ICH E17 and Multi-Regional Clinical Trials (MRCTs)

Aloka Chakravarty, Ph.D.

Deputy Director, Office of Biostatistics

CDER, FDA

This is excerpted from a short course taught jointly with Dr. Lisa LaVange (FDA), Dr William Wang (Merck & Co, Inc) and Dr. Bruce Binkowitz, (Shionogi Inc) – co-authors are duly acknowledged

Outline

- Motivation and Introduction
- ICH E5 overview and its relation to E17
- ICH E17 Basic Principle
- ICH E17 Statistical Considerations
- E17 Comment/Responses
- Concluding Remarks

ICH

International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use

- Begun in 1990
- Originally three ICH regions: EU, US and Japan
- Regulators and representatives from the pharmaceutical industry at the table
- Developed guidelines recognized by regulatory agencies
- Recent reorganization (Oct 2015)
  - New regions added as members and/or observers

ICH E17 Concept Paper

- Statement of Perceived Problem (Dated 21 May 2014)
  - Multi-regional clinical trials (MRCTs) are conducted to provide data in support of regulatory submissions in different regions, including non-ICH regions - regulatory agencies face challenges in evaluating data
  - No harmonized guidelines on designing or conducting MRCTs
  - An international guideline that harmonizes regulatory expectations about the use of MRCTs for global drug development will be useful to both sponsors and regulators
- Issues to Be Resolved (Endorsed in June 2014)
  - Main objective of this guideline is to provide common points to consider for planning/designing MRCTs and to minimize the amount of conflicting advice provided by regulatory agencies on the trial design
  - Issues about data analysis and interpretation may be discussed in the process of developing the guideline but are considered out of scope for the guideline itself

ICH E17 Guideline

ICH E17: Proposal, Expert Working Group, Status

ICH
harmonisation for better health

Final Concept Paper
E17: General principle on planning/designing Multi-Regional Clinical Trials
dated 21 May 2014
Endorsed by the ICH Steering Committee on 5 June 2014

Type of Harmonisation Action Proposed

This Concept Paper supports a proposal for a new harmonised tripartite guideline on general principles on planning/designing Multi-Regional Clinical Trial (MRCT).

Statement of the Perceived Problem

Drug development has rapidly been globalized recently and MRCT for regulatory submission has widely been conducted in non-ICH regions as well as ICH regions. Regulatory agencies currently face challenges in evaluating data from MRCTs for drug approval. However, there is currently no harmonised ICH Guideline on MRCTs, especially focusing on scientific issues in planning/designing MRCTs, although Q&A of ICH E5 Guideline partly covers issue relating to MRCTs. An international guideline will be needed to promote conducting MRCT appropriately. A lack of harmonisation on this topic may cause additional burden for sponsor and difficult situation for conducting MRCTs.

Issues to be Resolved

The new guideline will describe practical issues in planning/designing MRCT. Issues on data interpretation may be discussed in a process of discussion for establishing this guideline, but are out of scope in this guideline. Main objective of this guideline is to provide common points to consider in planning/desingning MRCTs and minimize conflicting opinions from regulatory bodies. The below may be examples of topics covered in this guideline, but more details will be determined by discussion among experts of the group.

- Issues in planning MRCTs
  - Usefulness of MRCTs in drug developments
  - Essential points for conducting MRCTs (GCP etc)
  - Importance of ethnic factors evaluation on drug efficacy/safety in MRCTs etc.
- Issues in designing MRCTs
  - Points to consider in dose determination for MRCT (exploratory and confirmatory)
  - How to control various concomitant medications in each country
  - Consideration on definition of a population and methods of sample size estimation for a population/region etc.
- Others
  - Encouraging a parallel scientific consultation with multiple regulatory agencies in advance

- E17 EWG: established in June 2014
  Rapporteur: PMDA

- Status:
  - Step 2b: ICH draft signed off Jun 2016
  - Step 3: public comments rec'd Jul –Jan 2017
  - Review of comments in progress
  - Finalization anticipated 4Q 2017

Members/Observers of the ICH E17 Working Group (ICH Meeting in Osaka, Japan, Nov 2016)

EU	EMA	Canada	Health Canada
	EFPIA	WHO	WHO
Japan	PMDA	GCC	Saudi Food and Drug Authority
	JPMA	Brazil	Brazilian Health Surveillance Agency
US	FDA	Singapore	Health Sciences Authority (HSA)
	PhRMA	Korea	Ministry of Food and Drug Safety (MFDS)
		Chinese Taipei	Center for Drug Evaluation (CDE)

Potential Impact of E17

- Give patients earlier access to innovative therapies
  - Provide an innovative drug to patients sooner by synchronizing clinical development programs across different geographic and regulatory regions
- Avoid duplication
  - Reduce the need to conduct standalone regional or national studies, including bridging studies.
- Promote international harmonization
  - Consider use of a global, harmonized approach to drug development first
- Provide better evidence for drug approval in each region
  - Encourage better planning and design of MRCTs based on the latest scientific knowledge and experience
- Build infrastructure to support global drug development
  - Plan and conduct high quality MRCTs early in a drug development program to build up the needed trial infrastructure and capability

E17 Overview

- Guidance to encourage use of MRCTs
  - Reduce the need for single-region studies
- Benefits (potential) construe to:
  - Patients, through earlier access to medicines in multiple regions
  - Sponsors, through acceptability of data from one trial to more than one agency
- Costs include:
  - Greater emphasis on up-front planning and coordination across different regulatory regions
  - More focused thinking about statistical concepts for sample size determination and analysis planning

Trial Design

- Emphasis on obtaining agreement from different regulatory agencies involved in the trial on important aspects of trial design, e.g.,
  - Objectives
  - Endpoints
  - Comparators
  - Population (inclusion/exclusion criteria)
- Goal of trial planning is to have clear, interpretable results that can support registration in multiple regions

Quality by Design

- Consistent with proposed revision of ICH E8, a quality by design approach is encouraged
- Identify critical quality factors during planning
  - E.g., appropriate application of inclusion/exclusion criteria, adherence to assigned treatment, etc.
- Implement procedures to address those factors across all regions during trial conduct
  - E.g., procedures to minimize attrition; collect follow-up data after treatment discontinuation, if called for, etc.
- Data monitoring to identify quality issues during trial
  - In time to remedy problems

Pooled Regions and Pooled Sub-populations

- Regions usually defined as geographical, geopolitical, or regulatory units
  - May be pooled to facilitate trial conduct and analysis, e.g., North America, Europe, East Asia
  - Recommend stratification at the design (randomization) stage and stratification or model-based adjustment at the analysis stage
- "Pooled sub-populations" may be pre-defined based on extrinsic or intrinsic factors, spanning regions
  - Potential to create more informed strata, e.g., by race/ethnicity, genetic markers, medical practice, availability of health care, other
- Homogeneity within strata can provide variance reduction

Considerations

- US FDA does not require demonstration of statistically significant effects in an MRCT based on US clinical sites alone
  - Have approved drugs based on trials with no US sites, but prefer some data to assess consistency
  - PLATO study provides an example where post-hoc examination of consistency supported US approval
- Quality issues have been encountered in some submissions with data from non-US sites
  - Planning for consistent quality across all regions is a key message in ICH E17
- MRCTs have an important place in drug development
- E17 intended to facilitate use of MRCTs globally
- Planning and coordination are key to success

ICH E5 Guidance - history

- Original E5 (1998):
  - Topic proposed to the ICH Steering Committee in 1992 by Japan
  - Guidance signed off in February, 1998 after many years of effort regarding what should be its purpose, focus, content, and guidance
  - Focus on ethnicity, foreign data , acceptance of clinical trial data, regulatory standards, among others

- E5 Q&A (2006)
  - Clarified some points of ambiguity in the initial guidance
  - Introduced the multi-regional trial concept for bridging

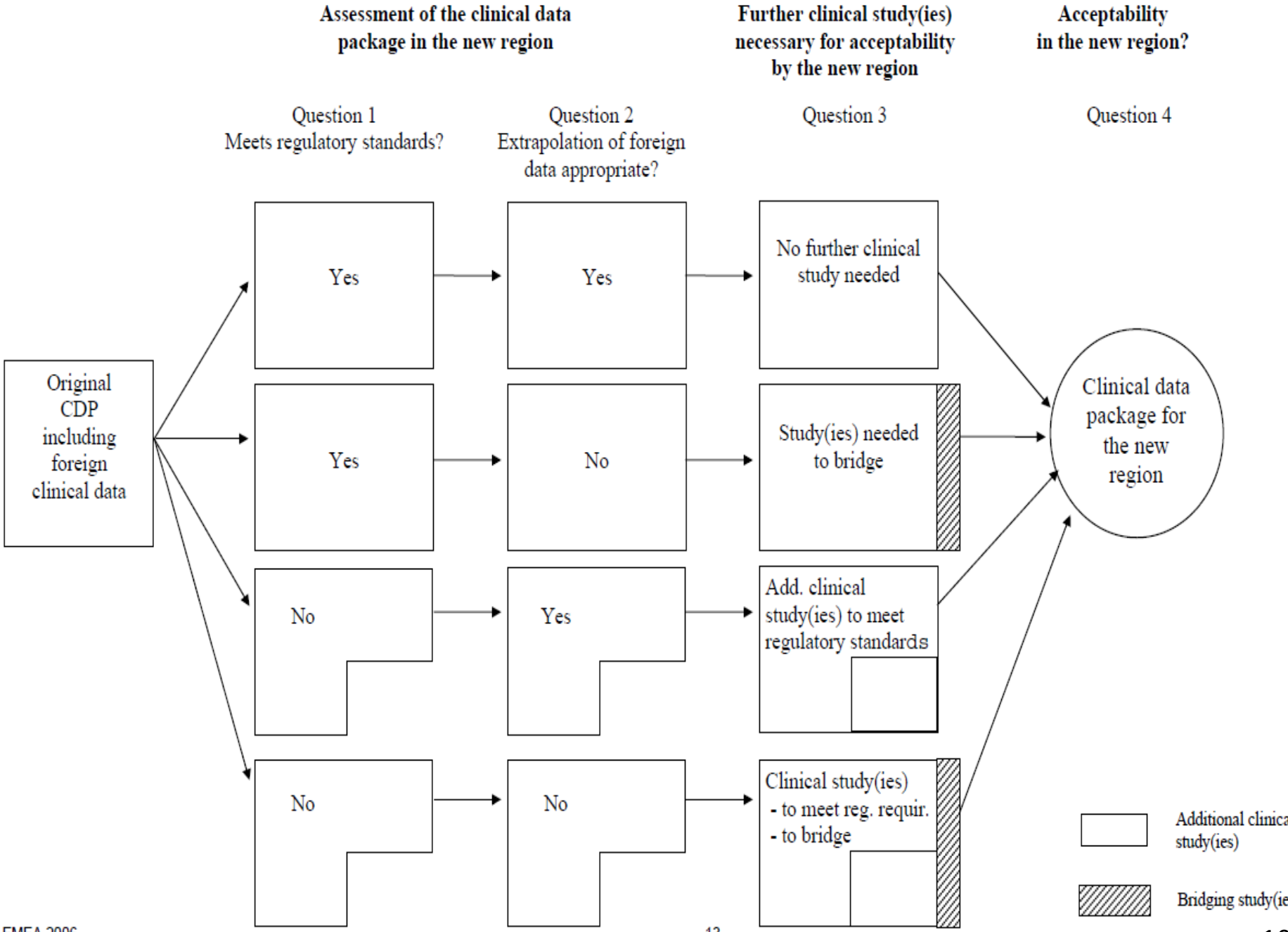
ICH E5 (1998)

APPENDIX A ICH E5

Classification of intrinsic and extrinsic ethnic factors

INTRINSIC			EXTRINSIC
Genetic		Physiological and pathological conditions	Environmental
Gender		Age (children-elderly)	Climate Sunlight Pollution
	Height Bodyweight		
		Liver Kidney Cardiovascular functions	**Culture** Socioeconomic factors Educational status Language
	ADME Receptor sensitivity		
Race			Medical practice Disease definition/Diagnostic Therapeutic approach Drug compliance
Genetic polymorphism of the drug metabolism			
			Smoking Alcohol
			Food habits Stress
Genetic diseases		Diseases	Regulatory practice/GCP Methodology/Endpoints

Appendix B: Assessment of the clinical data package (CDP) for acceptability



The Q & A addendum was very helpful and stimulated new thinking, especially Q11 (2006)

Guidance for Industry

E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data

---

Questions and Answers

The Multi-Regional Trial for Bridging

Q11: ***There seems to be an impression that the E5 bridging study would always be conducted after data in the original region is complete. Is this correct?***

It may be desirable in certain situations to achieve the goal of bridging by conducting a multi-regional trial under a common protocol that includes sufficient numbers of patients from each of multiple regions to reach a conclusion about the effect of the drug in all regions. Please provide points to consider in designing, analyzing and evaluating such a multi-regional trial.

A11: Bridging data should allow for extrapolation of data from one region to another. Although E5 speaks generally to extrapolation of data to a new region, E5 was not intended to suggest that the bridging study should necessarily follow development in another region. In the answer to Q1, it is made clear that it is also possible to include earlier studies conducted in several regions in a global drug development program so that bridging data might become available sooner. This can expedite completion of a global clinical development program and facilitate registration in all regions. A bridging study therefore can be done at the beginning, during or at the end of a global development program. For a multi-regional trial to serve as a bridging study for a particular region, it would need to have persuasive results in that region, because it is these regional results that can convince the regulators in that region that the drug is effective, and can "bridge" the results of trials in other regions in the registration application.

The Multi-Regional Trial for Bridging

A multi-regional trial for the purpose of bridging could be conducted in the context of a global development program designed for near simultaneous world-wide registration. The objectives of such a study would be: (1) to show that the drug is effective in the region and (2) to compare the results of the study between the regions with the intent of establishing that the drug is not sensitive to ethnic factors. The primary endpoint(s) of the study should be defined and acceptable to the individual regions and data on all primary endpoints should be collected in all regions under a common protocol. In instances where the primary endpoints to be used by the regions are different, data for comparison purposes on all primary endpoints should be collected in all regions.

Relevance to E17 – Using the MRCT without bridging

- E5 expressed the opinion that with increased experience with studies, including MRCT's, the need for bridging studies would lessen (see Q & A 10)
- After years of experience with MRCT's, some lessons learned can be incorporated into E17 to further advance the use of MRCT's without separate bridging studies

From ICH E5 to ICH E17: A 20+ Year Journey

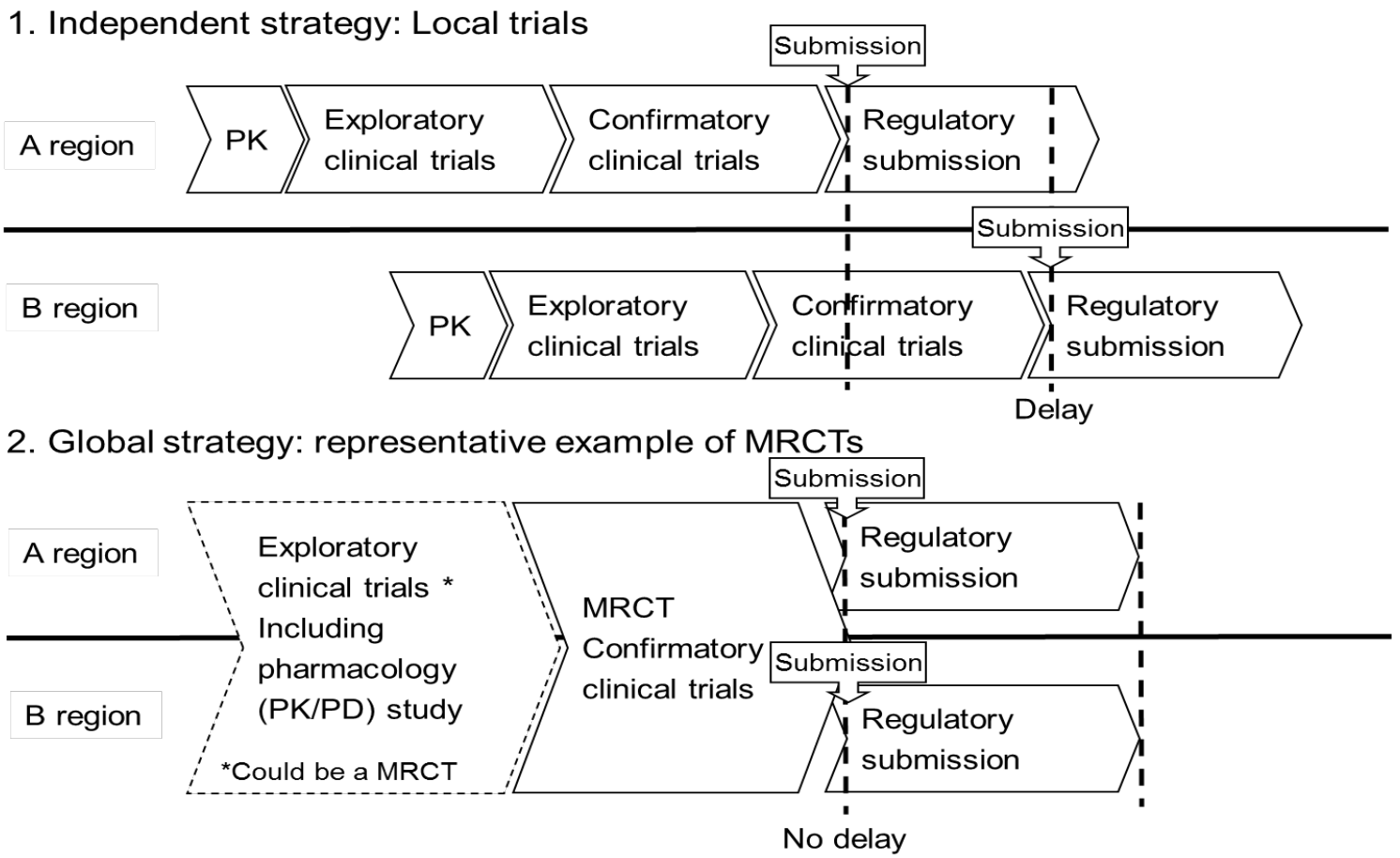
- Continuous learning intrinsic/extrinsic factors
- Design the development strategy holistically
  - From bridging to simultaneously confirming
  - From sequential to parallel
  - From a local mindset to a global mindset
  - From retrospective to prospective approaches

E17 and E5 should be used in combination

Promoting Conduct of MRCTs

- MRCTs are generally the preferred option for investigating a new drug for which regulatory submission is planned in multiple regions. The underlying assumption of the conduct of MRCTs is that the treatment effect is clinically meaningful and relevant to all regions being studied.
  - This assumption should be based on knowledge of the disease, the mechanism of action of the drug, on a priori knowledge about ethnic factors and their potential impact on drug response in each region, as well as any data available from early exploratory trials with the new drug.
  - The study is intended to describe and evaluate this treatment effect, acknowledging that some sensitivity of the drug with respect to intrinsic and/or extrinsic factors may be expected in different regions and this should not preclude consideration of MRCTs.

Encouraging Simultaneous Global Drug Development



Careful Consideration of Intrinsic/Extrinsic Factors

- To increase an acceptability of MRCT data in the review by multiple regulatory agencies for drug approval, a sponsor should carefully consider the planning and design of MRCTs in advance
  - Ethnic factors are a major point of consideration
    - identified during the planning stage,
    - information on them collected and evaluated during MRCTs.
  - Based on the understanding of accumulated knowledge about these intrinsic and extrinsic factors, MRCTs should be designed to provide information to support an evaluation of whether the overall treatment effect applies to subjects from participating regions.

Sample Size Allocation

- The guiding principle for determining the overall sample size in MRCTs is that the test of the primary hypothesis can be assessed, based on combining data from all regions in the trial
- The sample size allocation to regions should be determined such that clinically meaningful differences in treatment effects among regions can be described without substantially increasing the sample size requirements based on the primary hypothesis.

  - The guideline provides some more details how to allocate sample size to region

Pooled Population

- Introduce a new use of "pooled population" to help regulatory decision making
  - Some regions may be pooled at the design stage, if subjects are similar enough with respect to intrinsic and/or extrinsic factors relevant to the disease area and/or drug under study.
  - Consideration could also be given to pooling a subset of the subjects from a particular region with similarly defined subsets from other regions to form a pooled subpopulation whose members share one or more intrinsic or extrinsic factors important for the drug development program.
  - Strategy for pooling regions and the principles for pooling subpopulations should be specified at the planning stage and described in the protocol.

Quality of MRCT

- Ensuring trial quality is of paramount importance for MRCTs.
- This will not only ensure the scientific validity of the trial results, but also enable adequate evaluation of the impact of intrinsic and extrinsic factors by applying the same quality standard for trial conduct in all regions.
- In addition, planning and conducting high quality MRCTs throughout drug development will build up trial infrastructure and capability, which over time will result in a strong environment for efficient global drug development.

Discussions with Regulatory Agencies

- Encourage discussions with regulatory authorities in the planning stage
  - In the planning and design of MRCTs, it is important to understand the different regulatory requirements in the concerned regions.
  - Efficient communication among sponsors and regulatory authorities at a global level can facilitate future development of drugs. These discussions are encouraged at the planning stage of MRCTs.

Key Statistical Considerations:
Choice of Endpoints and Multiplicity

- The primary endpoint should be clinically meaningful, accepted in medical practice , and sufficiently sensitive and specific to detect the anticipated effect of the treatment
  - It should be acceptable to all concerned regulatory authorities. Agreement on the primary endpoint ensures that the overall sample size can be determined for a single (primary) endpoint based on the overall study population
  - If, in rare instances, agreement cannot be reached, a single protocol should be developed with endpoint-related subsections tailored to meet the respective requirements of the regulatory authorities. In this case, no multiplicity adjustment is needed for regulatory decision-making

Key Statistical Considerations:
Pooled Region and Pooled Subpopulation

- Introduce the concepts as tools to evaluate treatment effect in multi-regional setting and to allocate sample size efficiently for regulatory decision-making; they should be specified in the planning stage

Pooled Region

- Pooling subjects across geographical regions, countries or regulatory regions based on a commonality of extrinsic intrinsic and/or factors
- Ex: North America, East Asia

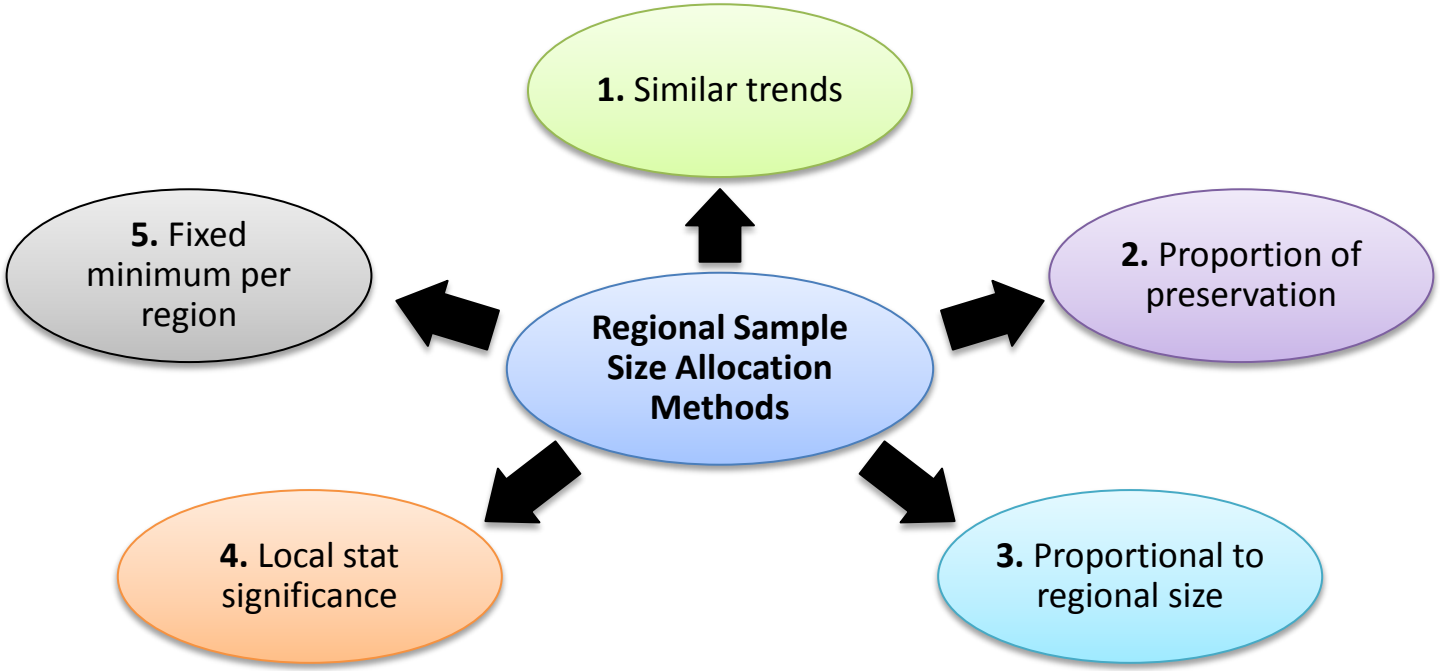
Pooled Subpopulation

- Pooling subsets of the subjects across geographical regions and regulatory jurisdictions, who share one or more key intrinsic or extrinsic factors
- Ex: Chinese/Japanese living in China/Japan and ROW; Biomarker+ patients across regions

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 regions, is of primary importance
- The sample size allocation to regions should be determined such that clinically meaningful differences in treatment effects among regions can be **described** without substantially increasing the sample size on the primary hypothesis

Key Statistical Considerations: Overall Sample Size and Its Allocation to Region



- In general, evaluation of regional consistency - not hypothesis testing; rather a **descriptive or qualitative** framework
- A balanced approach is needed to ensure feasibility and to describe the treatment effect in its regional context
- It should take into consideration region size and patterns of disease prevalence, as well as other logistical considerations

Key Statistical Considerations: Subgroup Analyses and Regional Evaluation

- **Evaluation of Subgroups Defined by Intrinsic/Extrinsic Factors**
  - Well-reasoned and prospective planning of the analysis of the impact of intrinsic and extrinsic factors can potentially minimise the need for data-driven investigations of subgroup findings and can establish a good foundation for evaluating the regional consistency
  - Furthermore, pre-specified key subgroup analyses for relevant study subpopulations that are defined beyond geographical boundaries and based on common intrinsic and/or extrinsic factors may be useful for generating key scientific evidence to support regional marketing authorisation

Key Statistical Considerations: Subgroup Analyses and Regional Evaluation (cont'd)

- **Examination of Regional Consistency**
  - The statistical analysis plan should include strategy for evaluating consistency of treatment effects across regions
  - Various analytical approaches, possibly used in combination, include:

- Descriptive summaries
- Graphical displays (eg, forest plots, funnel plots)
- Model-based estimation (including covariate-adjusted analysis)
- Test of treatment by region interaction, although it is recognized such tests often have very low power

Key Statistical Considerations: Subgroup Analyses and Regional Evaluation (cont)

- **Primary analysis and estimation of regional treatment effects**
  - If randomization is stratified by region, the primary efficacy analysis should adjust for regions using appropriate statistical methods
  - If sample sizes in one or more regions are too small, methods borrowing information from other regions should be considered
  - The estimations of treatment effects should be planned to enable the qualitative/quantitative benefit-risk evaluation in subgroups and regions

Questions and Comments: What's the scope of the E17 guidance?

- MRCTs for registration purpose and for post-marketing commitment
- It does cover exploratory MRCTs
- It includes vaccine products
- It does not cover requirements for observational trials (may be covered in a future renovation of the ICH E6)

Questions and Comments: How to ensure discussion across agencies?

- The WG had a lot of discussion on this.
- The WG acknowledged the cross-agency communication could facilitate the planning of the MRCTs; but the mechanism of cross-agency communication is out of scope
- Might consider a statement acknowledging the advantage of joint regulatory/sponsor discussion
- Might include as an example, in a Q&A format, the EMA-FDA Parallel Scientific Advice Process http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500014868.pdf

Questions and Comments: Will the guidance require longer time to setup/execute

- The guidance promotes a holistic and systematic planning and execution at program level
- For a single MRCT, it may require longer time to plan and setup the trial, but it should result in high quality design/execution, high quality global filing package and regulatory review/approval, and the ability to examine regional differences
- A good example is the recent FDA draft guidance on "Collection of Race & Ethnicity Data in Clinical Trials". It may take longer time to setup the trial the first time, it will allow collection of data to answer key questions on ethnicity *www.fda.gov/RegulatoryInformation/Guidances/UCM126396* .

Questions and Comments: Definition of Region(s) and Pooled

Two different definitions for different purposes:

- Regulatory region (for regulatory jurisdiction):
  - A region for which a common set of regulatory requirements applies for drug approval (e.g., European Union, Japan).
- Pooled regions (for design and analysis):
  - To increase sample size for evaluation of regional consistency, geographical regions, countries or regulatory regions can be pooled
  - Must be reasonable to pool based on intrinsic and/or extrinsic factors (e.g., practice of medicine) for purpose of regulatory decision-making

Questions and Comments: What's the value of pooled subpopulation vs. subgroup?

- Pooled subpopulations are introduced to emphasize the consideration of key intrinsic/extrinsic factors during the design/planning; these are not just any subgroup analyses
  - Help prioritize the intrinsic/extrinsic factors of interest
  - Help plan for collection of sufficient information to answer the questions of interest on key factors
  - Promote the consideration of sample size allocation going beyond the typical regional distribution
  - Facilitate early scientific discussion and agreement with regulatory agencies
  - Note: Subpopulation can be defined by variety of factors, eg, race, ethnicity, and molecular/genotypic categorization (more in the future)

Pooled Subpopulation and Pooled Region

Concept	Example Scenario	Example Regulatory Context	Pooling Strategy at the Design Stage	Comments on Regulatory Filings
Pooled Subpopulation (Ethnic Factor)	A drug that may be sensitive to ethnicity, but not extrinsic factors	**Region 1** is largely populated by the ethnic group B. **Region 2** also has ethnic group B. **Region 1** has minimum sample size requirement	Sample size requirement for **Region 1** can be met by enrolling subjects in **Region 1** and **Region 2**	Use pooled subpopulation to provide key supportive evidence for registration in **Region 1**. eg: - Caucasian in EU& US - Japanese in Japan & US - Chinese in China & EU
Pooled Subpopulation (Genomic Factor)	A drug that may be sensitive to biomarker status	MRCT with strong interest in BM+ and General interest for BM+/BM- combined	Stratify by region but have a sample size requirement for BM+	Use pooled subpopulation to plan sufficient evidence for BM+ and overall population
Pooled Region	A drug that may be sensitive to a few environmental factors and a few intrinsic factors	**Region 1a**, **Region 1b**, **Region 1c**, under jurisdiction of different regulatory authorities, shared similarity in these environmental factors as well as these intrinsic factors	Define **Region 1** by pooling **Regions 1a**, **1b**, and **1c**. Sample size allocation strategy can be based on the pooled region	Use the pooled region to provide key supportive evidence for registration in **Regions 1a**, **1b**, and **1c**. eg: • European Union • North America • Asia tripartite

Question and Comment: Regional Consistency – Definition and Application

- Evaluation of regional consistency - not hypothesis testing; rather a descriptive or qualitative framework
- The goal is **NOT** to confirm its consistency across region, but
  - To evaluate the regional difference
  - To describe/explain them by intrinsic/extrinsic factors
- Interpretation of variability – in light of biological plausibility, consistency with findings from other trials, strength of evidence, statistical uncertainty
- For a given trial, a working definition of consistency (see the 5 approaches) can be used to justify the amount of information to be allocated at the regional (or pooled-region) level

Questions and Comments: How to balance the overall sample size and local regulatory requirement?

- The inherent heterogeneity of a MRCT compared to a single-region trial will usually result in a relatively larger sample size requirement for 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.

Questions and Comments: How to balance the overall sample size and regional requirement? (cont)

- ICH E17 gives an overview of several approaches, ranging from equal allocation in each region to allocation proportional to disease risk or prevalence
  - Pros and cons of each approach provided
- Discourage allocation based on the need to demonstrate significant effects within each region
- Recommendation is to balance statistical efficiency with feasibility of enrollment, while ensuring trial objectives can be met
  - Pooled subpopulation and pooled region are tools to help achieve these.

Questions and Comments: Do we need special monitoring by region

- Consistent with proposed revision of ICH E6, a quality by design approach is encouraged
- Identify critical quality factors during planning
  - Appropriate application of inclusion/exclusion criteria, adherence to assigned treatment, etc.
- Implement procedures to address those factors across all regions during trial conduct
  - Procedures to minimize attrition; collect follow-up data after treatment discontinuation, if called for, etc.
- Data monitoring to identify quality issues during trial
  - In time to remedy problems

Concluding Remarks

- ICH E17 is built on top of the key concepts of the ICH E5, and they should be used in combination
- ICH E17 promotes the use of MRCTs for global drug development
- ICH E17 is principle driven - it introduces important concepts for sample size calculation and allocation
- Public Comments received to date ask for more clarity on key concepts; revisions should result in a better guidance

References

- *Mohamed Alosh, Kathleen Fritsch, Mohammad Huque, Kooros Mahjoob, Gene Pennello, Mark Rothmann, Estelle Russek-Cohen, Fraser Smith, Stephen Wilson & Lilly Yue (2015) Statistical Considerations on Subgroup Analysis in Clinical Trials, Statistics in Biopharmaceutical Research, 7:4, 286-303, DOI: 10.1080/19466315.2015.1077726*
- *ICH E5. Ethnic Factors in the Acceptability of Foreign Clinical Data (R1). 1998. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E5_R1/Step4/E5_R1__Guideline.pdf (accessed July 14, 2017).*
- *ICH E5. Implementation Working Group Questions & Answers. 2006. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E5_R1/Q_As/E5_Q_As__R5_.pdf (accessed July 14, 2017)*
- *ICH E17 Final Concept Paper 2014. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E17/E17_Final_Concept_Paper_July_2014.pdf (accessed July 14, 2017)*
- *ICH E17 : General Principles for Planning and Design of Multi-Regional Clinical Trials June 2016 Step 2 draft available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E17/E17_Step2.pdf (accessed July 14, 2017)*

References (2)

- Ministry of Health, Labour and Welfare of Japan. *Basic Principles on Global Clinical Trials*. 2007. Available at http://www.pmda.go.jp/files/000153265.pdf (accessed July 14, 2017).
- EMA draft guidance: "Guideline on the investigation of subgroups in confirmatory clinical trials" http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500160523.pdf (accessed July 14, 2017)
- Wedel H, DeMets D, Deedwania P et al. Challenges of subgroup analyses in multinational clinical trials: Experiences from the MERIT-HF trial. *Am Heart J* 2001;142:502–511. syndromes. *Eur Heart J* 2000;21:371–381
- Wallentin L, Becker RC, Budaj A et al., for the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–105
- Akkerhuis KM, Deckers JW, Boersma E et al., for the PURSUIT Investigators. Geographic variability in outcomes within an international trial of glycoprotein IIb/IIIa inhibition in patients with acute
- Pfeffer MA, Claggett B, Assmann SF et al. (2015). Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 131: 34–42