4.2 – Concept of Benefit / Risk

Presentation to APEC Preliminary Workshop on Review of Drug Development in Clinical Trials

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Disclaimer: the information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
Benefit / Risk Concept

Risk to subjects

Societal benefit

Regulatory rejection

Regulatory approval
Benefit / Risk

- Assessing benefit / risk involves:
  - Analysis of unmet medical need and disease characteristics
  - Analysis of data accumulated through product development

- Both the regulator and the sponsor assess benefit / risk continuously
Design study protocol with measures to mitigate risks

Continuously evaluate safety

Benefit / risk assessment cycle

Revise plans if benefit/risk changes

Define the benefits and potential risks
Extrinsic Factors in Benefit / Risk Balance

Societal benefit

Risk to trial subject

- Morbidity and mortality of disease
- Unmet medical need
- Validated methods are available to measure efficacy and safety

- New target with unknown effects or target known to be high risk
- Drug class has known risks
- Uncertainty about efficacy and safety measures
Benefit / Risk – Phase I (1)

• Healthy volunteers:
  – Benefits: societal benefit only (monetary benefit is not taken into account in regulatory decision)
  – What are the risks?
    • Drug type and target
    • Drug product quality
    • Potential toxicity based on pre-clinical studies
    • Proposed starting dose and dose-escalation method
    • Route of administration
    • Single vs repeat-dose
    • Sample size
    • Tests and procedures

• What are the risk mitigation measures?
Benefit / Risk – Phase I (2)

• Patients:
  – Benefits: societal benefit; potential for patient benefit in some studies
  – What are the risks?
    • Patient population
    • Drug type and target
    • Drug product quality
    • Potential toxicity based on pre-clinical studies
    • Proposed starting dose and dose-escalation method
    • Route of administration
    • Single vs repeat-dose
    • Sample size
    • Tests and procedures

• What are the risk mitigation measures?
Benefit / Risk – Phase II

• Benefits: societal benefit; potential benefit to trial subjects

• What are the risks?
  – Patient population
  – Potential toxicity based on pre-clinical studies
  – Safety data from phase I studies
  – Changes in drug product quality
  – Proposed phase II starting dose and dose-range
  – Study design and endpoints
  – Duration of trial
  – Sample size
  – Tests and procedures

• What are the risk mitigation measures?
Benefit / Risk – Phase III

• Benefits: societal benefit; potential benefit to trial subjects

• What are the risks?
  – Patient population
  – Safety data from phase I & II studies
  – Changes in drug product quality
  – Proposed dose or dosage regimen
  – Study design and endpoints
  – Statistical plan
  – Duration of trial
  – Tests and procedures

• What are the risk mitigation measures?
Discrete time points in benefit/risk assessment

Continuous benefit/risk assessment

Data accumulation

Preclinical

Healthy Volunteers

Phase I Patients

Phase II

Phase III

Phase IV

Do benefits outweigh risks?
Real World

- Previous trials often not conducted in own region
- Use of a comparator product not marketed in own region but marketed in another region
- Multiple investigational products
- Manufacturing changes in between phases (e.g., impact on more complex products such as biologics)
- Reconciling differences in clinical practices between regions
- Reconciling differences in marketing requirements between regions
Conclusion

• The outcome of the benefit / risk assessment is a judgement call that is based on:

  – Extrinsic factors:
    • Morbidity and mortality of the disease
    • Extent of unmet medical need
    • Availability of validated safety & efficacy measures
    • Knowledge about the drug target and drug class
    • Marketing requirements

  – Factors related to the drug and the trial:
    • All accumulated data on the drug product
    • The proposed trial itself (e.g., design, population, dosage regimen, safety and efficacy measures, risk mitigation measures, etc.)
    • Adequate risk communication to trial subjects
## References