Elements of Design of FIM Clinical Trials

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Points to Consider:

- Subject safety is paramount; efficacy is not expected
- Choice of subjects
- Route and rate of administration
- Calculation of dose
- Precautions to apply between doses within cohorts

Points to Consider (continued):

- Precautions to apply between cohorts
- Dose escalation scheme
- Stopping rules and decision making
- Monitoring for adverse events
- Site of clinical trial

General Considerations

- Subjects safety rights and well being are paramount

- In general, the higher the potential risk associated with the type of medical product and its target, the greater the precautionary measures that should be applied

Choice of Subjects

- Healthy subjects or patients
  - Fully justified by sponsor on a case-by-case basis considering
    - Risks inherent in type of medicinal product
    - The target; presence of target in normal vs. disease state
    - Potential for toxicity; short and long term
    - Possible higher variability in patients
    - Relevance of data to intended clinical use
- Clear inclusion/exclusion criteria
- Subjects should not simultaneously be in another trial

Route and Rate of Administration

- Carefully considered and justified
- iv administration: slow infusion over several hours, preferable to slow bolus

Precautions to apply between doses within cohort

- Sequential design
- Adequate period of observation between administration
  - Justified on a case by case basis taking into account all available information
- Number of subjects depends on trial objectives and variability of PK/PD parameters

Precautions to apply between cohorts

- Prior to dose escalation, results from prior cohort fully considered (and all subjects dosed) including PK, PD, safety
- Assumptions made in designing dose escalation regime should be revisited as new data becomes available
- Time interval between cohorts should be guided by existing non-clinical and clinical PK/PD data and, if available, already existing experience with comparable products

Precautions to apply between cohorts (continued)

- Dose escalation increments justified on case by case basis taking into account PD aspects including steepness of dose response curve, and other available information, dose/toxicity and dose/effect relationship in non-clinical studies should guide dose increments until clinical data becomes available.

- Steeper the increase in dose toxicity or dose effect curves, lower dose increment that should be selected.

- Choice of dose level should include some estimate of potential PD/or adverse effects

Stopping Rules

- Protocol should define stopping rules
- Consider use IDSMB
- Define clear procedure for decision making

Monitoring for Adverse Events/Reactions

- Provide specific plan for monitoring for AE's
- Consideration of likely AE's
- Training in identification and management of AE's
- Define treatment strategy for predictable adverse reactions
- Consider antidotes, supportive treatment, access to treatment allocation codes
- Clear procedures for communication of SUSAR's
- Consider potential long term safety issues and therefore duration of monitoring period

Site of Clinical Trial

- Appropriate facilities
- Appropriate training and expertise
- Understanding of IMP, target, mechanism
- Immediate access to facilities for treatment of medical emergencies, stabilising individual and readily availability of ICU
- Preferably conduct at single site

Comments

- Is there too much focus on healthy volunteer trials
  - Not sufficiently covering issues in patient trials eg oncology
- Guidance not acknowledging that toxicity may be endpoint of trial
- Site – not overly restrictive
  - Not restrict to single site if patient trial
  - More clarity in relation to ICU
- IDSMB
  - Use fairly uncommon
  - Could IEC role be enhanced
  - Is it appropriate?
  - ? Case by case

Comments continued)

- Greater definition of what constitutes acceptable level of risk
- Section on consent
  - Basis of R/B analysis
  - Degree to which factors are unknown
  - Information
- Multiple single doses
- Possible benefit
- Degree of uncertainty around risk
- Long term monitoring/consequences
  - Little likely to be known at this stage
  - Some difficulties, lack of clarity
  - Targeted, case by case

Comments (continued)

- More emphasis that same or slower rate administration as used in animal trials
  - Control of dose
  - Discussion of duration
- Uncertainty in estimated first dose should be quantified and explained
- More specific recommendations on drug dosing and number of subjects, recommendation that at least 1 subject be dosed with placebo on same day
- All data before dose escalation?
  - Impractical
  - Relevant data
  - Sufficient data
  - Prespecify what