, Exploratory and Programme Medical Statistics, **Eli Lilly**

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11.40 Get the dose right

- Best approaches and recent applications for designing adaptive dose-finding trials
- Why it's important to study more than one dose and which specific adaptive approaches are particularly well suited
- A comparative look at the most popular design methods for adaptive dose finding - both frequentist and Bayesian - and their relative strengths and weaknesses
- Simulation-driven decision-making: comparing different trial design options to arrive at the study best qualified to achieve developmental objectives
- Scenarios and the considerations for combining/consolidating traditionally separate studies into a single adaptive study: integrating PoC with dose-finding in a single trial

James Bolognese, Senior Director for Clinical Trial Services, **Cytel**

12.20 Networking lunch

1.50 Group sequential tests for delayed response: a case study

- Current group sequential tests stop with a final decision once a stopping rule is satisfied
- However, often the response of clinical interest is to be measured some time after commencement of treatment, meaning there will be subjects at each interim analysis who have been randomised to a treatment but are yet to respond
- We derive a new form of group sequential test which gives a proper treatment to these "pipeline" subjects
- We use optimal versions of our designs to measure the impact on efficiency of the length of delay in response
- We discuss the use of adaptive group sequential procedures for monitoring delayed responses, concentrating on two-stage designs

Lisa Hampson, Research Associate in Medical Statistics, **University Of Bristol**

2.30 Case study: combined phase I/PoC study with adaptive dose selection

- A combined MAD and POC study
- Planned trial
- Key design features
- Benefits of the design

Paul Jordan, Senior Statistician, **Roche**
Annette Sauter, **Roche**

3.10 The use of efficient trial design in Phase II to choose the right dose in Phase III

- Objective of Phase II is to choose the dose for later confirmatory studies
- According to the FDA - 20% of post approval changes were to the dose
- Large number of compound failures in Phase III - dose finding is clearly not done in the most efficient manner
- Model-based designs, coupled with Bayesian methods and adaptive designs (where appropriate) can improve dose finding by modelling the whole of the dose response curve
- The talk will highlight the use of model-based approaches and illustrate using real-life examples

Alun Bedding, Director, Biostatistics and Programming Development Partners, Drug Development Sciences, **GlaxoSmithKline**

3.50 Chairman's closing remarks

4.00 Afternoon tea and close of conference