



Module 5

Pooling strategies

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

- **Why consider pooling?**
- **Definition of Pooled Region and Pooled Subpopulation**
- **How to pool regions and subpopulations**
- **Potential applications of pooling strategies**
- **Additional considerations**
- **Concluding remarks**

Why consider pooling?

E17 introduces concepts of pooled regions and pooled subpopulations as pooling strategies. (section 2.2.5 and 1.4)

[Basic principle #4, Section 1.4]

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.*



E17 states usefulness of prespecified pooling, but does not mandate pooling.

Definition of pooled regions and pooled subpopulations

Pooled Regions

[Glossary] *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

[Glossary] *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 are assumed as ethnicity-related subgroups and are particularly important in the MRCT setting.*



Both pooling strategies are defined based on intrinsic and/or extrinsic factors known to potentially affect the treatment effect. Science based strategic pooling can bring efficiency and knowledge to enable regulatory decision making.

What is a “Region”?

[Glossary]

Region: A geographical region, country or regulatory region

Pooled Region

Commonality in intrinsic and/or extrinsic factors known to potentially affect the treatment effect

Regulatory Region

Commonality in regulatory requirements

Geographical Region

Commonality in locational proximity



Regions or pooled regions should be pre-specified in the protocol for stratification, sample size allocation, and consistency evaluation.

How to define pooled regions

- A pooled region is a group of regions based on the commonality in intrinsic and/or extrinsic factors known to potentially affect the treatment effect and in the distributions of those factors

[Section 2.2.5 Sample Size Planning]

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



Even distant regions can be pooled

- ✓ Regions in tropical areas may be pooled for some infectious diseases.
- ✓ Regions in the similar latitude may be pooled for some skin diseases, where UV exposure is the prognostic factor.

How to define pooled subpopulation

[Section 2.2.5 Sample Size Planning]

If there is sufficient knowledge about these factors at the trial design stage, it may be possible to define subpopulations based on those factors, and then incorporate these newly defined subpopulations in the stratification and analysis, in addition to region.

Stratification by an intrinsic and/or extrinsic factor known to potentially affect the treatment effect

	Stratum①	Stratum②	Stratum③	total
Region A				
Region B				
Region C				
Region D				
total				

Pooled Subpopulation

How to pool regions and subpopulations

1. Identify intrinsic and/or extrinsic factors which may affect the treatment effect from early trials or existing data

- Factors known to be prognostic for the disease under study
 - may be known in the therapeutic area or in the drug class.
- Factors known to be predictive for the drug response
 - From early trials or previous experience of the drug class

2. Consider the extent to which these factors may explain the anticipated variability among regions or subpopulations



The process to determine these factors for pooling is similar to that used to determine stratification factors or covariates in the primary analysis

How to pool regions and subpopulations (continued)

3. Define pooled regions and/or subpopulations based on similar distribution of the identified factors.

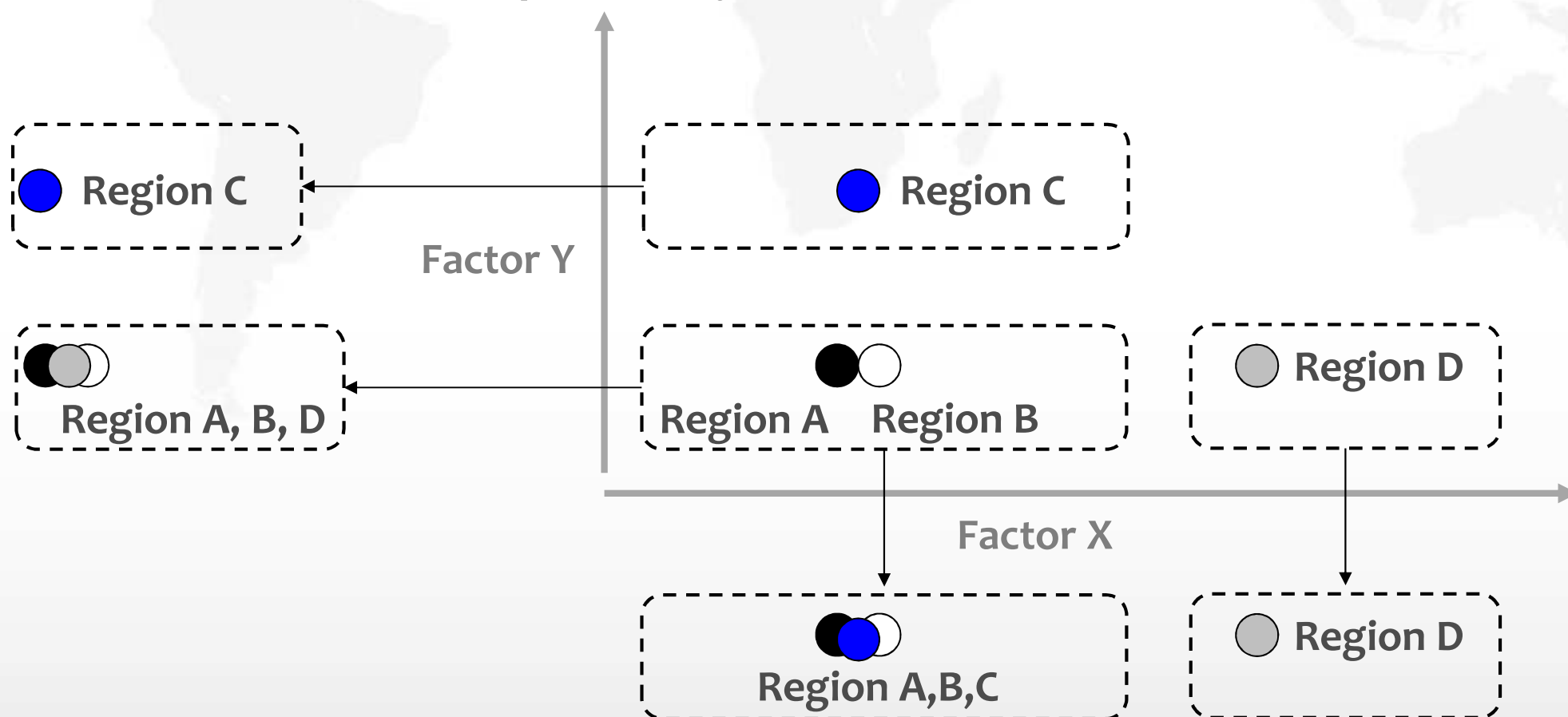
- For a single factor, it may be easy to consider pooling regions and/or subpopulations
- For multiple factors to be considered, multivariate approaches may be useful

[Section 2.2.5 Sample Size Planning]

Note that information about the extrinsic and intrinsic factors used to define pooling strategies should be collected for subjects enrolled in the trial to be able to monitor the recruitment strategy and ensure adequate regional and subpopulation representation.

How to pool regions and subpopulations: pooling based on relevance of factors

Suppose Factor X and Y are intrinsic and/or extrinsic factors known to potentially affect the treatment effect



Potential applications of pooling strategies

The potential applications of pooling strategies are not limited to analyses of efficacy endpoints, but may include:

- **Sensitivity analyses**
 - Exploratory analyses to support the predefined evaluation of the regional consistency
- **Safety evaluation**
 - For some adverse events, pooling strategies defined by known risk factors may be useful to identify populations at risk.

More flexibility for exploratory purposes



- Learning more about factors influencing drug responses
- Providing justification for pooled regions and/or subpopulations in future trials

Additional considerations

- **E17 can be applied even if pooled regions and/or subpopulations cannot be defined.**
- **Pooling across regions based on intrinsic and extrinsic factors known to potentially affect the treatment effect may reduce chance findings of regional differences, but may also reduce the chance of detecting true inconsistent findings. It is important to balance these considerations.**

Concluding remarks

- **MRCTs are usually stratified by region for both randomization and analysis.**
- **Pre-specified pooling of regions or subpopulations may help to provide flexibility in sample size allocation to regions and to facilitate the assessment of consistency in treatment effects across regions.**
- **Choice of pooling strategies depends on knowledge about the relevance of intrinsic and/or extrinsic factors known to potentially affect the treatment effect.**