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

Legal Notice

This module addresses different aspects of pooling strategies mentioned in the E17 guideline.

ICH E17 encourages identification and evaluation of intrinsic and/or extrinsic factors known to potentially affect the treatment effect. This helps to justify pooling strategies.

Why consider pooling?

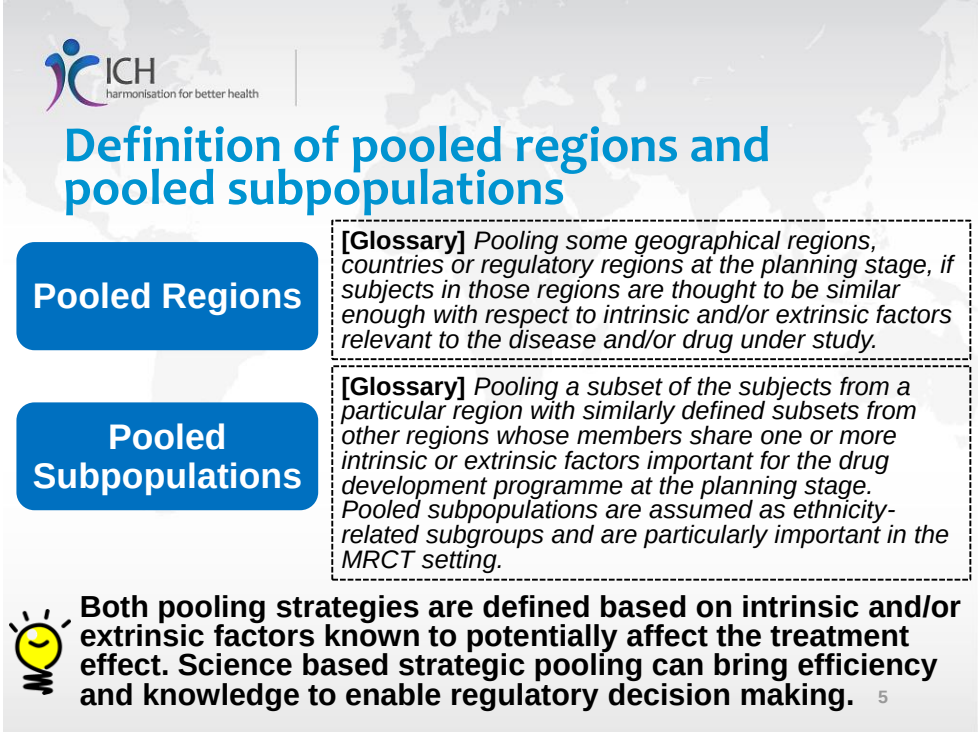
E17 introduces concepts of pooled regions and pooled subpopulations as pooling strategies. (section 2.2.5 and 1.4)

[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.



Intrinsic and extrinsic factors known to potentially affect the treatment effect may also be "effect modifiers" in the statistical or epidemiological context.

Effect modification occurs when the magnitude of the effect of the primary exposure on an outcome differs depending on the level of covariate, i.e., an effect modifier.

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

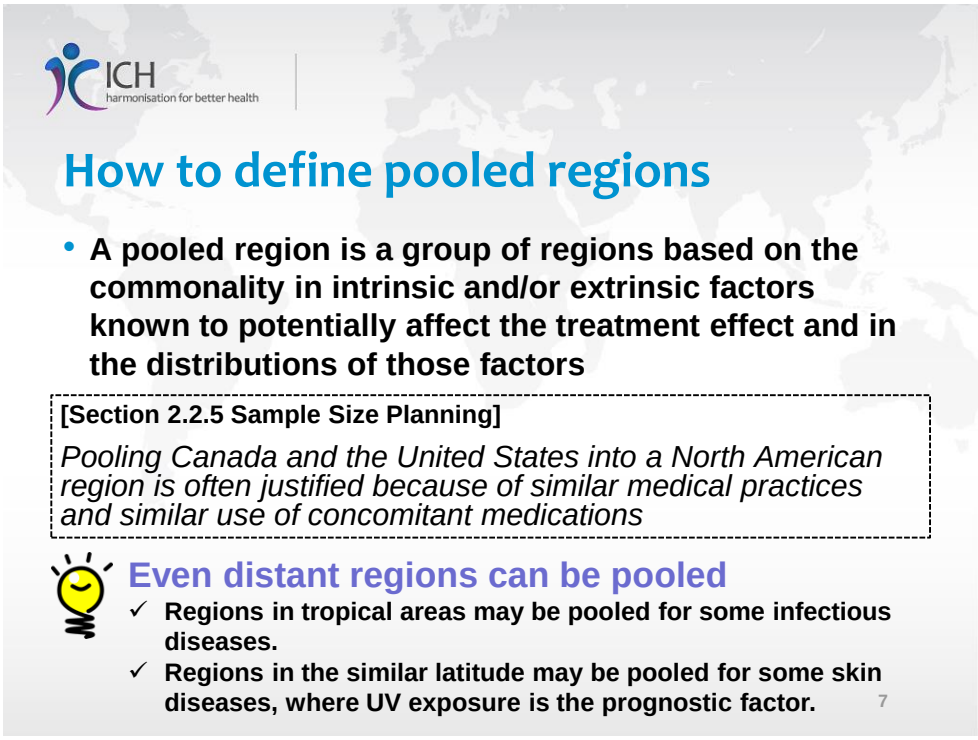
Regulatory Region

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.



The example of pooled region, Canada + US, shown in section 2.2.5 is justified by the commonality in extrinsic factors, i.e. medical practices and similar use of concomitant medications. According to the definition of pooled region, even distant regions can be pooled.

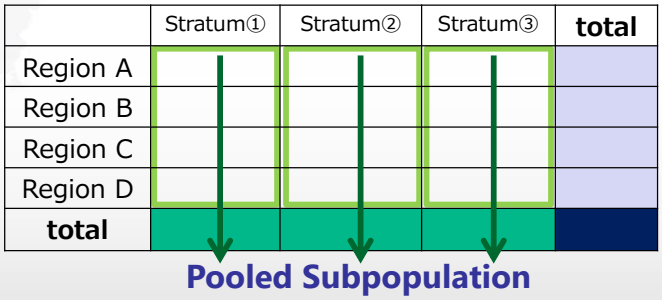
These considerations may encourage pooled subpopulation defined by those factors.

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



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A pooled subpopulation is like a stratum defined by an intrinsic and/or extrinsic factor known to potentially affect the treatment effect, assuming other relevant intrinsic and extrinsic factors are similar among regions.

Pre-specification of pooled subpopulations requires sufficient knowledge about prognostic relevance of these factors.

Pooled subpopulations defined in the protocol should be incorporated in the stratified randomisation and stratified analysis.

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.

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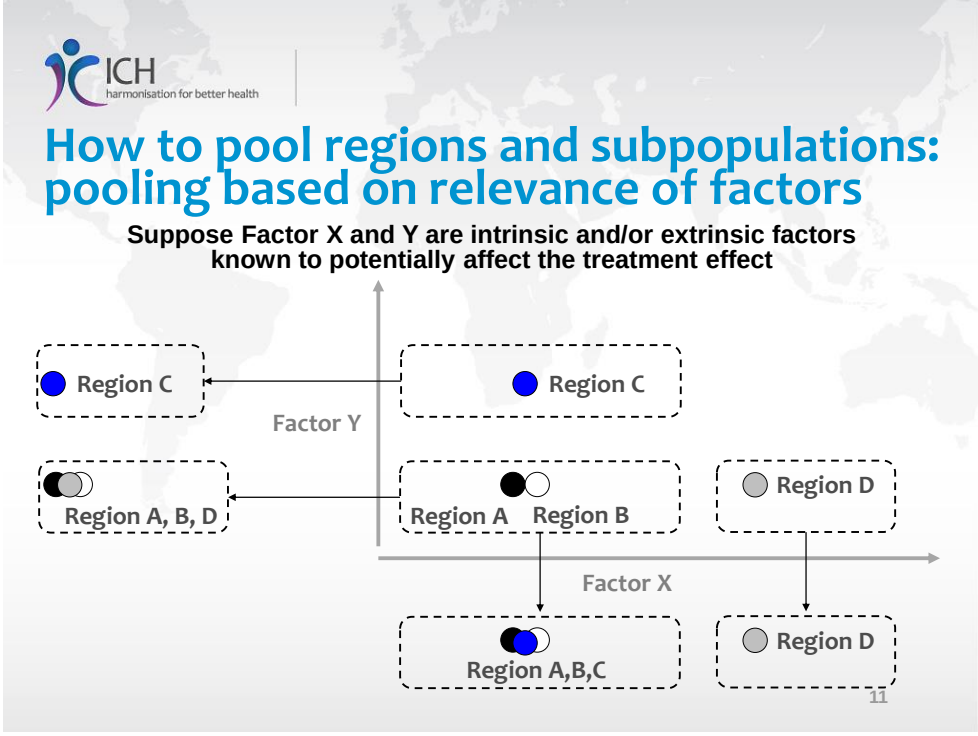
Regarding prognostic or predictive factors, see BEST (Biomarkers, Endpoints, and other Tools).

Resource;
https://www.ncbi.nlm.nih.gov/books/NBK338448/.

Also see Module 2 for further considerations.



Justification of pooling involves considerations of a large number of different aspects of the trial population.

Suppose subjects can be described in two dimensions (Factor X, Factor Y) where Factor X could be disease severity and Factor Y could be a biomarker. If both factors are relevant in the treatment context, only Region A and B can be pooled.

If Factor X is of limited relevance, Region A, B, and D can be pooled. If Factor Y is of no relevance, Region A, B and C can be pooled.

Thus, at the planning stage, justifications should be provided regarding which factors are relevant based on available knowledge from the different regions.

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.**