Implementing ICH M14 in Fragmented Claims-EMR Settings

A Practical Framework for Real-World Safety Studies

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ICH M14: a harmonized baseline

Milestone	Date
ICH Step 4 adoption	4 September 2025
EU effective date	18 March 2026
FDA final guidance	March 2026

Harmonized principles for non-interventional safety studies using real-world data: research question, data suitability, feasibility, design, bias, validation of key variables, and reporting.

M14 harmonizes the principles, not the underlying data infrastructures.

ICH M14 Final Guideline (4 Sep 2025); EMA Step 5; FDA guidance for industry (Mar 2026).

The principles are harmonized. The infrastructures are not.

Linkage and coordinated access available

Claims ↔ EHR ↔ Registry

- Patient-level information can be combined where permitted
- Linkage quality and completeness require assessment

Sources accessed separately

Claims | Hospital EMR | Registry

- Study populations and records remain separate
- Access, coverage and definitions require source-specific assessment

Same principles. Different implementation conditions.

Comparison adapted from ICH M14 §5.3 considerations for multiple data sources. Presenter's framing.

M14 tells us WHAT. Fragmentation makes the HOW explicit.

Domain	Decision to make explicit
Fitness-for-use	Which source can serve which role?
Feasibility	What evidence is available at each decision point?
Comparator strategy	What question does the selected design answer?
Validation	What supports the operational definition in this population?

These questions arise in many settings. Fragmentation makes them difficult to leave implicit.

Related M14 scope: §3, §4.2, §5.1, §5.3, §5.6. Domain arrangement is the presenter's implementation format.

Evidence roles when sources remain separate

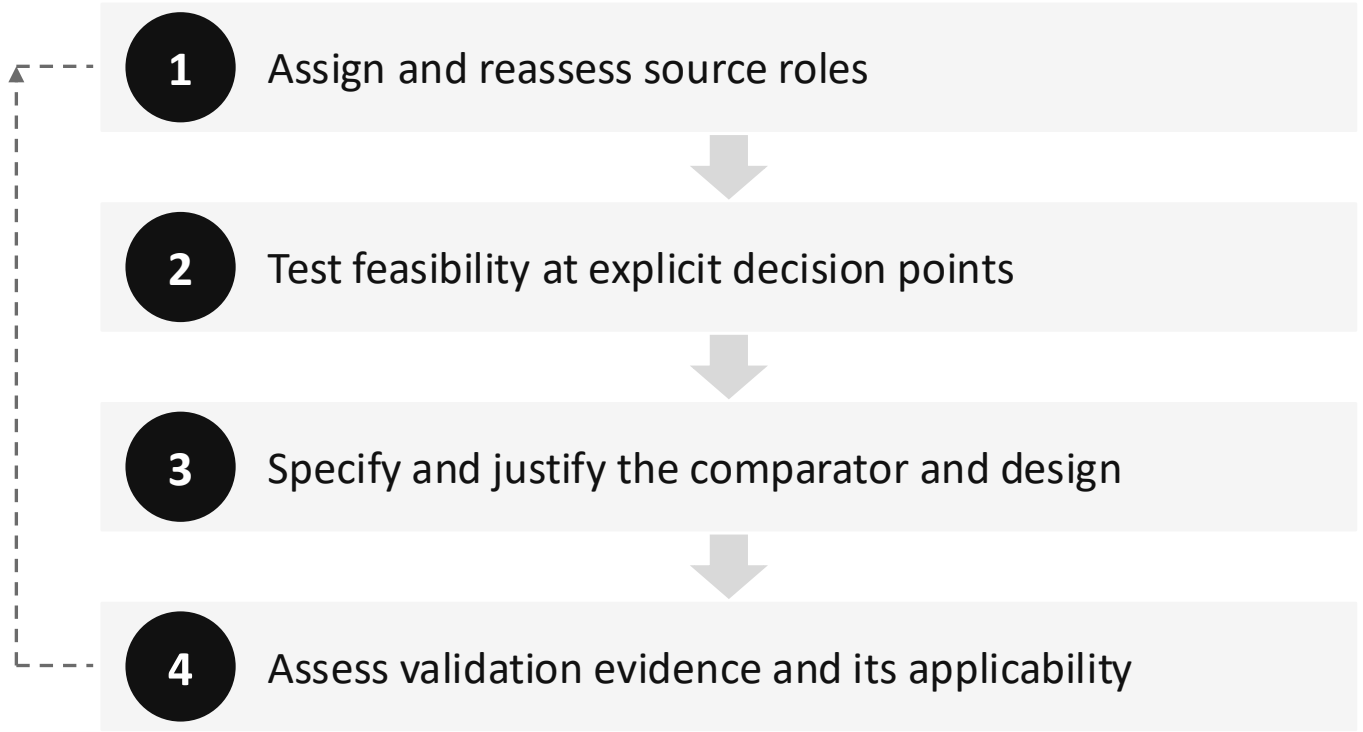
Primary analysis	Supporting evidence	Validation evidence	Not used
The source used to answer the study question	A defined contribution to interpretation, where justified	Evidence about the performance or suitability of an operational definition	No justified role in this study

Claims, EMRs and registries can each be primary sources in different studies.

Separate sources do not become one causal dataset.

A four-domain implementation framework

Starting point: the safety question and intended use of the evidence



Redesign returns to earlier decisions

Across all domains

Record the basis, the decision and the remaining uncertainty

Overall assessment

Can the proposed study support its intended purpose?

Fitness-for-use: fit for what role?

Question requirements

Population · exposure · comparator · outcome · covariates · follow-up

Assessment for each candidate source

Requirement	What is recorded?	What remains uncertain?
Relevant study element	Availability and observation conditions	Completeness, measurement and coverage

Output: a source-by-role assessment

Fitness is question- and role-specific. More sources is not automatically better.

Implements M14 §5.3 relevance and reliability as a question- and role-specific matrix.

Feasibility: staged decision gates

	Gate 1	Gate 2
Information	Documentation, literature, coverage, approximate volumes	Eligible counts, observation history, expected events, completeness
Decision	Proceed / Redesign / Stop	Confirm / Refine / Redesign / Stop
Meaning	Provisional commitment to further assessment	Decision about the proposed study

Define decision criteria before inspecting treatment-effect results.

Where access takes months, Gate 1 carries the cost of being wrong.

An access-constrained operationalization of M14's two-phase feasibility process (§4.2). Gate names are the presenter's.

Comparator strategy: start from the causal question

1. What is the target causal contrast?
2. Is the preferred design feasible and clinically meaningful?
3. If the design changes, what changes with it?

An active-comparator new-user cohort is one example for an appropriate medication-safety question — a design choice driven by the question, not a universal M14 requirement.

Record changes to

- Population
- Estimand
- Time zero
- Bias structure

Alternative designs are not interchangeable.

ICH M14 §4.1, §5.1, §5.5.1.

Validation evidence, applicability and robustness

Component	Question
Validation evidence	What supports the operational definition, and how was it assessed?
Applicability assessment	Does that evidence apply to this algorithm, population and setting?
Robustness analysis	How do results change under alternative definitions?

Robustness does not establish validity.

A published algorithm and a validated algorithm are not automatically the same thing.

ICH M14 §5.6, §7.1.3.

Implementation Decision Record

For M14-aligned studies in fragmented settings · Template — filled in for the worked illustration on slides 17–18

Decision	Choice and status	Basis	Remaining uncertainty or action
Source role	*candidate / proposed / confirmed*	*why this source, for this role*	*what still has to be assessed*
Feasibility gate	*go / redesign / stop*	*information available at the gate*	*what the gate could not establish*
Objective and design	*selected / reassessing*	*reason for the design choice*	*what changed, and residual bias*
Outcome definition and validation	*under assessment / supported*	*evidence and its applicability*	*next validation action*

Each decision links to its supporting assessment.

A presenter-proposed format, not an ICH template. M14 §2, §10 recommend documenting key decisions and rationale.

Korea: the implementation setting

Source	Assessment focus
National claims	Coverage of relevant care, exposure history and follow-up
Hospital EMRs	Recorded clinical information and the care captured by the institution
EMR-derived registries	Registry entry, collected study variables and follow-up procedures

Separate access processes and study populations. Patient-level linkage is not a routine pathway in the studies discussed here.

Practice background

Claims-based studies; safety and effectiveness studies using hospital EMRs, including registry-based studies within RMPs. The primary source follows the study question.

The illustrative question and candidate sources

Among patients initiating an anti-inflammatory biologic, how does the risk of hospitalized serious infection compare with initiation of an appropriate alternative therapy?

Composite design-stage illustration. No study results are presented.

Assessment focus for each candidate source

Requirement	Claims candidate	EMR-derived registry
Exposure and prior history	Covered use, observable history	Recorded treatment, prior care
Outcome and follow-up	Hospitalization capture	Registry follow-up, outside events
Clinical variables	Measured variables, justified proxies	Actual collection, completeness
Study population	Eligible observable cohort	Registry population

For this illustration: assess claims as the primary candidate.

Gate 1: reimbursement and exposure observability

A drug can be perfectly coded in claims and still be unusable for the study if the clinically relevant use is not reimbursed.

Before detailed assessment

- Is use in the target indication observable?
- Is the alternative therapy used in a comparable clinical setting?
- Do approximate volumes justify further assessment?
- What evidence or further work could support the outcome definition?

Illustrative decision

GO to detailed feasibility

Eligible cohort size and measurement adeq uacy remain to be established.

Gate 2: the planned initiator cohort is insufficient

Illustrative finding

Eligible observed initiators do not support the planned precision for the comparison.

Known constraint

Direct clinical severity measurement remains limited.

Decision

REDESIGN

Including current users would change the population and the treatment period being observed.

Finding is illustrative. Selection differences between initiators and current users: ICH M14 §5.5.1.

The proposed descriptive question

Among patients receiving the biologic at a prespecified cohort-entry date, what is the observed incidence rate of hospitalized serious infection during on-treatment follow-up?

	Original plan	Proposed redesign
Population	Eligible initiators	Patients receiving treatment at cohort entry
Objective	Comparative initiation effect	Descriptive event occurrence
Start of follow-up	Treatment initiation	Prespecified cohort entry



Treatment initiation — not observed as follow-up in the redesign

Cohort entry → on-treatment follow-up (observation window)

Selected for reassessment. The original initiation comparison remains unanswered.

Decision Record: the original comparative plan

Composite planning illustration

Source role	Choice and status **Claims proposed as primary can didate**	Basis Selected for exposure history and longitudinal hospital capture	Remaining uncertainty or action Still to assess: coverage of relevant use, outcome measurement
Gate 1 — original comparis on	Choice and status **GO to detailed feasibility**	Basis Plausible coverage, comparator and volume	Remaining uncertainty or action Public volume is not an eligible cohort count
Gate 2 — original comparis on	Choice and status **REDESIGN**	Basis Initiator yield does not support the planned comparison	Remaining uncertainty or action Original initiation question unresolved

Decision Record: the revised study and what remains

Composite planning illustration

	Choice and status	Basis	Remaining uncertainty or action
Objective and design	**Descriptive current-user cohort — selected for reassessment**	A separate descriptive information need	Selected population and clinical case mix limit interpretation
Outcome and validation	**Algorithm and external evidence under assessment**	No local chart validation in this illustration	Next: assess whether external validation applies to this algorithm and population

Next decision: can the revised study support its descriptive purpose?

What the record gives us — and what it does not

Intended use	Assessment in this illustration
Estimate the comparative effect of initiation	Not answered by the revised design
Describe event occurrence in the defined current-user cohort	A candidate purpose, subject to reassessment
Describe all treated patients or early initiation risk	Beyond what the proposed cohort alone supports

None of that is hidden. A reviewer can see the limits of this study before reading a single result.

Before proceeding: reassess eligibility, person-time, precision and outcome measurement.

What the framework does — and does not do

It does

- Assign explicit source roles
- Make design changes and their reasons visible
- Surface remaining uncertainty before results
- Give early regulatory dialogue something concrete to review

It does not

- Make unlinked populations equivalent to linked data
- Recover clinical information that was never recorded
- Turn an unsuitable source into a fit-for-use one
- Establish regulatory acceptance

The purpose is not to lower the standard. It is to make the evidence boundary visible.

Fragmentation differs. The implementation questions recur.

National claims and separately accessed hospital records

Registries and separate claims sources

Research networks with uneven data depth

Health-system records with incomplete observation of outside care

Recurring decisions

- Source role
- Feasibility
- Design
- Validation
- Intended use of the evidence

Korea is one illustration of a broader problem.

Three messages

1. M14 harmonizes principles. Implementation depends on the study setting.

2. Make source roles, feasibility decisions, design changes and validation evidence explicit and traceable.

3. State what the selected evidence can support, and which questions remain unanswered.

Fragmentation should not lower the evidentiary standard.

It should raise the standard for transparency.

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