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

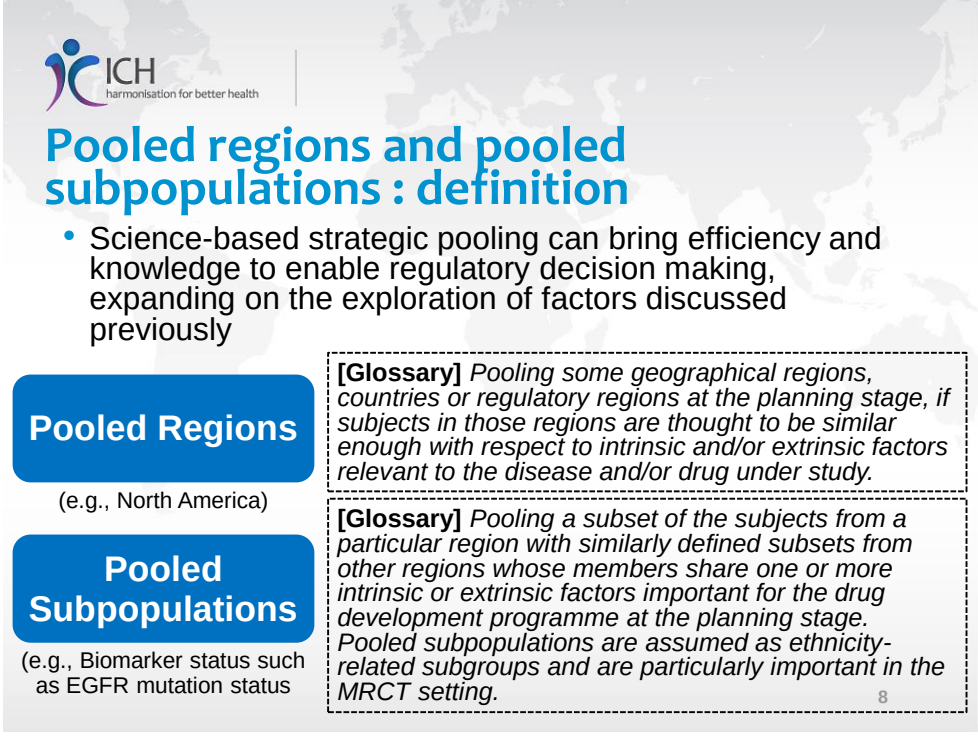
[General Considerations, Section 2.2.5]

- *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.*

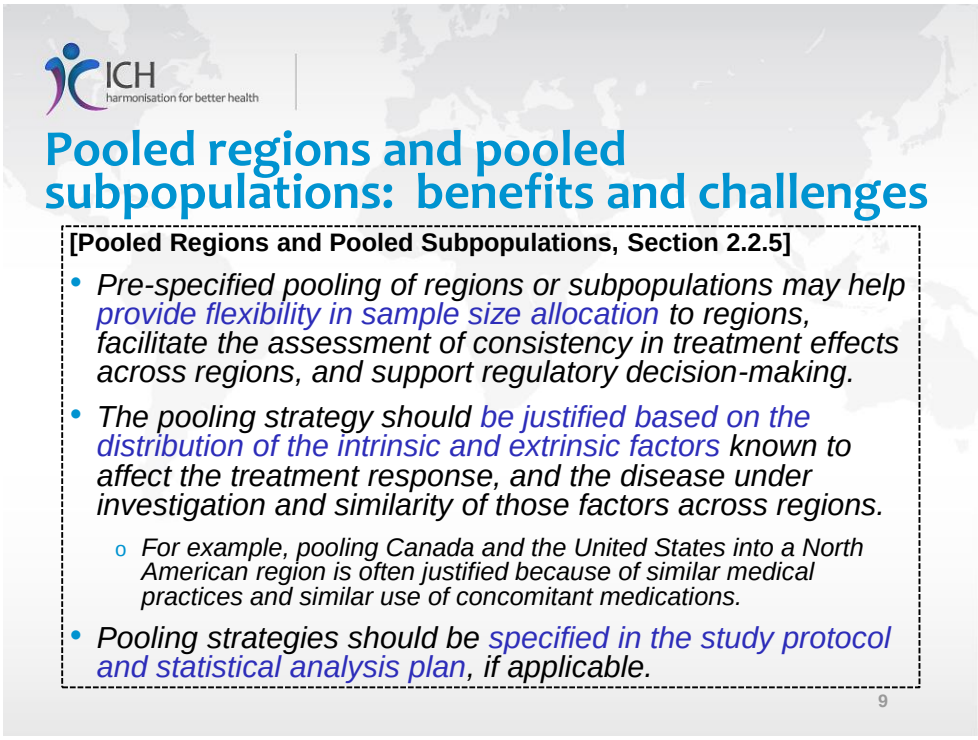
Consistency is defined as lack of clinically relevant differences. This concept is discussed further in another E17 training module 6; please refer to it for additional details.



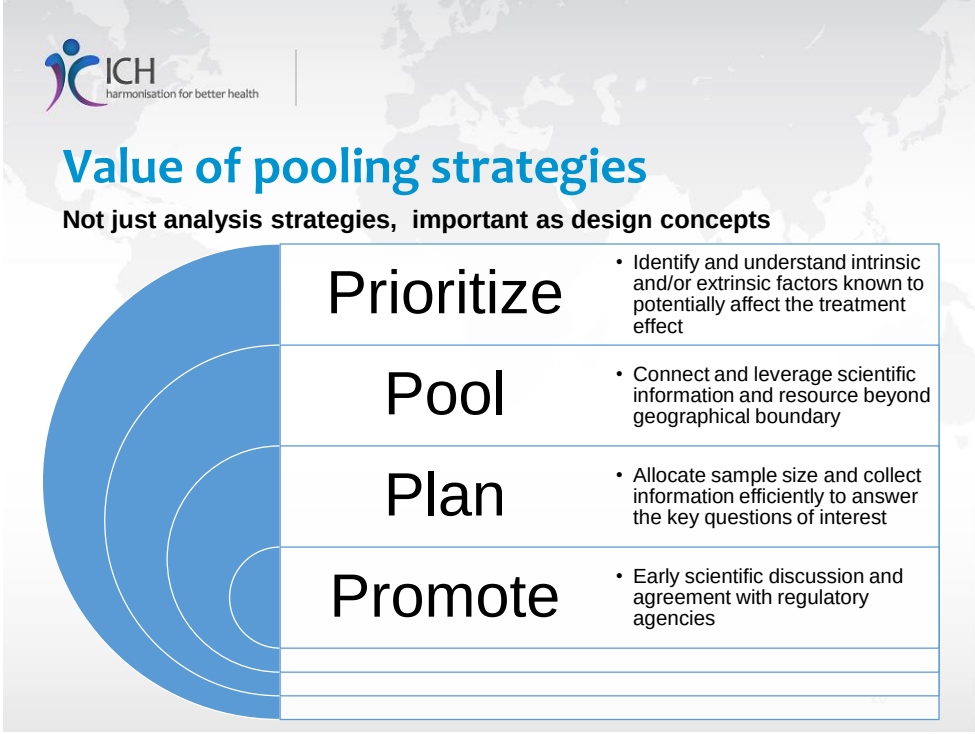
In planning for sample size, two important concepts are introduced.

The first one is that of a pooled region. It refers to pooling of geographical regions, countries or regulatory regions based on a commonality of extrinsic and/or intrinsic factors. For example, North America is often pooled together for similarities in medical practice.

The second one is that of pooled subpopulation. It refers to pooling subsets of the subjects across geographical regions and regulatory regions, who share one or more intrinsic or extrinsic factors which may affect the treatment effect. Examples may include biomarker status such as EGFR mutation status.



Please refer to Module 5: Pooling strategies for additional details.



Pooled regions and pooled subpopulations are not just analysis strategies – they are important design concepts.

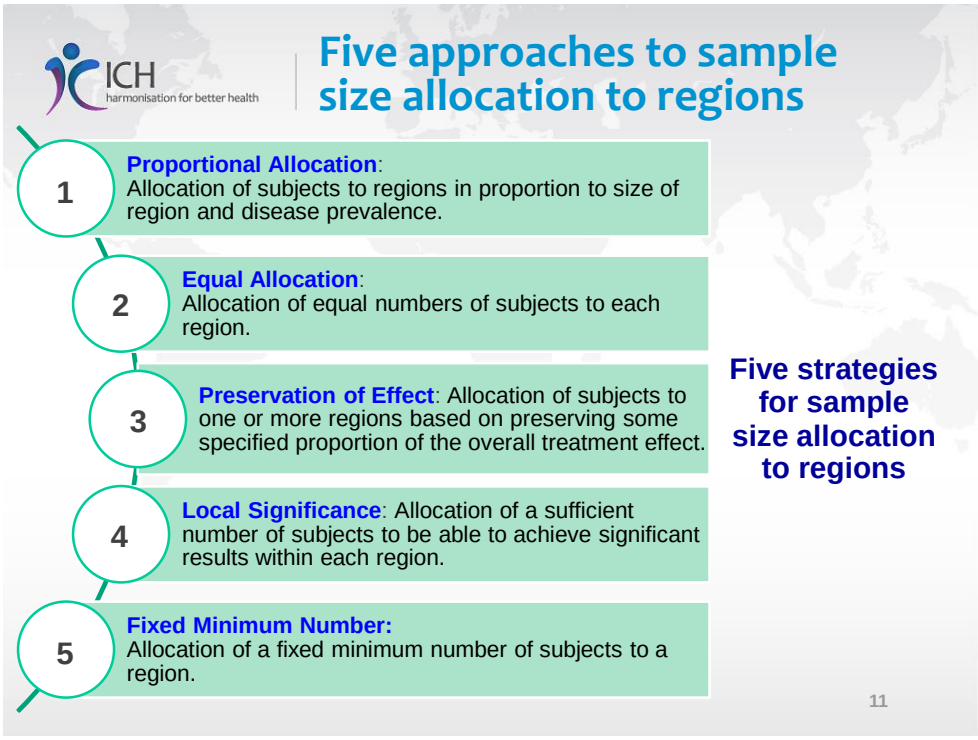
There are four major reasons for considering use of pooled regions and pooled subpopulations.

The first one is to prioritize – to identify and understand intrinsic and/or extrinsic factors known to potentially affect the treatment effect.

The second one is to pool - to connect and leverage scientific information and resources beyond geographical boundaries.

The third one is to plan - to allocate sample size and collect information efficiently to answer the key questions of interest.

The fourth one is to promote early scientific discussion and agreement with regulatory agencies.



There are five common strategies for sample size allocation to region which will be discussed one by one, including the pros and cons for each. Note that these are not the only possible strategies; others may be considered, if deemed appropriate.

1. Proportional Allocation

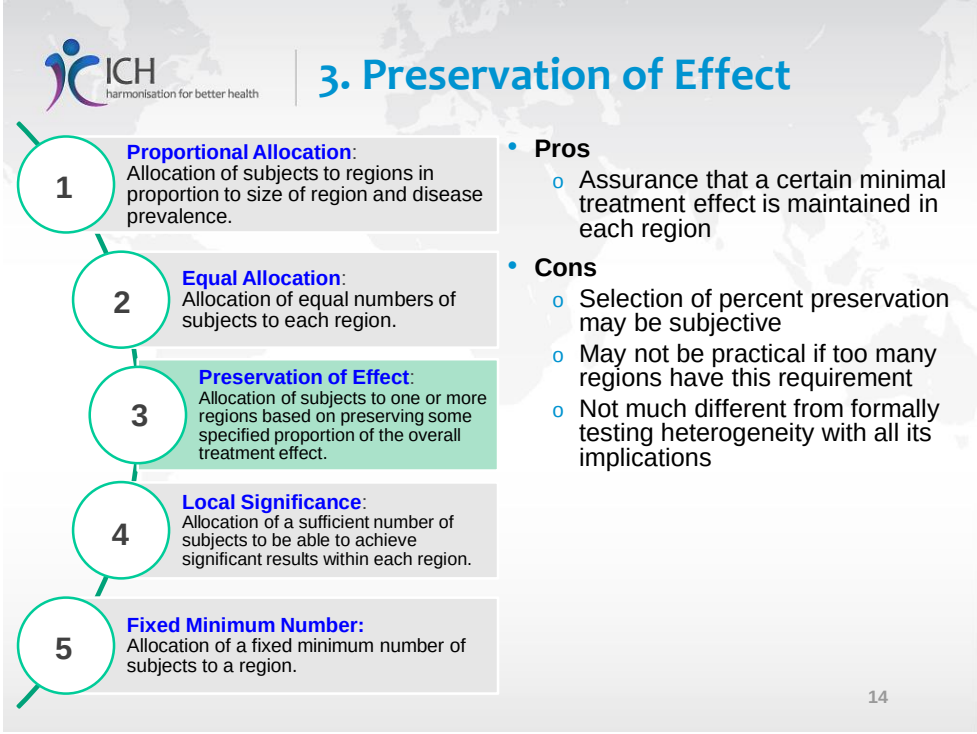
1. **Proportional Allocation**: Allocation of subjects to regions in proportion to size of region and disease prevalence.
2. **Equal Allocation**: Allocation of equal numbers of subjects to each region.
3. **Preservation of Effect**: Allocation of subjects to one or more regions based on preserving some 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**
  - 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

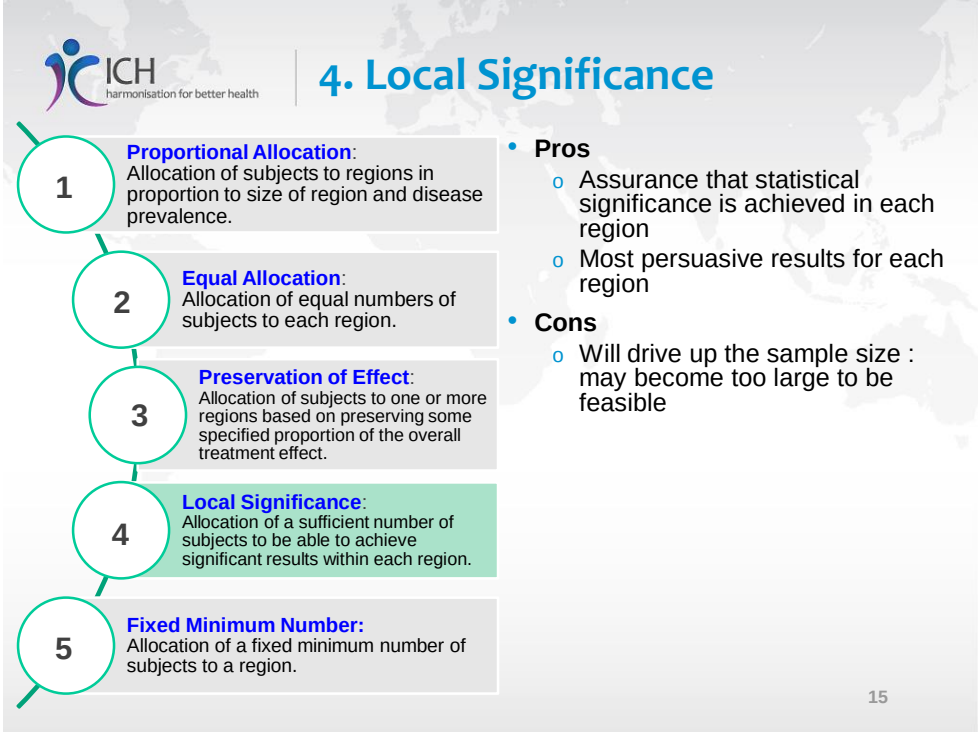
2. Equal Allocation

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.

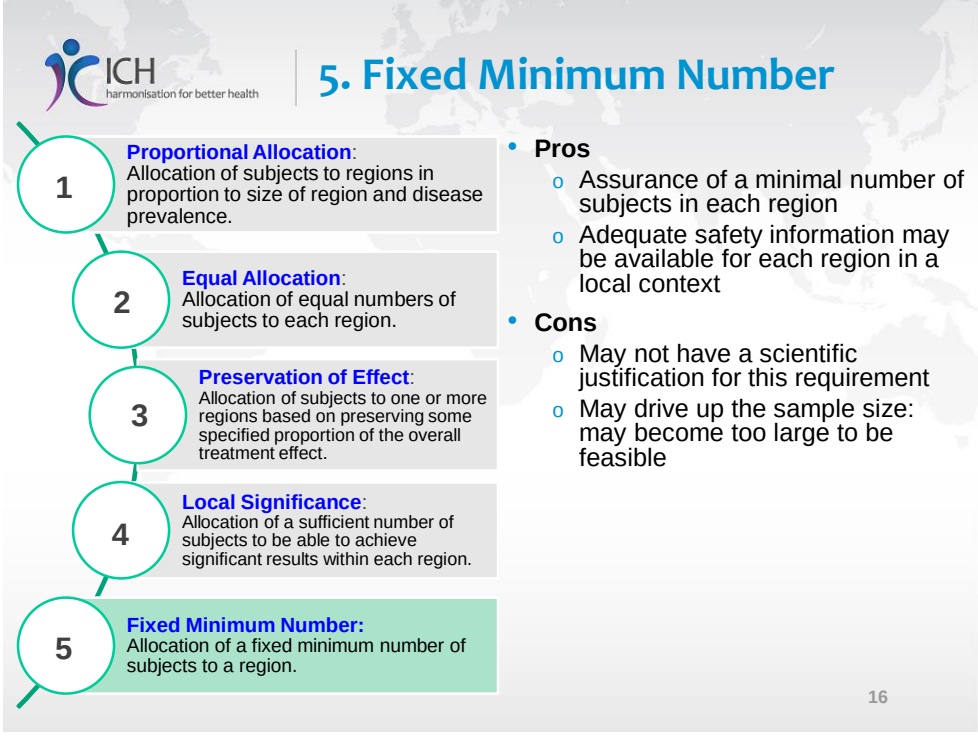
- **Pros**
  - Easily comprehensible
  - Maximizes opportunity to examine consistency
- **Cons**
  - Recruitment may not be feasible or able to be completed in a timely fashion
  - Difficult if disease incidence and/or prevalence would affect recruitment from all participating regions



Practically, this is not really different from testing for heterogeneity with either low power, or substantial increases in sample size. If clinically relevant differences in treatment effects are seen between regions, it is important to explore whether there are any underlying reasons for the observed differences.

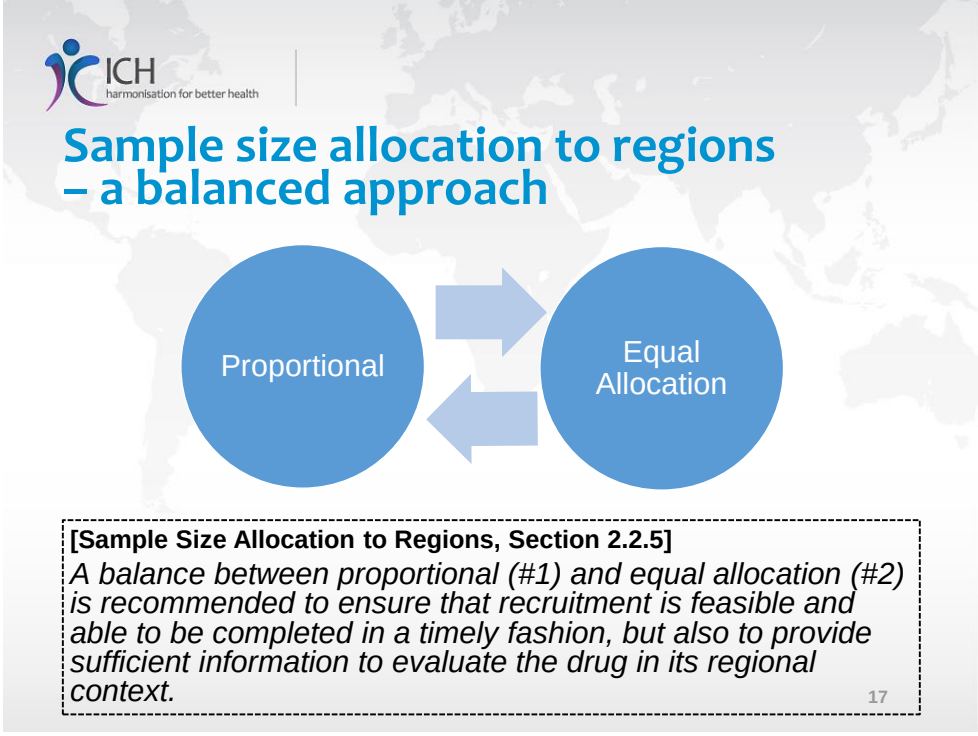


Allocation based on the need to demonstrate significant effects within each region contradicts the idea of an MRCT, which should, within one protocol, demonstrate that (beyond clinically irrelevant differences), the treatment can achieve the same benefit in all regions. Mandating that there is significance in each of the regions would mean that separate studies with similar (but not identical) protocols could be planned, which would be less informative than investigation in one MRCT.



If chosen without a scientific argument (e.g., this minimum is needed to have stable estimates for the evaluation of consistency and information to evaluate inconsistency), the strategy does not benefit interpretability or logistics of the trial.

It is noted, however, that a scientifically justified minimum number of subjects per region would allow competitive recruitment after the agreed number of subjects per regions has been recruited.



The question arises how a balance between not increasing the overall sample size and having a sufficient sample-size per region for examining consistency can be achieved?

The inherent heterogeneity of an MRCT compared to a single-region trial will usually result in a relatively larger sample size requirement for the assessment of a given hypothesis. MRCTs should be designed to provide enough information to allow an evaluation of the consistency of effect across regions and subpopulations. Evaluation of consistency is qualitative and descriptive; this evaluation should not drive the sample size requirement up so much that the MRCT is no longer feasible or practical.

Pooled regions and pooled subpopulations can be useful tools to increase efficiency without substantially increasing the overall sample size and still enable evaluation of consistency.

Approaches of sample size allocation to regions based on preservation of effect, local significance or fixed minimum number (without scientific justifications) are not practical and generally not recommended.

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