



Module 7

Selection of comparators

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

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Outline

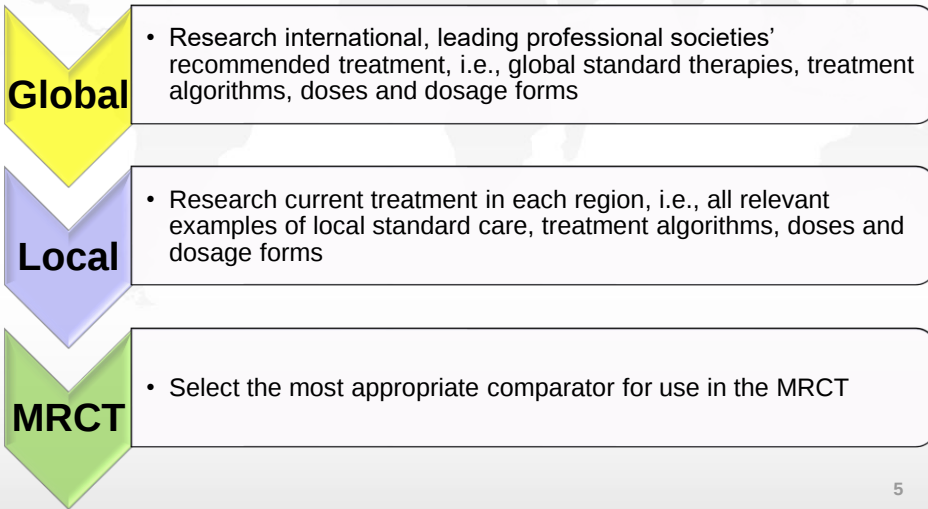
- Introduction
- How to select a comparator
- Using comparators not approved in some regions
- Concluding remarks

Introduction

- **Comparators in an MRCT should be considered in the context of available standard therapies.**
- **In principle, the same approved comparators (e.g., same indication, dose, dosage form and route of administration) should be used in participating regions to enable interpretation of trial results.**
- **In some cases, the selected comparator is not approved in some regions. This module will provide considerations for such situations.**

The purpose of this module is to identify potential issues when selecting comparators in MRCTs and to provide considerations on how to handle these issues.

How to select a comparator



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It is important to understand the global standards first, but also to consider local standards of care.

Treatment algorithms are sometimes proposed by international associations of physicians. By consulting such international treatment guidelines, the sponsor can get information about which comparator is the most appropriate choice. Information about available treatments should be collected from all regions. Based on international treatment guidelines and local treatment guidelines, the most appropriate comparator can be selected.

Situations where an unapproved comparator may be considered

- There is no established standard treatment for the target disease
- The comparator is in late stage of development (e.g., ongoing confirmatory study) in the region in question
- There is documented clinical experience of the comparator in one or more ICH regions included in the trial
- The comparator has been recognised as a standard therapy in an international clinical treatment guideline
- There are no concerns related to safety or lack of efficacy of the comparator in existing clinical study data and/or in the post-marketing data
- The comparator is unlikely to be sensitive to intrinsic and/or extrinsic factors relevant for the regions in question

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The comparators used in MRCTs should in principle be the same across regions.

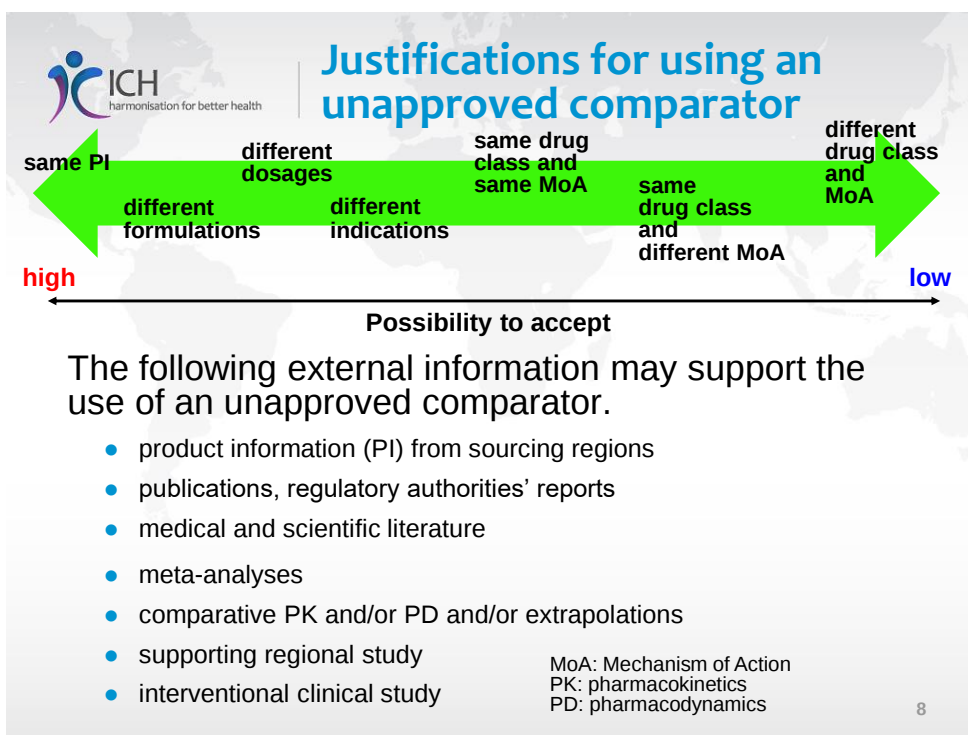
However, it may be necessary and acceptable to use an unapproved comparator or a comparator approved with different indications, dose strengths or formulations in a region. It is important to understand how the new drug can be used locally and how the data for the new drug can be translated into local standard care.

Selection of comparators should be discussed and agreed with relevant regulatory authorities to ensure that the planned MRCT is acceptable. Justification for choice of comparators and comprehensive product information should be provided with the protocol.

Considerations for use of unapproved comparators

- Justification for the use of an unapproved comparator should be based on scientific information (e.g., from comparisons against treatments which are approved in the region in question). A risk assessment of the unapproved comparator is also needed.
- If a non-inferiority trial is planned:
 - Is sufficient information available to select an appropriate non-inferiority margin?
 - Is sufficient information available to establish product similarity with approved therapies in the region in question? (see next slide)

In a non-inferiority trial, it may be problematic to use an unapproved comparator. It is important to consider differences between the comparator and approved therapies in the region in question and discuss with relevant regulatory authorities.



The larger the differences between the unapproved comparator and approved therapies, the more information is needed to support the use of the unapproved comparator.

Additional considerations

- In order to ensure consistent quality of the active comparators, it is recommended to use comparators from the same manufacturing source in all participating regions.
- Quality and sourcing of the comparator is particularly important for biologicals.
- The most comprehensive product information used in a participating region should be used consistently in all participating regions.

Concluding remarks

- Comparators in MRCTs should ideally be approved in all participating regions.
- However, there could be situations where the most appropriate comparator:
 - is not approved in a particular region, or
 - is approved but has different indications, dose strengths or formulations
- If a comparator not approved in some regions is selected, scientific justifications should be provided for use of the unapproved product in those regions.
- The selection of comparators should be discussed and agreed with relevant regulatory authorities.