Safeguarding public health

Adaptive Designs

- Latest thinking from this regulator!

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Objectives / Topics for Discussion

- Summarise the **DRAFT** CHMP Reflection Paper
  - Comment on ‘unresolved’ / ‘priority’ issues.
- Describe process for finalising the Reflection Paper
- Describe benefits of European Scientific Advice
- Review experience in European Scientific Advice to date
- QUESTIONS / DISCUSSION

Producing ‘guidelines’

- Committee for Human Medicinal Products (CHMP)

- Working parties include
  - Efficacy Working Party (EWP) - responsible for development of ‘general’ guidance
  - Scientific Advice Working Party (SAWP) - responsible for advice on particular development programmes

Scene-setting
- Quotes from Dr Simon Day

•“First to market with a new chemical entity is a good thing… first to regulation with a new [statistical] method may not be”

•“EWP is interested in innovative ways of designing and analysing clinical trials... the role of the EMEA is to regulate and not to initiate methodological research.”

Scene-setting (continued)

- (selective) advertising from another ‘adaptive designs’ meeting

- *“Ensure your organisation improves it’s Clinical Development practices, by playing an integral role in reducing your organisations (sic) costs, improving time to market and increasing the studies (sic) success rate. Innovate your organisation’s development procedures by introducing flexibility into your studies … Improving the quality of your trials …”*

- *“Nothing in life is free”*

‘Draft’ guidance

- Note - **confirmatory** clinical trials

- Exploratory clinical trials are considered the domain / risk of the sponsor

- Introduction / Scope

- General discussion of Interim Analyses

- Interim Analyses with Design Modifications
  - minimal requirements
  - scenarios

Introduction / Scope

- ‘without lowering regulatory standards’
- ‘contradiction to confirmatory nature of phase III studies’
- ‘use in difficult experimental situations’
- ‘in general changes are not recommended’

- Statistical possibilities -vs- Regulatory requirements

Introduction / Scope

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- Statistical possibilities -vs- Regulatory requirements

- *“We spent so long thinking about whether we could, we didn’t stop to think about whether we should”*

‘Minimal requirements’ (FDA – Sue Jane Wang)

- Is prospectively planned
- Has valid statistical approaches on modification of design elements that have α-control (ICH E-9I)
- Has valid point estimate and CI estimates
- *Utility of drawing strength from external trials, but, not too much*
- Careful use of “learning phase” in “confirming” phase
- *Has SOP/infrastructure/firewalls on adaptive process monitoring* – bias issue & trial integrity
- Has SOP/logistics on adaptive design decision
- Includes documentation of actual monitoring process, extent of compliance, potential impact on study results

- Compare with draft Reflection Paper – similar principles

Scenarios

- Sample size re-assessment
- Change in primary endpoint
- Discontinuing treatment arms
- Switching from ‘non-inferiority’ to ‘superiority’
- Randomisation ratio
- Phase II/III combinations; applications with one pivotal study
- Substantial changes of trial design
- Futility

- **Is there a good reason to adapt?**

- **How many of these have been deemed ‘acceptable’ trial designs?**

Unresolved Issues

- Sponsor Involvement
  - Usual regulatory standards are compromised. Does this matter?

- Phase II / III trials
  - Which data might be considered confirmatory?
  - The benefits of replication
  - How much to 'spend' in Phase II

- How to assess sponsor involvement?
  - Assessment of 'firewalls'?
  - Assessment of heterogeneity?
  - 'Worst-case' (?) scenario – no involvement, no contamination

- Concurrent controls

- 'should' vs 'must'; 'never' vs 'infrequently' etc.

Process for finalising the Reflection Paper

- Consultation period ended 30th September 2006
- Plenty of comments received!

- Sponsor Involvement
  - None, Limited / Controlled, Open?
  - Assess through homogeneity only?
- Phase II / III studies
  - Depends on sponsor involvement?
- Too strict?

- Further drafting and discussion at EWP

The benefits of European Scientific Advice

•General guidance can only give general principles - this may be enough!

•Specific guidance and discussion is available through SAWP

•Guidance is not obligatory ...
•… but is **strongly recommended** for most confirmatory trials with adaptive design

• Exceptions ...

Experience in European Scientific Advice to date

- Results of my quick survey…

- **How many of these have been deemed ‘acceptable’ trial designs?**

Use of data from interim analyses – dissemination of interim information

•Principle: Data from interim analyses not disseminated until the trial has answered all important questions of interest / has completed.

•Book(s) by Ellenberg et al
•EU guidance

•How does this fit with conditional approval?
- With great difficulty!
- Double-blind versus open-label trials, Objective versus subjective endpoints
- Is the treatment period complete?
- Proving that two parts of a trial are consistent (not proving that they are not inconsistent!)
- Ethics / Practicalities of continued treatment

QUESTIONS / DISCUSSION