What ICH E17 will bring us?

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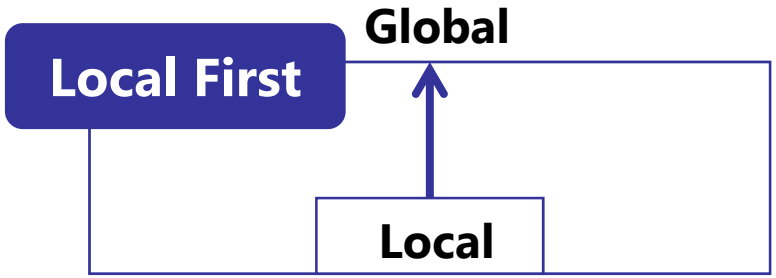
6th Joint Conference of Taiwan and Japan on Medical Products Regulation

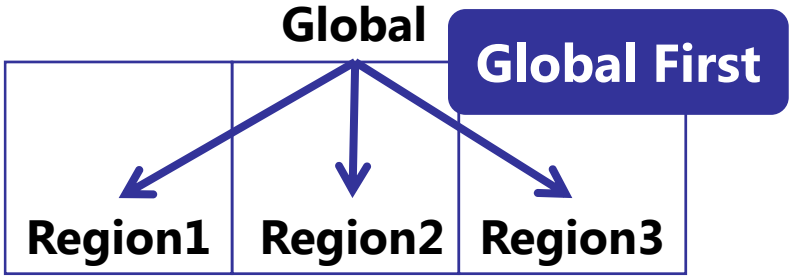
Paradigm shift E17 brings us

MRCT
under ICH E5



- Supremacy of local data actually collected, even if the size is very small
- Comparison b/w local vs. global had been a common approach

MRCT
in the era of E17



- Look at global data first
- Identify/determine factors affecting the MRCT result by using overall data
- During this exploration, evaluate consistency among regions, irrespective of individual countries
- Then think locally; allow to *estimate* local results without depending on local data actually collected

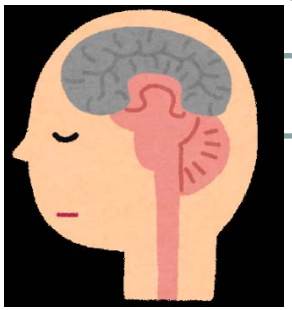
Local First paradigm

Local First paradigm has dominated our way of thinking

How many subjects from my country?

Comparison b/w local vs overall is the norm.

Even if the # of subjects is very small, I believe my country's data is a reflection of reality

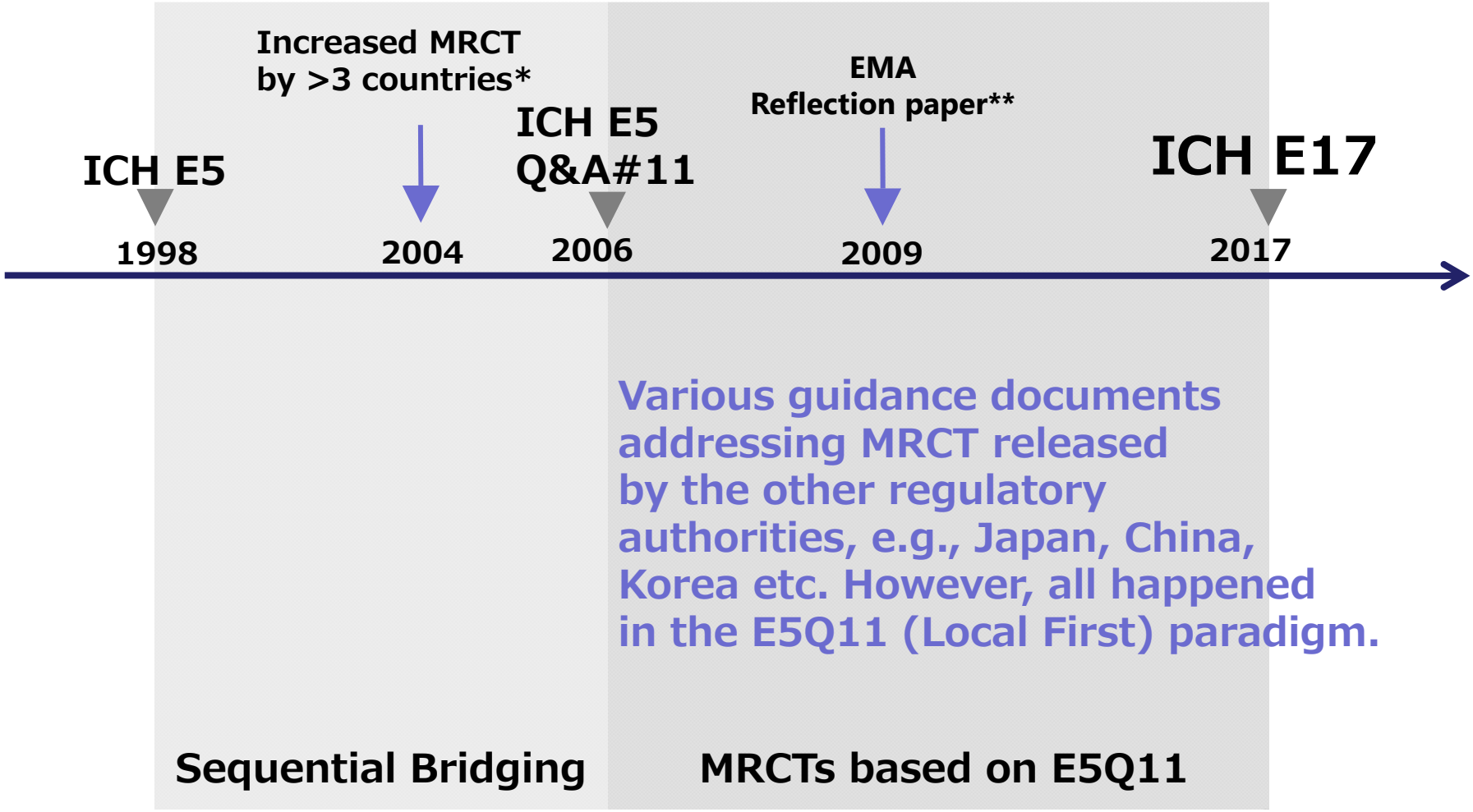


The followings should be evaluated in subjects from my country:

- ✓ Safety
- ✓ Tolerability
- ✓ Dose selection
- ✓ Long term safety

Even a few subjects should join early phase studies from my country.

“Local first” Paradigm



**EMA Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU-population」

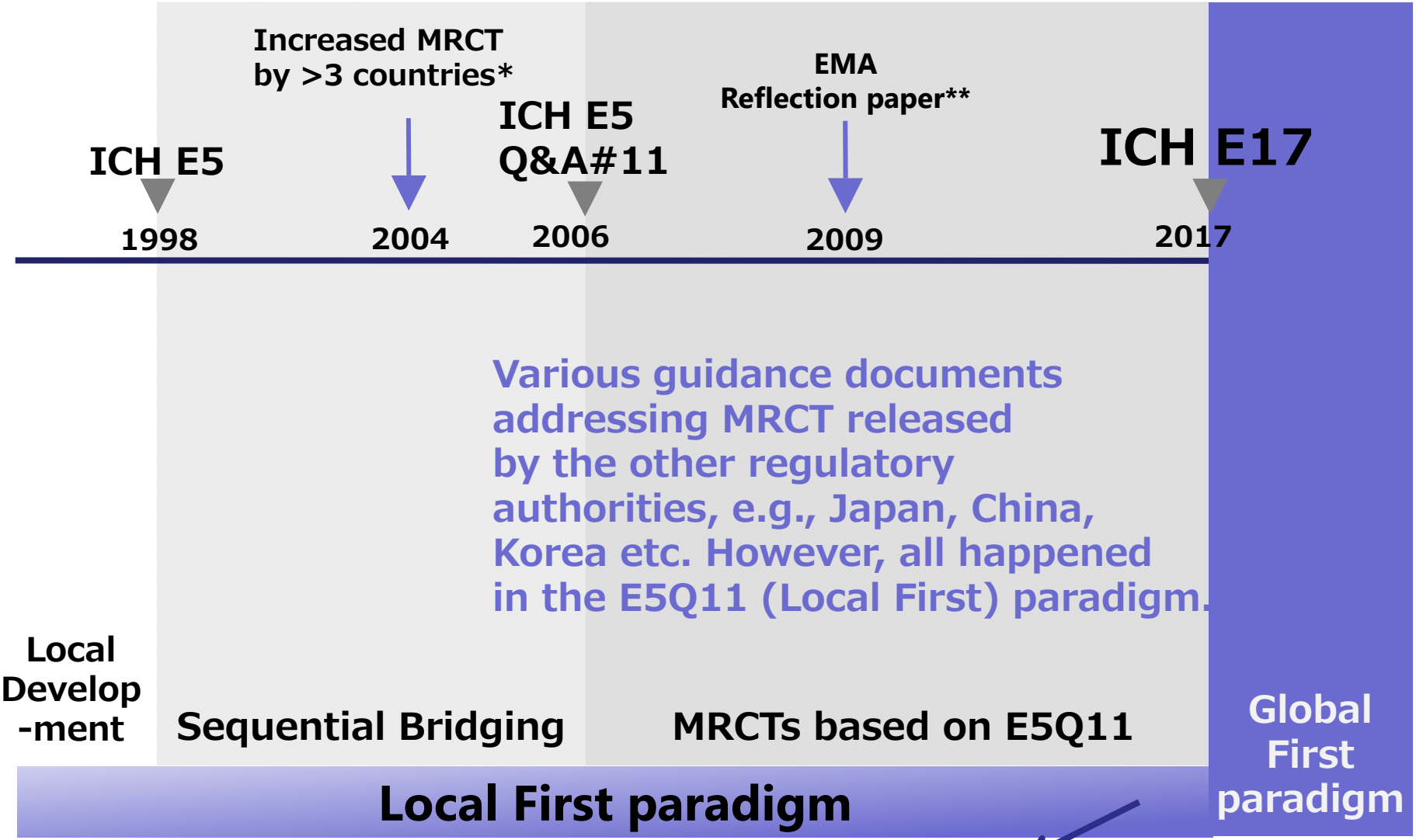
E5 Q&A#11

Characteristic description in E5 Q&A#11

[Evaluation]
It is difficult to generalize about what study results would be judged persuasive, as this is clearly a regional determination, but a "hierarchy of persuasiveness" can be described.
1. Stand Alone Regional Result ***←Statistically significant result BOTH in overall AND in the "region of interest"***
2. No Significant Regional Result but Similar Results across Regions

- **At that time, "Region" basically meant the ICH region (EU, US, Japan), or region including neighboring countries of Japan, EU, or US.**
- **At the face-to-face meeting of E5 IWG, a representative from EMEA said, "Statistical significance in EU population is welcome. I'm not interested in the results outside EU, basically."**
  → EU regulatory authority also had Local First thinking.
- **Around 2006, it was the time US-based data fell below 50% in the data submitted to FDA.**
  →FDA had mainly looked at their local data

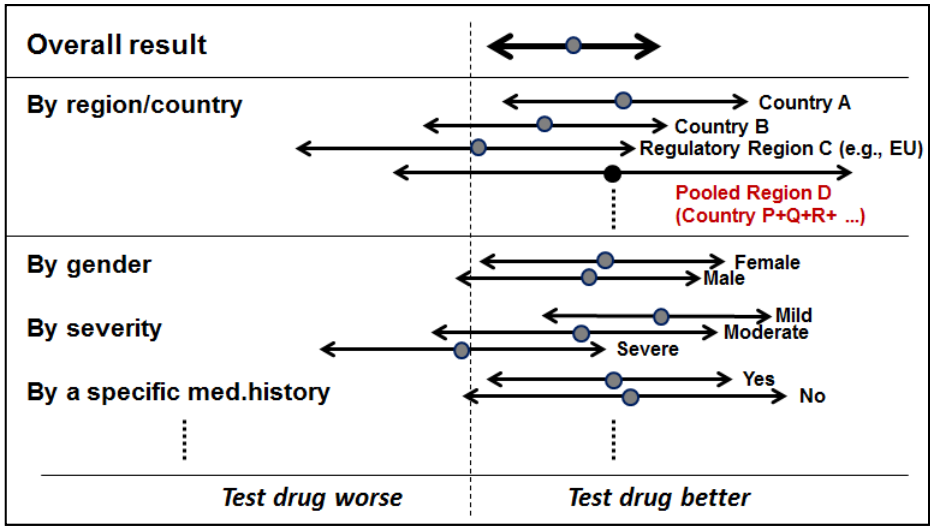
Towards “Global First” Paradigm



Global First is…

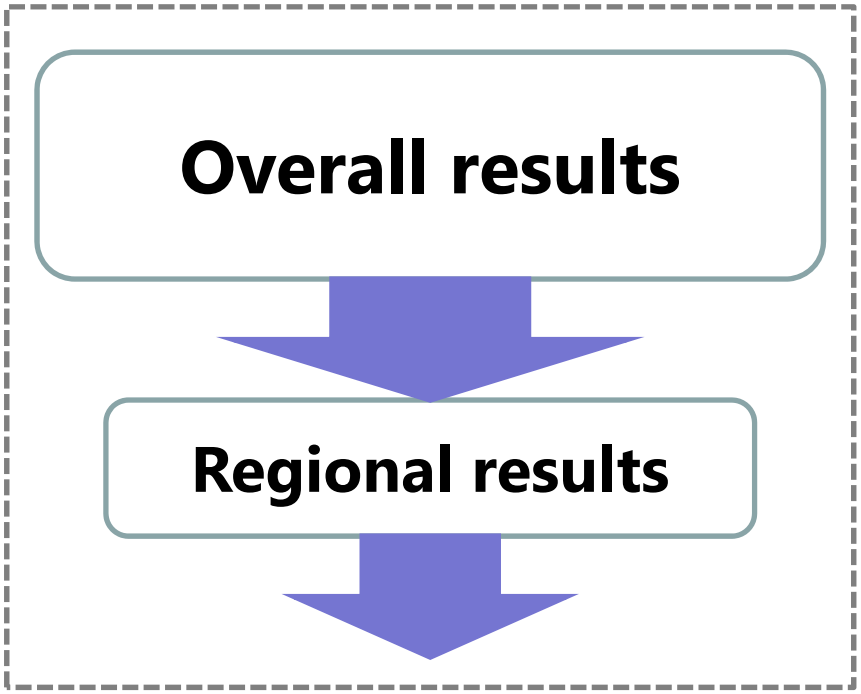
Overall results

- ✓ **Drilling down from overall results**
- ✓ **Using the overall MRCT data, we will explore what kind of factors cause different results? (including evaluation of consistency among regions)**



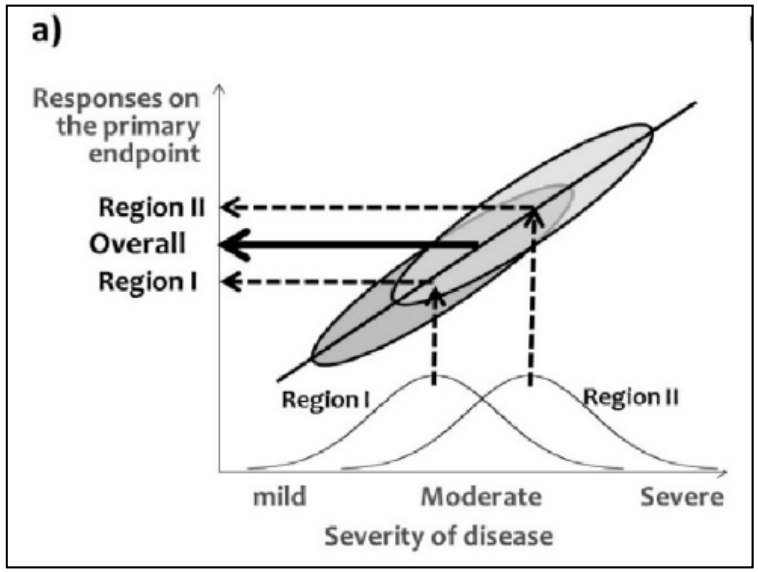
Forest plot is
the simplest way
to show these explorations.

Global First is…

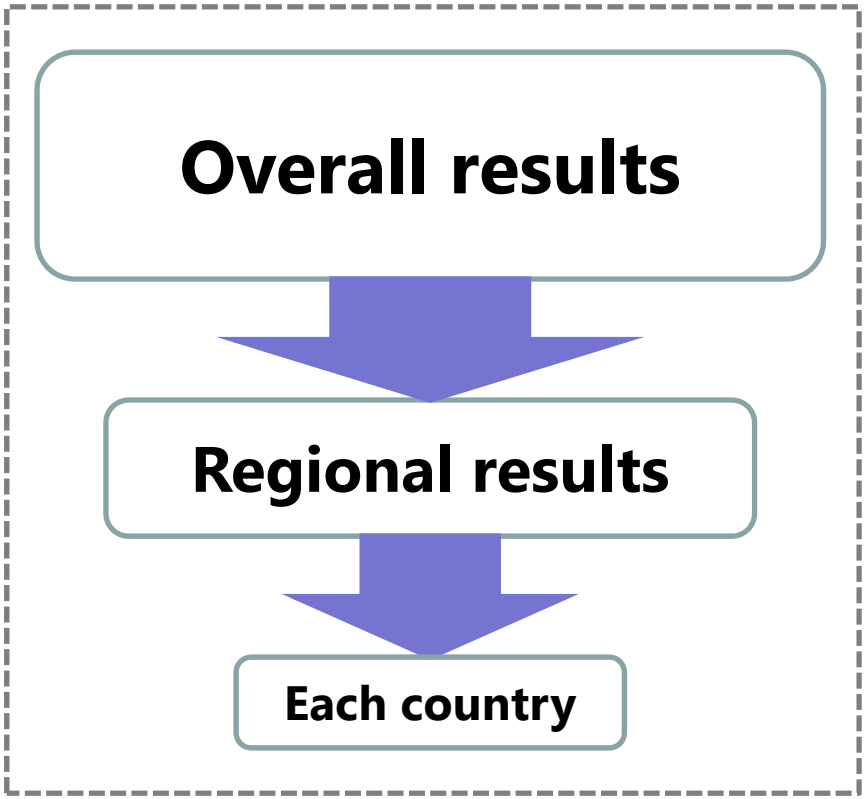


- ✓ **If the factor(s) affecting the result was identified/suggested, and if regional differences were observed, we would try to explain the regional differences by the identified/ suggested factors.**

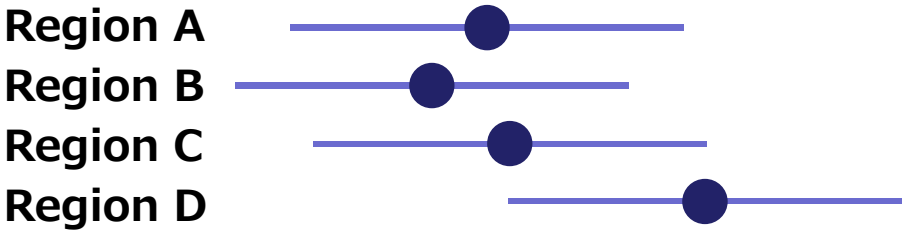
Can we explain like fig.2?



Global First is…



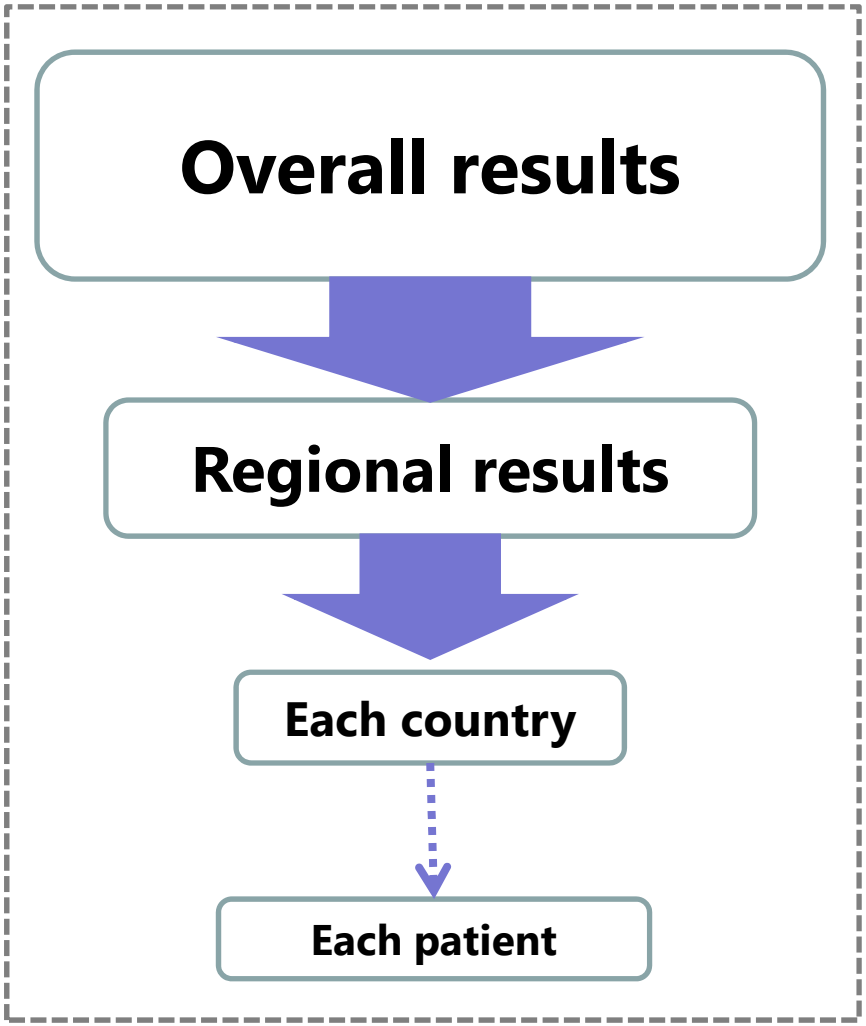
When we look at consistency among regions, we may also look at the data from each country included in each region.



- ✓ **Doesn't a specific country with large sample size bias the result of the region?**
- ✓ **Is there a country in the region that gives far different values?**

Like this, the results of each country are <u>in a deep part of the hierarchy</u>. Ideally, the sample size of each country is nearly equal in the region. However, is it really necessary to plan the sample size of each country for such consideration?

Global First is…



- ✓ **Statistically, our goal is to develop a predictive model with influential factors based on the overall data.**
- ✓ **If we can characterize each country/ region with the influential factors, we could estimate the result of each country/region. Global First allow us to do that.**

- ✓ **Furthermore, If the useful model is developed, the model could be use to predict each patient's outcome.**
- ✓ **Such a predictive model will be a useful tool for individualized medicine.**

Global First is…

Global First also means that
we do not shut our eyes to the drawbacks of Local First

the drawbacks of Local First

The smaller the local sample size,
1. The easier it is for local results to be away from *true value* just due to play of chance
2. The lower the precision of estimation is
3. The more questionable the representativeness of local patient population is

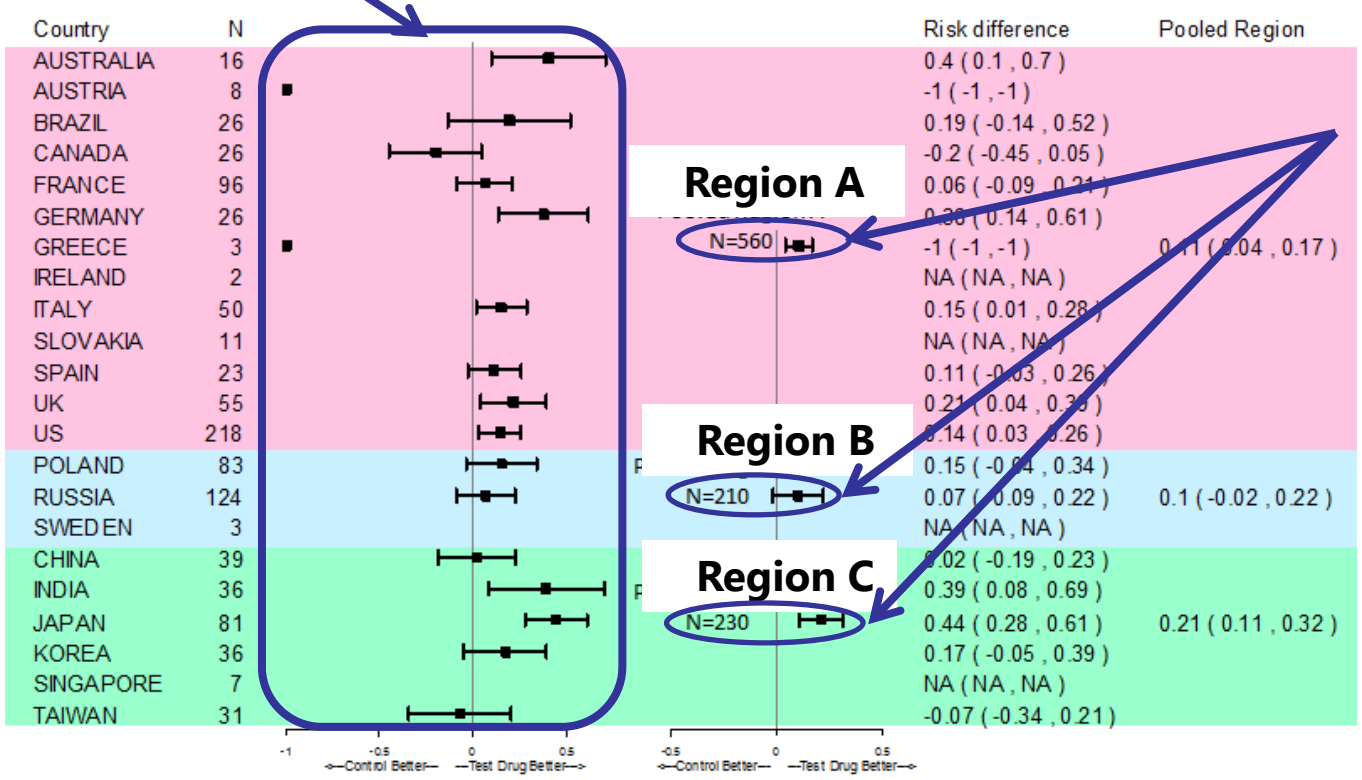
Use of Regions is an approach for overcoming the drawbacks of country-wise data

The smaller the local sample size,

1. The easier it is for local results to be away from *true value* just due to play of chance
2. The lower the precision of estimation is
3. The more dubious the representativeness of local patient population is

\+ **Big countries affect the overall results**

Results from each country



Results from each Region

Note:

If you increase the number of regions *too much*, the goodness of the region would fade away…

E17 describes Pooling Strategies

Pre-specified pooling of regions or subpopulations 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.** **[from E17]**

Pooled Region

Pooled Subpopulation

- ➢ **Both pooling strategies are paying attention to ethnic factor(s) known to affect the treatment effect.**
- ➢ **Unless we have such factors at the planning stage of the MRCT, we cannot pre-specify pooled region/subpopulation.**
- ➢ **However, E17 does not require pooling in any case.**

Common misconceptions?

Unless Pooled Region/Subpopulation can be defined, E17 cannot be applied

Unless ethnic factors affecting the MRCT result are identified in advance, Pooled Region/Subpopulation can not be defined.

Before confirmatory MRCT, such investigation must be completed

In this TA, such factors are unknown.

Though we have potentially influential factors, such info. will not be available from all par-ticipating countries.

Cost for exploratory studies will increase.

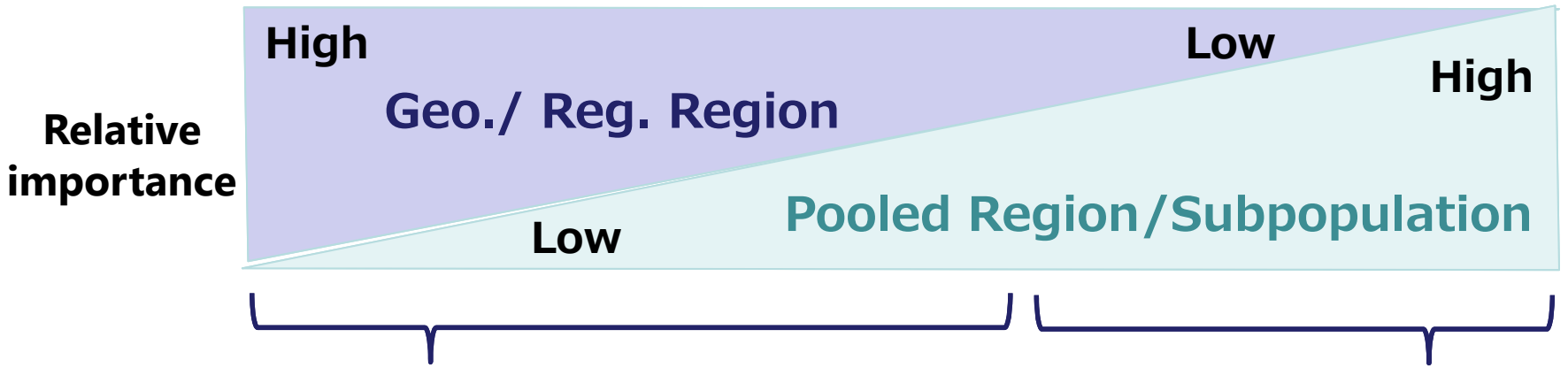
Due to cost issues

We cannot apply E17

Relative importance of pooling strategies depends on our knowledge

Knowledge of ethnic factors affecting the MRCT result

Unknown or weak to explain ⟷ **Well known and strong to explain**

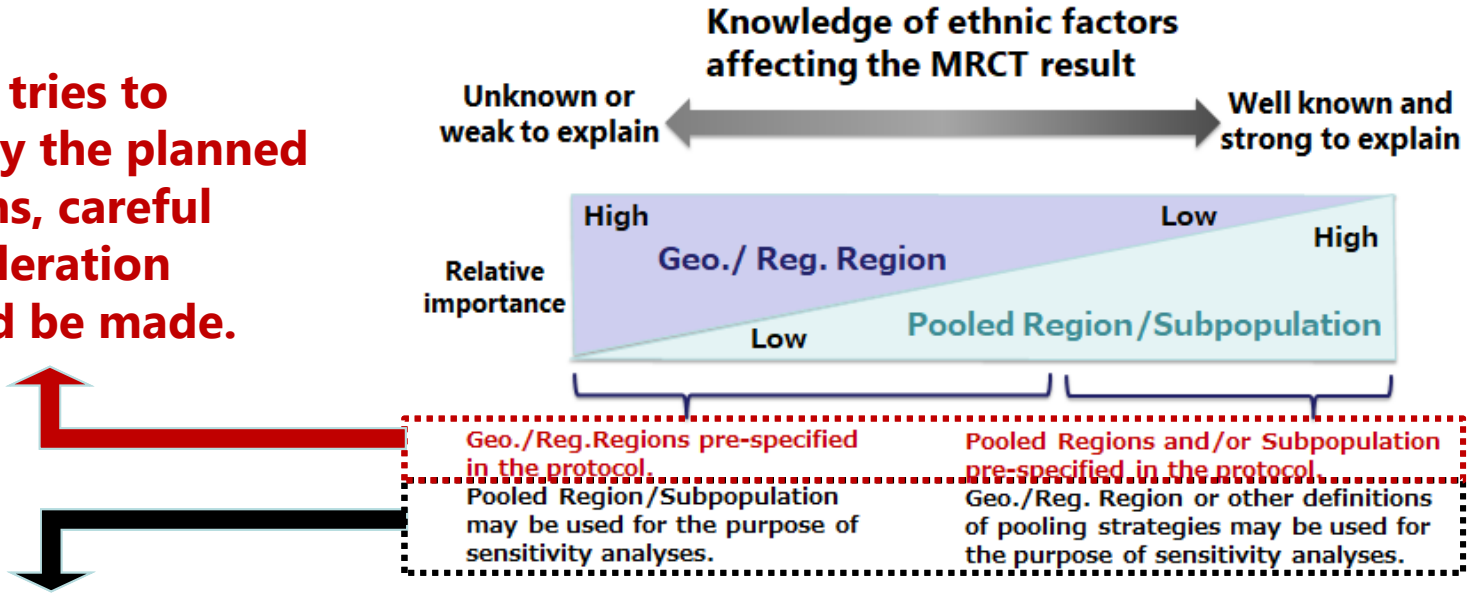


Geo./Reg.Regions pre-specified in the protocol.
Pooled Region/Subpopulation may be used for the purpose of sensitivity analyses.

Pooled Regions and/or Subpopulation pre-specified in the protocol.
Geo./Reg. Region or other definitions of pooling strategies may be used for the purpose of sensitivity analyses.

Pre-specified vs. Exploratory

If one tries to modify the planned regions, careful consideration should be made.



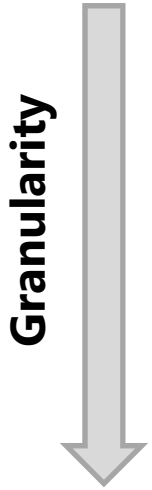
As these are exploratory, flexible approaches will be acceptable

One can define more than one set of regions, and one can define regions *post hoc* by using actually collected data in the MRCT. *However, please note* that the weight of evidence of the findings from exploratory analyses will *decrease* in the order below:

- Prespecified in the protocol/SAP
- Defined prior to Unblinding
- Defined after Unblinding

2nd & 3rd practices could be applied to on-going/completed MRCT

Each factor is a gateway to explore more specific factors



Geo.Region/Country	…Mixture of so many ethnic factors
Ethnicity	… Mixture of so many ethnic factors
Race or other intrinsic factors*	…relatively specified but still rough factors
Particular factors (very specified factors)	…specified, e.g. mutation of specific molecule

***Race or other intrinsic factors:**
[Race] …mixture of many intrinsic factors
[Sex] …mixture of sex-related intrinsic factors, e.g., e.g., Sex hormones, sexual function, body fat percentage, etc.
[Body Weight] …mixture of intrinsic factors, e.g., body fat percentage, life-style habit, concomitant illness, genetic factors, etc.

The possible obstacle to healthier implementation of E17

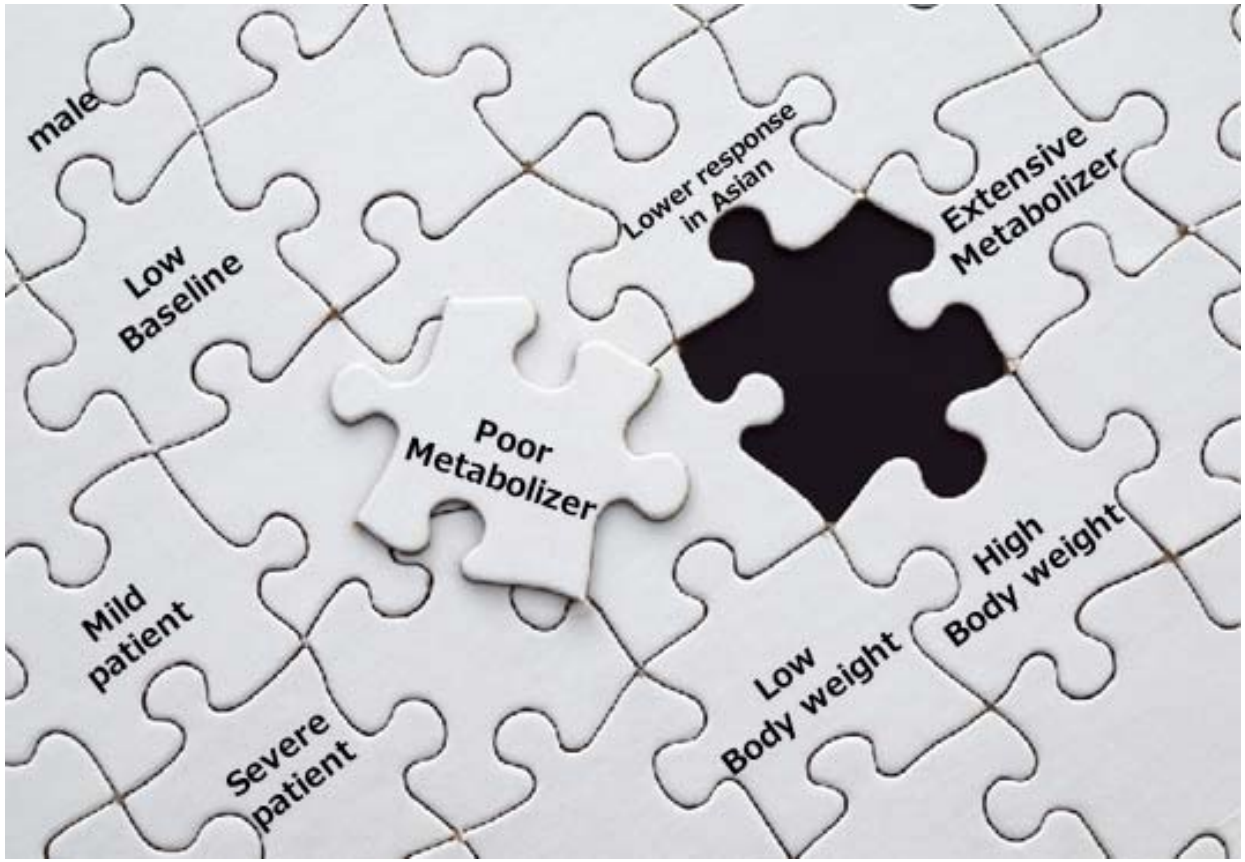
Local First backed with safety evaluation

"We need look at our country's data."
"For safety evaluation, we require >xxx subjects' data from our country." etc.

If we have some regulatory authorities requiring like that, planning, design, and interpretation of MRCT may be distorted!

- However, safety evaluation is even more compatible with Global First.
  - Until information is sufficiently accumulated, any ADRs should be regarded as common risks of mankind.
  - Firstly, take off the regional/national boundaries and look at the globe from bird's-eye view, then only when we recognize that the risk is high in a specific country/region, that become a local matter.

Which pieces can your country/region contribute to?



The art and science of global development is to take all the available data and present it in such a way that the data tell a story about the efficacy/safety profile of the drug. This story should be fact based. The data that tell the story are like pieces of *a jigsaw puzzle* that must be correctly interlocked to allow the reviewers to see the overall picture of the drug.

To obtain data from patients in your country is not to explain to people in your country. The data of the patients who participated in the MRCT contributes to the information to explain to *the patients in the world* having the common background of interest. That is Global first.

Messages

- **Paradigm shift from Local First to Global First is a challenge for every country/region, more or less…**
- **E17 provides general principles of planning and design of MRCTs, and covers MRCTs *in various setings*.**
- **E17 provides a *toolbox* to tell a story for explaining efficacy/safety profile of the drug to people all over the world.**
- **Our question is NOT "Can we apply E17 to the drug project?", BUT "How do we use E17 for the drug project?"**

Messages

- **There may be room for re-considering our "Commonplace" in the Local First paradigm**
  - ✓ **Phase I should be conducted in our country before joining global development program**
  - ✓ **Our country's subjects should be included in the early phase clinical trials, e.g., POC, dose selection, etc., *even if the sample size is very small*.**
  - ✓ **To know about safety profile in our country, minimum xxx subjects should be enrolled from our country**
  - ✓ **Long-term safety study should be conducted in our country**