Latest trend of clinical trial requirements (Japan)

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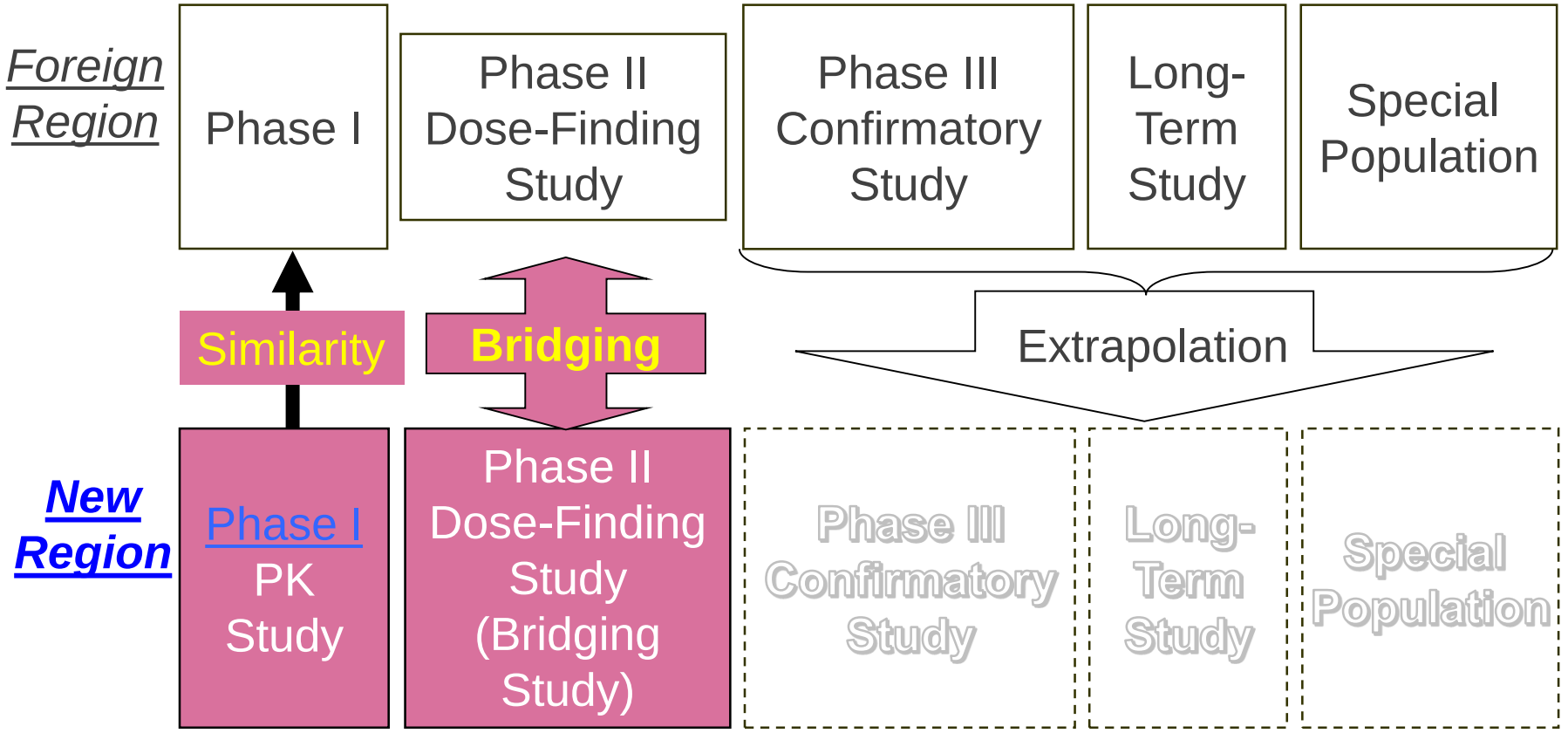
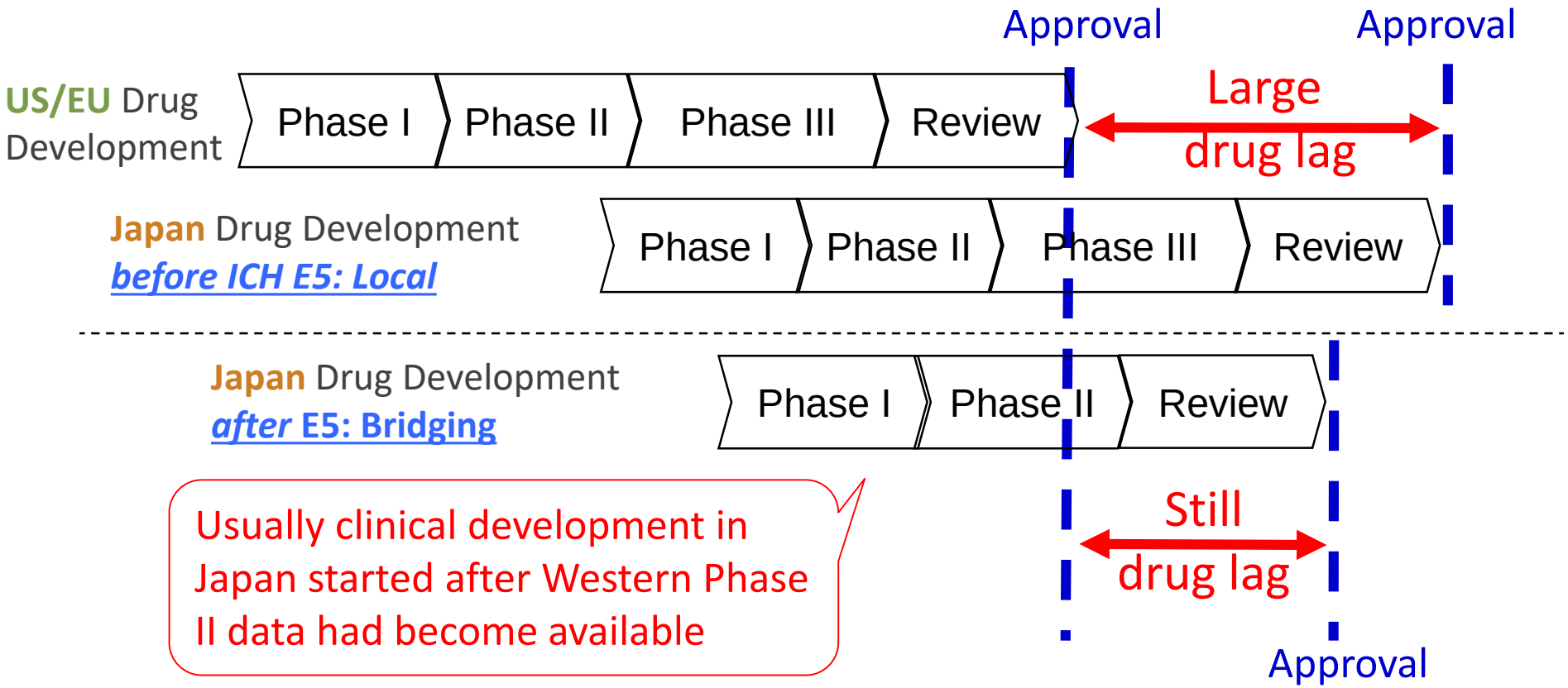
History of Drug Evaluation using Foreign Clinical Data in Japan

		Drug development in Japan
Early 1990s	• No guideline for using foreign clinical data	Local (only Japanese) clinical trials
1998	• ICH E5: Ethnic Factors in the Acceptability of Foreign Clinical Data	Bridging strategies
2006~ 2007	• E5 Implementation Working Group Questions & Answers (R1) • Basic Principles on Global Clinical Trials	A multi-regional trial for the purpose of bridging could be conducted in the context of a global development program
2018	• ICH E17: General Principles for Planning and Design of Multi-Regional Clinical Trials • ICH E17: Training Materials	**Japanese original guidelines on MRCTs**

Typical clinical data based on ICH E5

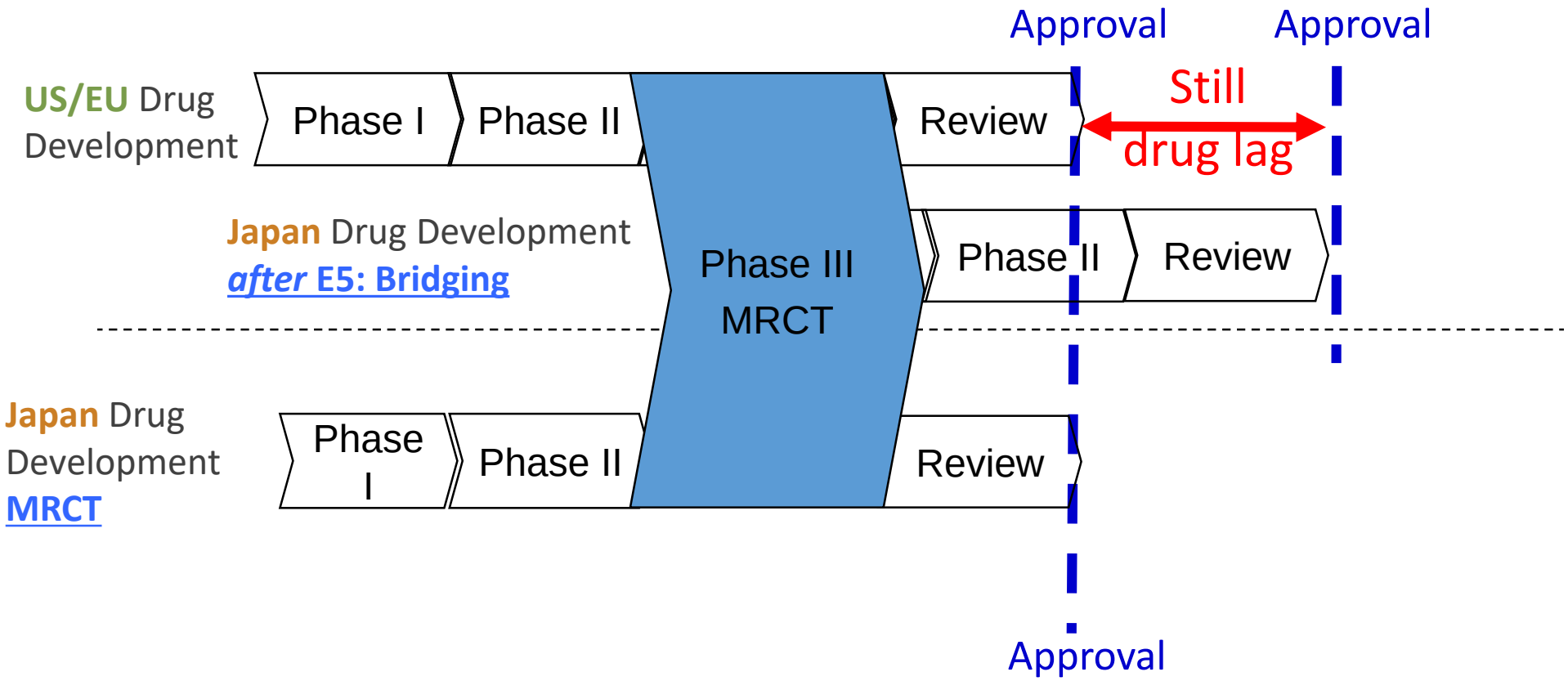


“ICH E5 Bridging” and “Drug Lag”



The “sequential” bridging could shorten the clinical development period but had only limited effects in resolving the “Drug Lag”

“ICH 17 MRCTs” and “Drug Lag”



It becomes easier to conduct large-scale trials by utilizing MRCTs.
Recently, patients can access new drugs earlier than in the past around the world.

Review in Later 2000s-

Series of Japanese guidelines on MRCTs

2007 Guideline

September 28, 2007
Notification No.0928010

Attention to:
Commissioner of Prefectural Health Supervising Department

- Planning of a MRCT
- Mainly based on our experience in clinical trial consultation meetings

Up to the present according to "Ethnic Factors in the Acceptability of Forei
based on ICH-E5 guideline (Notification No. 762, Director of Evaluation and Lic
Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated A
utilizing foreign clinical trial data in a new drug application what is called "Bri
accepted in Japan, and post-marketing data in USA and EU have been taken into c
review for regulatory approval where necessary.

Japanese : http://www.pmda.go.jp/files/000157000.pdf
English : http://www.pmda.go.jp/files/000157900.pdf

2012 Guideline

Basic Principles on Global Clinical Trials (Reference Cases)

September 5, 2012
Pharmaceuticals and Medical Devices Agency

- East Asian development
- Evaluation of MRCT results
- Based on our experience in clinical trial consultation meetings and new drug review

(1) What are the special points to consider when conducting a global clinical trial in East Asia?	The types and frequency of metabolic enzyme polymorphisms and gene profiles are thou Asian ethnicities in Japan, China and Korea. Some drugs have recently been approved ma pivotal global clinical trials conducted in East Asia. Data from well-designed and conducted Asia is acceptable for documents of new drug application in Japan. However, the difference in ethnic factors (intrinsic factors as well as extrinsic factors such socioeconomic condition) may affect the efficacy and safety of drugs (effects not only on the

Japanese : http://www.pmda.go.jp/files/000157901.pdf

2014 Guideline

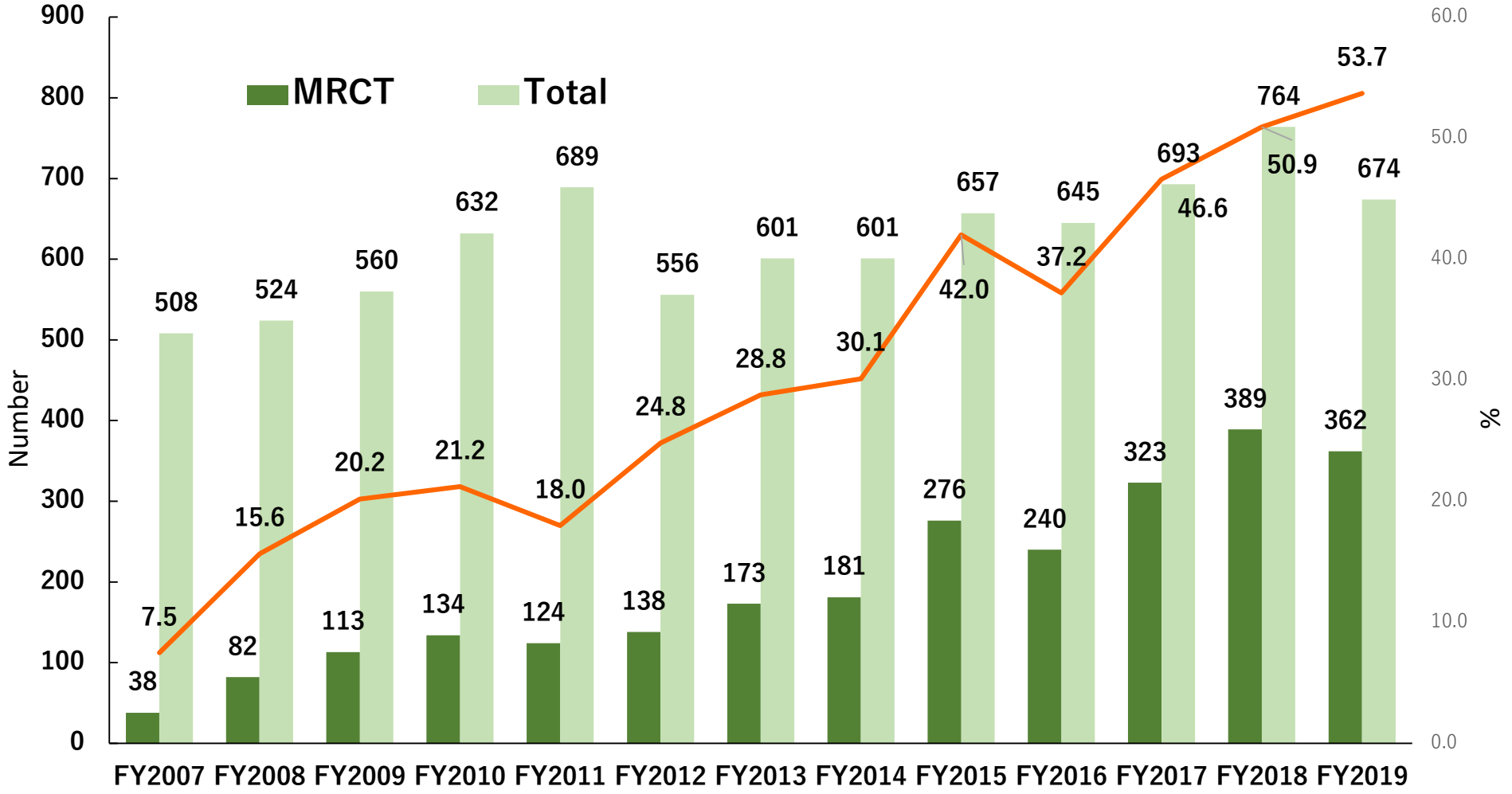
Administrative Notice
October 27, 2014

- Necessity of Phase I trials in the Japanese population prior to global clinical trials

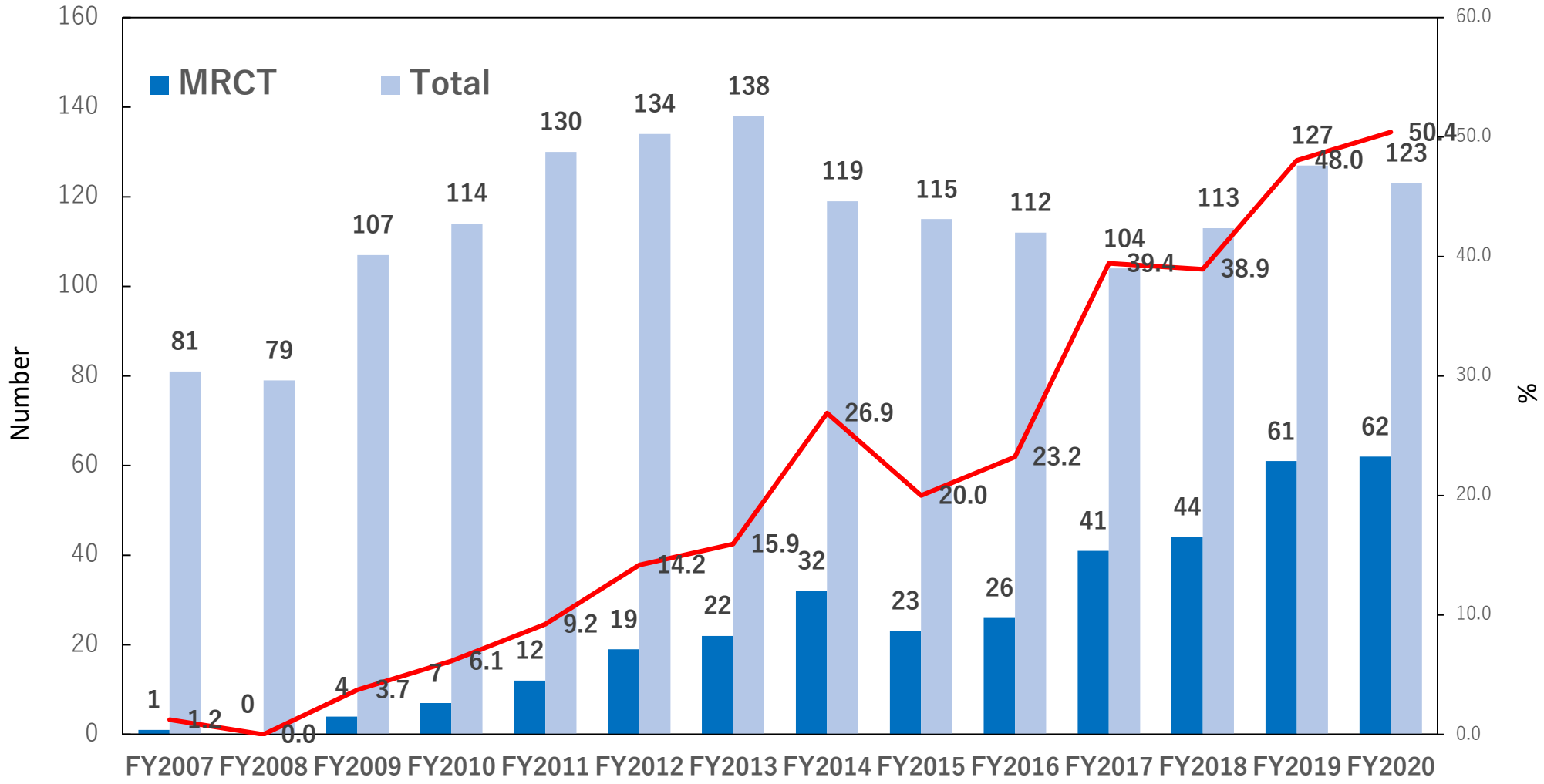
and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007) and the "Basic Principles on Global Clinical Trials (Reference Cases)" (Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 5, 2012) have been issued from the perspective of promoting Japan's active participation in global clinical trials.

Japanese: http://www.pmda.go.jp/files/000157480.pdf
English: http://www.pmda.go.jp/files/000157777.pdf

Trends of MRCT-related Clinical Trial Notifications in Japan



Trends of MRCT-based New Drug Approvals in Japan



Overview of ICH E17

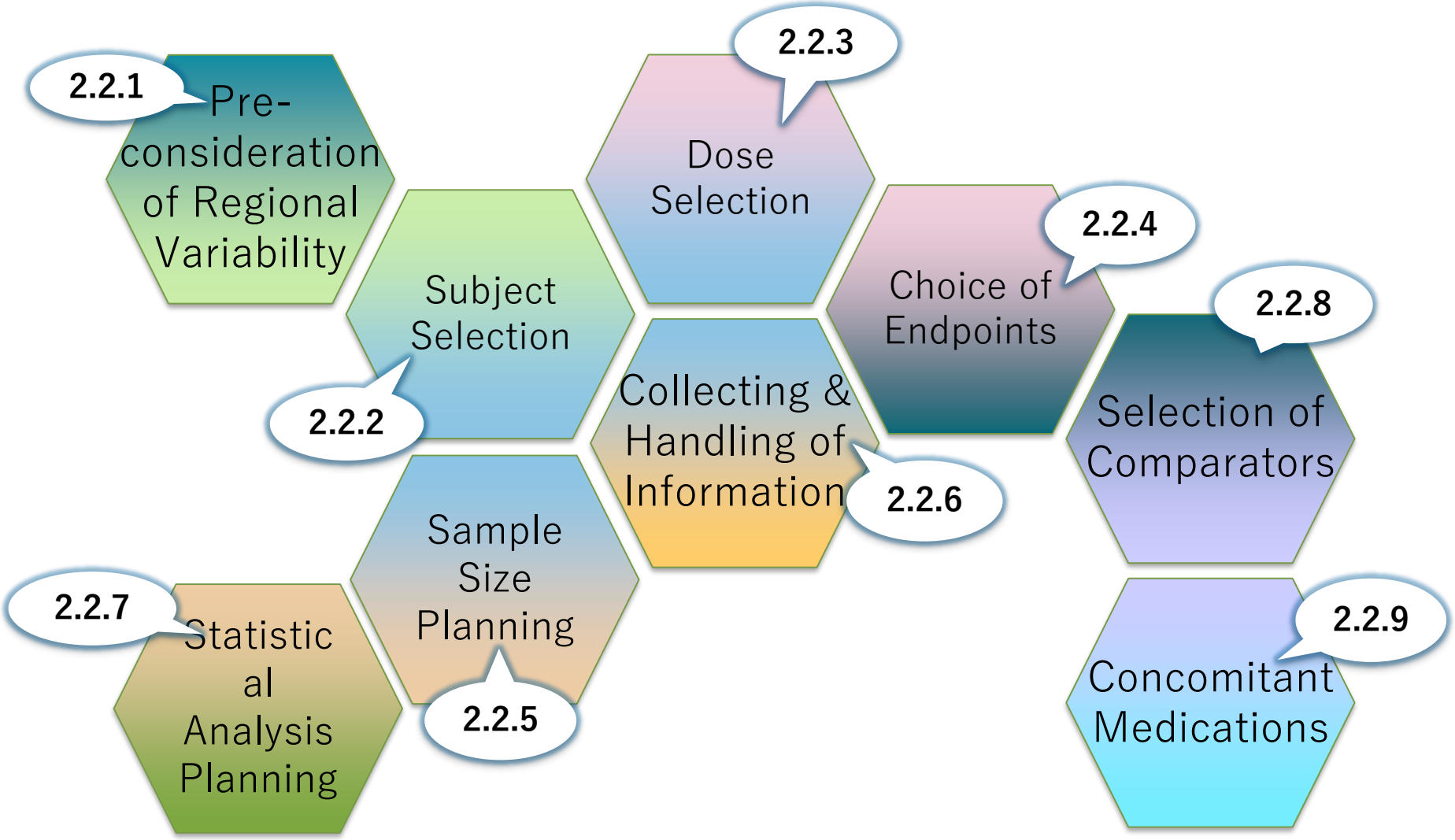
【Objective】

With the increasing globalisation of drug development, it has become important that data from multi-regional clinical trials (MRCTs) can be accepted by regulatory authorities across regions and countries as the primary source of evidence, to support marketing approval of drugs (medicinal products). The purpose of this guideline is to describe general principles for the planning and design of MRCTs with the aim of increasing the acceptability of MRCTs in global regulatory submissions.

【Scope】

- ICHE17 is focusing on "Planning and Design" of MRCTs
- Analyses and interpretation of MRCT results are out of scope
- Operational aspects are out of scope
- How to consult with the various regulatory authorities is out scope but there is reference in Section 2.1.3
- Cross reference to multiple ICH guidelines, especially to ICHE5

E17 addresses various topics



Impacts of ICH E17 guideline

- Earlier access to innovative therapies
  - Provide an innovative drug earlier to patients by synchronizing the timing of clinical drug development across different regions
- Avoid duplication
  - ➢ Reduce the need to conduct standalone regional or national studies including bridging studies.
- Promote international harmonization
  - ➢ A globally harmonized approach to drug development should be considered first.
- Provide better evidences for drug approval in each region
  - ➢ Encourage better planning and design of MRCTs based on the latest scientific knowledge and experiences
- Longitudinal build-up of capability and infrastructure for global drug development
  - ➢ Planning and conducting high quality MRCTs throughout drug development will build up trial infrastructure and capability

ICH E17 is trying to convey that…

- Points to consider for successful MRCT, rather than a single solution
- Differences among regions are nothing special. Such differences are NOT barrier against conduct of MRCTs in most cases
- Not finding differences, but identifying differences which affect treatment effect is of paramount importance
- How to manage such differences in order to conduct MRCTs or participate in MRCTs

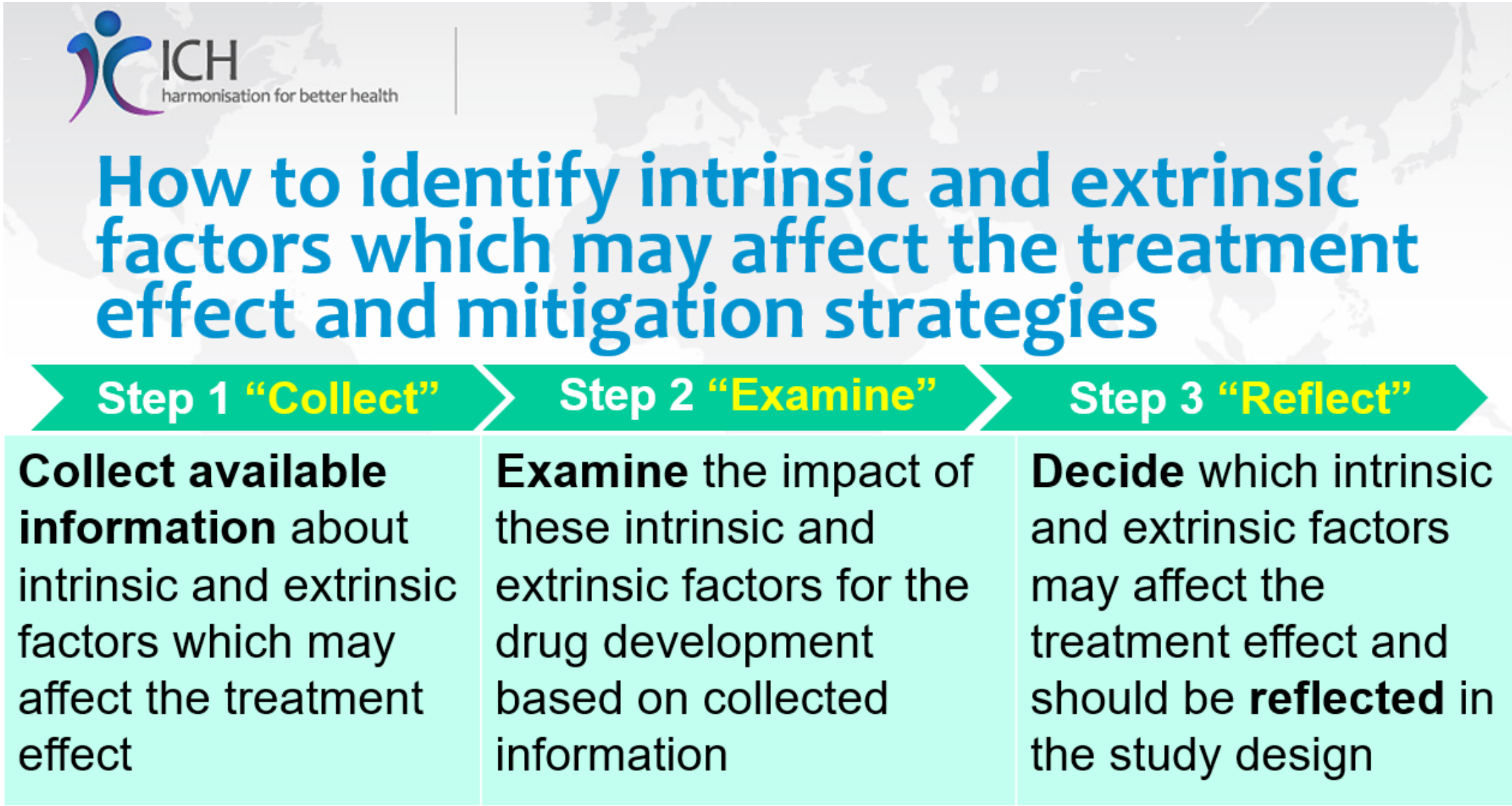
See ICH E17 training material Module 2

An extensive set of training materials has been developed **to promote the efficient and consistent implementation of the E17** in the context of an evolving drug development environment.

Why important in the design of an MRCT?

- Intrinsic and/or extrinsic factors may impact the treatment effect
- Pre-consideration and mitigation of large differences across regions can support adequate interpretability of the results of an MRCT in different regions
- Pre-consideration of regional variability should be reflected in the trial design to lead to a successful MRCT

Steps to identify ethnic factors affecting the treatment effect



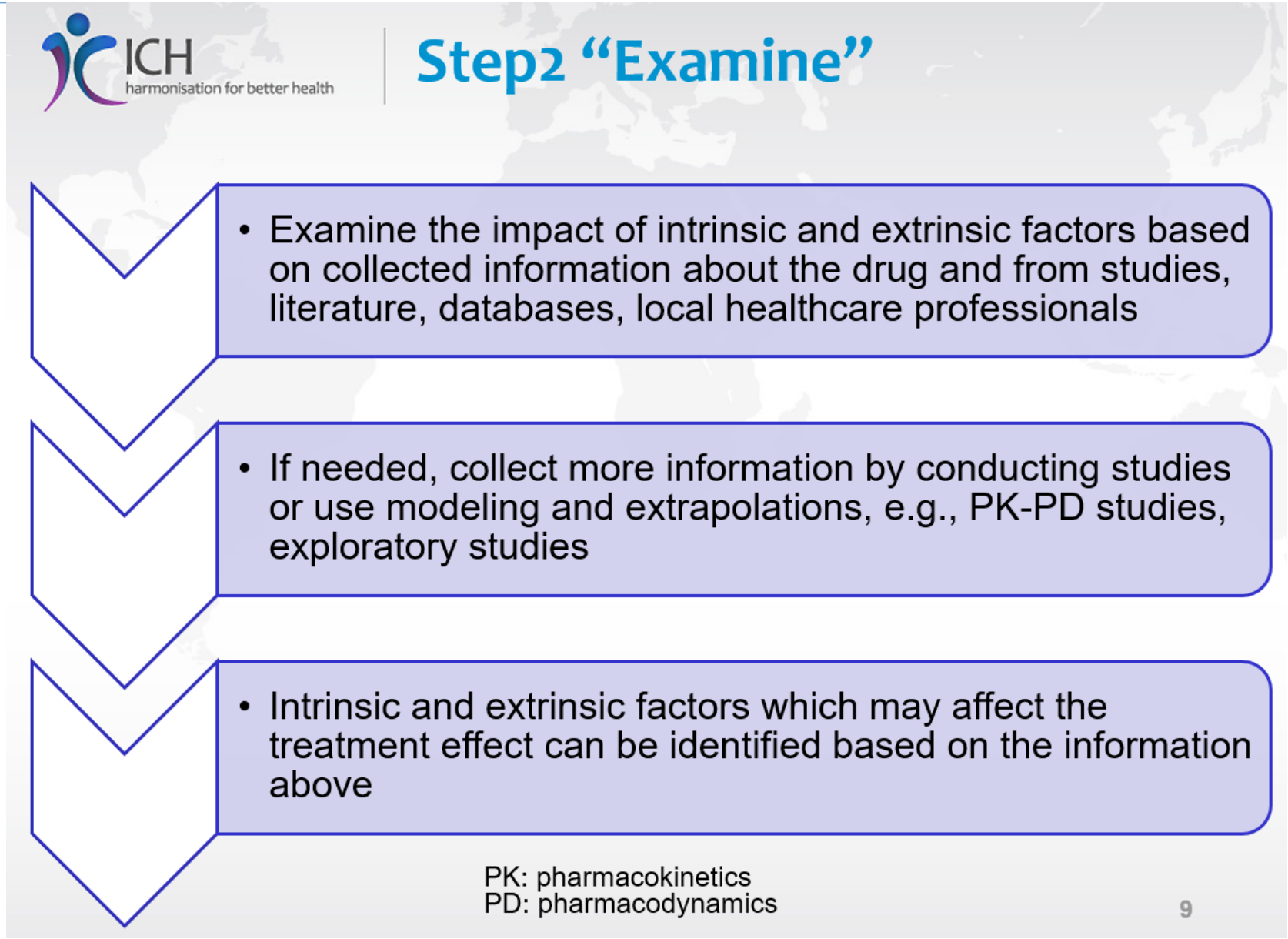
Step1 “Collect”

Step1 “Collect” information

- **Search medical and scientific literature, guidelines and other publicly available information**
  - disease information
  - genetic information
- **Search databases (e.g., WHO disease database, registries)**
  - epidemiological data
  - historical data
- **Consult local healthcare professionals**
  - clinical practice, therapeutic approach in their region

WHO: World Health Organization

Step2 “Examine”



Step3 “Reflect”

ICH harmonisation for better health

Step3 “Reflect”

Some possible mitigation and design strategies include:

- Define clear and specific inclusion and/or exclusion criteria
- Decide on stratification and/or pooling for the factors which may affect the treatment effect
- Consider study power and proper allocation of subjects to (pooled) regions and/or pooled subpopulations

➔See Module 4, 5 and 6 for further consideration

How to review/interpret MRCT data (1)
(Out of scope in the ICH E17)

In advance, confirm acceptability and validity of the hypothesis that benefit/risk in own population can be evaluated based on MRCT data

Evaluate overall treatment effects in all population enrolled in an MRCT

Evaluate consistency between regional population and overall population

In case of inconsistency, conduct more careful review and analysis to understand factors affecting drug responses (or chance finding?)

(If the drug can be approved)

Providing accurate and enough information on a drug label and/or other materials to help its proper use

How to review/interpret MRCT data (2)

(Out of scope in the ICH E17, but related principles are described in the ICH E17)

- The primary objective of an MRCT generally corresponds to an evaluation of the treatment effect in the overall population.
- The assumption to conduct an MRCT is that there is no clinically relevant differences in distribution of ethnic factors which may affect the treatment effect between regions to be participated.

- During regulatory review, regulators should evaluate benefit/risk of the product based on results of the overall population.
- At the same time, regulators should evaluate the consistency of treatment effect between regions and the overall population in order to examine whether ethnicity could affect benefit/risk of the product.

Example：Dapagliflozin for CHF

- Dapagliflozin : SGLT2 inhibitor
- CHF : Chronic heart failure

DAPA-HF Trial（Feb 2017～Jul 2019）；
Phase III MRCT evaluating the efficacy and s
in patients with HF and reduced ejection frac

Dapagliflozin was approved for CHF based on the same data from DAPA-HF Trial;
- in Japan in Nov 2020
- in US in May 2020
- in EU in Nov 2020

- Result：

Composit endpoint of CV death, Hospitalization for heart failure, and Urgent heart-failure visit

Subgroup	Dapagliflozin (N=2373)	Placebo (N=2371)	Hazard Ratio (95% CI)
	no. of patients/total no.		
All patients	386/2373	502/2371	0.74 (0.65–0.85)
Geographic region			
Asia	77/543	114/553	0.65 (0.49–0.87)
Europe	193/1094	218/1060	0.84 (0.69–1.01)
North America	54/335	73/342	0.73 (0.51–1.03)
South America	62/401	97/416	0.64 (0.47–0.88)

th America
17, 17%

Europe
54, 46%

20

Global approach

MRCT is one of the powerful tool to cope with global public health issues and rapid paradigm shift.

We live in an age where drug development should be advanced in cooperation with regulators in the world as well as other stakeholders such as industries and academia.

We also live in an age where experiences and knowledge sharing is necessary.