

Evaluating the Quality of Real-World Evidence Used to Support Regulatory Decision-Making for Medical Devices

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Evaluating the **Quality of Real-World Evidence** Used to Support **Regulatory Decision-Making** for Medical Devices

1. Regulatory Decision Making
2. Quality of the Evidence
3. Real-world Data & Real-world Evidence
4. Risk of Bias assessment

Contains Nonbinding Recommendations

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 30, 2019.

Document originally issued on March 28, 2012.

This document supersedes “Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications” issued August 24, 2016.

For questions about this document concerning devices regulated by CDRH, contact the Office of Policy at 301-796-5441. For questions about this document concerning CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD) by calling 800-835-4709 or 240-402-8010.

Benefit-Risk Assessment Summary

Based on the totality of the data Device Name: PMA/De Novo Number: <input type="checkbox"/> Interim <input type="checkbox"/> Final	Proposed Indications for Use
Assessment of Benefit	Considering benefit in terms of <ul style="list-style-type: none"> • Type • Magnitude • Probability • Duration of effects <ul style="list-style-type: none"> • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable) • Other
1. Is there any evidence of clinical benefit?	<input type="checkbox"/> YES → Q2 <input type="checkbox"/> NO → Do not approve/grant for proposed Indications for Use; proceed to Q9
2. What is the extent of uncertainty for the Benefits?	<input type="checkbox"/> High <input type="checkbox"/> Med <input type="checkbox"/> Low Continue to Q3
Assessment of Risk	Considering risk in terms of <ul style="list-style-type: none"> • Severity, types, number and rates of harmful events • Probability of a harmful event • Duration of harmful events • Risks from false-positive or false-negative results <ul style="list-style-type: none"> • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable)
3. Are known/probable risks more than minimal?	<input type="checkbox"/> YES → Q4 <input type="checkbox"/> NO → Q4
4. What is the extent of uncertainty for the risks?	<input type="checkbox"/> High <input type="checkbox"/> Med <input type="checkbox"/> Low Continue to Q5
Assessment of Benefit-Risk	
5. Do the Benefits outweigh the Risks?	<input type="checkbox"/> YES → Worksheet complete <input type="checkbox"/> Unable to conclude that benefits outweigh the risks → Q6
6. Do the Benefits outweigh the Risks, taking into account additional considerations?	<input type="checkbox"/> YES → Worksheet complete <input type="checkbox"/> Unable to conclude that benefits outweigh the risks → Q7
7. Can the risks be mitigated, so that Benefits outweigh the Risks?	<input type="checkbox"/> YES → Worksheet complete <input type="checkbox"/> Unable to conclude that benefits outweigh the risks → Q8
8. Do the Benefits outweigh the Risks considering the use of postmarket actions?	<input type="checkbox"/> YES → Worksheet complete <input type="checkbox"/> Unable to conclude that benefits outweigh the risks → Q9
9. Is there any evidence of clinical benefit for a modified Indications for Use?	<input type="checkbox"/> YES → Return to Q1 and proceed with modified Indications for Use <input type="checkbox"/> NO → Do not approve/grant

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Assessment of Risk	Considering risk in terms of <ul style="list-style-type: none"> • Severity, types, number and rates of • Patient perspective (or care-partner and/or
Strength + Uncertainty	
negative results	
3. Are known/probable risks more than minimal?	<input type="checkbox"/> YES → Q4 <input type="checkbox"/> NO → Q4
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2. What is the extent of uncertainty for the benefits?

Recognizing that some extent of uncertainty always exists, select the sources of uncertainty, if applicable, in the data that affect your assessment of the clinical benefit. Consider sources of uncertainty related to clinical and/or analytical performance characteristics (e.g., sensitivity, specificity, accuracy, precision, reproducibility, as applicable). *Select any of the following that demonstrate sources of uncertainty for the benefits, and then answer the question in the box below.*

- Inconsistent or conflicting results between studies
- Wide confidence intervals surrounding the point estimate(s) and/or odds ratio(s)
- A significantly underpowered study with statistical insignificance in outcome measure(s)
- High subject or specimen loss-to-follow-up at critical assessment point(s)
- Large amount of missing data at critical assessment time(s) +/- imputation
- Significant number of major protocol deviations
- Impact of confounding interventions or physiological factors
- Inconsistent user experience or user experience not representative of likely real-world user
- Unclear correlation between non-clinical data, pre-selected enriched data, or computer modeling and clinical performance
- Surrogate endpoint has not yet been demonstrated to correlate with a clinical outcome
- Real-World Evidence (RWE) is not relevant or reliable for the purposes of the proposed analysis
- Inspectional findings
- Study design or results lead to lack of generalizability for the intended use population or specific clinical subpopulations.
- Physiological or clinically meaningful range of the diagnostic output is unknown, or generalizability of proposed clinical cut-off is unknown
- Imperfect comparator method used to calculate performance characteristics
- Other(s): The duration of benefit is unclear.
- None

Q2: What is the extent of uncertainty for the benefits?

- Low → Continue to Question 3
- Med → Continue to Question 3
- High → Continue to Question 3

Hierarchy of Evidence

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

2.2. Assessment of Cardiovascular Risk

Recommendations for Assessment of Cardiovascular Risk		
Referenced studies that support recommendations are summarized in Online Data Supplement 3.		
COR	LOE	Recommendations
I	B-NR	1. For adults 40 to 75 years of age, clinicians should routinely assess traditional cardiovascular risk factors and calculate 10-year risk of ASCVD by using the pooled cohort equations (PCE) (S2.2-1, S2.2-2).
Ila	B-NR	2. For adults 20 to 39 years of age, it is reasonable to assess traditional ASCVD risk factors at least every 4 to 6 years (S2.2-1–S2.2-3).
Ila	B-NR	3. In adults at borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk (≥7.5% to <20% 10-year ASCVD risk), it is reasonable to use additional risk-enhancing factors to guide decisions about preventive interventions (e.g., statin therapy) (S2.2-4–S2.2-14).
Ila	B-NR	4. In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk) or selected adults at borderline risk (5% to <7.5% 10-year ASCVD risk), if risk-based decisions for preventive interventions (e.g., statin therapy) remain uncertain, it is reasonable to measure a coronary artery calcium score to guide clinician–patient risk discussion (S2.2-15–S2.2-31).
Iib	B-NR	5. For adults 20 to 39 years of age and for those 40 to 59 years of age who have <7.5% 10-year ASCVD risk, estimating lifetime or 30-year ASCVD risk may be considered (S2.2-1, S2.2-2, S2.2-32–S2.2-35).

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) Benefit >>> Risk

Suggested phrases for writing recommendations:

- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
 - Treatment/strategy A is recommended/indicated in preference to treatment B
 - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) Benefit >> Risk

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
 - Treatment/strategy A is probably recommended/indicated in preference to treatment B
 - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) Benefit ≥ Risk

Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) Benefit = Risk

(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:

- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) Risk > Benefit

Suggested phrases for writing recommendations:

- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A

- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)

- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)

- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

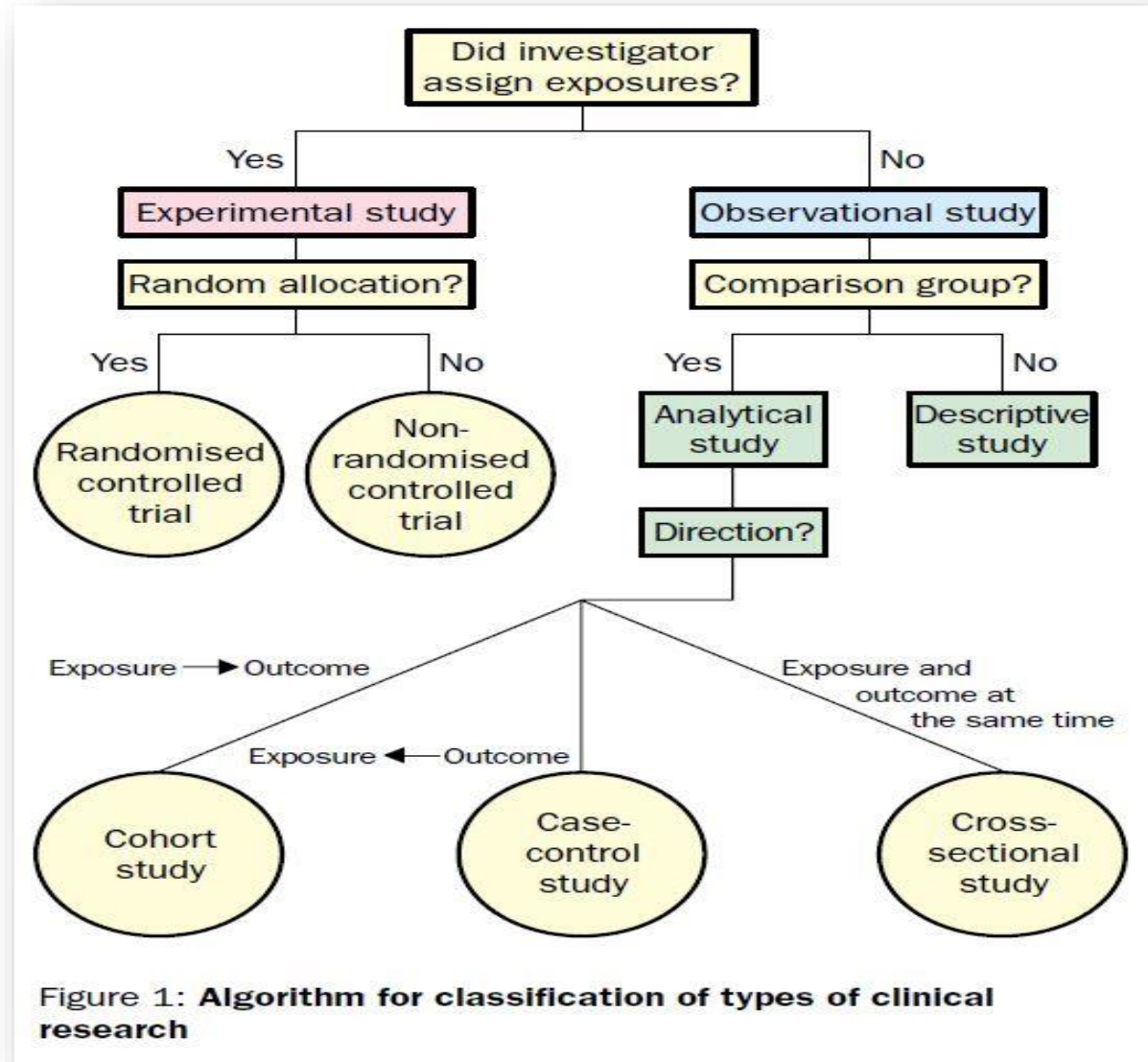
A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.



China CDE Definition (Center for Drug Evaluation):

"Data collected from routine sources about various aspects of patient health status and/or healthcare."
“来源于日常所收集的各种与患者健康状况和/或诊疗及保健有关的数据”

Source: *Guiding Principles for Real-World Evidence Supporting Drug Development and Evaluation (Trial Version)*
《真实世界证据支持药物研发与审评的指导原则》 (试行)

China CMDE Definition (Center for Medical Device Evaluation):

"Data collected from various sources other than traditional clinical trials, including information on patient health status and/or routine diagnosis and healthcare."
“传统临床试验以外的，从多种来源收集的各种与患者健康状况和/或常规诊疗及保健有关的数据”

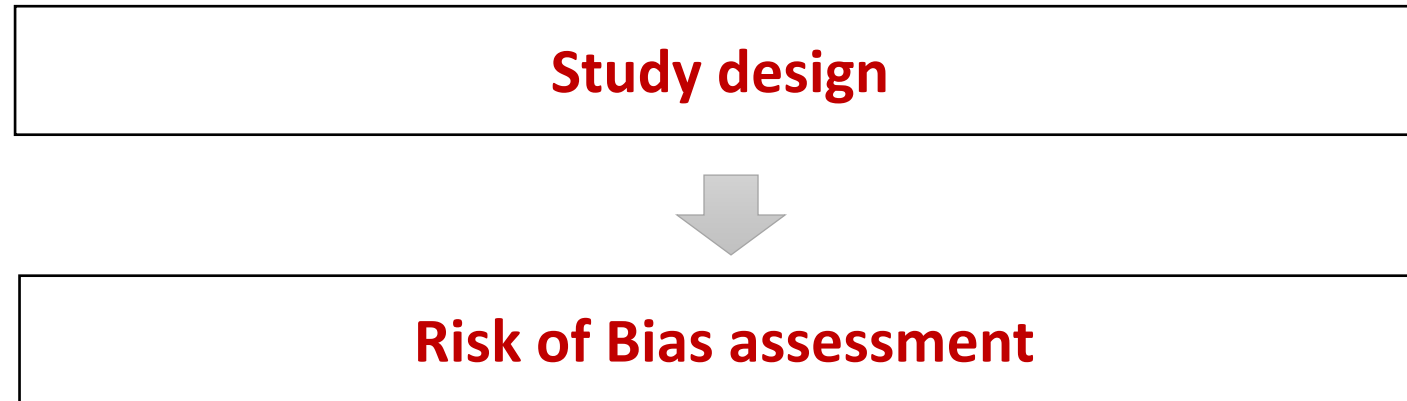
Source: *Guiding Principles for Real-World Data Used in Medical Device Clinical Evaluation (Trial Version)*
《真实世界数据用于医疗器械临床评价技术指导原则》 (试行)

FDA Definition

"Data relating to patient health status and/or the delivery of healthcare that are routinely collected from a variety of sources other than traditional clinical trials."

Source: *FDA Guidance for Industry: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*

- ✓ **Hospital Information System (HIS):** Structured and unstructured patient records, including demographics, clinical features, diagnoses, treatments, lab tests, safety, and outcomes.
- ✓ **Health Insurance System:** Data on patient information, medical service utilization, diagnoses, prescriptions, billing, and preventive care.
- ✓ **Disease Registry System:** Databases for specific diseases, often chronic, derived from hospital-based disease cohort registries.
- ✓ **ADR Sentinel Surveillance Alliance:** Monitoring and evaluation of drug and medical device safety using electronic healthcare data.
- ✓ **Natural Population and Disease-Specific Cohort Databases:** Cohort databases for natural populations and specific diseases.
- ✓ **Omics-Related Databases:** Information on pharmacogenomics, metabolomics, proteomics, and other biological interactions.
- ✓ **Mortality Registry Database:** Death records confirmed by hospitals, disease control centers, and household registration departments.
- ✓ **Patient-Reported Outcome Data:** Self-reported assessments or measurements by patients.
- ✓ **Data from Mobile Devices:** Data collected via wearable or mobile medical devices.
- ✓ **Other Special Data Sources:** Data for imported overseas drugs for specific medical purposes; infectious disease reporting databases; immunization program databases.....



Etiological Research

- Studies the relationship between risk factors and diseases, as well as the mechanisms causing diseases.

Diagnostic Research

- Focuses on the accuracy of new methods for diagnosing specific diseases and evaluates their clinical value.

Therapeutic Research

- Investigates the efficacy and side effects of specific treatment plans for diseases.

Prognostic Research

- Predicts possible outcomes of disease progression and identifies factors influencing prognosis.

Other Research

- Includes studies such as pharmacoeconomic research.

Question



Study design

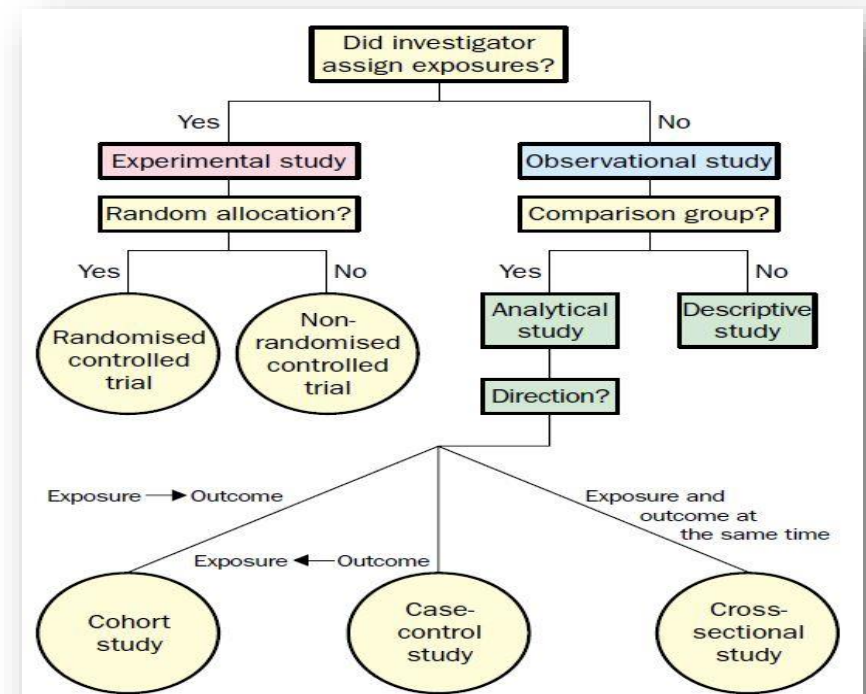


Figure 1: Algorithm for classification of types of clinical research

Research case example

MY ALERTS SIGN IN

Circulation

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AHA JOURNALS

ORIGINAL RESEARCH ARTICLE

Magnitude of Soluble ST2 as a Novel Biomarker for Acute Aortic Dissection

Yuan Wang, Xin Tan, Hai Gao, Hui Yuan, Rong Hu, Lixin Jia, Junming Zhu, Lizhong Sun, Hongjia Zhang, Lianjun Huang, Dong Zhao, Pei Gao, Jie Du



Patients available from the hospital*

Patients with Aortic Dissection[‡]

- Total: 719 patients[‡]
- Time onset ≤ 24 hours: 259 patients
- Time onset ≤ 14 days: 462 patients
- Time onset > 14 days: 257 patients

Patients with Myocardial Infarction[‡]

- Total: 6142 patients from the hospital
- Acute MI: 2183 patients

Patients with Pulmonary Embolism[‡]

- Total: 209 patients from the hospital
- Time onset ≤ 14 days: 117 patients

Healthy participants[‡]

- Total: 426 participants with blood sample available to measure sST2

Discovery study set (1027 participants)

AAD vs AMI (479 patients)

- ≤ 24 hours after symptoms onset
- Frequency-matched case-control design
- Complete information on D-Dimer & sST2
- 245 patients with AAD
- 234 random-selected frequency matched AMI patients without heart failure

AAD vs Pulmonary Embolism (492 patients)

- ≤ 14 days after symptoms onset
- Complete information on D-Dimer & sST2
- 443 patients with AAD
- 49 patients with PE after excluding patients already treated in other hospitals

sST2 Distribution Comparison (301 participants)

- Complete information on D-Dimer & sST2
- Additional participants included:
 - 234 patients with AD: time onset >14 days
 - 67 healthy participants

Objectives

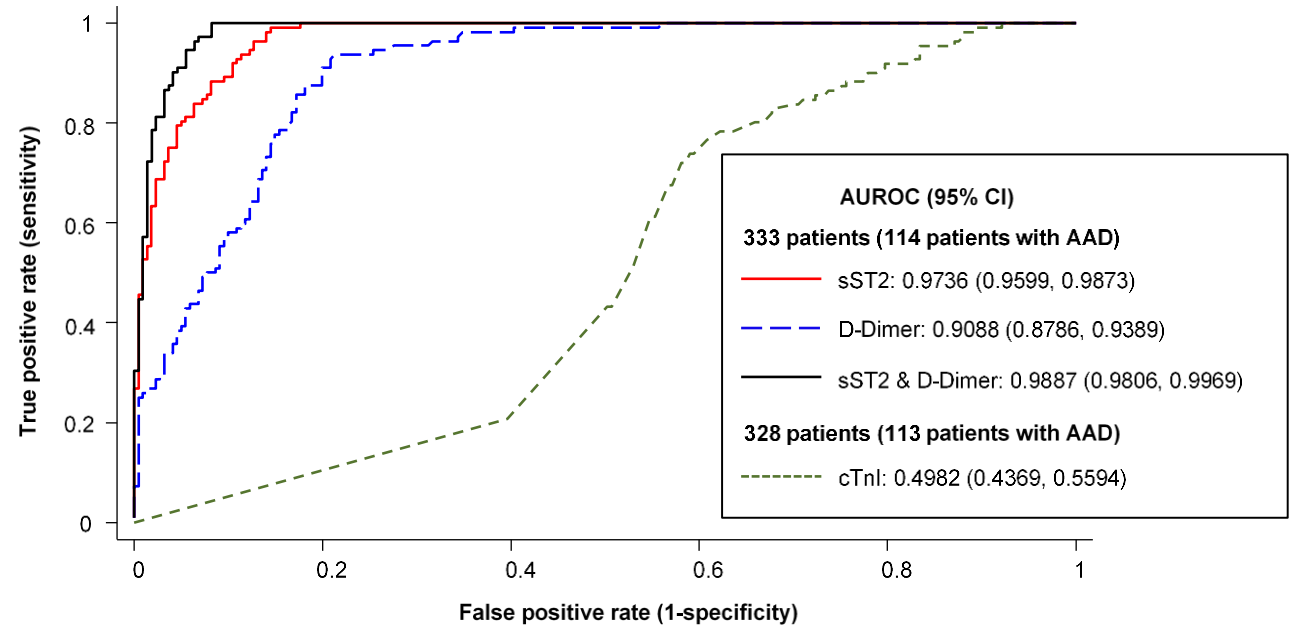
(1) To evaluate the diagnostic performance for the magnitude of levels of sST2 to discriminate AAD from AMI

(2) To evaluate the diagnostic performance for the magnitude of levels of sST2 to discriminate AAD from PE in acute phase

Definitive diagnose is to distinguish AAD from other sudden-onset severe chest pain diseases

Research case example

Study set	Discovery Set* (n=1027)		
Study population	AAD vs AMI	AAD AMI	n=245 n=234
	AAD vs PE	AAD PE	n=443 n=49
	sST2 distribution	AD Healthy control	n=677 n=67
Study design	Retrospective		



Research case example

Validation cohort (n=333)	
AAD	n=114
AMI	n=72
PE	n=24
Angina	n=54
Others	n=69

Table. Diagnostic Performance of Patients With AAD Versus Others Using sST2 Compared With D-Dimer in the Validation Cohort

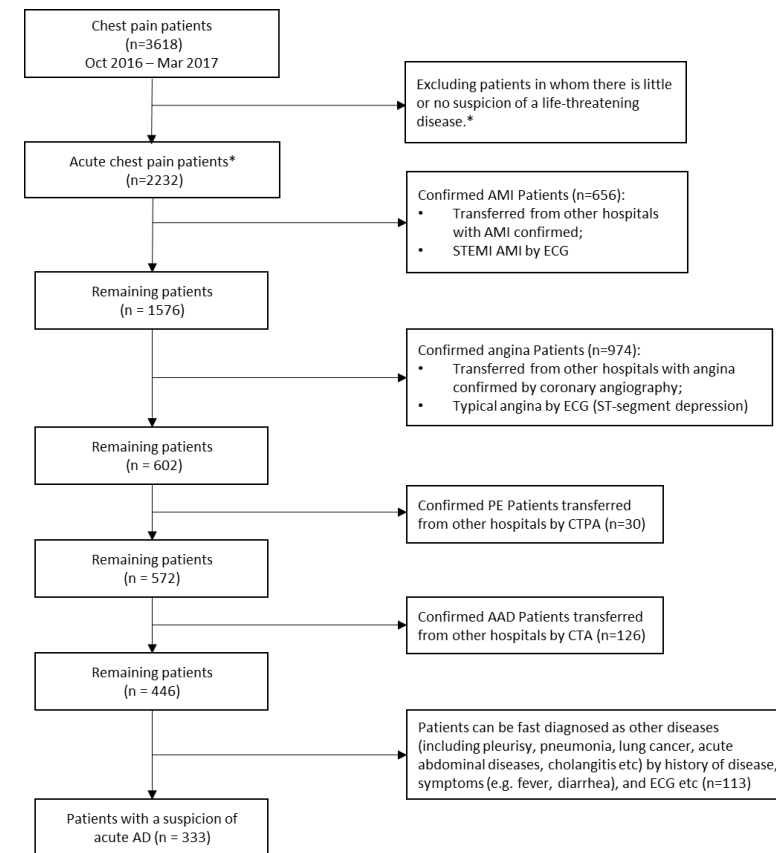
	Threshold	Sensitivity, %	Specificity, %	Accuracy, %	PLR	NLR	PPV, %‡	NPV, %‡
Patients (n=333, with AAD n=114)								
sST2, ng/mL	34.6*	99.1	84.9	89.8	6.6	0.01	68.7	99.7
	36	93.0	88.1	89.8	7.8	0.08	72.3	97.4
	40	87.7	91.3	90.1	10.1	0.13	77.1	95.7
	50	74.6	95.0	88.0	16.3	0.27	83.2	91.8
D-dimer, ng/mL	323*	93.9	78.5	83.8	4.4	0.08	59.3	97.5
	500 (recommended)†	87.7	82.2	84.1	4.9	0.15	62.2	95.3

AAD indicates acute aortic dissection; NLR, negative likelihood ratio; NPV, negative predictive value; PLR positive likelihood ratio; PPV, positive predictive value; and sST2, soluble ST2.

*Optimal threshold value obtained from the data, which was the threshold leading to the maximum summation of sensitivity and specificity (ie, the Youden index).

†Predefined threshold values based on information from previous literature.

‡Because the prevalence of aortic dissection in patients presenting with suspicion of aortic dissection is poorly understood, to ease the generalization of our estimations, we used 25% (ie, 1 in 4 patients) as suggested in the previous literature.



Perspective



Key elements evaluated in the study design

PICOTS elements

Elements	Relevant questions
<u>P</u> opulation	Which patients / population? and what problem(s) will the study address?
<u>I</u> ntervention or <u>E</u> xposure(s)	What is the intervention or exposure being studied? (e.g., drugs, devices, surgery, or tests)
<u>C</u> omparator	What is the comparator intervention or exposure for evaluating the target intervention's effect?
<u>O</u> tcomes	What are the outcomes or endpoints of interest?
<u>T</u> iming	What is the time frame for evaluating outcomes? Short-term or long-term outcomes?
<u>S</u> etting	What is the setting of interest? (e.g., hospitals, private clinics, community health centers, etc.)

Selection Bias

Bias caused by the **selection process of study samples**, leading to results that do not represent the entire population.

Information Bias

Systematic errors caused by **inaccurate measurement** of exposures, outcomes, or other key factors during data collection.

Confounding Bias

Bias caused by confounding factors related to both the exposure and the disease, distorting the true relationship between them.

Randomized trials: Risk of Bias

To assess the risk of bias in **randomized trials** included in systematic reviews. The tool is designed to ensure a more **structured and transparent evaluation of bias**, improving the reliability and validity of systematic reviews. Assess across five key domains:

1. **Bias arising from the randomization process:** Ensures that randomization was conducted properly to avoid selection bias.
2. **Bias due to deviations from intended interventions:** Assesses whether participants received the intended interventions and whether deviations could affect outcomes.
3. **Bias due to missing outcome data:** Evaluates the impact of incomplete data on the reliability of results.
4. **Bias in measurement of the outcome:** Checks whether outcomes were measured consistently and without influence from knowledge of the intervention.
5. **Bias in selection of the reported result:** Ensures that the reported results are not selectively chosen based on their significance.



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Risk of Bias 2 (RoB 2) tool

Observational studies: ROBINS-I V2

✓ Purpose:

- To assess the **risk of bias** in a specific result from an individual non-randomized study.
- Focuses on studies examining the **effect of an intervention on an outcome**.

✓ Launch Date: November 22, 2024.

✓ Target Studies: Follow-up (cohort) studies.

☰  Risk of bias tools

ROBINS-I V2 tool

We are pleased to announce Version 2 of the ROBINS-I tool, launched on 22 November 2024.

Access the tool here:

[ROBINS-I V2 \(editable document\)](#) or [ROBINS-I V2 \(PDF document\)](#)

The Risk Of Bias In Non-randomized Studies – of Interventions, Version 2 (ROBINS-I V2) aims to assess the risk of bias in a specific result from an individual non-randomized study that examines the effect of an intervention on an outcome. The document describes the ROBINS-I V2 tool for follow-up (cohort) studies.

The development group for ROBINS-I V2 was led by Jonathan Sterne and Julian Higgins. A full list of contributors will appear here soon.



□ Bias Focus:

- Evaluates bias that could cause a significant change in the estimated effect compared to the true value.

□ Hypothetical ‘Target Trial’:

- Defines a hypothetical randomized trial to estimate causal effects and guide bias assessment.
- essential for assessment of risk of bias, because the causal effect defines the result that would be seen (other than the impact of sampling variation) in the absence of bias.

□ Seven Bias Domains:

- Risk of bias **due to confounding.**
- Risk of bias in **classification of interventions.**
- Risk of bias in **selection of participants.**
- Risk of bias due to **deviations from intended interventions.**
- Risk of bias due to **missing data.**
- Risk of bias in **measurement of the outcome.**
- Risk of bias in **selection of the reported result.**

1. Planning Stage

Identify important **confounding factors** that could influence the intervention-outcome relationship.

Specify these factors in the protocol or systematic review.

2. Assessment Process

Answer **signaling questions** for each bias domain (e.g., Yes, Probably Yes, Probably No, No, No Information).

Use an **algorithm** to map responses to a proposed risk-of-bias judgment.

3. Judgment Levels

Low Risk of Bias: Little or no concern.

Moderate Risk of Bias: Some concern, but not critical.

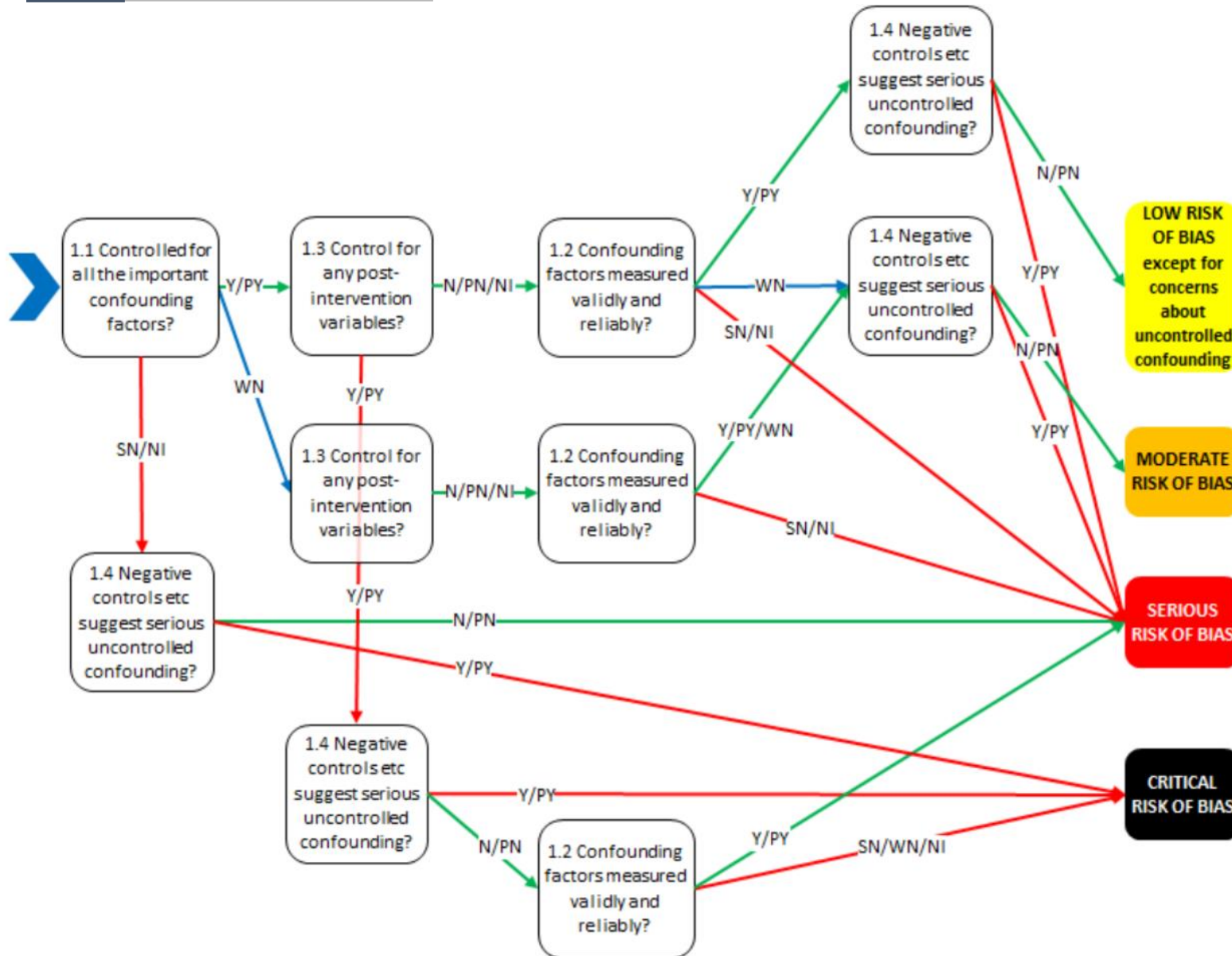
Serious Risk of Bias: Important problems in the domain.

Critical Risk of Bias: Severe issues; result should be excluded from evidence synthesis.

4. Override Option

Users can override algorithm-generated judgments with justification for transparency.

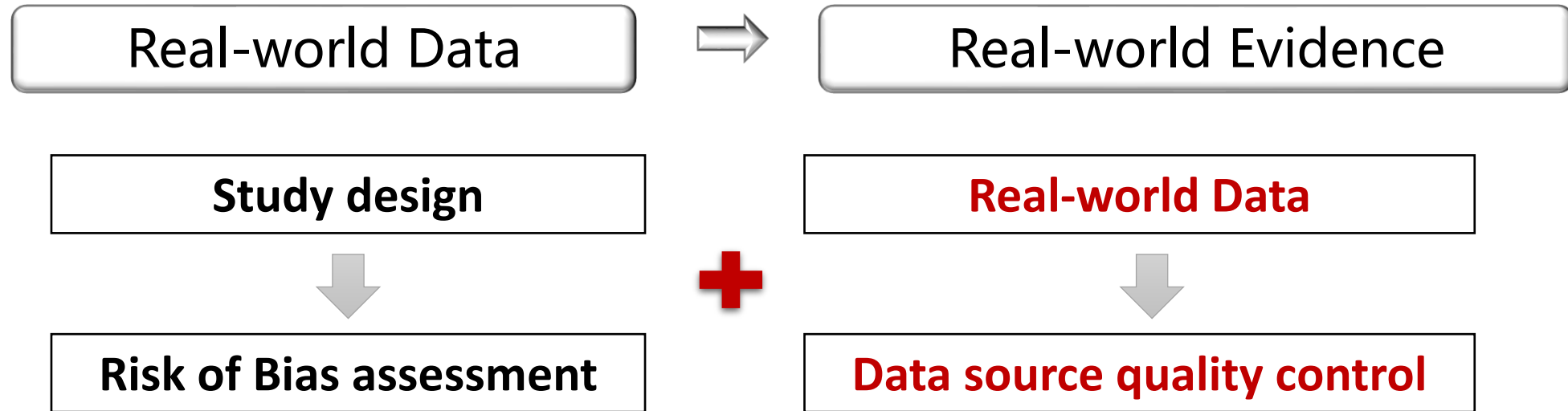
How Does ROBINS-I V2 Work?



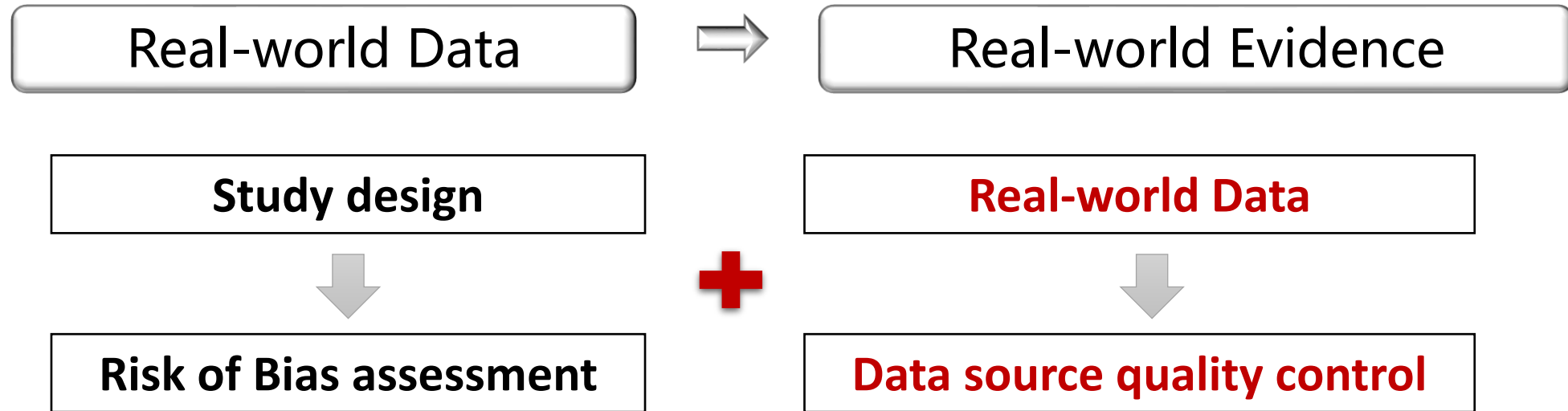
When to Stop Assessment?

Critical Risk of Bias:

If confounding is not controlled or the outcome measurement method is inappropriate, the result is judged at **Critical Risk of Bias**, and no further assessment is required.



- **Background:**
 - Importance of study design in minimizing bias risk for Real-World Evidence (RWE) in regulatory decisions.
 - **Growing maturity of linked large-scale databases and their role in RWE generation.**
- **Objective:**
 - Propose the addition of a dedicated session on data source quality control to enhance the reliability of RWE for regulatory use.



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Proposed Key Topics to Cover



北京大学
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Global Harmonization Working Party
GHWP Towards Medical Device Harmonization

Data Source Selection

- Criteria for selecting reliable and representative data sources.
- Evaluating the completeness, accuracy, and timeliness of data.

Data Linkage and Integration

- Addressing challenges in linking multiple data sources.
- Ensuring consistency and reducing errors in integrated datasets.

Data Cleaning and Validation

- Methods for identifying and correcting errors or inconsistencies.
- Validation techniques to ensure data reliability.

Metadata Documentation

- Importance of documenting data provenance, transformations, and quality checks.

Regulatory Expectations

- Aligning data quality control practices with regulatory requirements.
- Case studies of successful RWE submissions supported by high-quality data.

Next Steps

❑ Implementation Plan

- Develop detailed session content and materials.
- Engage experts in data quality and RWE for session delivery.

❑ Integration into RWE Framework

- Incorporate data source quality control as a standard component to evaluate quality of RWE evidence.
- Promote collaboration between database providers, researchers, regulators and other stakeholders.

Conclusion

- ✓ Emphasize the critical role of study design as well as the data source quality in generating reliable RWE.
- ✓ Advocate for the inclusion of a dedicated part on data source quality control to evaluate the quality of RWE to support regulatory decision-making for medical devices.

Thank you
