



Module 1

Basic principles and overview of training modules

ICH E17: General principles for planning and design of Multi-Regional Clinical Trials

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

1

This presentation will give you an introduction to the basic principles of the ICH Guideline E17: General principles for planning and design of Multi-Regional Clinical Trials, as well as give you an overview of the training materials so that you can easily find information in this guidance.

Legal Notice

- This presentation is protected by copyright and may, with the exception of the ICH logo, be used, reproduced, incorporated into other works, adapted, modified, translated or distributed under a public license provided that ICH's copyright in the presentation is acknowledged at all times. In case of any adaption, modification or translation of the presentation, reasonable steps must be taken to clearly label, demarcate or otherwise identify that changes were made to or based on the original presentation. Any impression that the adaption, modification or translation of the original presentation is endorsed or sponsored by the ICH must be avoided.
- The presentation is provided "as is" without warranty of any kind. In no event shall the ICH or the authors of the original presentation be liable for any claim, damages or other liability arising from the use of the presentation.
- The above-mentioned permissions do not apply to content supplied by third parties. Therefore, for documents where the copyright vests in a third party, permission for reproduction must be obtained from this copyright holder.

ICH HARMONISED GUIDELINE

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

November 16th, 2017

ICH E17 guideline

- Work started in June 2014
- Finalised in November 2017
 - **Multi-Regional Clinical Trial (MRCT) = a clinical trial conducted in more than one region under a single protocol.**
 - **Region = a geographical region, country or regulatory region.**

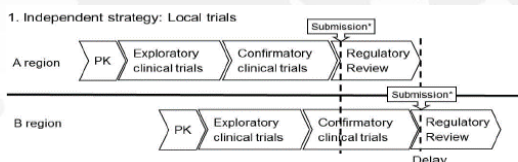


The drafting of the E17 guideline started in 2014 and the guideline was finalized in November 2017. It has since then been adopted by regulators and pharmaceutical industry in all ICH regions.

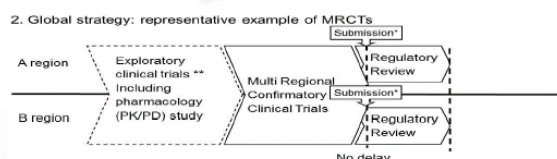
During the time the guideline was drafted, a large number of comments were received, requesting additional clarification of some of the principles in the guideline. Therefore, it was considered important to develop training and presentation materials to ensure that the E17 guideline is well understood and is implemented consistently amongst different stakeholders in both ICH and non-ICH regions.

Why was the E17 Guideline drafted?

- Historically, clinical trials of a new medicine were often performed separately in different regulatory regions to fulfil the requirements of each region.



- More recently, global regulatory strategies are also used to plan and conduct studies



The purpose of E17 is to describe general principles and strategic programme issues for the planning and design of multi-regional clinical trials to ensure that data from such trials can be accepted by regulatory authorities across regions and countries as the primary source of evidence, to support marketing approval of medicinal products

Before presenting the training material itself, we will present a summary of the main messages of the E17 guideline.

Historically, clinical trials of new medicines were often performed separately in different regions to fulfil the local requirements for approval of the medicine. However, in more recent times, it is common that new drug development trials occur in several geographical regions at the same time under a single protocol. This is what is meant by the expression “multiregional clinical trial”. As a result of this development, it was considered important to have a guideline with the main objective to provide guidance on optimal planning and design of multiregional clinical trials and thereby ensure that data from such trials can be accepted for approval in different parts of the world at the same time.

Which are the advantages associated with MRCTs according to E17?

- **Facilitates a more efficient development of new medicines and increase the possibility of having the new medicine approved in several different regions at the same time**
- **Efficient way to be able to recruit a sufficient number of trial subjects within a reasonable timeframe**
- **Provides an opportunity to learn more about how treatment effects can vary between different regions and populations and may explain reasons for differences**

5

So, what are the advantages with multiregional clinical trials compared to trials performed in a single region? Multiregional clinical trials can facilitate more efficient development of new medicines and increase the possibility of having the new medicine approved in several different regions at the same time. Thereby, patients may have earlier access to new medicines worldwide.

To perform a multiregional clinical trial is also an efficient way to be able to recruit a sufficient number of trial subjects within a reasonable timeframe. This may be particularly important when either the disease being treated is rare or when large numbers of subjects are required.

Multiregional clinical trials may also provide an opportunity to learn more about how treatment effects can vary between different regions and populations and may also help us to understand the reason why these differences exist.

Which challenges need to be considered when planning an MRCT?



**Conducting an MRCT may be possible in spite of these concerns!
Challenges at the planning stage may translate into new knowledge!**

6

There may be challenges associated with conducting multiregional clinical trials and therefore, the E17 guideline emphasises that regional differences that may have impact on the results of treatment with the new medicine should be considered at the planning stage. Such differences may include medical practice, diet, socio-economic factors as well as differences in the response to the treatment due to variations in the subject's metabolism of the medicine.

We hope that you will find the E17 guideline helpful in providing suggestions on how to plan and design a study despite these potential differences, as well as how to interpret the results. In fact, a thorough planning that includes accounting for the possibility of regional differences, may ultimately increase our knowledge about the importance of such differences.

2.1 Strategy-related Issues

2.1.1	<i>The Value of MRCTs in Drug Development</i>	3
2.1.2	<i>Good Clinical Practice (GCP) Requirements and MRCTs</i>	6
2.1.3	<i>Scientific Consultation Meetings with Regulatory Authorities</i>	6

2.2 Clinical Trial Design and Protocol-related Issues

2.2.1	<i>Pre-consideration of Regional Variability and its Potential Impact on Efficacy and Safety</i>	7
2.2.2	<i>Subject Selection</i>	9
2.2.3	<i>Selection of Doses for Use in Confirmatory MRCTs</i>	10
2.2.4	<i>Choice of Endpoints</i>	11
2.2.5	<i>Sample Size Planning</i>	13
2.2.6	<i>Collecting and Handling of Efficacy and Safety Information</i>	18
2.2.7	<i>Statistical Analysis Planning</i>	20
2.2.8	<i>Selection of Comparators</i>	23
2.2.9	<i>Handling Concomitant Medications</i>	25

So, how can the E17 guideline help to handle challenges that may arise when you plan a multiregional clinical trial? As you can see from the table of contents, the guideline includes sections handling both strategy-related issues, as well as design and protocol related concerns. These sections provide guidance on many aspects such as selection of subjects, doses, comparators and endpoints as well as how to plan and allocate the sample size.

Overview of training materials

- Training material intended to provide clarity on key aspects of the guideline in order to facilitate a harmonized interpretation and implementation by industry and regulators in the ICH and non-ICH regions
- Training material does not provide additional guidance beyond E17

We hope you found this introduction of the basic principles helpful. You may now wish to review the other training modules! This material is intended to provide clarity on some of the key aspects of the guideline, but it will not introduce any new concepts or additional guidance to what is currently in the E17 guideline.

Overview of Training material

General modules

- o Animated video; Main message of MRCTs
- o Module 1; Overview of training material/Basic principles

Technical modules

- o Module 2; Preconsideration of regional variability when recruiting diverse populations in global development
- o Module 3; Selection of doses
- o Module 4; Sample size allocation
- o Module 5; Pooling strategies
- o Module 6; Evaluation of consistency
- o Module 7; Selection of comparators

The training material is divided into modules. The first two modules aim at providing a general overview of the main messages and basic principles of the E17 guideline while module 2 – 7 are focused on specific sections of the E17 guideline and provides a more in-depth explanation. In the technical modules you will also find written notes that will further explain and expand on important issues.

Table of Contents and related training modules

1. INTRODUCTION	1
1.1. Objectives of the Guideline	1
1.2. Background	1
1.3. Scope of the Guideline	2
1.4. Basic Principles	2
2. GENERAL RECOMMENDATIONS IN THE PLANNING AND DESIGN OF MRCTs	3
2.1 Strategy-related Issues	3
2.1.1 <i>The Value of MRCTs in Drug Development</i>	3
2.1.2 <i>Good Clinical Practice (GCP) Requirements and MRCTs</i>	6
2.1.3 <i>Scientific Consultation Meetings with Regulatory Authorities</i>	6
2.2 Clinical Trial Design and Protocol-related Issues	7
2.2.1 <i>Pre-consideration of Regional Variability and its Potential Impact on Efficacy and Safety</i>	7
2.2.2 <i>Subject Selection</i>	9
2.2.3 <i>Selection of Doses for Use in Confirmatory MRCTs</i>	10
2.2.4 <i>Choice of Endpoints</i>	11
2.2.5 <i>Sample Size Planning</i>	13
2.2.6 <i>Collecting and Handling of Efficacy and Safety Information</i>	18
2.2.7 <i>Statistical Analysis Planning</i>	20
2.2.8 <i>Selection of Comparators</i>	23
2.2.9 <i>Handling Concomitant Medications</i>	25
3. GLOSSARY	26

This slide shows the table of contents of the E17 guideline and in which module of the training material you can find specific topics addressed.

Finally...

- We hope this training material will be useful and help you to understand and use the E17 guideline in your planning and/or assessment of multiregional clinical trials



Finally, we hope that the training material will be useful and help you to understand and use the E17 guideline in your planning or assessment of multiregional clinical trials.