June 7, 2015.
Revised Aug 10, 2015
Revised Nov 18, 2015
Revised Aug 23, 2018

MRCT-GCP inspection Regulatory Science Center of Excellence
Core curriculum

Basics of MRCT

1) Introductory session: how a regulatory decision is made
2) Trend of Clinical Development for Medicinal Product
3) Expectation on MRCT
   - Industry's view point
   - Regulator's view point
4) Essential information for MRCT
   - Disease prevalence (Epidemiological Data)
   - Healthcare System and Medical Practice
   - Medical needs
   - Utilization of IT
5) Regulatory Requirements
   - Difference between MRCT and Domestic Study
   - How to meet different regional requirements
6) Relevant ICH Guidelines for MRCT
   - E2A, E2F, E5(R1), E6(R1, R2), E8, E9, E10, E17

Development Strategy

1) Current issues on product approval
   - Industry's view point
   - Regulator's view point
2) MRCT or Domestic Development?
   - MRCT for all trials?
   - Stepwise Expansion of Regions?

Protocol Design and Statistical Analysis Plan

1) Selection of Geographical Regions to include

2) Number of Patients in Each Region
   - Method of Dynamic Enrollment of Subjects
3) Primary/Secondary Endpoint?
4) Statistical Analysis Plan
5) Determination of standard drug as comparator
   - How to determine a comparator in a trial, such as when to use the placebo as an adequate comparator or how to choose a standard drug as comparator.
6) Determination of efficacy parameters
   - How to determine whether the parameters used in a trial are adequate to assess the efficacy of a drug.

Finding Optimal Dosage

1) For Next Stage/Trial
   - The possibility to test the optimal dosage in phase III trial which is not covered yet in phase II trial.
2) For Special Population
   - Population with renal or hepatic impairment: How to determine adequate number of subjects for the trial.
   - Pediatric and elderly population: How to determine the appropriateness of extrapolating adult dosage to pediatric/elderly dosage
3) Ethnic Difference / Genomic Difference
   - Type of drugs that will need specific studies among Asian population, such as due to different kinds of enzymes in Asian population.
4) For rare disease indication
   - Number of subject adequate for rare disease indication and the possibility to assess the efficacy from only phase II trial.

Clinical Data Analysis

1) Difference between Statistical Significant and Clinical Significant
2) How to set sub-set for Sub-population Analysis?
3) Signal detection
4) How to determine the need to conduct the sub-group analysis
5) The use of sub-group analysis data for the indication extension
   - Will it be permitted to use sub-group analysis data for the extension of an indication, and how far the sub-group analysis data can be used to claim

the extension of an indication?

Handling of ADR report

1) ADR Report timeline
2) How to evaluate ADR report so that the Regulatory can take an action to the clinical trial conduct

Assessment of Mock Marketing Authorization Application

1) Assessment by Attendees (Small groups), Presentation and Discussion

Risk Management Plan (RMP)

1) Development Stage
   - To avoid failure in development
   - Safety signal management
2) RMP for Market Authorization Application

GCP inspection in the review of MRCT data

1) Lecture on real world GCP inspection by PMDA and EMA (30 min x 2 sessions = 1hr)
2) Presentation from ThaiFDA (20 min)
3) Workshop: How to assess the findings of GCP inspection, which are significant/grave deviation and which are not? (60 min)
   For example, unexpected report, deviations, etc
4) Presentation on outcome of discussion (40 min)
5) Wrap-up (5min)

Potential Discussion topics in Session of GCP inspection in the review of MRCT data

- Difficult Areas: *Computer system, Lab/Test procedure, Grading of Observation*
- New, specific, and advance Knowledge / Technology
- To become Trainer on Basic GCP inspection, for other NRAs
- Inspection of BE study
- Inspection of Pharmacogenomic study
- Electronic record keeping system