



Introduction to the ICH M14 Guideline (Step 4):

General Principles on Planning, Designing, Analysing, and Reporting of Non-interventional Studies that Utilize Real-World Data for Safety Assessment of Medicines

실사용 자료 활용한 약물 안전성 평가를 위한 비중재 연구 계획 및 설계에 대한 원칙들

2025. 9. 24

BongKyoo Choi, ScD MPH RPh

Head, AI & Data Science Center, GC Biopharma
Expert member, IFPMA TF on ICH M14

▼ M14 EWG

General Principles on Plan, Design, Analysis, and Reporting of Non-Interventional Studies That Utilize Real-World Data for Safety Assessment of Medicines

This topic was endorsed by the ICH Assembly in June 2021.

The ICH M14 Guideline reached *Step 4* of the ICH process on 04 September 2025.

The M14 Guideline:

- Provides recommendations for generating real-world evidence (RWE) from real-world data (RWD) for regulatory submissions on post-marketing safety, acknowledging regional differences in RWD definitions and allowing supplementary data, including primary data collection where appropriate (see ICH E8);
- Provides recommendations with the intent to harmonise expectations for the design, planning, analysis, and reporting of non-interventional safety studies to facilitate regulatory review.

Rapporteur: Dr. David Moeny (FDA, United States)

Regulatory Chair: Dr. Kazuhiro Kajiyama (MHLW/PMDA, Japan)


Date of *Step 4*: 4 September 2025


Status: *Step 5*

Guideline

 M14 Guideline


Endorsed Documents

 M14 Concept Paper

 M14 Business Plan

 M14 Work Plan

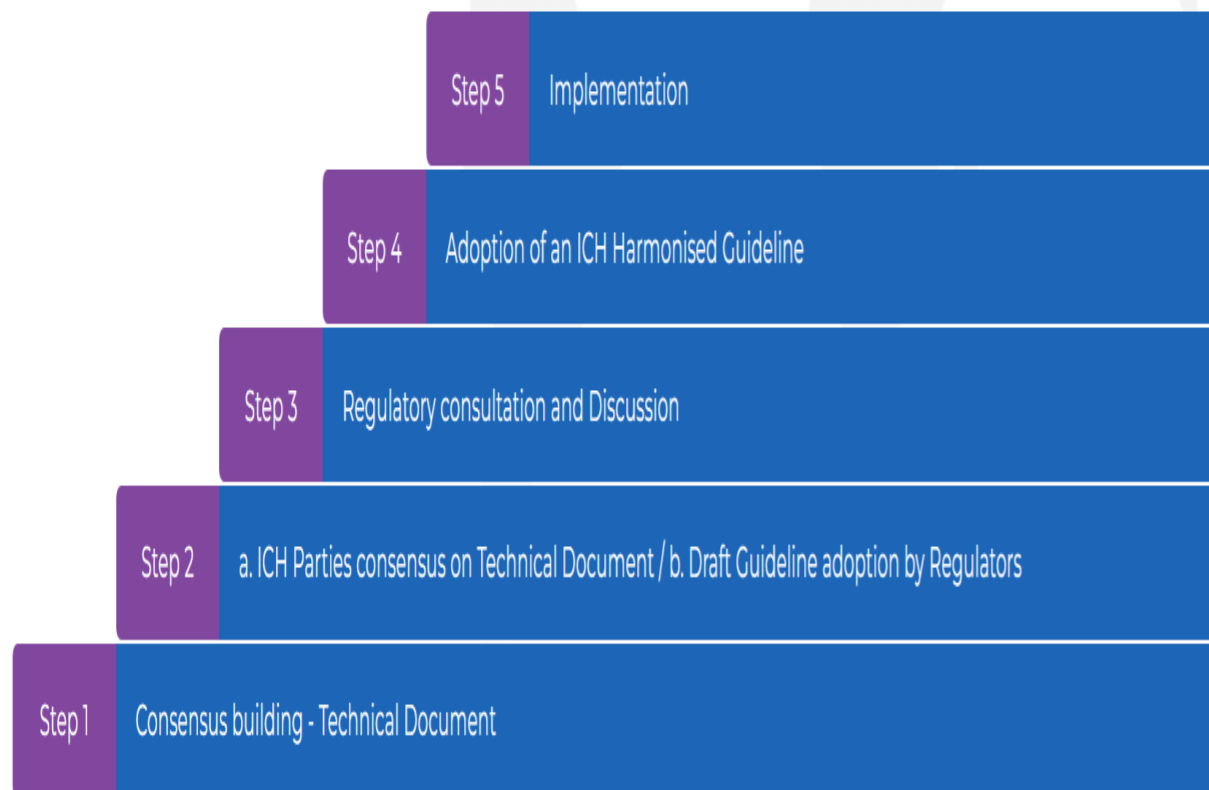
WG Presentation / Trainings

 M14 Step 4 presentation

WG list

Formal ICH Procedure

The Formal ICH Procedure is a step-wise procedure consisting of 5 steps (see below, click to have information on a particular step). This procedure is followed for the harmonisation of all new ICH topics.



M14 EWG General Principles on Plan, Design, Analysis, and Reporting of Non-Interventional Studies That Utilize Real-World Data for Safety Assessment of Medicines

Experts

ANVISA, Brazil

Ms. Flávia Regina Souza Sobral

CDSCO, India

Dr. Rubina Bose

EFPIA

Dr. Kimberley Brodovicz
Dr. Daniel Rosenberg

Global Self-Care Federation

Dr. Matthew Francis

Health Canada, Canada

Dr. Melissa Kampman

IGBA

Dr. Ayush Patel

MFDS, Republic of Korea

Dr. Seo Hyun Ok

NMPA, China

Dr. Jun Wang

SFDA, Saudi Arabia

Dr. Fawaz Alharbi

TFDA, Chinese Taipei

Ms. Jhih-Yu Syu

BIO

Dr. Brian Bradbury
Dr. Rachel Sobel

EC, Europe

Dr. Annalisa Capuano
Dr. Catherine Cohet

FDA, United States

Dr. Wei Hua
Dr. Yun Lu

HSA, Singapore

Dr. Sreemane Dorajoo

IFPMA

Mr. Tong Guo

JPMA

Prof. Makoto Miyazaki
Mr. Akinori Yuri

MHLW/PMDA, Japan

Dr. Kazuhiro Kajiyama
Dr. Takashi Waki

PhRMA

Mr. Robert Reynolds

Swissmedic, Switzerland

Dr. Renate Essen

WHO

Dr. Noha Iessa

Rapporteur

Dr. David Moeny (FDA, United States)

Regulatory Chair

Dr. Kazuhiro Kajiyama (MHLW/PMDA, Japan)



IFPMA

(International Federation of
Pharmaceutical
Manufacturers and
Associations):

IFPMA

Task Force on ICH M14

(Experts from China,
China Taipei, Brazil,
Republic of Korea)



KPBMA

Korea Pharmaceutical and Bio-Pharma
Manufacturers Association

Disclaimer: Expert Working Groups members are appointed by their nominating ICH Member or Observer party and are responsible for representing the views of that party, which may not necessarily reflect their personal views. Working Group experts do not respond personally to external inquiries but are directed to forward any inquiries they receive to their nominating party or the ICH Secretariat for a response on behalf of either their ICH party or the ICH Association as appropriate. For questions to the ICH Secretariat, please use the contact form on the ICH website.



Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products

AUGUST 2023

Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products

MARCH 2024



Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence - Scientific guideline

MARCH 2025




MFDS (Korea) Guidelines on RWD and/or non-interventional studies

가이드라인 등록번호
[안내서-1128-01]

의료정보 데이터베이스 연구에 대한 가이드라인
(민원인 안내서)

2021. 6.

 식품의약품안전처


목 차

- I. 서론 2
 - 1. 배경 및 목적 2
 - 2. 적용 범위 3
 - 3. 용어의 정의 3
- II. 데이터베이스의 종류 및 사용 시 고려사항 6
 - 1. 국내 RWD 자료원 현황 6
 - 2. 주요 데이터베이스 종류 및 특징 7
 - 가. 건강보험 청구자료 7
 - 나. 전자의무기록 8
 - 다. 환자등록자료 9
 - 3. 데이터베이스 사용 시 유의사항 9
 - 가. 적절성 10
 - 나. 신뢰성 10
- III. 연구설계 및 선정 시 고려사항 12
 - 1. 연구설계 12
 - 가. 코호트 연구 12
 - 나. 환자-대조군 연구 13
 - 다. 코호트 내 환자-대조군 연구 14
 - 라. 환자군 연구 15
 - 2. 연구설계 선정 시 고려사항 18
 - 가. 연구대상의 정의 18
 - 나. 노출 및 결과의 정의 18
 - 다. 비뮌됨, 교란요인 및 효과변경인자 19
 - 3. 데이터 관리 22
 - 4. 분석 22
 - 5. 개인정보보호 및 윤리 23
- IV. 연구계획서 및 보고서 작성 24
 - 1. 연구계획서 작성방법 24
 - 2. 연구보고서 작성방법 29

가이드라인 등록번호
[안내서-0019-06]

**- 의약품 등 시판 후 안전관리 -
신약 등의 재심사 업무 가이드라인**
(민원인 안내서)

2021. 11.

 식품의약품안전처

시판 후 조사 (PMS)

1. 사용성적조사
2. 특별조사

시판 후 데이터베이스 연구 (Database Study):

의료 정보 데이터베이스 취급자가 제공하는 의료 정보 데이터베이스를 이용하여 의약품의 이상 사례에 의한 질병 등의 종류별 발현 상황 및 품질, 유효성 및 안전성 등에 관한 정보의 검출 또는 확인을 위해 수행하는 연구방법

3. 시판 후 임상 시험

ICH M14: General Principles on Planning, Designing, Analysing and Reporting of Non-Interventional Studies That Utilise Real-World Data for Safety Assessment of Medicines

Step 4 document – to be implemented

September 2025

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

- This presentation is protected by copyright and may, with the exception of the ICH logo, be used, reproduced, incorporated into other works, adapted, modified, translated or distributed under a public license provided that ICH's copyright in the presentation is acknowledged at all times. In case of any adaption, modification or translation of the presentation, reasonable steps must be taken to clearly label, demarcate or otherwise identify that changes were made to or based on the original presentation. Any impression that the adaption, modification or translation of the original presentation is endorsed or sponsored by the ICH must be avoided.
- The presentation is provided "as is" without warranty of any kind. In no event shall the ICH or the authors of the original presentation be liable for any claim, damages or other liability arising from the use of the presentation.
- The above-mentioned permissions do not apply to content supplied by third parties. Therefore, for documents where the copyright vests in a third party, permission for reproduction must be obtained from this copyright holder.

Background

- **This document has been signed off as *Step 4* document (4 September 2025) to be implemented by the ICH Regulatory Members.**
- **This document was developed based on a Concept Paper (5 April 2022) and Business Plan (5 April 2022).**

Introductory Note

These slides were produced as training material to accompany the ICH M14 Guideline.

The intention is to assist the scientific community in the understanding of the new guideline to support the development of high-quality evidence regarding the safety of medicines to address regulatory questions.

For this purpose, the training material highlights selected sections of the guideline content, and for practicality purposes, is also accompanied by an example that is illustrative of the conceptual framework that was drafted based on the experience of the Expert Working Group members.

Training Objective

- **To understand the purpose, scope and considerations related to designing and executing non-interventional studies (NIS) fit for regulatory decision-making.**

Key steps in the conceptual framework for designing and executing NIS are illustrated with a worked example.

Key Principles

- **Provides recommendations on the planning, designing, analysing, and the reporting of non-interventional studies that utilise fit-for-use data for assessment of medicines (drugs, vaccines, and other biological products)**
 - Guideline addresses safety evaluations, but the principles presented may apply to effectiveness studies when real-world data are included.
- **Outlines an evidence-based approach to the development of high-quality evidence regarding the safety of medicines to address regulatory questions**
 - Recommends an iterative approach to study development, focusing on assessment of data fitness for use, the application of feasibility assessments to guide study design, further refinement of design based on feasibility results.
 - Recommends interaction with regulators for key decisions throughout the process.
- **Emphasises the importance of prespecifying and documenting key decisions around exposure, outcome, and covariate definitions, analysis plans, data management, and other aspects.**
- **Encourages transparency in study conduct, reporting, and dissemination of results.**

Expected Benefits

- Address gap in harmonised guidance on the development, conduct, and implementation, and regulatory use of non-interventional studies utilising real-world data.
- Provide recommendations and high-level best practices for study conduct of these studies.
- Improve efficiency and transparency in the development, reporting, submission and review of non-interventional studies and resultant regulatory actions.
- Improve the ability of the study protocol and report to be accepted across regulatory authorities.

Summary of Guideline Content

- Emphasises the importance of **fit-for-use real-world data** to address specific research questions via a stepwise, **iterative process** for study design and data source selection.
- Recommends an integrated assessment to determine if the evidence generated will be adequate, based on:
 - Data **relevance** and **reliability**;
 - Appropriateness of study **design** and **analytic** methods;
 - Robust assessment of study **limitations** and their impact on validity of the findings.
- Provides recommendations for **protocol** development including considerations for data sources, study population, exposures/outcomes/covariates, comparators, bias and confounding, and validation. Importance of **prespecifying** and **documenting** key decisions is stressed.
- Early **engagement** with regulatory authorities is encouraged.
- Emphasis is placed on **transparency** in study conduct, reporting, and dissemination of results.
- **Target audience** includes regulatory agencies, sponsors of non-interventional studies, researchers/study teams, data source holders/owners, public health organizations/agencies, scientific journals/outlets for dissemination.

Table of Contents

Section 1: Introduction

Section 2: General Principles

Section 3: Conceptual Framework for Generating Adequate Evidence using Real-World Data

Section 4: Initial Design and Feasibility

- Development of research question and feasibility assessments

Section 5: Protocol Development

- Study Design, Target/Study Population, Data Sources, Exposures/Outcomes/Covariates, Bias and Confounding, Validation

Section 6: Data Management and Curation

- Data Management, Quality assurance and control, Roles of data holders and researchers

Section 7: Analysis

Section 8: Reporting and Submission

- Adverse event reporting, regulatory submission of safety studies

Section 9: Dissemination and Communication of Study Materials and Findings

Section 10: Study Documentation and Record Retention

Section 11: Considerations in Specific Populations

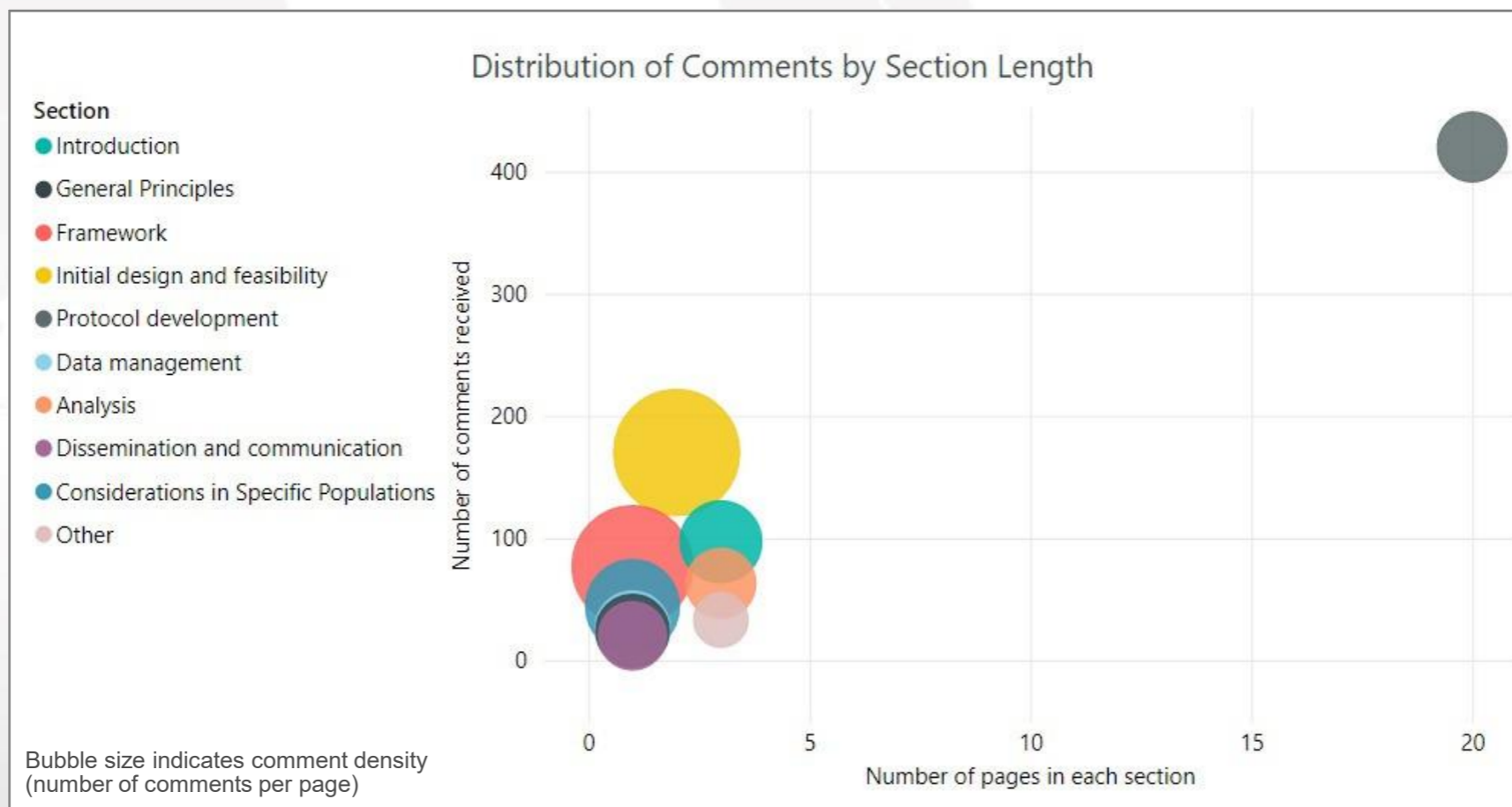
Section 12: Glossary

Section 13: References

Results of Public Consultation

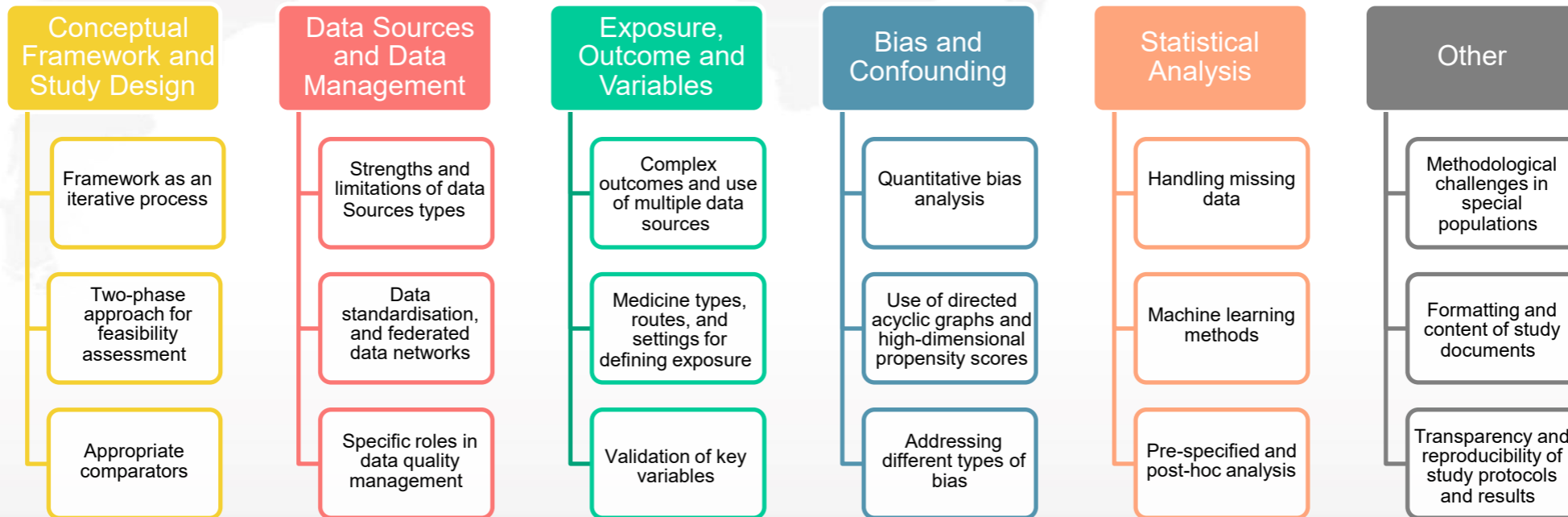
- Strong interest from the community - approximately 1600 comments received
 - AI was used for the initial processing and deduplication (e.g., fuzzy matching and semantic clustering)

The figure below shows that, while “Protocol Development” section had the highest number of comments, it also had the highest number of pages. Sections “Initial Design and Feasibility” and “Framework” received a higher density of comments relative to their length.



Results of Public Consultation (cont.)

- Improvements to the guideline
 - Public comments resulted in changes to the guideline, incorporating more advanced methodological concepts and addressing a broader range of potential challenges in study design and execution.
 - Below is a visual summary of content areas where the guideline now provides additional detail or clarification.



Objectives of the ICH M14



The purpose of this guideline is to recommend international standards for, and promote harmonization of, the general principles on planning, designing, analysing, and reporting of non-interventional studies that utilize fit-for-use (frequently referred to as fit-for-purpose) data for safety assessment of medicines (drugs, vaccines, and other biological products).

Scope of the ICH M14



Although there are slight differences between regions with regard to what constitutes **real-world data** (RWD), this guideline provides recommendations for the generation of **real-world evidence** (RWE) that is submitted to regulators for the purpose of evaluating post-marketing safety of medicines. At times, RWD sources alone may be insufficient to answer the research question of interest and a study will require additional data for the purposes of the study. Because **primary data collection** may be relevant to non-interventional studies using RWD, this guideline also includes considerations for primary data collection (see ICH E8 for additional information on this topic(7)).

The following are out of scope:

- Pharmacovigilance studies relying only on routine spontaneous reports obtained from national or regional data sources (e.g., pharmacovigilance systems at national level);
- Studies involving treatment assignment, including randomized controlled trials, pragmatic trials, single arm clinical trials with treatment assignment defined per protocol, and trials using external comparators;
- Studies primarily involving user-generated health data extracted from other sources (e.g., websites, blogs, social media, chat rooms); and
- Studies evaluating the effectiveness of risk minimization programs (e.g., Risk Evaluation and Mitigation Strategy or additional Risk Minimization Measures studies), unless the evaluation takes the form of a non-interventional study to evaluate the safety concern

Characteristics of Data Source Types in the ICH M14



Examples of data source types include data derived from **Electronic Health Records (EHRs)**, **administrative claims data**, patient registries, patient-generated data, and data gathered from other sources that can inform on health status, such as interviews, mail surveys, computerized or mobile-application questionnaires, and measurements through **digital health technologies** (DHTs; see Data Collected by Digital Health Technologies). Regardless of the data source(s) used, information on the context of the evidence generation should be obtained (e.g., geographic location, setting in which the data were generated, period during which the data were collected, and demographic information distribution of populations included in the data source).

A high-level summary of commonly used data source types is provided in the sections below.

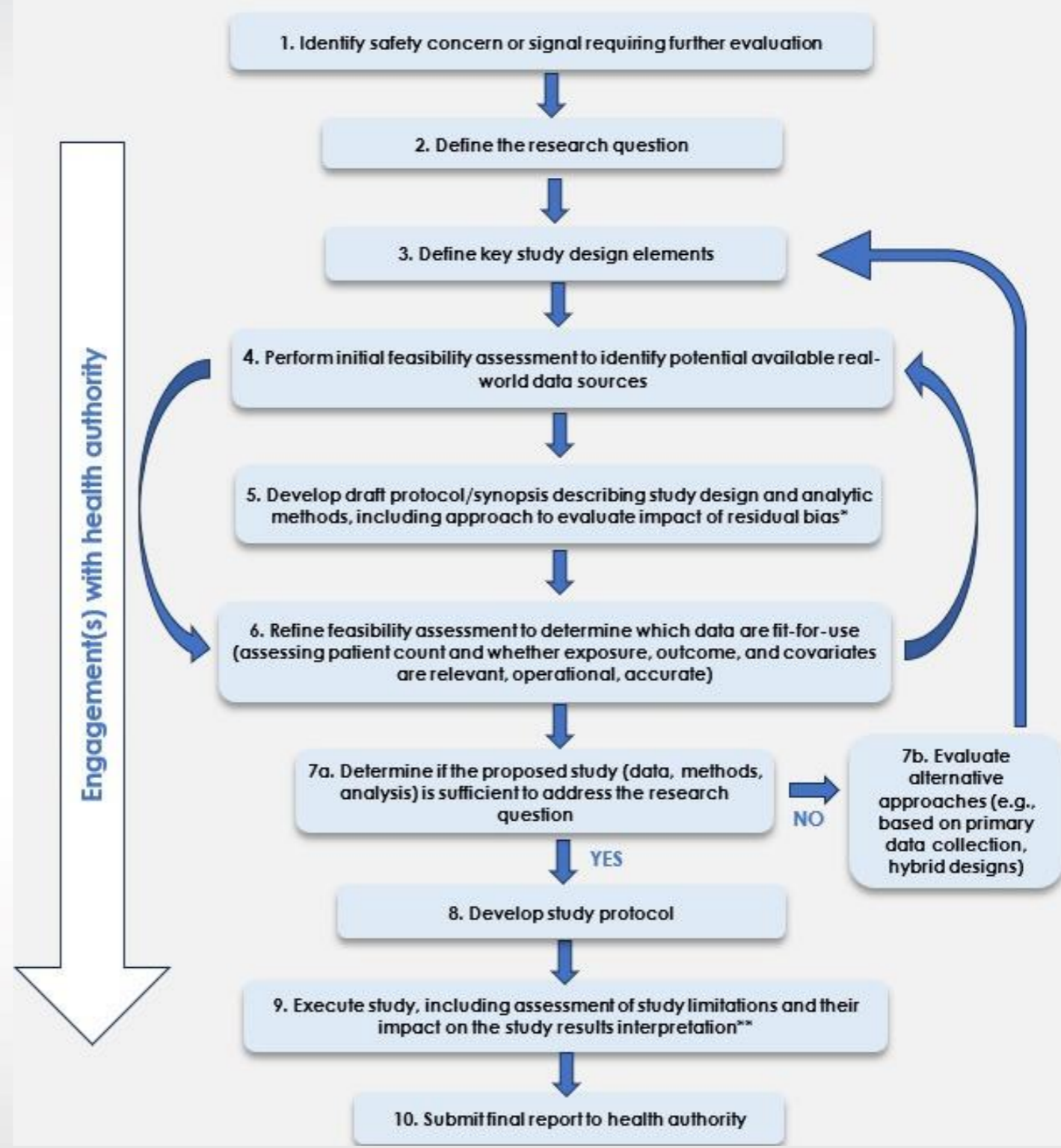
- **Electronic Health Record Data**
- **Administrative Claims Data**
- **Registries**
- **Data Collected by Digital Health Technologies**

Considerations at Study Kickoff

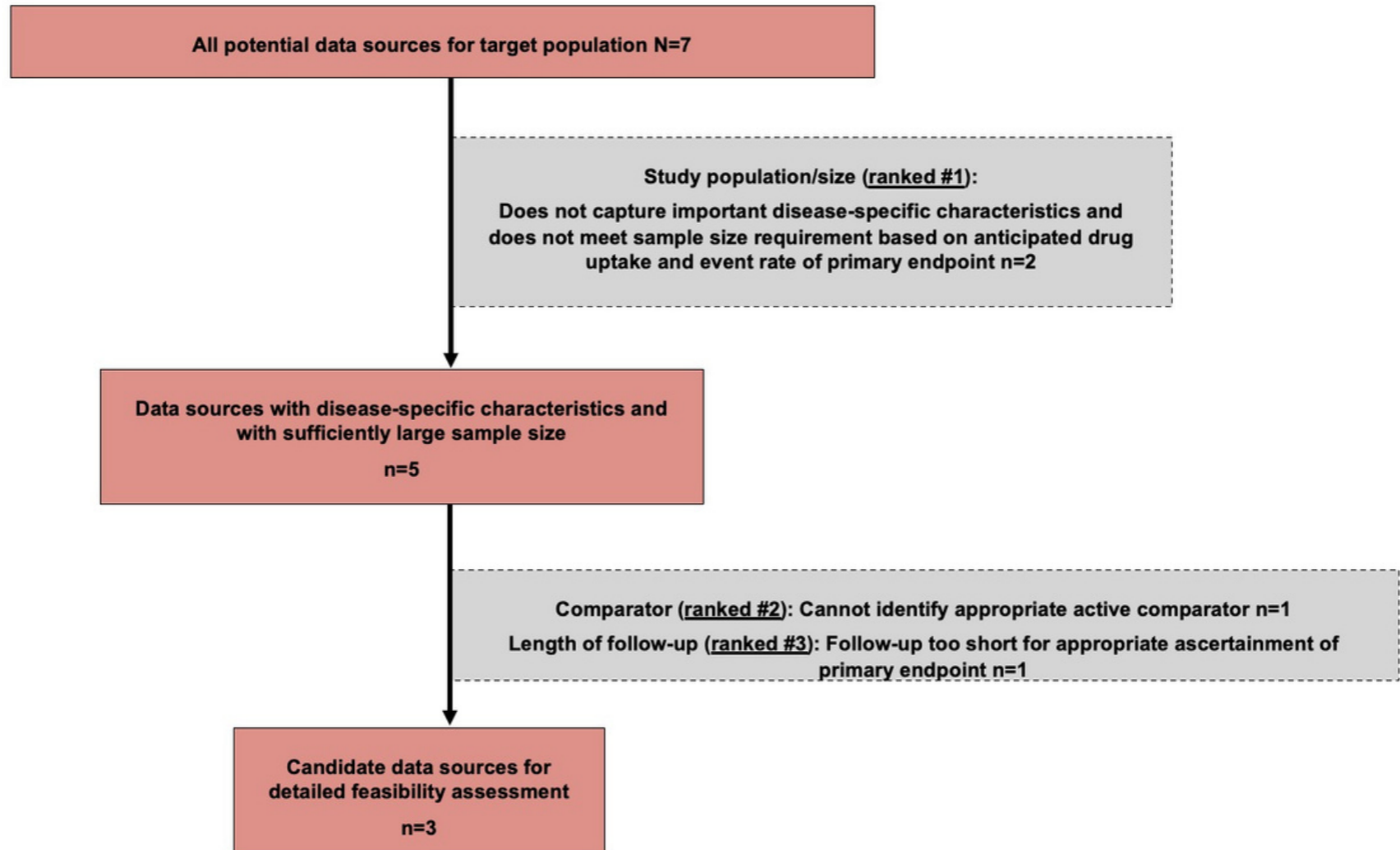
- Align on research question & study objective(s);
- Identify appropriate subject matter experts;
- Identify and plan for key stakeholder engagement (e.g., health authority(ies));
- Define key milestones and timelines (e.g., protocol/statistical analysis plan (SAP) finalization, final report);
- Identify known or anticipated risks to study design, execution; plan mitigation strategies;
- Clarify operational aspects including meeting logistics for the study team (frequency, decision log, etc.).

ICH M14 Step 4

Conceptual Framework for Generating Adequate Evidence using Real-World Data



Initial Feasibility Scan to Identify Fit-For-Purpose Data Sources (Steps 4-5)



Detailed Feasibility Assessment of Candidate Data Sources with Heatmap (Step 6)

	Data source 1	Data source 2	Data source 3
Study population - Ability to meet target sample size - Ability to capture important disease-specific characteristics	4	4	4
Identification of treatment group	5	5	5
Identification of active comparator group	5	3	3
Length and frequency of follow-up	4	3	3
Generalizability	5	2	2
Ascertainment of primary endpoint	4	3	3
Ascertainment of secondary endpoint	3	4	4
Historical use of data source for <u>postmarketing commitments</u>	4	4	4
Timelines - Time to fully executed contract, data access, and analysis	Fast	Slow	Slow
Final data source selection	SELECTED		

Legend: (5) Many or nearly all data requirements met (4) Several data requirements met (3) Likely that several data requirements met but requires further investigation (2) Some data requirements met or unable to assess at this time (1) Data requirements not met

Determine if Proposed Study, Including Selected Data Source(s), is Sufficient (Step 7a, 7b)

Data Source 1 selected. Further investigate availability of key elements of the secondary endpoint

Key elements of the secondary endpoint are available

Continue to Steps 8, 9, 10

If no existing data sources can be identified (e.g. rare disease), consider alternative approaches.

[See next slide]

Key elements of the secondary endpoint are missing

Evaluate alternative approaches

Can the missing data elements be collected by Data Source 1?

Is Data Source 1 still fit for use despite missing these key data elements?

Is linkage to another data source containing the missing data elements possible?

Add variables to existing registry

Consider *de novo* primary data collection

Return to Step 3

Iteration and Refinement

No data sources identified in feasibility assessment (Step 6)

Define specific data needs –specific measurement required to assess outcome:
e.g. sexual maturity assessment using Tanner stage questionnaire

Choose alternative approaches: *De novo* primary data collection
(e.g. registry) or hybrid approach (add questionnaire to existing
data asset) (Step 7b)

Define study elements and evaluate the feasibility of each approach and choose
approach (Steps 3-7a)

Develop protocol (Step 8)

Safety Reporting

Reporting of Adverse Events (AEs), Adverse Drug Reactions (ADRs) and product quality complaints

- **ICH E2D- Guidance for Market authorization holder (MAH) on reporting individual case safety reports (ICSRs)- “may require reporting to regulatory authority”**
- **Requirements can vary by:**
 - MAH, other sponsors, or applicant investigator.
 - Regions.
- **Refer to applicable laws and regulations (if ICH E2D not applicable).**

Study Reporting and Regulatory Submission

- **Consult guidance and engage early**
 - Refer to available guidance on document structure and content.
 - Initiate early discussions with regulatory agencies (agree on required documents and submission schedules).
- **Document variability (depending on local/regional requirements)**
 - Feasibility assessment
 - Protocol
 - SAP
 - Progress/interim and final reports
 - Reporting of AE / ADR / Product quality complaints
- **Leverage existing frameworks**
 - In the absence of specific regulatory guidance, use or adapt established frameworks from the scientific community.
 - For example: ISPE/ISPOR HARPER template



Considerations for Guideline Implementation

- **Regional differences exist regarding:**
 - Patient privacy requirements;
 - Requirements for reporting adverse events;
 - Requirements for study reporting and record retention;
 - Data accessibility, readiness.
- **Other ICH guidelines to review in relation to ICH M14**
 - [ICH E2D](#) Post-Approval Safety Data Management
 - [ICH E8 \(R1\)](#) General Considerations for Clinical Studies
 - [ICH E6\(R3\)](#) Guideline for Good Clinical Practice
 - ICH E23 - Pursuing Opportunities for Harmonisation in Using Real-World Data to Generate Real World Evidence, with a focus on Effectiveness of Medicines (in development, [reflection paper](#))

Dissemination and Communication

- **Public protocol availability**
 - Researchers are **encouraged** to make protocols publicly available in appropriate public registers of studies. This may be a regional requirement.
 - This should occur **after** protocol finalization.
- **Dissemination and communication of study results**
 - Registration of study reports may be required in accordance with local regulatory requirements.
 - Non-regulatory submission in scientific fora (e.g., conferences, workshops).
 - Peer-reviewed Scientific publications.
 - Communications tailored for patients and practitioners.
- **Leverage existing best practice recommendations for reporting studies in scientific literature**
 - **RECORD** (The Reporting of studies Conducted using Observational Routinely collected health Data).
 - **ENCePP** (The European Network of Centers for Pharmacoepidemiology and Pharmacovigilance) - Guide on Methodological Standards in Pharmacoepidemiology.
 - **HMA-EMA** (Heads of Medicines Agencies – European Medicines Agency) - Catalogues of real-world data sources and studies.
 - **ICMJE** (International Committee of Medical Journal Editors) - Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals.

EMA (2012): Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies



1. Table of contents

The study protocol should include a table of contents. The following table of contents can be used if this guidance serves as a template (select the table of content and press "F9" to update the page numbers).

- 1. Table of contents..... 4**
- 2. List of abbreviations 5**
- 3. Responsible parties 5**
- 4. Abstract..... 5**
- 5. Amendments and updates 6**
- 6. Milestones 6**
- 7. Rationale and background 6**
- 8. Research question and objectives 7**
- 9. Research methods 7**
 - 9.1. Study design7
 - 9.2. Setting.....7
 - 9.3. Variables.....7
 - 9.4. Data sources8
 - 9.5. Study size8
 - 9.6. Data management.....8
 - 9.7. Data analysis8
 - 9.8. Quality control8
 - 9.9. Limitations of the research methods9
 - 9.10. Other aspects.....9

From 10 January 2013, marketing authorisation holders have the obligation to comply with the format and content of the study protocol for post-authorisation safety studies (PASS), as specified in Art 36 to 38 and Art 40 of the Commission Implementing Regulation (EU) No 520/2012. Use of the format is encouraged for PASS protocols submitted before that date.

- 10. Protection of human subjects 9**
- 11. Management and reporting of adverse events/adverse reactions 9**
- 12. Plans for disseminating and communicating study results 9**
- 13. References 9**
- Annex 1. List of stand-alone documents 10**
- Annex 2. ENCePP checklist for study protocols..... 10**
- Annex 3. Additional information..... 10**

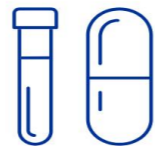
HMA-EMA Catalogues of real-world data sources and studies

The Catalogues for real-world data sources, studies, institutions and networks replace and enhance the previous EU PAS Register® and ENCePP Resource Database.



263

Data sources



3167

Studies



799

Institutions



185

Networks

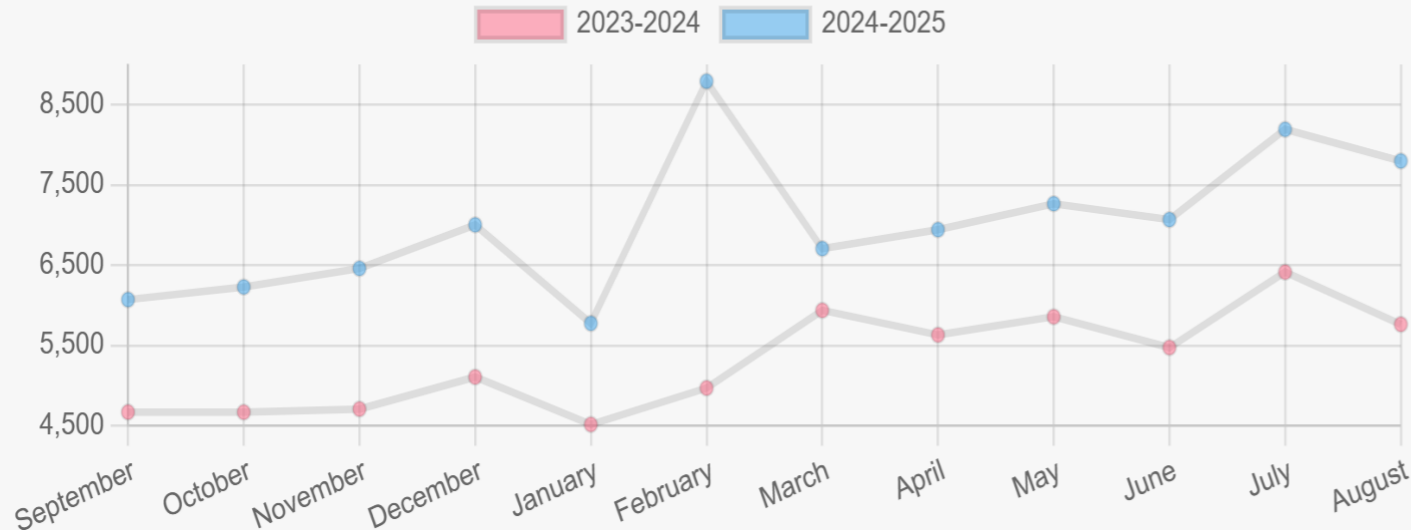
What is PROSPERO?

PROSPERO is an international systematic review registry that aims to promote transparency and open science, reduce reporting bias and help prevent unintended duplication and research waste.

The PROSPERO database currently includes records of over **373000** prospectively registered systematic reviews with health related outcomes, providing easy access to key information about planned, in-progress and completed reviews.

PROSPERO is produced by the Centre for Reviews and Dissemination (CRD) and funded by the National Institute for Health and Care Research (NIHR)

Recent PROSPERO registrations



BongKyo Choi, Eun-Kyoung Lee, Ju-Yeun Lee, Sangbaek Koh, Hyunjeong Cho, Sujin Lee. Incidence of Bacille Calmette-Guérin (BCG) vaccine-associated lymphadenitis in healthy children: a systematic review and meta-analysis. PROSPERO 2024 Available from <https://www.crd.york.ac.uk/PROSPERO/view/CRD42024531072>

Additional Suggested Literature

- **It is beyond the scope of ICH M14 Guideline to provide detailed instruction for the design and execution of non-interventional safety studies.**
- **The Guideline provides references to literature providing additional detail on topics such as quantitative bias assessment and the design and conduct of studies on special populations.**

Conclusions

- **ICH M14 harmonises the general principles on planning, designing, analysing, and reporting of non-interventional studies.**
- **An iterative, data driven approach to identify fit-for-use data and to inform subsequent study design is provided.**
- **Goals include streamlining study design, facilitating Submission of study protocols or reports across regulators, and supporting decision making.**

Contact

- **For any questions please contact the ICH Secretariat:**

admin@ich.org

Thank You!

Qs: b.choi@gccorp.com