8. Clinical Trial Assessment
Phase II

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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.
Overview

- Purpose
- Type of Study
- Type of Control
- Endpoint
- Selection of population
- Risk vs benefit
- Risk mitigation
- Risk communication
- Reference
- Exercises
Purpose of phase II

- Link animal and human findings
- Estimate efficacy and Safety
- Select dose and dose interval
- To success phase III studies, furthermore to success development of the drug!
Type of Study

- Comparative vs non-comparative
- Randomized
- Blind vs unblinded
- Proof of concept
Comparative or non-comparative?

- If comparator is not included in the studies...
  - How to measure the magnitude of efficacy and safety?
  - Are results of past studies useful for evaluation of developing drug?
Randomized Control Study

Why an intervention group and a control group are needed?

- To remove investigator bias in allocation of participants
- To guarantees that statistical tests will have valid significance levels
Blind vs unblinded

- To avoid potential problems of bias during data collection and assessment
- Should have a double-blind design. If impossible, a single-blind approach and other measures to reduce potential bias are favored.
Proof of concept

- Important studies in drug development
- Provide evidence that the hypothesized mechanism is affected by the drug
- Provide evidence that the effect on the mechanism leads to a desired short-term clinical outcome
Type of Control

- Placebo control
- Specified active agent
- Optimal Basic Therapy
  - Any medicines
  - Any therapy (Surgical treatment etc.)
Objectives

- Efficacy
- Safety
- Pharmacokinetic in patients
  - Condition of disease
  - Concomitant drugs
- Interaction with food/drugs
Example

- Antibiotics
- Identified what PK/PD parameter is depend on efficacy
- Approved in over 80 countries some years ago
- An industry would like to launch it in our country
- PK in our healthy volunteer is similar with foreigners
Selection of population

- Group of which benefit is expected
- What population is target of the drug after launched?
- At beginning of clinical development, inclusion criteria is so restricted.
  - Age (not include elderly, pediatrics, etc)
  - Organ dysfunction (liver, renal, etc.)
  - Severe
Risk and benefit on participants

- Risk
  - Unknown effects
  - First trial for patients

- Benefit
  - More sufficient effect than current drugs?
Risk and benefit on development

- **Risk**
  - Prolong of development periods
  - Failure of development

- **Benefit**
  - Improve the probability of success
Risk mitigation

- What is identified risks of developing drugs?
  - Fully grasp character of developing drug
- Make a system for early detection of risks
- Timely and appropriate evaluation through trials
- Back to non-clinical, if necessary
Risk communication

- Share information on developing drugs
  - What AEs are detected in development?
  - What is risk factors in each AEs?
  - What method is available for early detection?
Reference

- Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

- General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products

- In Vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and Recommendations for Dosing and Labeling
  http://www.fda.gov/cder/guidance/2635fnl.pdf

APEC Preliminary Workshop on Review of Drug Development in Clinical Trials
2007.3.17 – 21, Bangkok, Thailand
Exercise

- One of fluoroquinolone injection
- Efficacy depend on AUC/MIC and Cmax/MIC
- Identified risks are liver and renal toxicity
- QT-prolongation, seizure and joint-/surrounding tissue problem in juvenile animals are known in same class.
Exercise (cont.)

- How to select dose (amount and interval) ?
- What population is suitable for early Phase II ?
- What should we do for risk minimization ?
  - Inclusion/exclusion criteria ?
  - What and how should we monitor ?