Impact of MRCT after ICH E17 fully implement
-Industry perspective-

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ICH E17 Guideline

JPMA

General Principles for Planning and Design of Multi-Regional Clinical Trials (MRCTs)

- Purpose
  - To describe general principles for the planning and design of MRCTs with the aim of increasing the acceptability of MRCTs in global regulatory submissions

✓ More efficient drug development
✓ Earlier access to medicines

Objectives of MRCT

- Primary Objective
  - To confirm treatment effect in the overall study population

- Key Secondary Objective
  - To investigate consistency in treatment effect across populations from different regions taking into account the potential impact of intrinsic and extrinsic factors

How much is MRCT different? b/w before and after ICH E17

What's change?

GV

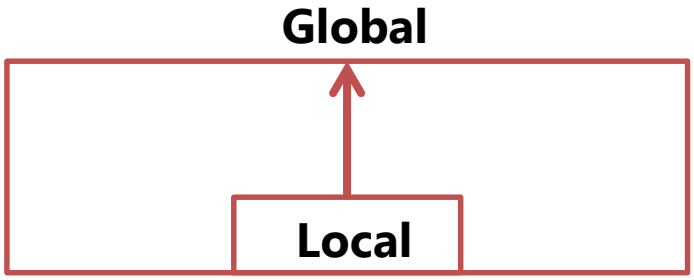
EV

What Impacts on MRCT are expected by ICH E17?

- Concept of population to enroll patients should be changed from “country” to “region”.
- Current Japanese GL for MRCT are not consistent with ICH E17 concept.
- Early communication with HAs is important to plan MRCT appropriately based on ICH E17.

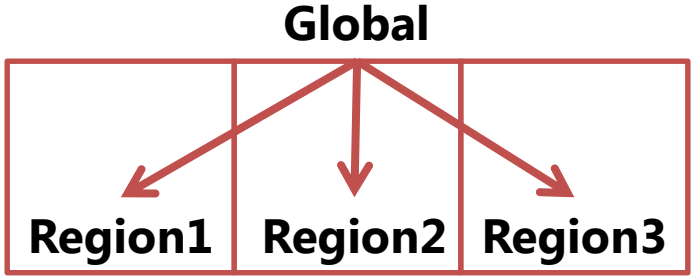
Shift from "Local First" to "Global First"

MRCT under
ICH E5



Looked at local data first
Then compared it with overall data
This is why PMDA typically wanted
to enroll 10-15% of sample size in Japan

MRCT under
ICH E17



Look at global data first
Then compare regions 1, 2 & 3,
instead of individual countries

Easy to say, but hard to do…

Should not heavily depend on "your country's data"

- Insufficient local sample size
  - "Play of chance" may mislead (apparently different from true value just by chance)
  - Lower precision of estimation
- Careful interpretation needed
  - local results are exploratory

What is “Region”?

Irrespective of Therapeutic area, Protocol, Endpoint

Note: One country may be a region

Regulatory Region

a common set of regulatory requirements applies for drug approval

Geographical Region

“Neighborhood”
(Some extrinsic factors may be common)

Pooled Region

There are **scientific grounds** for pooling
(intrinsic factors of interest or those distribution)

Depends on Therapeutic area, Protocol, Endpoint

NO **YES**

Do you have scientific grounds for pooling?

e.g., Japan + Korea + Taiwan + China …

How to construct “Pool Regions”?

Country-level background data:
Potential influence factors on treatment effect

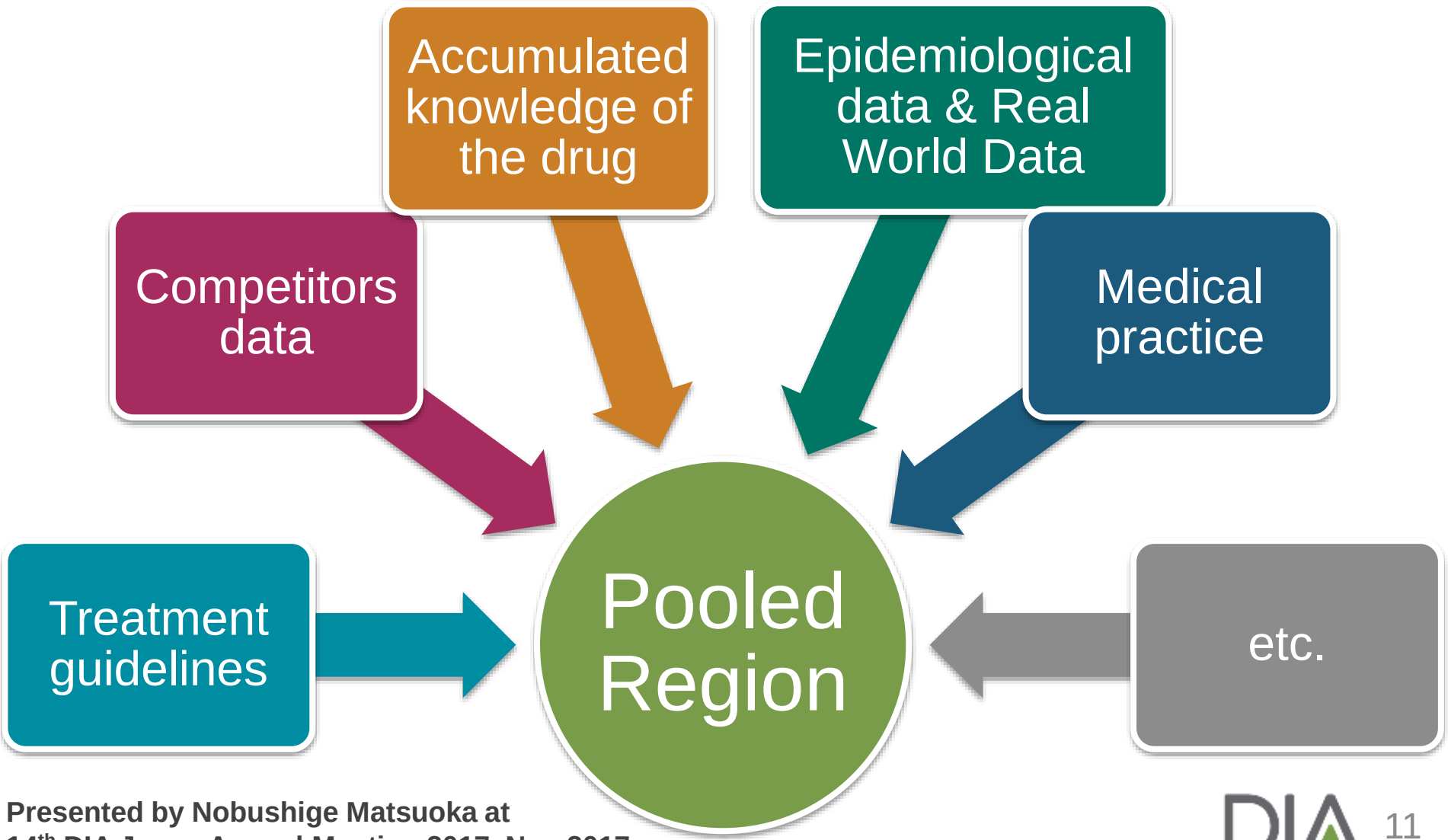
e.g., Age, Gender, Body weight, BMI, Prior medication, Comorbidities, Severity of disease…

Clustering Analysis

Pooled regions can be defined using a measure of **“similarity”** across regions

Analytical approach to defining region
→Data-driven approach

Information source for defining pooled regions



Presented by Nobushige Matsuoka at
14th DIA Japan Annual Meeting 2017, Nov 2017

Countries in Each Pooled Region

Region A (N: 25.8%)	Region B (N: 13.1%)	Region C (N: 45.9%)	Region D (N: 15.1%)
• Argentina	• Austria	• USA	• Russia
• Colombia	• Denmark	• Canada — NA	• Ukraine — EU
• Mexico	• Finland	• Brazil	
• Peru — LA	• Netherlands	• Chile — LA	
• Belgium	• Norway	• Puerto Rico	
• Italy — EU	• Sweden	• Czech Rep	
• South Africa	• Turkey — EU	• France	
• China	• UK	• Germany	
• India — AP	• **Japan**	• Hungary	
• Philippines	• South Korea — AP	• Israel — EU	
• Singapore		• Poland	
• Taiwan		• Romania	
		• Spain	
		• Australia — AP	
		• Hong Kong	
		• Malaysia	

NA: North America;
LA: Latin America;
EU: Europe;
AP: Asia/Pacific

Summary

- Let’s start planning MRCTs based on ICH E17 guideline after Step 5 with Try and Error to deliver innovative medicine to patients faster.
- Collaborate and share our roles with diversity in MRCTs through ICH E17.
- Can increase efficiency for new drug development and to save cost and resource which are limited.