ICH M14：
General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines

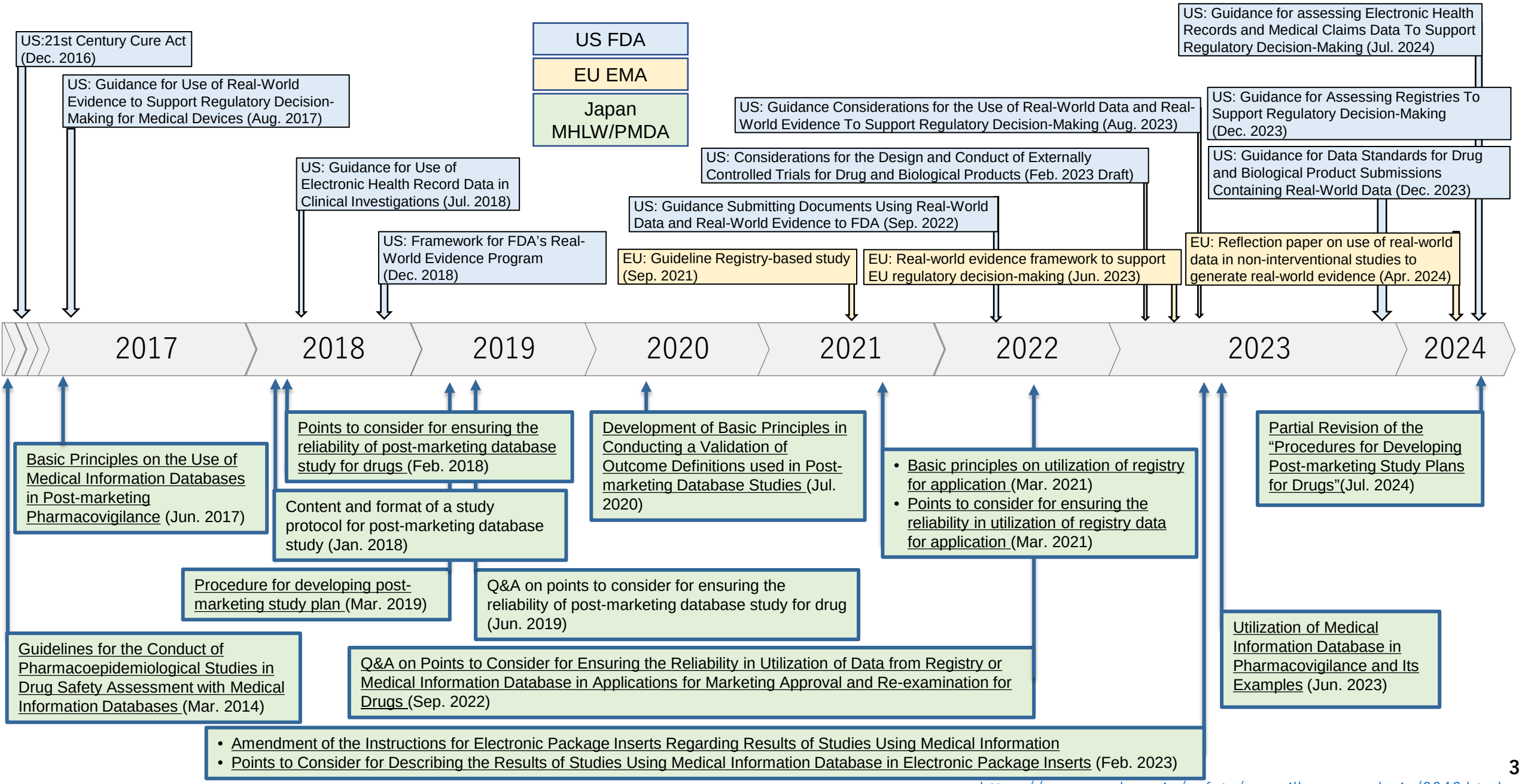
医薬品の安全性評価においてリアルワールドデータを活用する薬剤疫学調査の計画、デザイン、解析に関する一般原則（案）

独立行政法人医薬品医療機器総合医機構
医薬品安全対策第一部　薬剤疫学課
梶山和浩

本日の内容

1. 本トピックの背景
2. 活動経緯
3. ガイドライン案の構成
4. 今後の予定

リアルワールドデータの活用に関する主なガイドライン



https://www.pmda.go.jp/safety/surveillance-analysis/0046.html

2019年　6月　Reflection paperの採択

■ 提案の目的

- **harmonize the technical scientific requirements related to pharmacoepidemiological studies submitted to regulatory agencies.**
- **promote a globally-harmonized approach in post-marketing safety-related regulatory actions based on the most current scientific evidence.**

ICH harmonisation for better health

ICH Reflection Paper
Endorsed by the ICH Assembly on 5 June 2019

ICH Reflection paper

Strategic Approach to International Harmonization of Technical Scientific Requirements for Pharmacoepidemiological Studies Submitted to Regulatory Agencies to Advance More Effective Utilization of Real-World Data

Background

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Strategic approaches

For achieving the objective, a step-wise approach is proposed as described below.

	Workload	Deliverable	Timing*
1st Stage	• Information exchange for mutual understanding of situations including contents of local guidelines in each region (mainly e-mail/TC based) • Considering the specific areas and opportunities for international harmonization	• List of Harmonizable areas in ICH	2019.Q4 -2020.Q2
2nd Stage	• Prioritizing harmonization area as ICH guidelines • Creating overall structure of these guidelines (i.e. the relationships between the different guidelines)	• Priority list and overall structure of all guidelines	2020.Q3 -2021.Q1
3rd Stage	• Creating opportunity proposal for high priority topics to propose a form of expert working group • Opportunity proposal for the other topic will be created in order of priority	• Opportunity proposal	2021.Q2 -2021.Q3
4th Stage	• Following regular ICH process; New Topic proposal, adoption and Steps 1-4	• ICH Guideline	2021.Q4 -20XX.QX

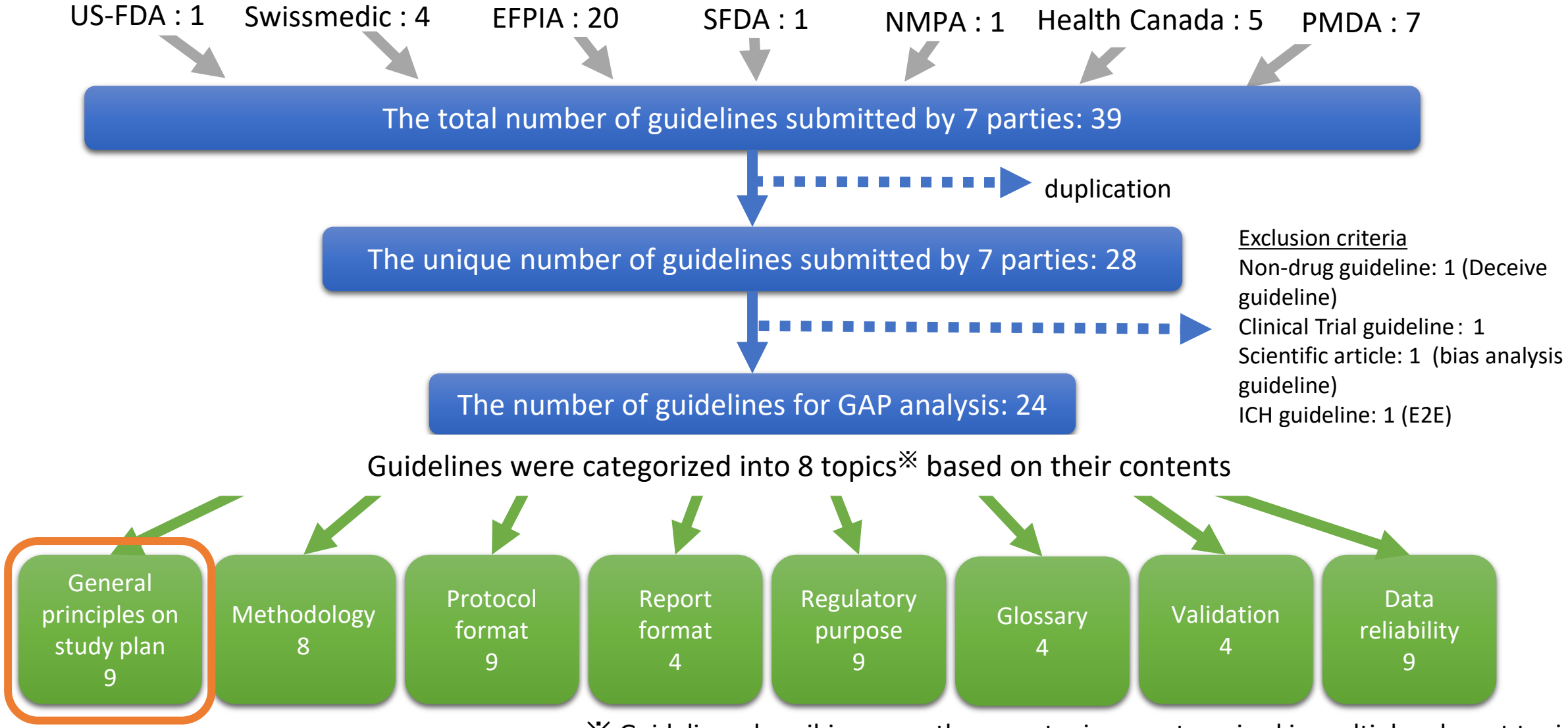
*Note: The timing will be optimized by the discussion group; some opportunity proposals may be reported in shorter term, whereas other topics may need a long-term discussion.

Pharmacoepidemiology Discussion Group

It is recommended to establish an informal pharmacoepidemiology discussion group (PEpi-DG) to accomplish this work. The PEpi-DG will serve for a two-year period.

https://admin.ich.org/sites/default/files/2019-08/ICH_ReflectionPaper_Pharmacoepidemiology_2019_0605.pdf

各地域のガイドラインの整理（GAP Analysis）



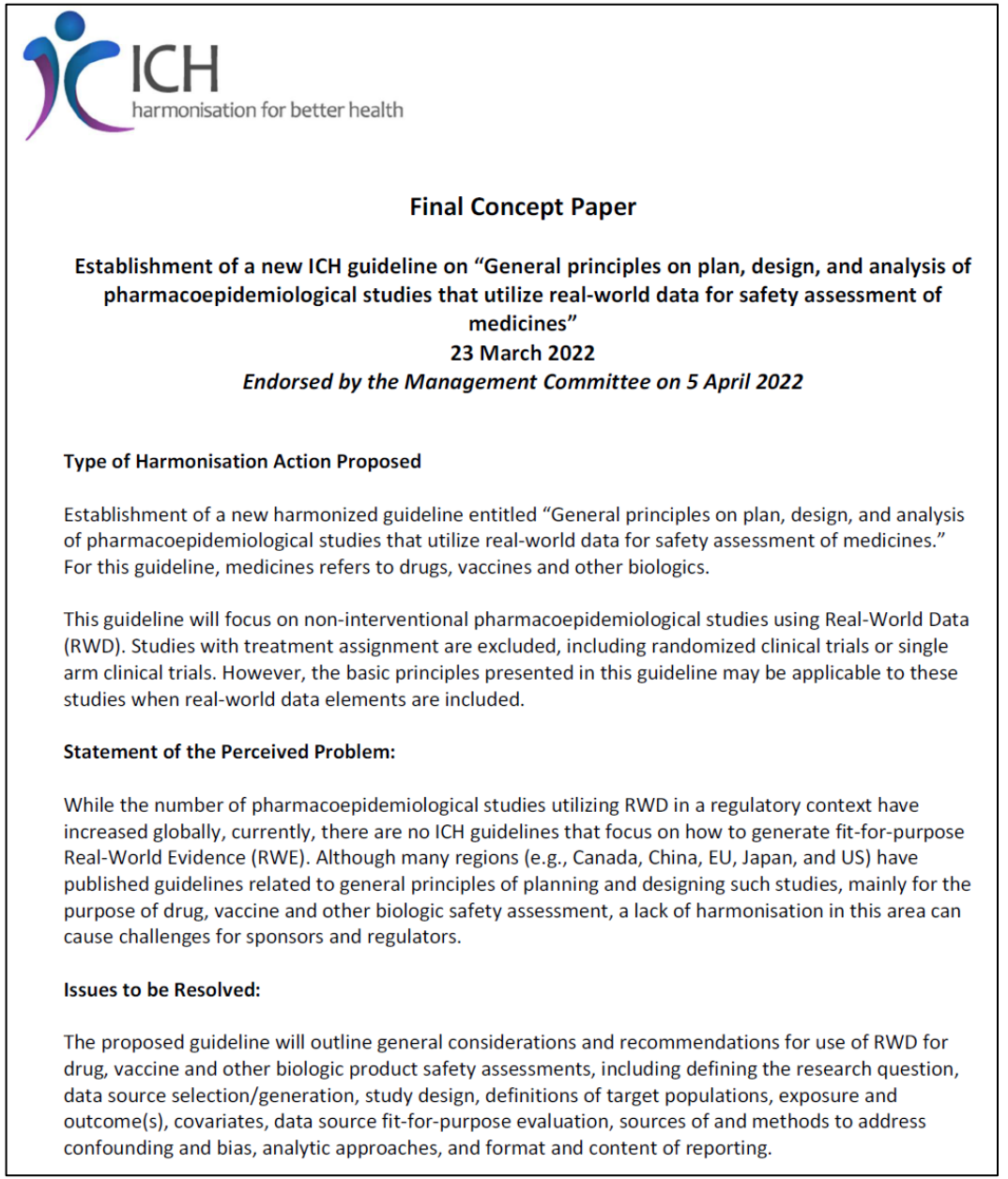
※ Guidelines describing more than one topic are categorized in multiple relevant topics.

https://www.pmda.go.jp/files/000241195.pdf より一部改変

2022年　3月　Concept paperの最終化

■ Type of Harmonisation Action Proposed

- This guideline will focus on non-interventional pharmacoepidemiological studies using Real-World Data.
- Studies with treatment assignment are excluded, including randomized clinical trials or single arm clinical trials.
- The basic principles presented in this guideline may be applicable to these studies when real-world data elements are included.



ICH
harmonisation for better health

Final Concept Paper

Establishment of a new ICH guideline on "General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines"

23 March 2022

Endorsed by the Management Committee on 5 April 2022

Type of Harmonisation Action Proposed

Establishment of a new harmonized guideline entitled "General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines." For this guideline, medicines refers to drugs, vaccines and other biologics.

This guideline will focus on non-interventional pharmacoepidemiological studies using Real-World Data (RWD). Studies with treatment assignment are excluded, including randomized clinical trials or single arm clinical trials. However, the basic principles presented in this guideline may be applicable to these studies when real-world data elements are included.

Statement of the Perceived Problem:

While the number of pharmacoepidemiological studies utilizing RWD in a regulatory context have increased globally, currently, there are no ICH guidelines that focus on how to generate fit-for-purpose Real-World Evidence (RWE). Although many regions (e.g., Canada, China, EU, Japan, and US) have published guidelines related to general principles of planning and designing such studies, mainly for the purpose of drug, vaccine and other biologic safety assessment, a lack of harmonisation in this area can cause challenges for sponsors and regulators.

Issues to be Resolved:

The proposed guideline will outline general considerations and recommendations for use of RWD for drug, vaccine and other biologic product safety assessments, including defining the research question, data source selection/generation, study design, definitions of target populations, exposure and outcome(s), covariates, data source fit-for-purpose evaluation, sources of and methods to address confounding and bias, analytic approaches, and format and content of reporting.

https://database.ich.org/sites/default/files/M14_ConceptPaper_2022_0405.pdf

活動経緯

2022年 4月　Final Concept Paper 採択

2024年 4月　EWGメンバーによるガイドライン案の合意。Step 1 Sign-off。

2024年 5月　Step 2a/b Sign-off。Step 3開始。

2024年 5～10月　各地域においてパブリックコメントを公募。

- **国内のパブリックコメント期間：6月17日～7月29日**
- **パブリックコメント説明会：7月8日**

2025年 3月　ブダペスト中間会合

2025年 5月　マドリード対面会合

M14ガイドラインの目的（パブリックコメント時点）

- **Many regions have published guidelines on the regulatory use of pharmacoepidemiological studies utilizing real-world data (RWD), but a lack of harmonisation in this area can cause challenges for sponsors and regulators**
- **Development of this guideline will promote harmonisation in the design and use of these studies, minimize the need to conduct multiple studies on the same safety concern for submission to multiple regulators, result in improved efficiency and transparency in the development, submission and review of pharmacoepidemiological studies and resultant regulatory actions**
- **Provides recommendations and high-level best practices for the conduct of these studies, with a goal of streamlining the development and regulatory assessment of study protocols and reports**

M14 Step2 Presentation(2024年5月21日公開)より抜粋

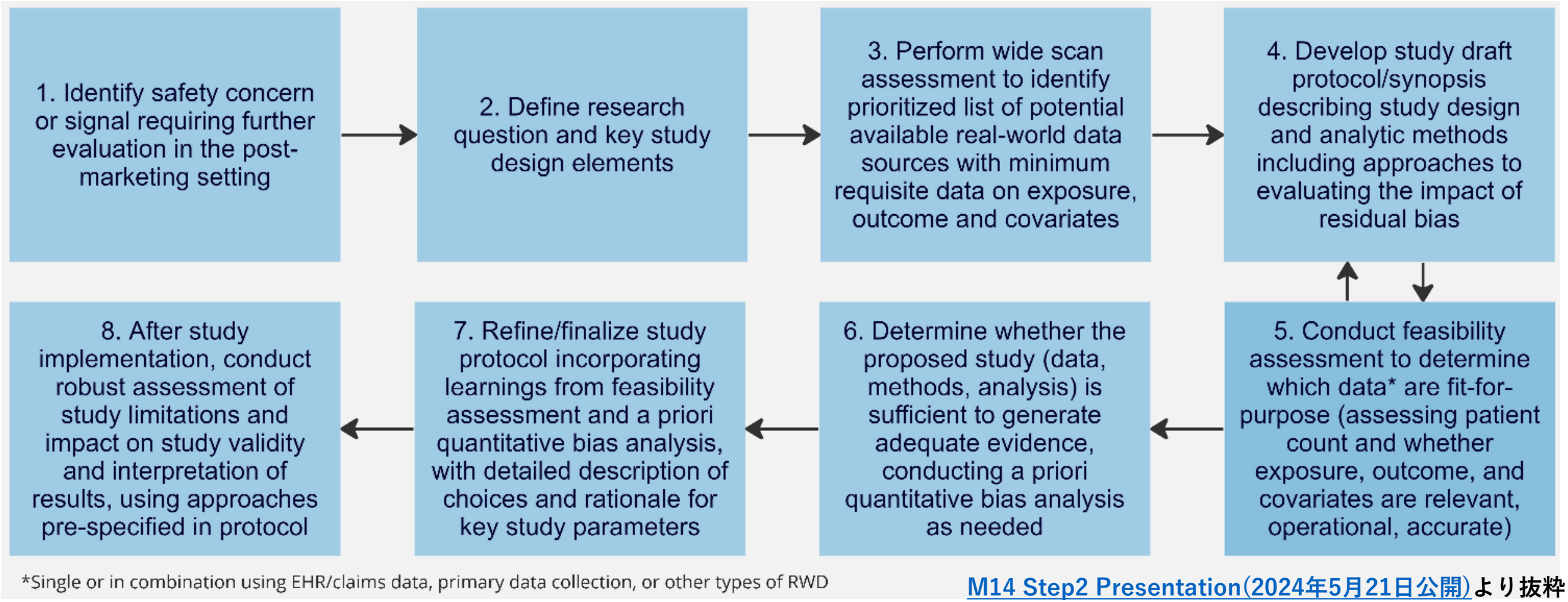
ガイドライン案の構成（パブリックコメント時点）

1. **INTRODUCTION：**
   - Objectives, Background, Scope
2. **GENERAL PRINCIPLES**
3. **FRAMEWORK FOR GENERATING ADEQUATE EVIDENCE USING REAL-WORLD DATA**
4. **INITIAL DESIGN AND FEASIBILITY：**
   - Research Question and Feasibility Assessments
5. **PROTOCOL DEVELOPMENT：**
   - Study Design, Data Sources, Target/Study Population, Exposures/Outcomes/Covariates, Bias / Confounding, Validation
6. **DATA MANAGEMENT**
7. **ANALYSIS**
8. **REPORTING AND SUBMISSION：**
   - Adverse Events, Adverse Drug Reactions, and Product Quality Complaints
   - Formatting and Content of Study Documents for Submission to Regulatory Authorities
9. **DISSEMINATION AND COMMUNICATION OF STUDY MATERIALS AND FINDINGS**
10. **STUDY DOCUMENTATION AND RECORD RETENTION**
11. **CONSIDERATIONS IN SPECIFIC POPULATIONS**

M14 Step2 Presentation(2024年5月21日公開)より抜粋

FRAMEWORK FOR GENERATING ADEQUATE EVIDENCE USING REAL-WORLD DATA （パブリックコメント時点）

The Guideline presents an overall framework for generating adequate evidence using fit-for-purpose real-world data to address regulatory questions on the safety of medicines, summarized in this diagram



M14 Step2 Presentation(2024年5月21日公開)より抜粋

今後の予定

Expected future completion date	Milestone
Sep. 2024 - May 2025	Review, evaluate, and revise guideline based on comments received; Complete draft training materials
Jun. 2025	Step 3 Sign-off by M14 EWG Topic Leaders Step 4 adoption of final Guideline

M14 Workplan(2025年2月13日公開)より抜粋

ご清聴ありがとうございました。