



ICH E17

General principle on planning and design of Multi-Regional Clinical Trials

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International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use



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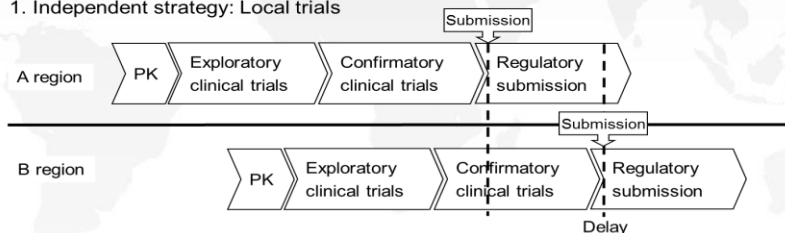
Objectives & Scope

- The purpose of this guideline is to describe general principles for the planning and design of Multi-Regional Clinical Trials (MRCTs) with the aim of increasing the acceptability of MRCTs in global regulatory submissions.
- The primary focus of this guideline is on MRCTs designed to provide data that will be submitted to multiple regulatory authorities for drug approval (including approval of additional indications, new formulations and new dosing regimens) and for studies conducted to satisfy post-marketing requirements.

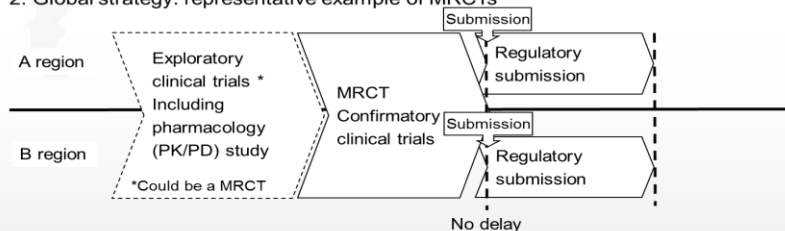
3

Encouraging simultaneous global drug development

1. Independent strategy: Local trials



2. Global strategy: representative example of MRCTs



4

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 underlying assumption of the conduct of MRCTs is that the treatment effect is clinically meaningful and relevant to all regions being studied.
 - This assumption should be based on knowledge of the disease, the mechanism of action of the drug, on a priori knowledge about ethnic factors and their potential impact on drug response in each region, as well as any data available from early exploratory trials with the new drug.
 - The study is intended to describe and evaluate this treatment effect, acknowledging that some sensitivity of the drug with respect to intrinsic and/or extrinsic factors may be expected in different regions and this should not preclude consideration of MRCTs.

5

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.
 - Ethnic factors are a major point of consideration.
 - They should be identified during the planning stage, and information about them should also be collected and evaluated when conducting MRCTs.
 - Based on the understanding of accumulated knowledge about these intrinsic and extrinsic factors, MRCTs should be designed to provide information to support an evaluation of whether the overall treatment effect applies to subjects from participating regions.

6

Pooled Population

- Introduce a new use of “pooled population” to help regulatory decision making
 - Some regions may be pooled at the design stage, if subjects in those regions are thought to be similar enough with respect to intrinsic and/or extrinsic factors relevant to the disease area and/or drug under study.
 - Consideration could also be given to pooling a subset of the subjects from a particular region with similarly defined subsets from other regions to form a pooled subpopulation whose members share one or more intrinsic or extrinsic factors important for the drug development program.
 - The strategy for pooling regions and the principles for pooling subpopulations should be specified at the planning stage and described in the protocol.

Sample size allocation

- The guiding principle for determining the overall sample size in MRCTs is that the test of the primary hypothesis can be assessed, based on combining data from all regions in the trial.
- 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 sample size requirements based on the primary hypothesis.
 - The guideline provides some more details how to allocate sample size to region in the guideline

Quality of MRCT

- Ensuring trial quality is of paramount importance for MRCTs.
- This will not only ensure the scientific validity of the trial results, but also enable adequate evaluation of the impact of intrinsic and extrinsic factors by applying the same quality standard for trial conduct in all regions.
- In addition, planning and conducting high quality MRCTs throughout drug development will build up trial infrastructure and capability, which over time will result in a strong environment for efficient global drug development.

MRCTs in an exploratory stage

- Encourage conduct of MRCTs as part of the early exploratory development program
 - MRCTs can play an important role in drug development programmes beyond their contribution at the confirmatory stage.
 - For example, exploratory MRCTs can gather scientific data regarding the impact of extrinsic and intrinsic factors on pharmacokinetics and/or pharmacodynamics (PK/PD) and other drug properties, facilitating the planning of confirmatory MRCTs.
 - MRCTs may also serve as the basis for approval in regions 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 drugs. These discussions are encouraged at the planning stage of MRCTs.

11

Impacts of E17 guideline in drug development

- Earlier access to innovative therapies
 - Provide an innovative drug earlier to patients by synchronizing the timing of clinical drug development across different regions
- 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
- Longitudinal build-up of capability and infrastructure for global drug development
 - Planning and conducting high quality MRCTs throughout drug development will build up trial infrastructure and capability

12



Thank You!

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