Safeguarding public health

Sponsor involvement - Current Regulatory Recommendations

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- Interim assessments can be mandatory from an ethical perspective

- Interim assessments have the potential to benefit experimental design, through:
  - Safety monitoring
  - Efficacy monitoring
  - Futility assessments
  - Monitoring of trial progress and conduct
  - Opportunity for adaptations based on accumulating data?

Available guidance

- CHMP Guideline on Data Monitoring Committees
  - CHMP/EWP/5872/03 Corr
- FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees
- Data Monitoring Committees in Clinical Trials: A Practical Perspective
  - Susan Ellenberg, Thomas Fleming, David DeMets
- Main Issues:
  - Multiple analyses / Type I error
  - Maintaining trial integrity - if treatment allocation or accumulating results are known or can be calculated / guessed, will trial conduct be influenced, will bias be introduced? How can absence of bias be established?

Basic requirements around interim analyses

- Interim analyses introduce a risk to trial integrity so …
  - Justify the need for interim analysis
  - Justify the number of interim analyses
  - Control the flow of interim information: **sponsor involvement discouraged**
  - Control Type I error via appropriate statistical methodology

- Protection of trial integrity and statistical validity is generally done very well in present-day submissions.
  - ‘Stopping rules’ e.g. O’Brien-Fleming
  - DSMB / DMC charters
  - ‘Independent statistician’ / Firewalls etc.

- But it is proposed that the status-quo changes …

- Argued that there is increased **need** for sponsor involvement
  - "Financial implications are too great"
  - "Increased complexity of decision-making"
  - How much can be asked of independent experts?

  - [Keeps senior management out of decision making process!!]

- Example is dose-selection in Phase II / III trial.
  - This is a multi-factorial problem and a critical decision. Criteria may be difficult to agree - i.e. to formulate into an algorithm - in advance.

How critical is it to control dissemination of interim information?

•“This happens anyway between Phases II and III in a standard development programme”

•“Actually, there may be advantages to a seamless trial by minimising dissemination of information” - less information passed between trial stages than between development phases?

• Some modifications will be incorporated by design.

• Different endpoints / centres / investigators / patient population

• Bias due to dissemination of information is not quantifiable. We just don’t know!

- **Risk** of sponsor involvement
  - Risk of damage to trial integrity remains (perhaps increases)
  - Regulatory perception
  - Establishing absence of ‘bias’, in particular when heterogeneity between trial stages exists.

- *“Nevertheless sponsor involvement introduces an additional risk when the credibility of the trial results is challenged: with sponsor involvement it would be more difficult to argue that importantly different results from different stages are only due to chance”*

- *“Sponsor involvement is discouraged.”*

Challenge to Applicants

- Why is sponsor involvement necessary?
- How can absence of bias be established?

Concluding remarks

- Bias due to dissemination of information is not quantifiable. Trial results may be compromised.
- Sponsor involvement represents a **risk**; it is discouraged.
- Plans to protect information are necessary but not guaranteed to be sufficient.
- Do the benefits outweigh the risks?
- Again, context of trial within development programme is key.