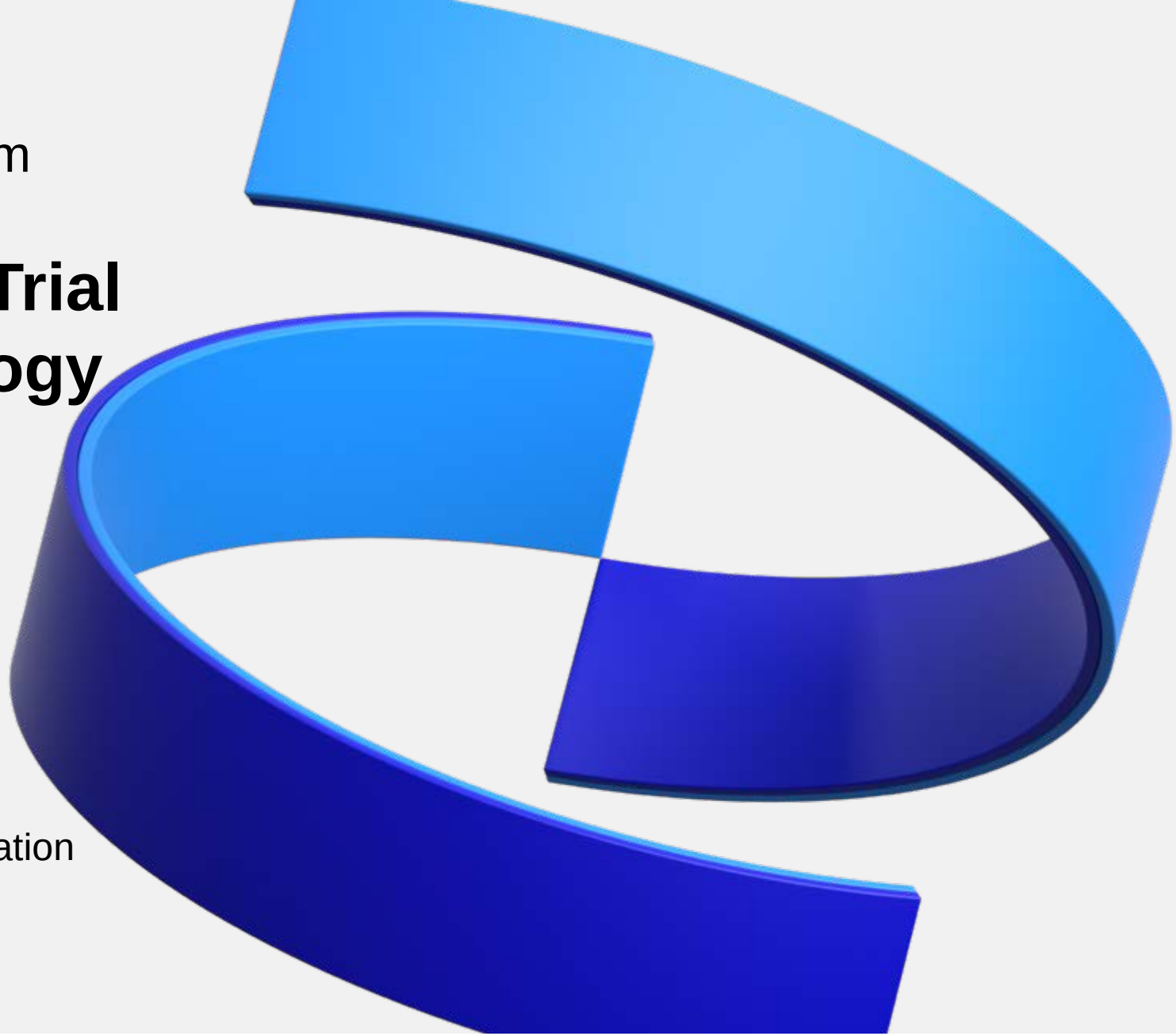
Japan-China ICH Joint Symposium

Multi-Regional Clinical Trial and Clinical Pharmacology Strategy



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Our Aspiration

Bring medicines to the world faster

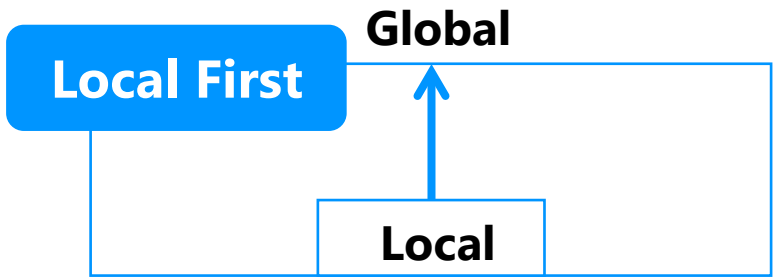
When a drug is developed globally,

- Simultaneous clinical development, NDA and approval in Asian region without delay from US/EU/UK
- Joining a **Multi-Regional Clinical Trial (MRCT)** from Japan, China and other Asian countries

are key strategies for Asian patients.

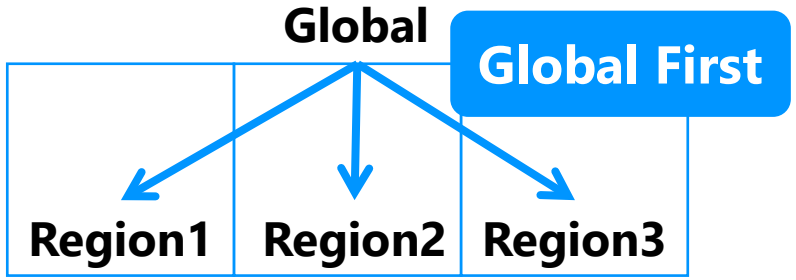
Paradigm Shift on MRCT by E17

MRCT
under ICH E5



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

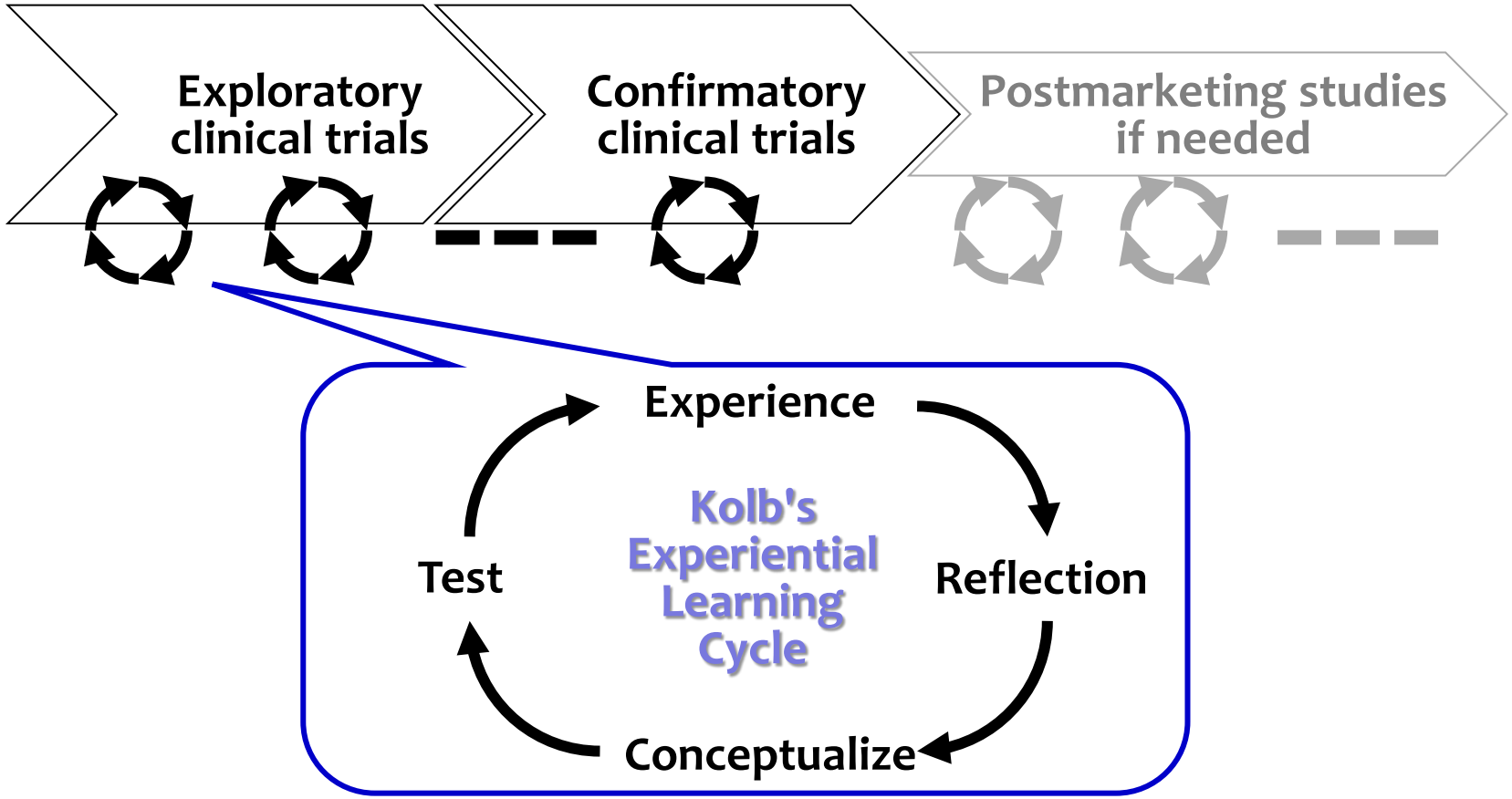
MRCT
in the era of E17



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

MRCT and Exploring Effect Modifiers

- Treatment effects vary from person to person because magnitude of **Effect Modifiers** (intrinsic or extrinsic factors which may affect treatment effect) are different among patients
- Exploring **Effect Modifiers** is program level consideration



How can Japan and China contribute a MRCT?

The sample size of countries participating in MRCT may vary, and it is difficult for any country to obtain high-evidence conclusions from their own data alone.

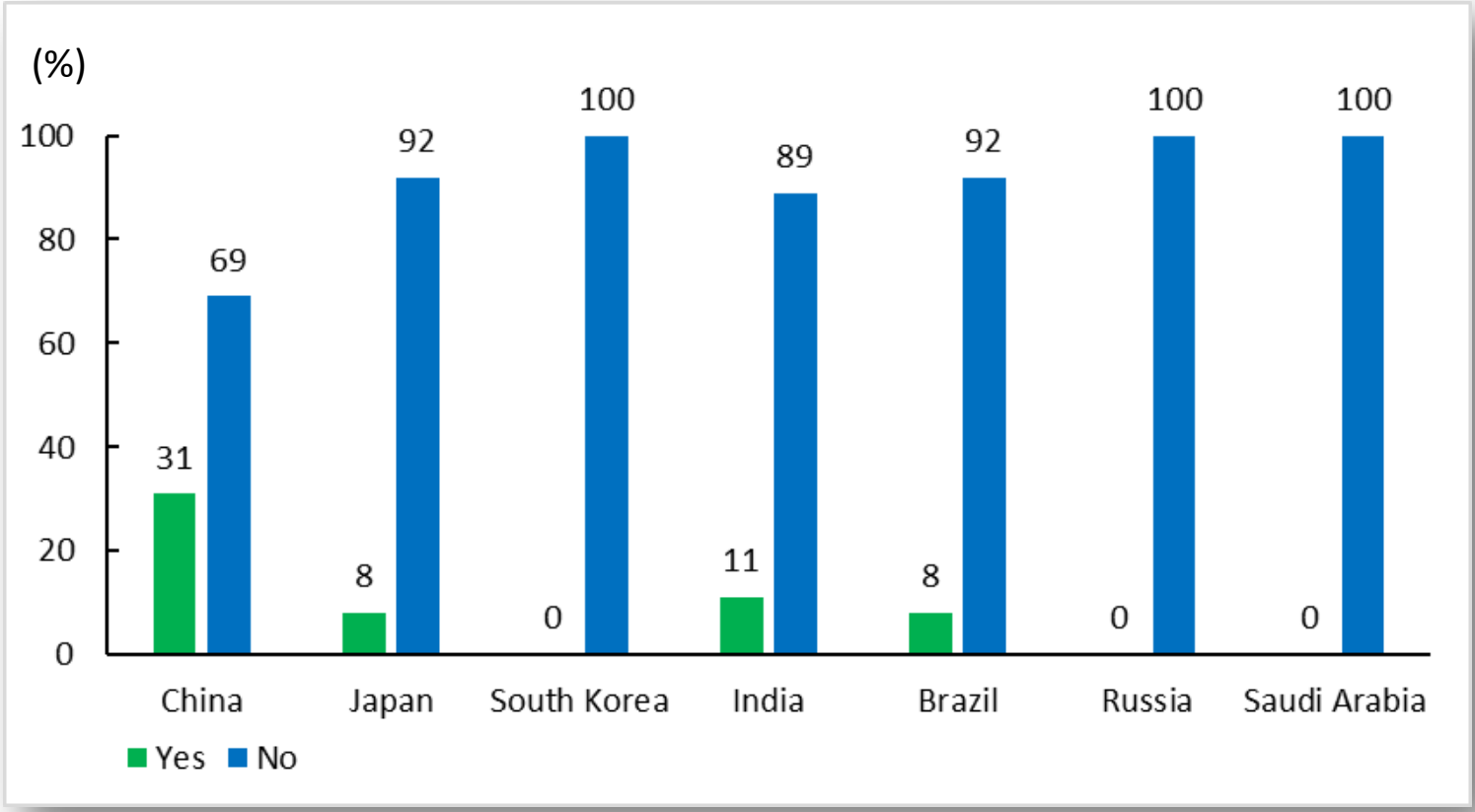
So, points to consider…

- **Which of countries, regions and races** are appropriate to identify effect modifiers?
- Investigate prospectively: "**When is the best timing** to include Japanese and Chinese **in which of MRCTs**?"
- Seeking a possibility to use **Japanese and Chinese data mutually**

In addition, for investigation of effect modifiers, calculation of sample size and extrapolation of outcomes from Country A to Country B, **Modeling and Simulation (M&S)** approach and **Model-Informed Drug Development (MIDD)** can be utilized.

Current Status of Implementation of E17

- To assess whether the ICH E17 guideline is fully utilized, the European Federation of Pharmaceutical Industry Associations (EFPIA) conducted a survey amongst its member companies
- The graph shows sponsor responses to the following survey question***: "In your view, have you noticed a difference in how often this regulatory authority requests local clinical data since implementation of the E17 guideline?"***



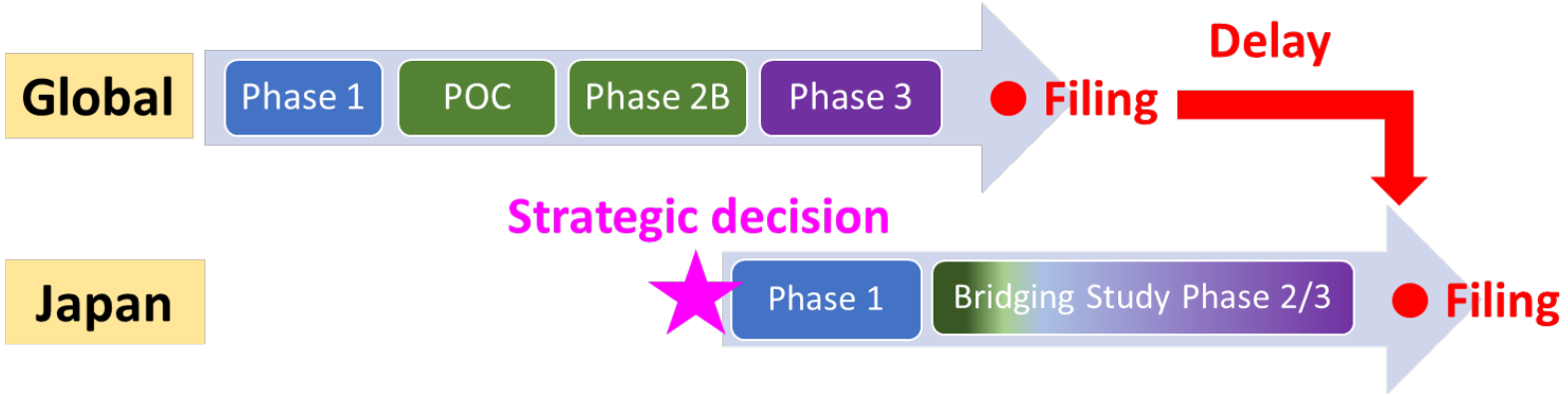
DIA Europe 2021 Figure 4 (Modified):
https://globalforum.diaglobal.org/issue/june-2021/industry-survey-on-implementation-of-ich-e17-guideline/

Current Status to Join a MRCT in Japan

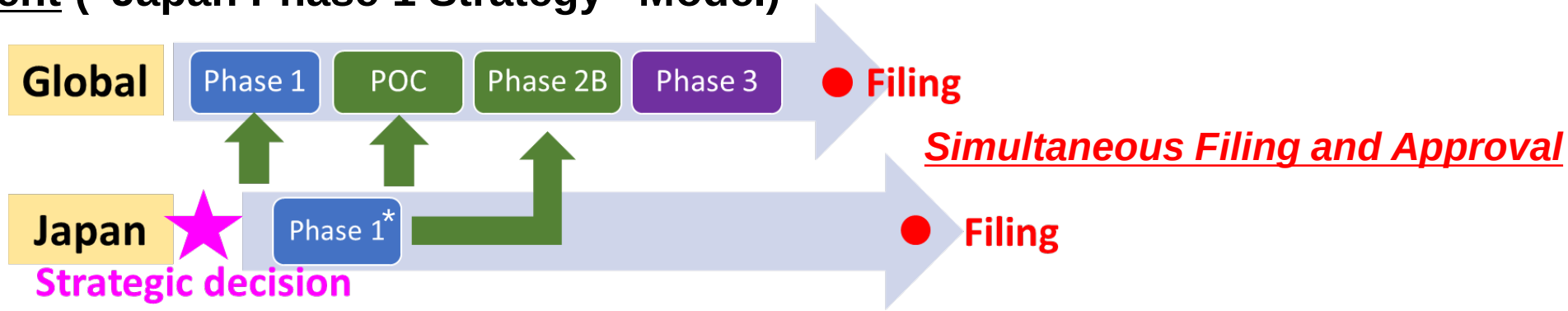
- **Global clinical trials** (MRCT) have been recommended by MHLW/PMDA as an efficient and rapid approach to develop new drugs to resolve the drug lag issue
- Early participation in global trials from at least the exploratory dose finding study is recommended
- Before participation, it should be confirmed by sponsor that there are **no particular safety concerns** for the **Japanese** for dosage regimen to be used in a global trial

Execute “Japan Phase 1 Strategy” to fully integrate Pfizer Japan into Global Development

Past



Present (“Japan Phase 1 Strategy” Model)



*In some cases, considering other Asian data instead of Japanese data

Is a specific local Phase I data always needed before joining a MRCT?

- The necessity of the local phase I data should be considered according to the research questions to be answered
  - ✓ What we need to know is NOT the average Pharmacokinetic (PK) parameters for each country with a large uncertainty, BUT the PK parameters for the compound in humans from different backgrounds.
  - ✓ If the metabolic enzymes are identified, we can predict the PK parameters in a given population if we know the PK of the poor metabolizers, the extensive metabolizers and so on.

    A similar scenario can be considered for genetic polymorphisms of transporters etc.
  - ✓ If the effect modifiers for PK are unknown, investigating it in a population with a broader background may lead to the identification of the effect modifiers. In such a case, there is no need to be concerned about including a certain number of subjects from each of Japan/China.

    For example, if we want to include a certain number of subjects from Asia, we can consider on a case-by-case basis which country to include rather than competing with Japan and China.
- As for safety, there are very few questions that can be answered in a Phase I study of at most a dozen patients. All the countries participating in the global simultaneous development share the data and assessment of risks.

Conclusion and Take-Home Message

- Aim to increase the number of cases of simultaneous clinical development, NDA and approval in Asian region without delay from US/EU/UK
- We need to jointly consider how we can contribute a MRCT to identify effect modifiers
- We need to streamline the Phase 1 strategy to join a MRCT
- M&S and MIDD can contribute global clinical development
- Regulatory Agency, Industry and Academia must cooperate to use Japanese, Chinese and other Asian data mutually to bring medicines to the world faster

Thank you very much