Joint Efforts for Innovative Drug Development in China

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Source:

ICH E17 Training Modules

RDPAC ICH E17 Blue Paper RDPAC Training-20240612

CDE 2023 Annual Reviw Report

RDPAC report on drug registration timeline survey 2024

Acknowledgement

RDPAC Stats Core Team

RDPAC

RDPAC ICH E17 MRCT Blue Book Project Team

DIA China biostatistics community

Yan Hou (Peking University)

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Cheery Chen (Novartis)

RDPAC: the R&D-Based Pharmaceutical Association Committee, representing 46 leading multinational pharmaceutical companies with R&D capabilities, is a committee under the China Association of Enterprises with Foreign Investment (CAEFI).

Outline

- **Background – China Regulatory Environment and ICH Journey**
- **Joint Efforts in Development and Implementation of ICH Guidelines**
  - ICH E17 MRCT Blue Book Project
  - ICH E9R1 Implementation in China
- **Summary**

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China Regulatory Reform

Encourage Innovative Drug Development and Access to Patients

Reform of the Review and Approval System (State Council) Aug 2015

NMPA joined ICH Jun 2017

Drug Administration Law Dec 2019

Drug Registration Regulation Jul 2020

Regulations for the Implementation of the Drug Administration Law [DRAFT], May 2022

2015 2016 2017 2018 2019 2020 2021 2022 2023

- Review and approval quality
- Application backlog
- Generic drug quality
- Research innovation
- Review and approval transparency

Re-define New drug registration category

Consultation pathway

Expedited program

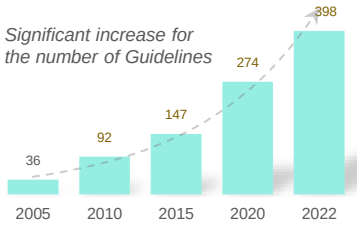
Technical guidance

CTA variation categories

Electronic submission

CTA approval in 60 Working days

NDA review report



China ICH Journey

- **Implement ICH guidelines and integrate China into global framework**
- **Accelerate CTA approval, clinical trial notification "approval" in 60 working days**
- **Enhance HA consultation (type I, II, III meeting)**
- **Shorten review timeline after introducing 4 expedited regulatory pathways**:
  1) conditional approval, 2) breakthrough therapy designation (BTD), 3) priority review, 4) special approval

As of 2023, China has implemented 100% ICH Guidelines.

Jun 2017, CFDA joined ICH

Jan 2018, NMPA released an announcement on the implementation of Tier-II guidelines

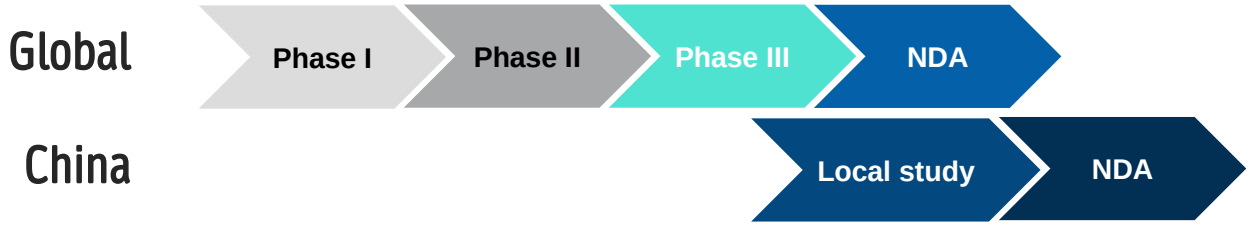
Jun 2018, NMPA became a member of ICH Management Committee

Jun 2021, NMPA was re-elected as a member of ICH Management Committee

Jun 2024, NMPA was elected as a member of ICH Management Committee for the 3rd time

China Regulatory Reform Enables Simultaneous Development

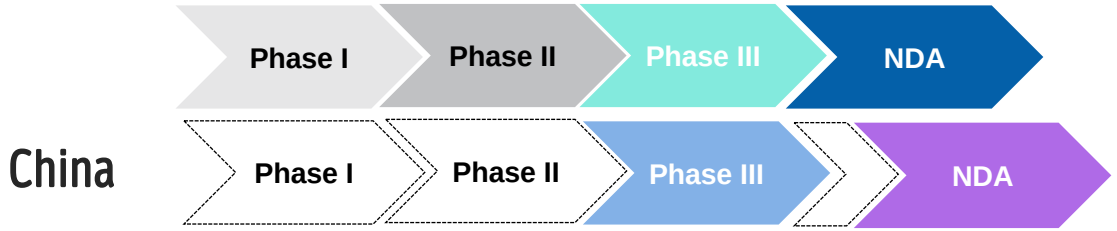
Prior to the regulatory reform, China stand-along study or bridging study is the main strategy



Local study includes stand-alone study, bridging study or MRCT extension

- Drug should at least be in Phase II trial stage before MRCT can be conducted in China
- Over 12 months CTA approval timeline
- Imported drug needs to be approved in another country before file NDA in China

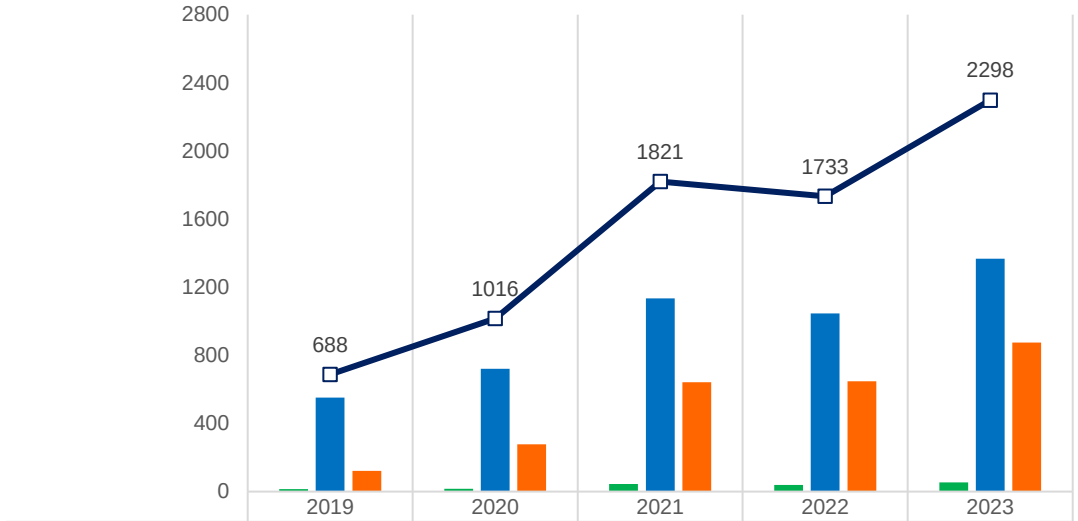
Since regulatory reform, MRCT becomes the preferred strategy and enables simultaneous registration



- Possible to join early phase development
- Adopt ICH guidelines
- CTA approval in 60 working days
- HA consultation (type I, II, III meeting)
- Expedited program

Rapid Increase in CTA and NDA Applications in China

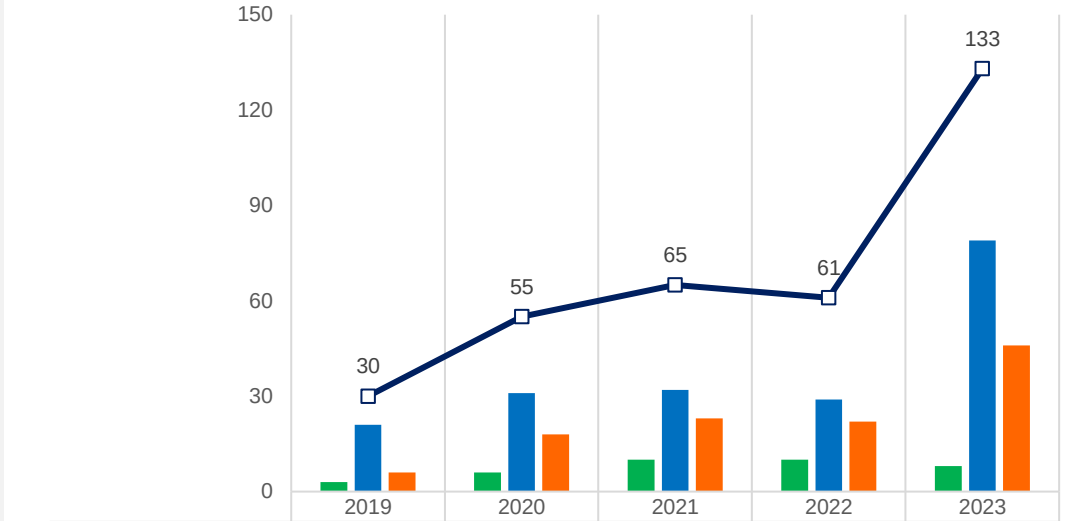
Quantity of IND-s acceptance of innovative drugs from 2019 to 2023



	2019	2020	2021	2022	2023
Chinese medicine	15	17	44	39	54
Chemical drug	552	721	1134	1046	1368
Biological drug	121	278	643	648	876
Innovative drug	688	1016	1821	1733	2298

IND acceptance of innovative drugs increased by 32.60%

Quantity of NDA-s acceptance of innovative drugs from 2019 to 2023



	2019	2020	2021	2022	2023
Chinese medicine	3	6	10	10	8
Chemical drug	21	31	32	29	79
Biological drug	6	18	23	22	46
Innovative drug	30	55	65	61	133

NDA acceptance of innovative drugs increased by 118.03%

Source: 2023 CDE annual review report

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Joint Efforts in Development and Implementation of ICH Guidelines in China

Development of ICH Guidelines

- Joining ICH WGs as EWG experts representing China Industry;
- Organizing workshops to collect inputs from industry and academia.

Implementation of ICH Guidelines in China

- Organizing the trainings for China drug development community cross industry, academia and HA;
  - **ICH E9R1 Estimand Training in 2022**
- Leading Blue Book Projects for selected ICH guidelines
  - **ICH E17 MRCT Blue Book Project**
  - **ICH E9R1 Blue Book**
- Organizing workshops to sharing experience and practice.

ICH E17 MRCT Blue Book Project (I)

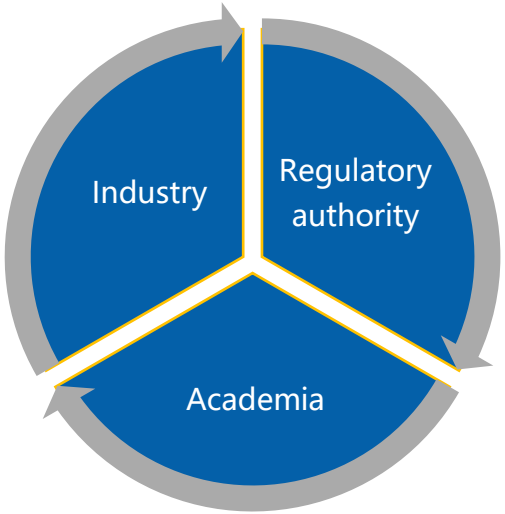
ICH E17: General Principles for Planning and Design of Multi-Regional Clinical Trials

Objectives:

- **Enhance the understanding of ICH E17**
- **Advance the implementation of ICH E17**
  - Status quo of research on ICH E17 in China and highlight China's specific conditions and requirements.
  - Analyze main challenges in implementing ICH E17 in China
  - Examine the strategies and methods to overcome challenges
- **Achieve consensus among regulatory authorities(HA), academia, and industry (RDPAC)**

ICH E17 Blue Book Project (II)

Tripartite Cooperation among HA, Academia and Industry (RDPAC)



Identification of research focus 2022-2023

Initiation Jan 2023

Literature search and review 1Q 2023

Tripartite close-door session May 2023

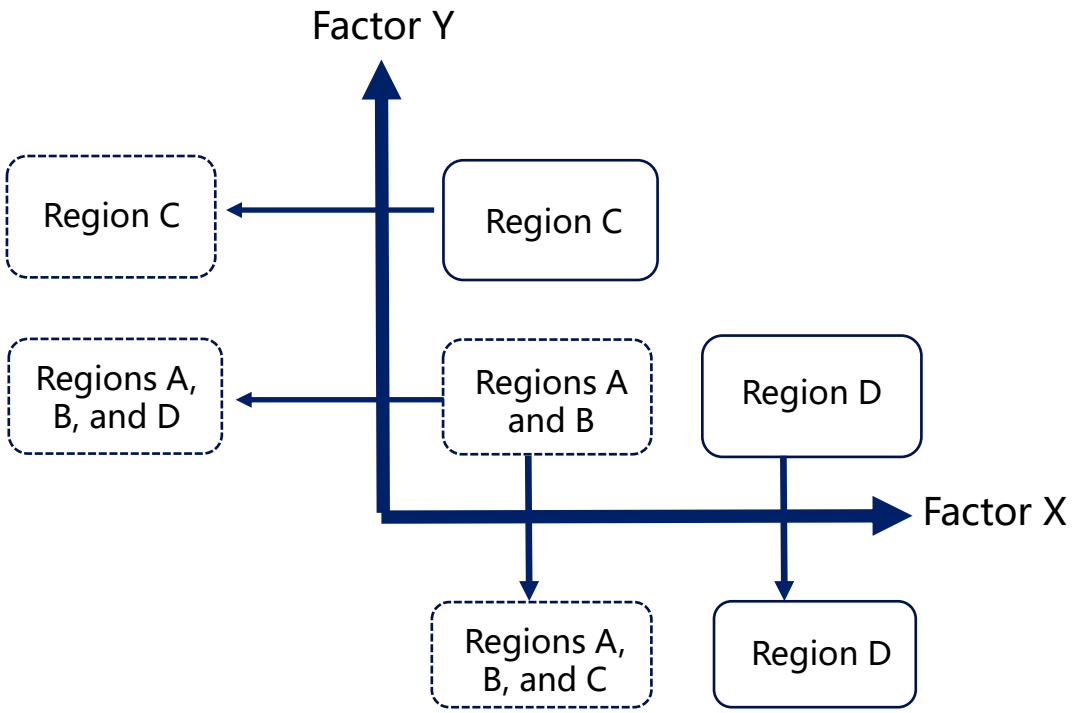
Draft for Comments 2Q 2023

Tripartite close-door session Aug 2023

Draft for Comments (Draft) 3Q 2023

Finalization 4Q 2023

Pooling Strategy - How to Pool Regions and Subpopulations Based on Relevant Factors



Obtain data from epidemiological and early clinical studies to identify true effect modifiers and appropriate pooling strategies

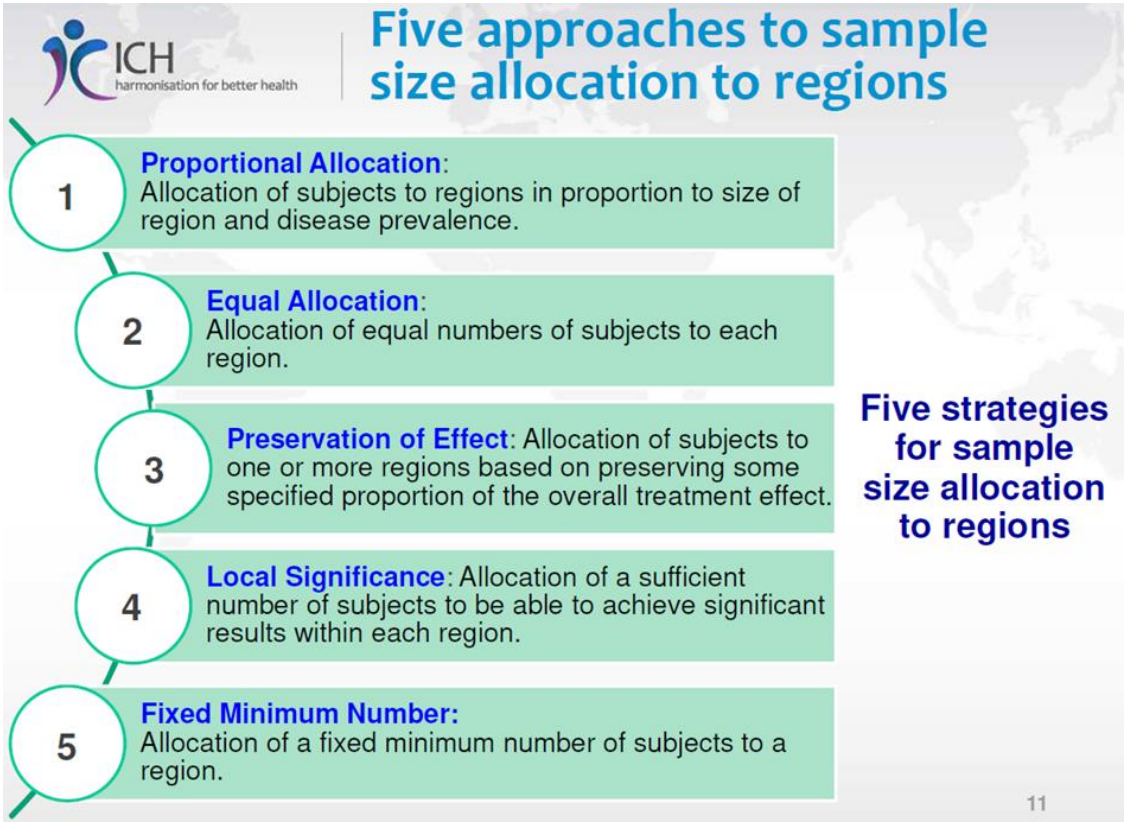
Based on the distribution of the intrinsic and extrinsic factors known to affect the treatment response, and the disease under investigation and similarity of those factors across regions

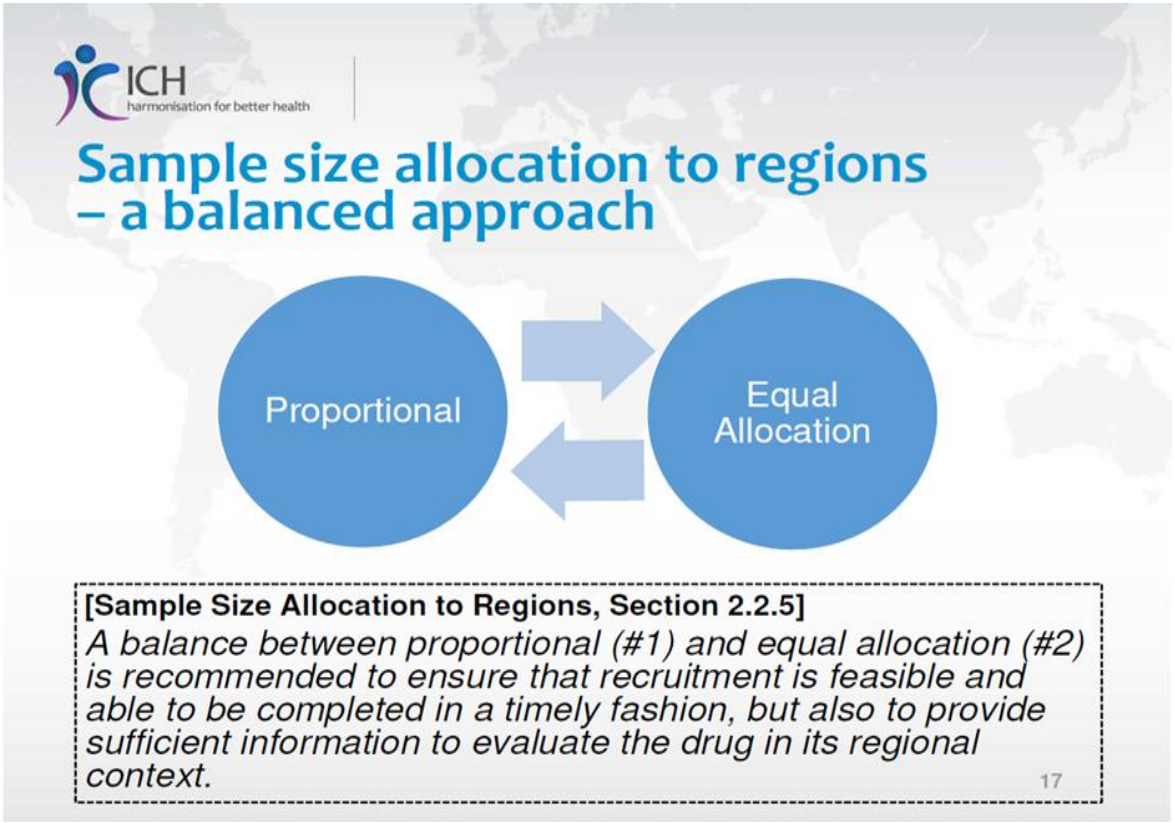
Map out the pooling strategy early, continuously collect and analyze relevant contributing factors, and assess and adjust the pooling strategy as needed. Pre-define the pooling strategy.

- **Pre-specified pooling of regions or subpopulations, based on established knowledge about similarities, may help facilitate the assessment of consistency in treatment effects across regions, and support regulatory decision-making**
- **Where available information is not yet complete, common region pooling strategies such as pooling East Asian, Asian and North American populations may be considered, and information on potential key factors can be collected on an ongoing basis during the global development process to aid in subsequent consistency evaluation**

Source: ICH E17 Training Modules; RDPARC ICH E17 Blue Paper Project RDPAC Training-20240612

Sample Size Allocation to Regions

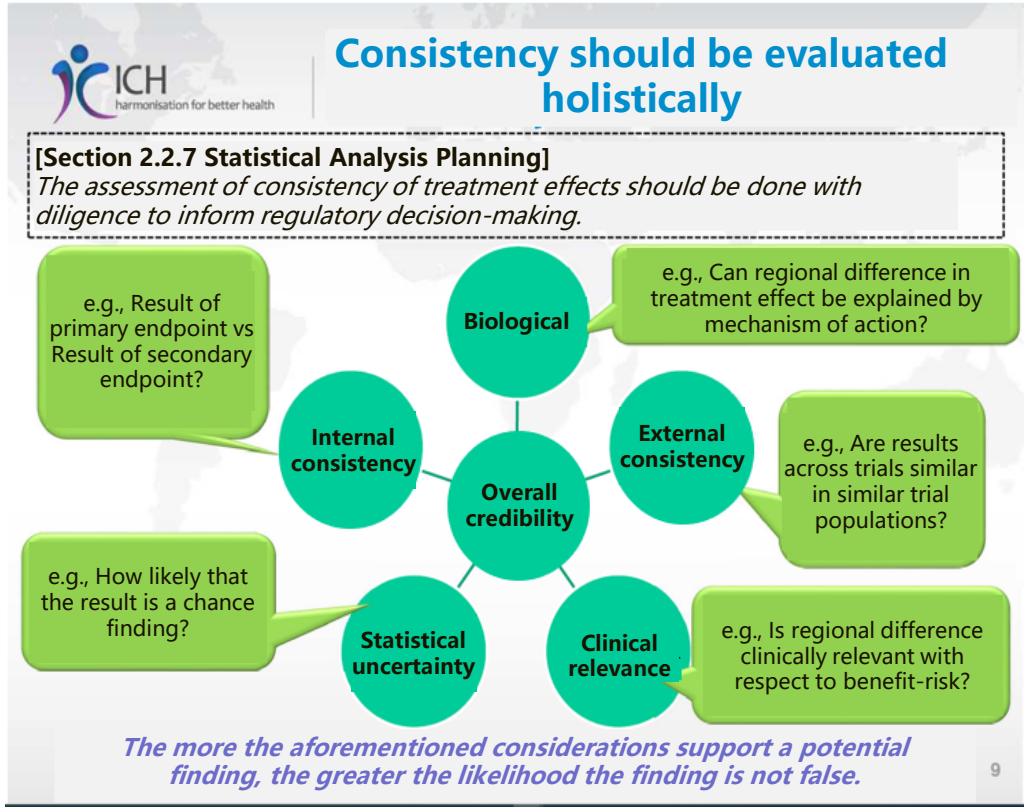


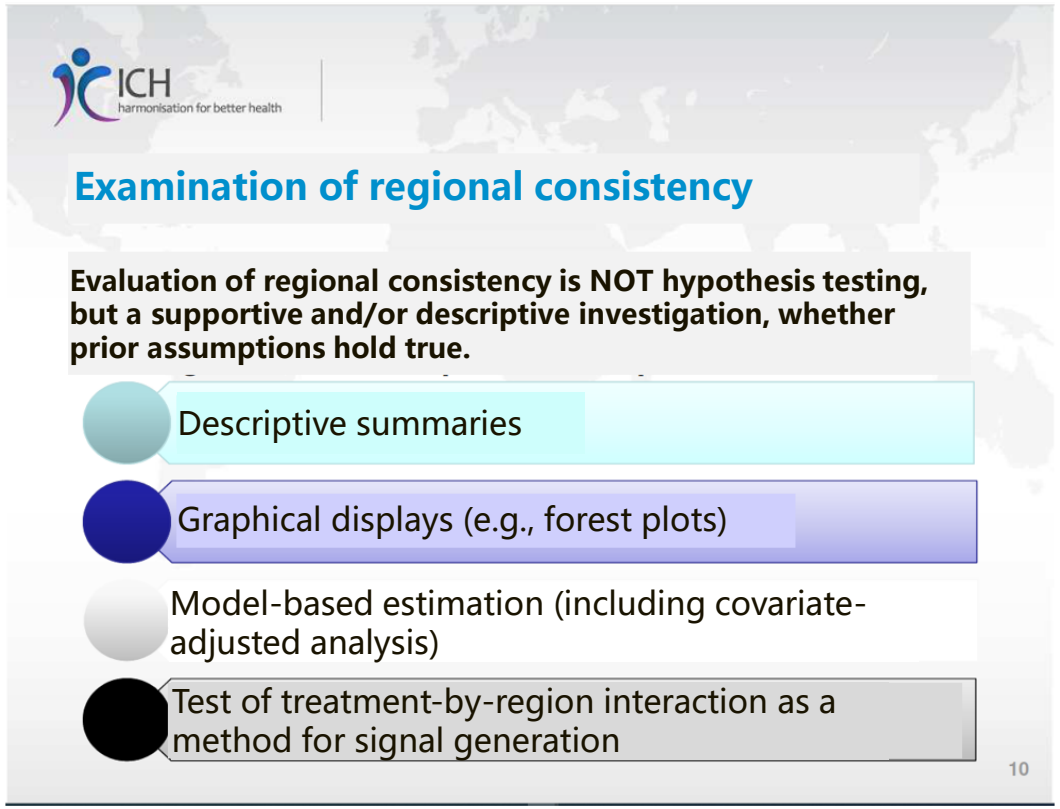


Pre-specified **pooling of regions or subpopulations**, based on established knowledge about similarities, may help provide flexibility in sample size allocation to regions, facilitate the assessment of consistency in treatment effects/safety/benefits and risks across regions, and support regulatory decision-making.

Source: ICH E17 Training Modules; RDPARC ICH E17 Blue Paper Project RDPAC Training-20240612

Assessment of Consistency in Treatment Effects across Regions in Benefit-risk Evaluation

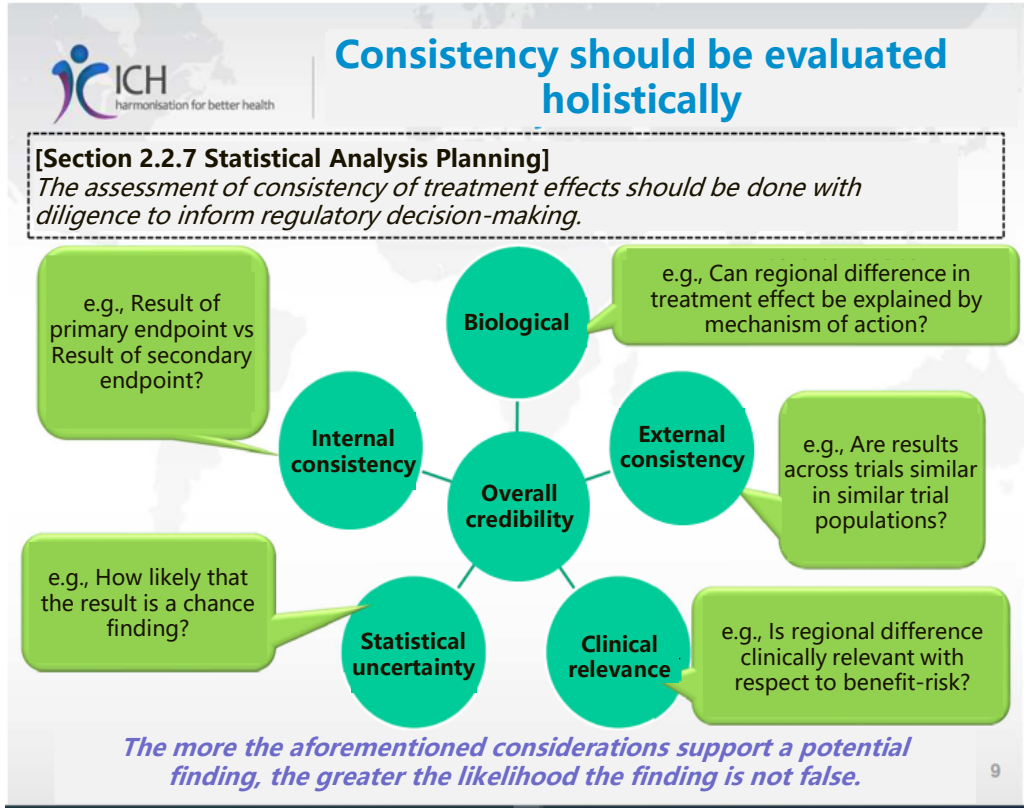




Consistency evaluation and analysis are supplementary rather than validation

Source: ICH E17 Training Modules; RDPARC ICH E17 Blue Paper Project RDPAC Training-20240612

Structured Consideration upon Identification of Benefit/Risk Inconsistency across Regions



- Clinical relevance
- Disease and treatment: Definition, diagnosis, treatment, guidelines, practice
- Clinical pharmacology: Dose, dose-exposure-response relationship
- Biological plausibility: Clinical, pharmacological, and mechanistic considerations
- Enrollment and sample size
- Balance of baseline parameters
- Exposure follow-up and distribution
- Internal consistency: Different endpoints, analyses, subgroups
- External consistency: Different trial conditions and data sources
- Statistical uncertainty: Pooling strategies, information borrowing
- Safety analysis and benefit-risk evaluation

If, through structured exploration, no sufficient reason is found to explain the inconsistency exhibited by the trial subgroup data, a comprehensive benefit-risk evaluation should be conducted based on totality of evidence

Source: ICH E17 Training Modules; RDPARC ICH E17 Blue Paper Project RDPAC Training-20240612

Special Considerations

- Non-inferiority
- Multiple primary endpoints
- Interim analysis
- Adaptive design
- Delayed treatment effect
- Single-arm study
- Rare disease
- Statistical analysis model
- Extension strategy

Source: ICH E17 Training Modules; RDPARC ICH E17 Blue Paper Project RDPAC Training-20240612

Joint Efforts on ICH E9(R1) Implementation in China

Purpose: To help the biopharmaceutical community in China better understanding the Estimand framework and support the implementation of ICH E9(R1) in China

Estimand Training in the 4th. Regulatory Biostats Submit Forum (Jan. 2022)

Estimand Blue Books (Oct. 2021 and Sept. 2022)

Estimand Training in 2022

One of the biggest statistical training in China which attracted 2000+ participants.

Speakers: 11 Experts from CDE (2 speakers), Academia (3 speakers) and Industry (5 speakers from 3 companies).

Participates:

Cross-function associates (biostats, clinical development, RA, data management, medical affairs, clinical operations ...) in biopharmaceutical industry;

Investigators from hospital and clinical centers;

Stats professors and graduate students;

Clinical and stats reviewers from CDE.

Scope:

Estimand and its value and impact, Estimand framework, Case studies from different therapeutic areas, Statistical analysis under Estimand framework.

Estimand Blue Books in China (I)

Purpose: To help the biopharmaceutical community in China better understanding the Estimand framework and support the implementation of ICH E9(R1) in China

- **Sponsor:** DIA China biostatistics community
- **Authors**: 30+ industry and academia experts on Estimand.
- **Reviewers**: global industry and academia experts from 20+ institutes, China CDE reviewers.
- **Target audience**: statisticians, clinicians and investigators from the pharmaceutical industry, clinical centers, and academia in China

Estimand Blue Books in China (II)

Estimand Blue Book v1.0 (Oct. 2021):

Support the implementation of E9(R1) in China via introducing Estimand framework, sharing detailed case studies and how to describe Estimand in the study protocol.

Estimand Blue Book V2.0 (Sept. 2022):

- Further enhance the Estimand concept
- Include regulatory guidelines with Estimand discussion to guide specific disease areas
- Introduce the impact on statistical analysis
- Discuss practical considerations in different scenarios during the implementation

Estimand Book to be Published in Springer

Book title: Estimands in Clinical Trials: A Practical Guide

- **Purpose**:
  - Further align the implementation practice in China with global.
  - Amend the Estimand Blue book by covering additional material and more recent developments. i.e. Regulatory guidelines and their relationship to the Estimand framework.
  - Engage global experts from industry, regulatory and academia and enhance the collaborations between China and global.
- **Authors**: 70+ experts from industry, regulatory, and academia.
- **Reviewers**: 40+ from industry, regulatory, and academia experts from 20+ institutes, finished two peer reviews for all 23 chapters.
- **Target audience**: statisticians, clinicians and investigators from the pharmaceutical industry, clinical centers, and academia in global.

Summary

- **China regulatory reform and ICH journey** facilitate simultaneous drug development and submission, promoting innovative drug development in China.
- **Cooperation among industry, health authorities, and academia** is essential for developing and implementing ICH guidelines, driving innovation in innovate drug development in China.

Thank you