



Module 4

Overall sample size and allocation to regions

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

- **Key statistical considerations**
- **Sample size planning for allocation to regions**
- **Pooled regions and pooled subpopulations**
- **Five approaches to sample size allocation to regions – pros and cons of each**
- **Concluding remarks**

Key statistical considerations: Overall sample size and its allocation to region

- The guiding principle for determining the overall sample size is that the test of the primary hypothesis, based on data from all enrolled regions, is of primary importance
- The sample size allocation to regions should be determined such that clinically relevant differences in treatment effects among regions can be evaluated without substantially increasing the sample size

This module expands on Principles 3 and 4 of E17

[Section 1.4 - Basic principles #3 and #4]

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.

Sample size planning for allocation to regions

[General Considerations, Section 2.2.5]

- *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*

[Overall Sample Size, Section 2.2.5]

- *Two additional factors are particularly important in the MRCT setting*
 - *the size of the treatment effect that is considered clinically relevant to all regions in the trial*
 - *the expected variability of the primary outcome variables based on combining data across regions.*

Sample size planning for allocation to regions (2)

[Sample Size Allocation to Regions, Section 2.2.5]

- 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 to collect information 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
 - should provide the information needed to support meaningful interpretation of results for regulatory decision-making in different regions

Pooled regions and pooled subpopulations : definition

- Science-based strategic pooling can bring efficiency and knowledge to enable regulatory decision making, expanding on the exploration of factors discussed previously

Pooled Regions

(e.g., North America)

Pooled Subpopulations

(e.g., Biomarker status such as EGFR mutation status)

[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.*

[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.*

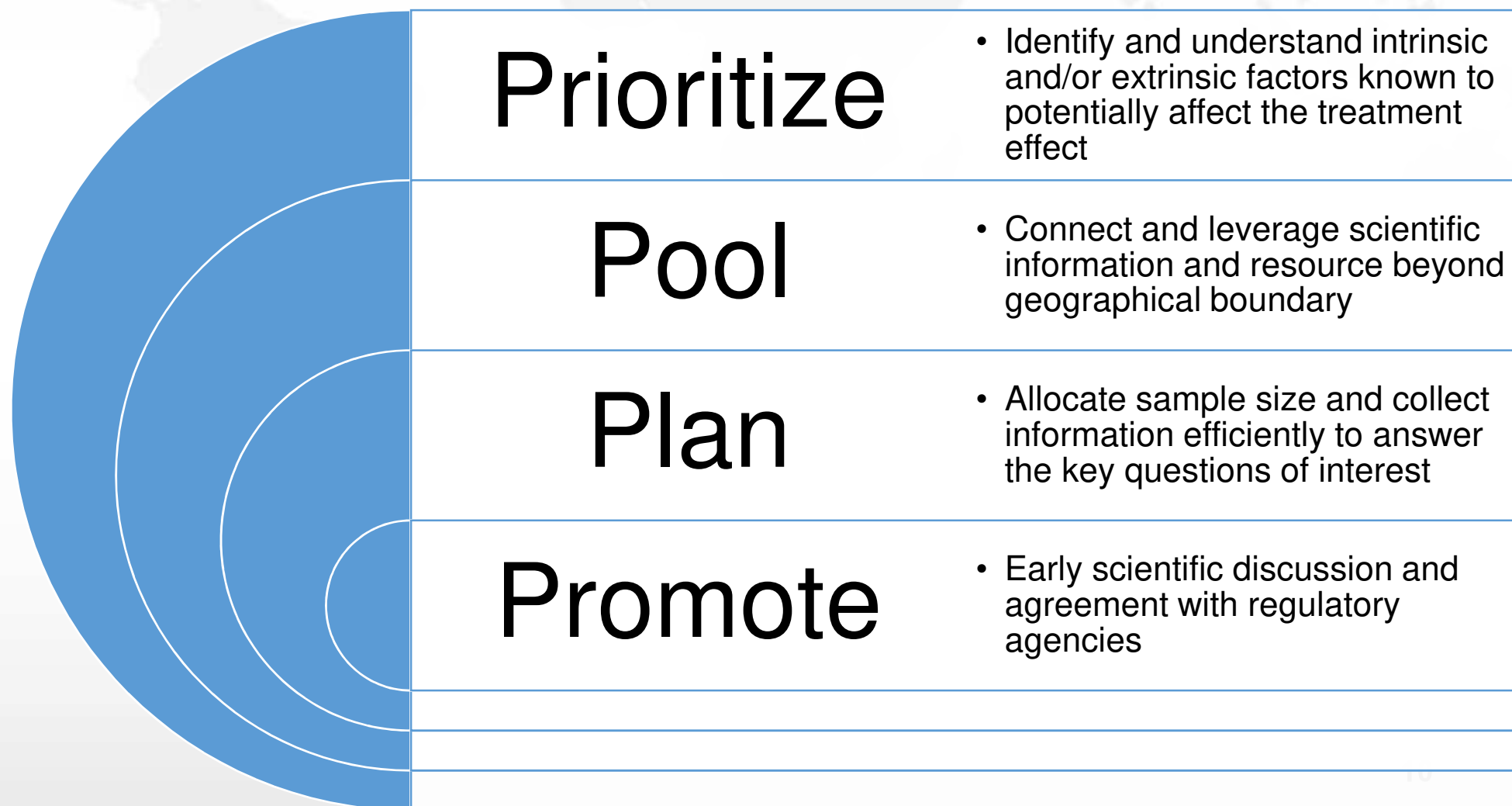
Pooled regions and pooled subpopulations: benefits and challenges

[Pooled Regions and Pooled Subpopulations, Section 2.2.5]

- *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.*

Value of pooling strategies

Not just analysis strategies, important as design concepts



Five approaches to sample size allocation to regions

1

Proportional Allocation:

Allocation of subjects to regions in proportion to size of region and disease prevalence.

2

Equal Allocation:

Allocation of equal numbers of subjects to each region.

3

Preservation of Effect: Allocation of subjects to one or more regions based on preserving some specified proportion of the overall treatment effect.

4

Local Significance: Allocation of a sufficient number of subjects to be able to achieve significant results within each region.

5

Fixed Minimum Number:

Allocation of a fixed minimum number of subjects to a region.

**Five strategies
for sample
size allocation
to regions**

1. Proportional Allocation

1

Proportional Allocation:

Allocation of subjects to regions in proportion to size of region and disease prevalence.

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Allocation of equal numbers of subjects to each region.

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Allocation of subjects to one or more regions based on preserving some specified proportion of the overall treatment effect.

4

Local Significance:

Allocation of a sufficient number of subjects to be able to achieve significant results within each region.

5

Fixed Minimum Number:

Allocation of a fixed minimum number of subjects to a region.

• **Pros**

- Focuses on regions of disease occurrence
- Recruitment is more feasible and able to be completed in a timely fashion
- May provide sufficient information to evaluate the drug in its regional context for the representative region

• **Cons**

- A single region or a cluster of regions may drive the overall result
- Adequate safety information in global context may not be available if information primarily comes from a single or cluster of regions

2. Equal Allocation

1

Proportional Allocation:

Allocation of subjects to regions in proportion to size of region and disease prevalence.

2

Equal Allocation:

Allocation of equal numbers of subjects to each region.

3

Preservation of Effect:

Allocation of subjects to one or more regions based on preserving some specified proportion of the overall treatment effect.

4

Local Significance:

Allocation of a sufficient number of subjects to be able to achieve significant results within each region.

5

Fixed Minimum Number:

Allocation of a fixed minimum number of subjects to a region.

- **Pros**

- Easily comprehensible
- Maximizes opportunity to examine consistency

- **Cons**

- Recruitment may not be feasible or able to be completed in a timely fashion
- Difficult if disease incidence and/or prevalence would affect recruitment from all participating regions

3. Preservation of Effect

1

Proportional Allocation:

Allocation of subjects to regions in proportion to size of region and disease prevalence.

2

Equal Allocation:

Allocation of equal numbers of subjects to each region.

3

Preservation of Effect:

Allocation of subjects to one or more regions based on preserving some specified proportion of the overall treatment effect.

4

Local Significance:

Allocation of a sufficient number of subjects to be able to achieve significant results within each region.

5

Fixed Minimum Number:

Allocation of a fixed minimum number of subjects to a region.

- **Pros**

- Assurance that a certain minimal treatment effect is maintained in each region

- **Cons**

- Selection of percent preservation may be subjective
- May not be practical if too many regions have this requirement
- Not much different from formally testing heterogeneity with all its implications

4. Local Significance

1

Proportional Allocation:

Allocation of subjects to regions in proportion to size of region and disease prevalence.

2

Equal Allocation:

Allocation of equal numbers of subjects to each region.

3

Preservation of Effect:

Allocation of subjects to one or more regions based on preserving some specified proportion of the overall treatment effect.

4

Local Significance:

Allocation of a sufficient number of subjects to be able to achieve significant results within each region.

5

Fixed Minimum Number:

Allocation of a fixed minimum number of subjects to a region.

- **Pros**

- Assurance that statistical significance is achieved in each region
- Most persuasive results for each region

- **Cons**

- Will drive up the sample size : may become too large to be feasible

5. Fixed Minimum Number

1

Proportional Allocation:

Allocation of subjects to regions in proportion to size of region and disease prevalence.

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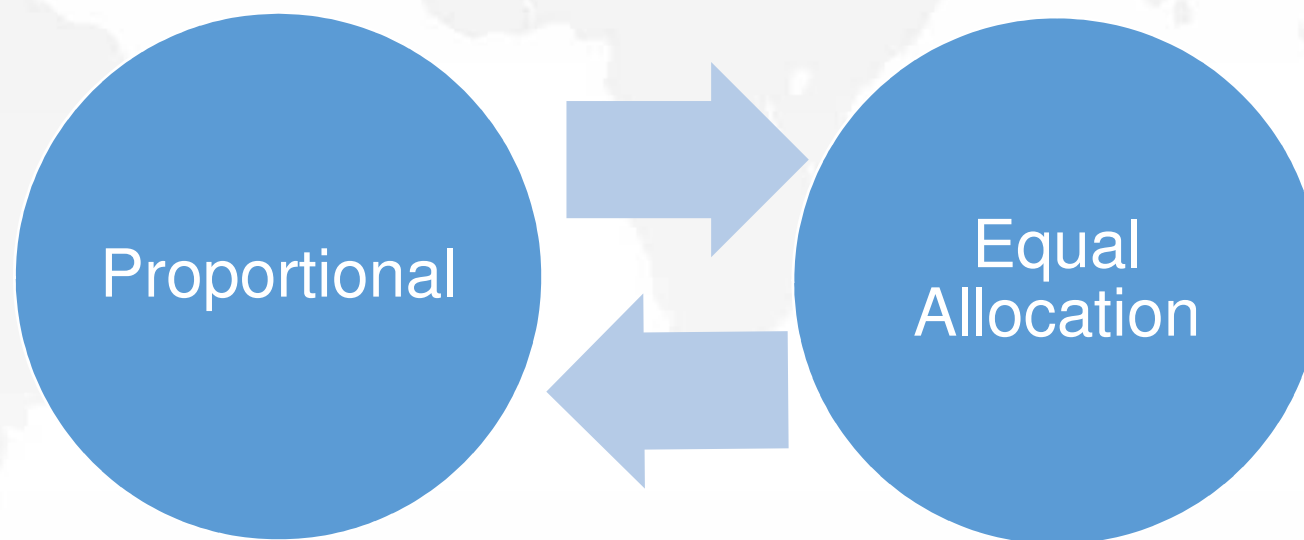
• **Pros**

- Assurance of a minimal number of subjects in each region
- Adequate safety information may be available for each region in a local context

• **Cons**

- May not have a scientific justification for this requirement
- May drive up the sample size: may become too large to be feasible

Sample size allocation to regions – a balanced approach



[Sample Size Allocation to Regions, Section 2.2.5]

A balance between proportional (#1) and equal allocation (#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.

Concluding remarks

- The guiding principle for determining the overall sample size is that the test of the primary hypothesis, based on data from all enrolled regions, is of primary importance
- The sample size allocation to regions should be determined such that clinically relevant differences in treatment effects among regions can be evaluated without substantially increasing the sample size
- Pre-specified pooling of regions or subpopulations may help provide flexibility in sample size allocation to regions, and facilitate consistency evaluation
- Recommendation is to balance statistical efficiency with feasibility of enrollment, while ensuring trial objectives can be met