第33回 ICH即時報告会

General Principles for Planning and Design of Multi-Regional Clinical Trials E17

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Objectives & Scope

- The purpose of this guideline is to facilitate the acceptance of MRCTs by regulatory authorities.
- This guideline describes basic principles for the planning and design of MRCTs with the aim of increasing the acceptability of the use of MRCTs in global regulatory submissions.

Activities before the Jacksonville meeting

- Five web-based conferences of whole group were held in July, September, October and November
  - ✓ Subgroup also had more conferences separately
- Active discussion by e-mail between the web-conferences
  - ✓ Enhanced and reviewed contents in all sections

Activities in Jacksonville

Date	Task / Activity
Day 1 (Mon)	➢ Revised contents in some parts (Stat. sections)
Day 2-3 (Tue-Wed)	➢ Crystallized key principle concepts
Day 4	➢ The assembly report ➢ Try to complete a line by line review as much as possible

Table of contents (tentative)

Promoting conduct of MRCTs

- **MRCTs are generally the preferred option for investigating a new drug for which regulatory submission is planned in multiple regions.**
  - ✓ The rationale for conducting the MRCT, rather than single-region trials, should be based on the assumption that there is a global treatment effect that is applicable to all regions being studied, while also acknowledging that some regional and/or national variation is expected.
  - ✓ This assumption should be based on a priori knowledge about ethnic factors and their potential impacts on drug response in each region as well as any data available from early exploratory trials with new drug.

Careful consideration

- **To increase an acceptability of MRCT data in the review by multiple regulatory agencies for drug approval, a sponsor should carefully consider the planning and design of MRCTs in advance.**
  - ✓ The MRCT should be designed to provide sufficient information for an evaluation of whether the overall treatment effect applies to subjects from different regions.
  - ✓ Ethnic factors are a major point of consideration when planning MRCTs.

Pooled population

- **Introduce a new use of "pooled population" to help regulatory decision making**
  - ✓ Subpopulations may be defined in MRCTs by one or more of intrinsic and/or extrinsic factors, and these subpopulations may span multiple regions.
  - ✓ Some regions may be pooled, if subjects in those regions are thought to be similar with respect to intrinsic and/or extrinsic factors which are relevant to the disease area and/or drug under study.
  - ✓ Both subpopulations and pooled regions should be specified at the study planning stage and may provide a basis for regulatory decision making for relevant regulatory authorities.

Sample size allocation

- **The guiding principle for determining the overall sample size in MRCTs is that the test of the primary hypothesis, based on combining data from all regions in the trial, is of primary importance.**
- **The sample size allocation to regions or pooled regions should be determined such that clinically meaningful differences in treatment effects among regions can be described without substantially increasing the overall sample size.**

MRCTs in an exploratory stage

- **Encourage to conduct MRCTs in an exploratory stage as well as a confirmatory stage**
  - ✓ MRCTs can play an important role in a drug development program beyond their contribution at the confirmatory stage.
  - ✓ For example, exploratory MRCTs can gather scientific data regarding the impact of extrinsic and intrinsic factors on PK/PD and other drug properties, facilitating better designs of confirmatory MRCTs.
  - ✓ MRCTs may also serve as the basis for approval in regions or countries not studied at the confirmatory stage through the extrapolation of study results.

Discussions with regulatory agencies

- **Encourage discussions with regulatory authorities in the planning stage**
  - ✓ In the planning and design of MRCTs, it is important to understand the different regulatory requirements in the concerned regions. Efficient communication among sponsors and regulatory authorities at a global level can facilitate future development of the drugs. These discussions are encouraged at the planning stage of the MRCT.

Impacts of the E17 guideline

- **Avoid duplication**
  - ✓ Reduce the need to conduct standalone regional or national studies including bridging studies.
- **Promote international harmonization**
  - ✓ A globally harmonized approach to drug development should be considered first.
- **Provide better evidences for drug approval in each region**
  - ✓ Encourage better planning and design of MRCTs based on the latest scientific knowledge and experiences
    - By implementing new use of “pooled population”

Next Steps

- Review all sections followed by completion of editorial change and grammatical check by e-mail and the web-conference by 1Q 2016
- Sign off as step 1 in written procedure in 1Q 2016
- Public consultation will be taken at the period between April and July 2016 after adoption as step 2a/b (Postal sign off procedure)
- Fourth face-to-face EWG Meeting in 4Q 2016 (in Japan) to revise the guideline based on comments received on the public consultation.
- The guideline will be finalized as *Step 4* possibly in 2Q 2017