



ICH
harmonisation for better health

ICH E17

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

January 14th, 2017

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



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ICH HARMONISED TRIPARTITE GUIDELINE

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

November 16th, 2017

ICH E17 Guideline

- Started in June 2014
- Draft in June 2016
- Finalised in November 2017

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1.1 Objectives of the Guideline

- With the increasing globalisation of drug development, it has become important that **data from multi-regional clinical trials (MRCTs)** can be accepted by regulatory authorities across regions and countries as the primary source of evidence, to support marketing approval of drugs (medicinal products)
- The purpose of this guideline is to describe general principles for the planning and design of MRCTs with the **aim of increasing the acceptability of MRCTs in global regulatory submissions**
- The guideline addresses strategic programme issues as well as issues that are specific to the planning and design of confirmatory MRCTs, and it should be used together with other ICH Guidelines, including E5, E6, E8, E9, E10, and E18.

1.3 Scope of the Guideline

- **MRCT is defined in the present guideline as a clinical trial conducted in more than one region under a single protocol.** In this context, a region may refer to a geographical region, country or regulatory region (see Section 3. Glossary)
- 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**
- Certain aspects of this guideline may also be relevant to studies conducted early in clinical development or in later phases. The present guideline **mainly covers drugs including biological products**, although some sections may not be applicable to all development programmes (e.g., pharmacokinetics (PK) not used for preventive vaccine dose-finding).

2.1.1 The Value of MRCTs in Drug Development

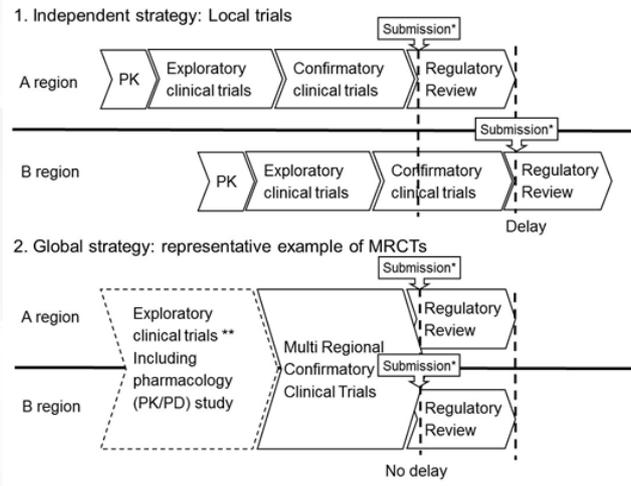


Figure 1. Illustrations of clinical drug development workflow across regions for drug submission and regulatory review in independent and global strategies

*: Marketing Authorization Application/New Drug Application
 **: could be parallel single region trials or MRCTs

1.4 Basic Principles

1.4 Basic Principles (1)

1. **Strategic use of MRCTs** in drug development programmes, properly designed and executed according to this guideline, can **increase efficiency** of drug development. MRCTs may enable **simultaneous submission** of marketing authorisation applications and support regulatory decision-making in multiple regions, allowing earlier access to new drugs worldwide. Although MRCTs may generally become the **preferred option for investigating a new drug for which regulatory submission is planned in multiple regions**, the potential for regional differences to impact the interpretability of study results should be carefully considered.
2. The **intrinsic and extrinsic factors** important to the drug development programme, should be **identified early**. The potential impact of these factors could be examined in the **exploratory phases** before the design of confirmatory MRCTs. Information about them should also be **collected during the confirmatory trial** for evaluation of their impact on treatment effects.

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1.4 Basic Principles (2)

3. MRCTs are planned under the assumption that the **treatment effect applies to the entire target population**, particularly to the regions included in the trial. Strategic allocation of the sample size to regions allows an evaluation of the extent to which this assumption holds.
4. **Pre-specified pooling of regions or subpopulations**, based on established knowledge about similarities, may help provide **flexibility in sample size allocation** to regions, facilitate the assessment of **consistency** in treatment effects across regions, and support regulatory decision-making.
5. A **single primary analysis approach** for hypothesis testing and estimation of the overall treatment effect should be planned so that it will be acceptable to all concerned regulatory authorities. A **structured exploration** to examine the **consistency of treatment effects** across regions and subpopulations should be planned.

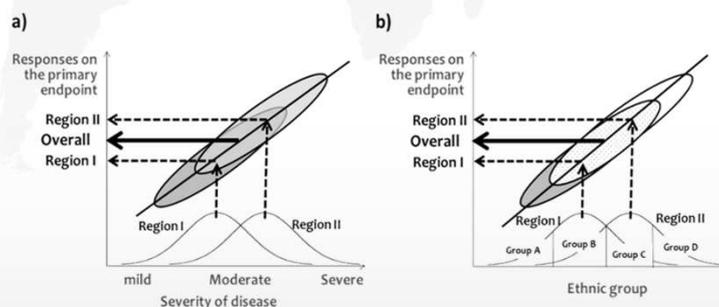
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6. In light of diverse regional practices, **ensuring high quality** of study design and conduct in accordance with ICH E6 in all regions is of paramount importance to ensure the study results are interpretable. Careful attention to quality during trial planning, investigator training, and trial monitoring will help achieve consistently high trial quality required for a successful MRCT.
7. **Efficient communication** among sponsors and regulatory authorities is encouraged at the planning stage of MRCTs, with the goal of obtaining acceptance of a global approach to study design across the different regulatory regions.

Major points described in Section 2

- At the planning stage, regional variability, the extent to which it can be explained by intrinsic and extrinsic factors, and its potential to influence the study results, should be carefully considered in determining the role MRCTs can play in the drug development strategy
- The intrinsic and extrinsic factors important to the drug development programme, should be identified during the planning stage of an MRCT.

Figure 2 illustrates the way in which intrinsic and/or extrinsic factors such as disease severity (Figure 2a) or ethnicity (Figure 2b) may manifest as regional differences in treatment response.



2.2.2 Subject Selection

- In MRCTs, **subject selection** should be **carefully considered** to better understand and possibly mitigate **potential sources of regional variability** and their impact on trial results
- **Clear** and **specific** inclusion and exclusion criteria, that are **acceptable** and can be **applied across regions**, should be included in the protocol
- To harmonise subject selection, **uniform classification and criteria** for diagnosis of the disease or definition of the at-risk population **should be implemented**, such as the use of relevant guidelines for disease definitions.

2.2.3 Selection of Doses for Use in Confirmatory MRCTs

- It is important to execute **well-planned early development programmes** that include PK and/or PK-PD studies of applicable parameters, in order to identify regional differences which may impact dose selection
- The **dose regimens** in confirmatory MRCTs (based on data from studies mentioned above) **should in principle be the same** in all participating ethnic population
- If earlier trial data show a clear difference in dose-response and/or exposure-response relationships for an ethnic population, it may be appropriate to **use a different dosing regimen**, provided that the regimen is expected to produce **similar therapeutic effects** with an **acceptable safety margin**, and provided it is **scientifically justified** in the study protocol. Prospective careful planning of assessment strategies where different doses are used should be tailored to each case and described in the analysis plans.

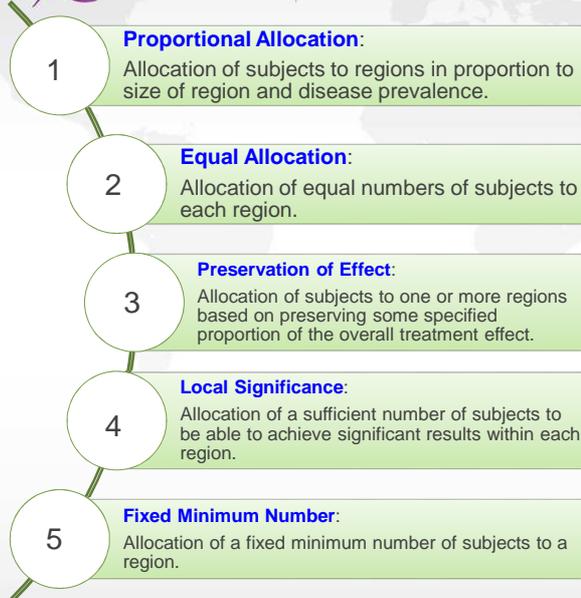
2.2.4 Choice of Endpoints

- The primary endpoint should be relevant to the target population. In MRCTs, this relevance needs to be considered for all regions in the trial and with respect to the various drug, disease and population characteristics represented in those regions
- An ideal clinical trial endpoint is one that is clinically relevant, accepted in medical practice (e.g., by regulatory guidance or professional society guidelines) and sufficiently sensitive and specific to detect the anticipated effect of the treatment
- The primary endpoint, whether efficacy or safety, should satisfy these criteria as well as being acceptable to all concerned regulatory authorities, to ensure that interpretation of the success or failure of the MRCT is consistent across regions and among regulatory authorities
- The primary endpoint of MRCTs should be one for which experience is already available in the participating regions.

2.2.5 Sample Size Planning

- The key consideration for sample size planning, is ensuring sufficient sample size to be able to evaluate the overall treatment effect, under the assumption that the treatment effect applies to the entire target population, particularly to the regions included in the trial
- Two additional factors are particularly important in the MRCT setting; (i) the size of the treatment effect that is considered clinically relevant to all regions in the trial, and (ii) the expected variability of the primary outcome variables based on combining data across regions.

- The MRCT should be planned to include an evaluation of the consistency of treatment effects among regions, where consistency is defined as a lack of clinically relevant differences
- If clinically relevant differences among regions are observed, then the MRCT provides a unique opportunity for additional learning about the factors that may explain these differences
- Regional allocation should have a scientific basis (rather than arbitrary targets), should support the evaluation of consistency and should provide the information needed to support regulatory decisions.



Five examples for sample size allocation to region

- ▶ **A balance between #1 and #2 is recommended to ensure that recruitment is feasible and able to be completed in a timely fashion, but also to provide sufficient information to evaluate the drug in its regional context.**

Pooled Regions and Subpopulations

- Pooled regions:

Pooling some **geographical regions, countries or regulatory regions** at the planning stage, if subjects in those regions are thought to be **similar enough with respect to intrinsic and/or extrinsic factors** relevant to the disease and/or drug under study.

- Pooled subpopulations:

Pooling a **subset of the subjects from a particular region** with similarly defined subsets from other regions whose members **share one or more intrinsic or extrinsic factors** important for the drug development programme at the planning stage. Pooled subpopulations is assumed as **ethnicity-related subgroup** particular important in the MRCT setting.

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Pooled Regions and Subpopulations

- Pre-specified pooling of regions or subpopulations may help **provide flexibility in sample size allocation** to regions, facilitate the assessment of consistency in treatment effects across regions, and support regulatory decision-making.
- The pooling strategy should be **justified based on the distribution of the intrinsic and extrinsic factors** known to affect the treatment response, and the disease under investigation and similarity of those factors across regions.
 - For example, pooling Canada and the United States into a North American region is often justified because of similar medical practices and similar use of concomitant medications.
- Pooling strategies should be **specified in the study protocol and statistical analysis plan, if applicable.**

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2.2.6 Collecting and Handling of Efficacy and Safety Information

- Adherence to GCP is critical for any clinical trial to meet its stated objectives and is particularly important in an MRCT, because of the coordination required to conduct a trial in diverse geographic regions.
- Methods of collecting and handling efficacy and safety information should be standardised across participating regions.
- It is also important to provide standardised training for investigators and study personnel in each region before initiating the trial in that region to ensure that the trial objectives are met through standardised implementation of the study protocol.

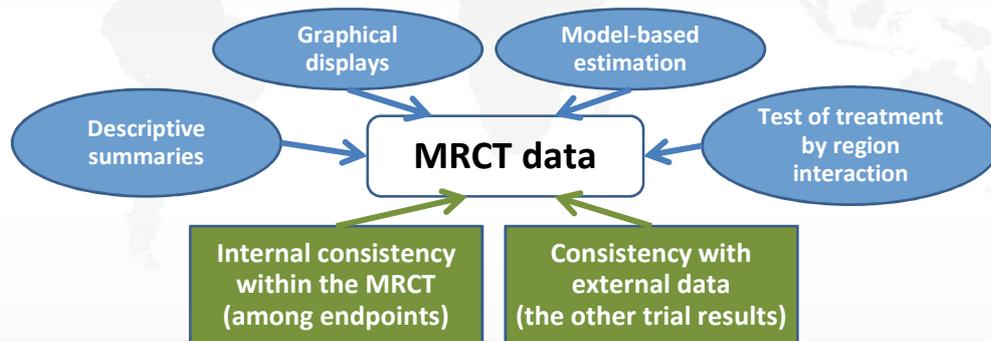
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2.2.7. Statistical Analysis Planning

- The analysis strategy should be planned to enable the qualitative and/or quantitative evaluation of benefit/risk across regions or important subpopulations represented in the MRCT.
- In planning an MRCT, the primary analysis strategy should carefully consider
 - (1) the target population,
 - (2) the endpoints/variables of primary interest
 - (3) the relevant intrinsic and extrinsic factors in the multi-regional, multi-subpopulation context
 - (4) the population-level summary of data required to describe the treatment effect.
- For most MRCTs, the primary analysis will correspond to a test of the hypothesis about the treatment effect and the estimation of that effect, considering data from all regions and subpopulations included in the trial.

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The statistical analysis strategy should include the evaluation of the consistency of treatment effects across regions and subpopulations



The evaluation of regional consistency is not considered a confirmatory exercise but rather a gateway for further exploration.

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- In case of **clinically relevant differences** in treatment effects among regions, a **structured exploration** of these differences should be planned.
 - **Factors known** a priori to vary among regions (e.g., disease severity, race, other subject characteristics) and hypothesized to be **prognostic or predictive** should be planned for and evaluated in the analysis model
 - **Unexpected regional differences** may be observed, and post-hoc analyses should be used for further investigation. **Factors known to be prognostic for the disease** would be examined first
 - Regional differences may require further **post-hoc investigation** to either identify plausible reasons for the differences or to better understand the observed heterogeneity. In some cases, **additional data**, including data from other clinical trials, or supportive evidence from other sources, may be needed to understand the regional differences observed
 - These **eventualities** should be carefully considered at the planning stage.

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2.2.8. Selection of Comparators

- The choice of control groups should be considered in the **context of the available standard therapies**, the **adequacy of the evidence** to support the chosen design, and **ethical considerations**.
- **Comparators** in MRCTs should in principle **be the same** in all participating regions.
- The **justification (including safety considerations)** for the use of **an unapproved drug** should therefore be described in the protocol based on scientific information, treatment guidelines and other relevant documents.

2.2.9. Handling Concomitant Medications

- In general, **drugs used concomitantly** with the investigational drug **should be the same** throughout the regions to the extent possible, but there may be **some differences** in the drugs and/or doses actually used due to variations in medical practices. This **could be acceptable** if not expected to substantially impact trial results.
- In circumstances where approved drugs are **combined** with an investigational drug, **the same dosage regimen** in all regions **should generally be applied**.
- If required by protocol, concomitant medications that are **not approved** in a region should have their use **justified** based on scientific information, treatment guidelines and other relevant documents.

- **Earlier access to innovative therapies**
 - Synchronize clinical drug development across different regions
- **Avoid duplication**
 - Reduce the need for region specific studies and 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**
 - Incorporate latest knowledge and experience from regions into one trial
- **Develop an infrastructure for global drug development**
 - Conducting high quality MRCTs is a valuable investment in modern drug development