Sentinel

Welcome to the Sentinel Innovation and Methods Seminar Series

The webinar will begin momentarily

Please visit www.sentinelinitiative.org for recordings of past sessions and details on upcoming webinars.

Note: closed-captioning for today's webinar will be available on the recording posted at the link above.

Sentinel

A PRocess guide for INferential studies using healthcare data from routine ClinIcal Practice to EvaLuate causal Effects of Drugs (PRINCIPLED)

Rishi Desai, MS, PhD
Mass General Brigham and Harvard Medical School

February 29, 2024

Process guide for inferential studies using healthcare data from routine clinical practice to evaluate causal effects of drugs (PRINCIPLED): considerations from the FDA Sentinel Innovation Center

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For numbered affiliations see end of the article

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Additional material is published online only. To view please visit the journal online.

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http://dx.doi.org/10.1136/

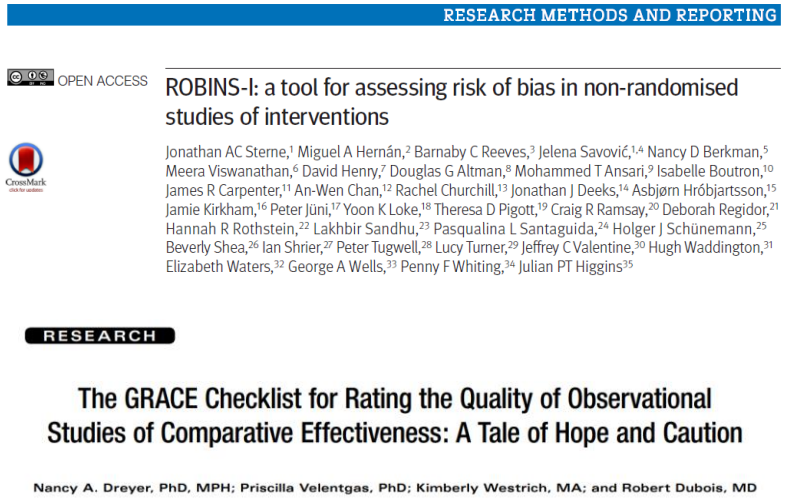
This report proposes a stepwise process covering the range of considerations to systematically consider key choices for study design and data analysis for non-interventional studies with the central objective of fostering generation of

Non-interventional studies, also referred to as observational studies, are conducted using real world data sources typically including healthcare data that are generated during provision of routine clinical care (including health insurance claims and electronic health records). These studies provide an opportunity to fill in evidence gaps for questions that have not been answered by randomized trials.[1] However, generating decision grade evidence from healthcare data requires

Motivation

Why do we need another framework?

Quality assessment tools



RESEARCH METHODS AND REPORTING

OPEN ACCESS

ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions

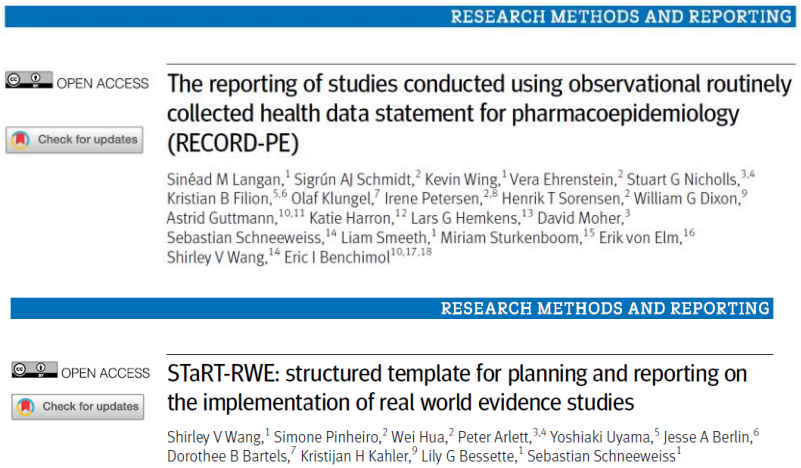
Jonathan AC Sterne,[1] Miguel A Hernán,[2] Barnaby C Reeves,[3] Jelena Savović,[1,4] Nancy D Berkman,[5] Meera Viswanathan,[6] David Henry,[7] Douglas G Altman,[8] Mohammed T Ansari,[9] Isabelle Boutron,[10] James R Carpenter,[11] An-Wen Chan,[12] Rachel Churchill,[13] Jonathan J Deeks,[14] Asbjørn Hróbjartsson,[15] Jamie Kirkham,[16] Peter Jüni,[17] Yoon K Loke,[18] Theresa D Pigott,[19] Craig R Ramsay,[20] Deborah Regidor,[21] Hannah R Rothstein,[22] Lakhbir Sandhu,[23] Pasqualina L Santaguida,[24] Holger J Schünemann,[25] Beverly Shea,[26] Ian Shrier,[27] Peter Tugwell,[28] Lucy Turner,[29] Jeffrey C Valentine,[30] Hugh Waddington,[31] Elizabeth Waters,[32] George A Wells,[33] Penny F Whiting,[34] Julian PT Higgins[35]

RESEARCH

The GRACE Checklist for Rating the Quality of Observational Studies of Comparative Effectiveness: A Tale of Hope and Caution

Nancy A. Dreyer, PhD, MPH; Priscilla Velentgas, PhD; Kimberly Westrich, MA; and Robert Dubois, MD

Reporting tools



RESEARCH METHODS AND REPORTING

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The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE)

Sinéad M Langan,[1] Sigrún AJ Schmidt,[2] Kevin Wing,[1] Vera Ehrenstein,[3] Stuart G Nicholls,[3,4] Kristian B Filion,[5,6] Olaf Klungel,[7] Irene Petersen,[2,8] Henrik T Sorensen,[2] William G Dixon,[9] Astrid Guttmann,[10,11] Katie Harron,[12] Lars G Hemkens,[13] David Moher,[3] Sebastian Schneeweiss,[14] Liam Smeeth,[1] Miriam Sturkenboom,[15] Erik von Elm,[16] Shirley V Wang,[14] Eric I Benchimol[10,17,18]

RESEARCH METHODS AND REPORTING

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STaRT-RWE: structured template for planning and reporting on the implementation of real world evidence studies

Shirley V Wang,[1] Simone Pinheiro,[2] Wei Hua,[2] Peter Arlett,[3,4] Yoshiaki Uyama,[5] Jesse A Berlin,[6] Dorothee B Bartels,[7] Kristijan H Kahler,[9] Lily G Bessette,[1] Sebastian Schneeweiss[1]

Best practices

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EMA/95098/2010 Rev.9

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology

(Revision 9)

Misc: Highly specific or focusing on parts of the process

Journal of the American Medical Informatics Association, 27(8), 2020, 1331–1337
doi: 10.1093/jamia/ocaa103
Perspective

AMIA

Perspective

Principles of Large-scale Evidence Generation and Evaluation across a Network of Databases (LEGEND)

Martijn J. Schuemie[1,2], Patrick B. Ryan[1,3], Nicole Pratt[4], RuiJun Chen[3,5], Seng Chan You[6], Harlan M. Krumholz[7], David Madigan[8], George Hripcsak[3,9], and Marc A. Suchard[2,10]

Clinical Pharmacology & Therapeutics

REVIEW | Open Access

The Structured Process to Identify Fit-for-purpose Data (SPIFD): A data feasibility assessment framework

Nicolle M Gatto, Ulka B Campbell, Emily Rubinstein, Ashley Jaksa, Pattra Mattox, Jingping Mo, Robert F Reynolds

First published: 30 October 2021 | https://doi-org.ezp-prod1.hul.harvard.edu/10.1002/cpt.2466

Why do we need another framework?

What do we have?

- Various tools exist in the literature for quality assessment, reporting, and describing best practices for pharmacoepidemiologic research

What don't we have?

- None of these tools offer a general framework to guide decision making at various steps when designing a study to answer a causal question

Vision for a framework to guide principled investigations using healthcare data

- The Sentinel Innovation Center has developed a causal inference framework proposing *a stepwise process that systematically considers key choices* with respect to design and analysis that influence the validity of non-interventional studies conducted with healthcare data
- A standardized process outlined in this framework will serve as *a guide to inform the conduct of* non-interventional studies using healthcare data for drug-outcome evaluation
- Key considerations to meet the FDA need of informing regulatory decision making based on such investigations
  - Limit variations in practice across investigators by outlining a general process
  - Focus on repeatability of the process
  - Written and endorsed by independent experts

Overview of the Process

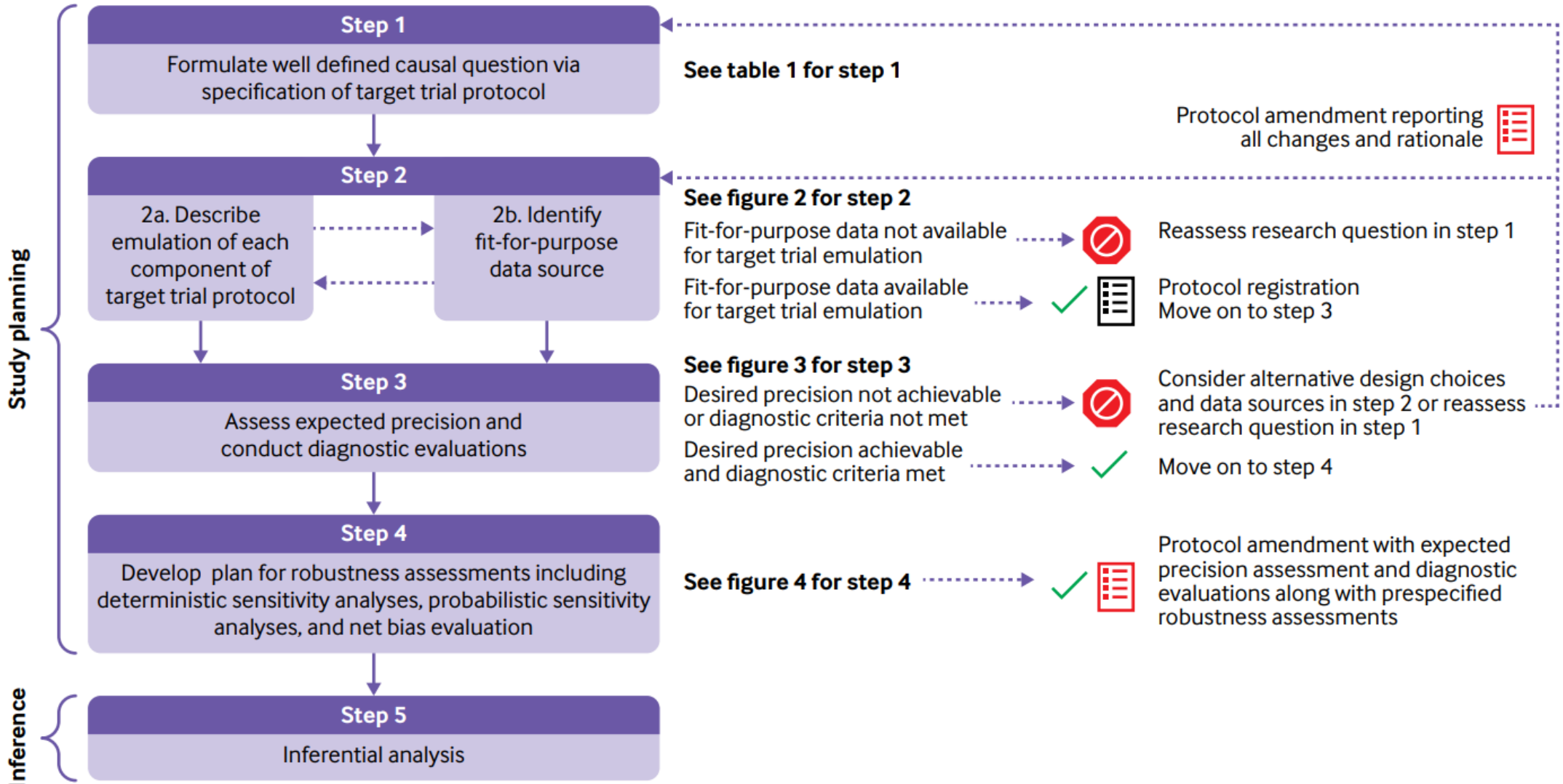


Fig 1 | Overview of the process guide for inferential studies using healthcare data from routine clinical practice

Step 1: Specification of the target trial protocol

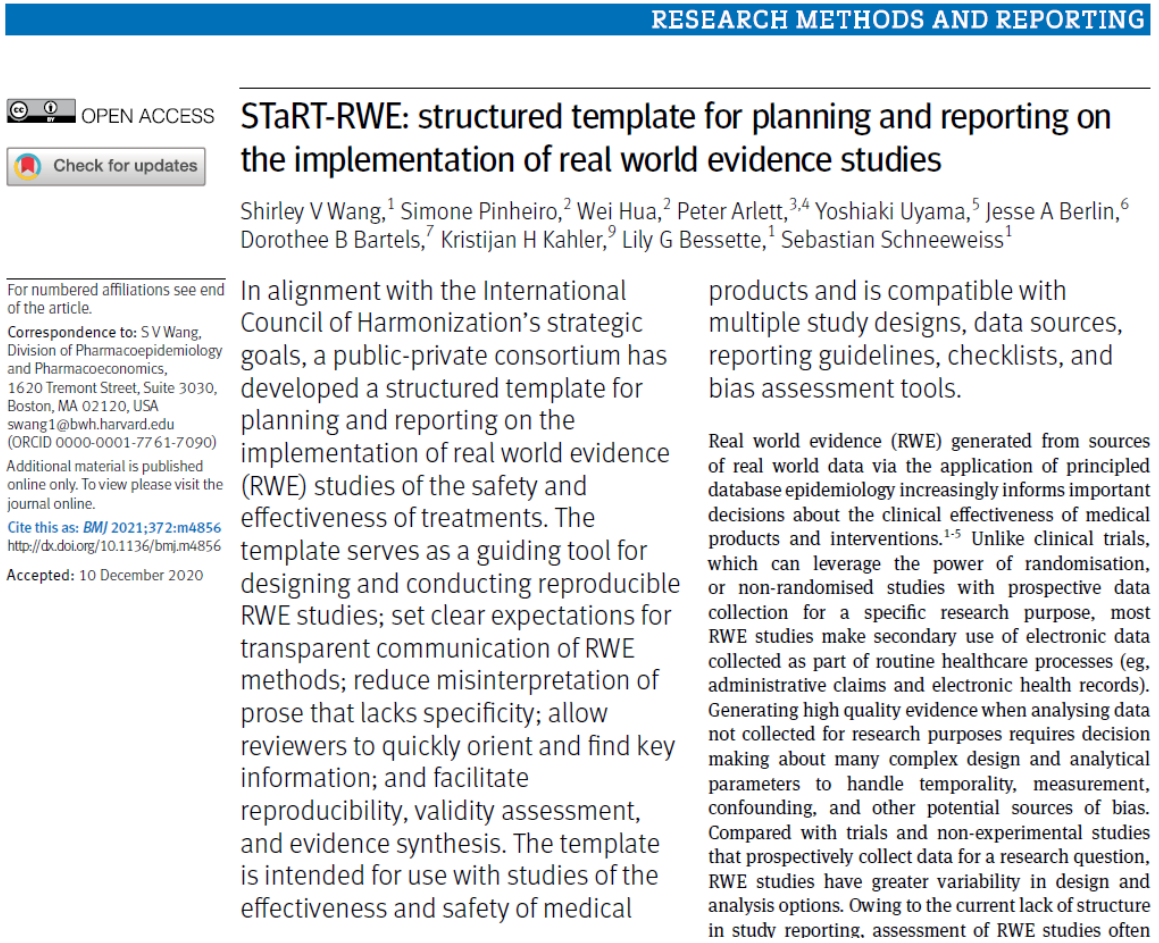
Table 1 | Target trial protocol for case example study evaluating the effect of sodium-glucose cotransporter-2 (SGLT-2) inhibitors on genital infections

Element	Specification	Emulation using real world data sources
Eligibility criteria	Patients with type 2 diabetes mellitus; aged ≥65 years; no use of study drug treatments before randomization; no history of end stage renal disease, HIV, or genital infections; continuous Medicare A, B, D enrolment for six months and recorded glycated hemoglobin (HbA_{1c}) test results in electronic health records in six months before treatment initiation	Same as target trial
Treatment strategies	Initiation of (1) SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin); or (2) DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin). Under both strategies, use of antidiabetic treatment after initiation is left to physician and patients' discretion	Same as target trial
Treatment assignment	Randomized, non-blinded	Non-blinded and assumed to be randomized within levels of measured confounders*
Follow-up start (time 0)	At assignment	Same as target trial
Follow-up end	First of administrative end of follow-up (day 365), loss to follow-up, death, or outcome occurrence	Same as target trial
Primary outcome	Genital infections	Same as target trial
Causal contrast	Intention-to-treat effect (effect of being assigned to the treatment)	Observational analogue of intention-to-treat effect

SGLT-2=sodium-glucose cotransporter-2; DPP-4=dipeptidyl peptidase-4; HbA1c=glycated hemoglobin.
*Measured confounders include demographics (age, sex, race, socioeconomic status markers), diabetes severity related variables including microvascular and macrovascular complications, measures related to diabetes control such as HbA_{1c}, comorbid conditions, cotreatments, markers for healthy behavior, and healthcare use.

Step 2a: Describing the emulation of each component of the target trial protocol

- A structured protocol detailing operationalization of variable definitions, including all codes and algorithms used for eligibility criteria, treatment strategies (including treatment initiation and discontinuation), outcomes, and confounders
- Other considerations include statistical analysis plans for the primary analysis
- Example of a template- STaRT RWE[2]



RESEARCH METHODS AND REPORTING

OPEN ACCESS

Check for updates

STaRT-RWE: structured template for planning and reporting on the implementation of real world evidence studies

Shirley V Wang,[1] Simone Pinheiro,[2] Wei Hua,[2] Peter Arlett,[3,4] Yoshiaki Uyama,[5] Jesse A Berlin,[6] Dorothee B Bartels,[7] Kristijan H Kahler,[9] Lily G Bessette,[1] Sebastian Schneeweiss[1]

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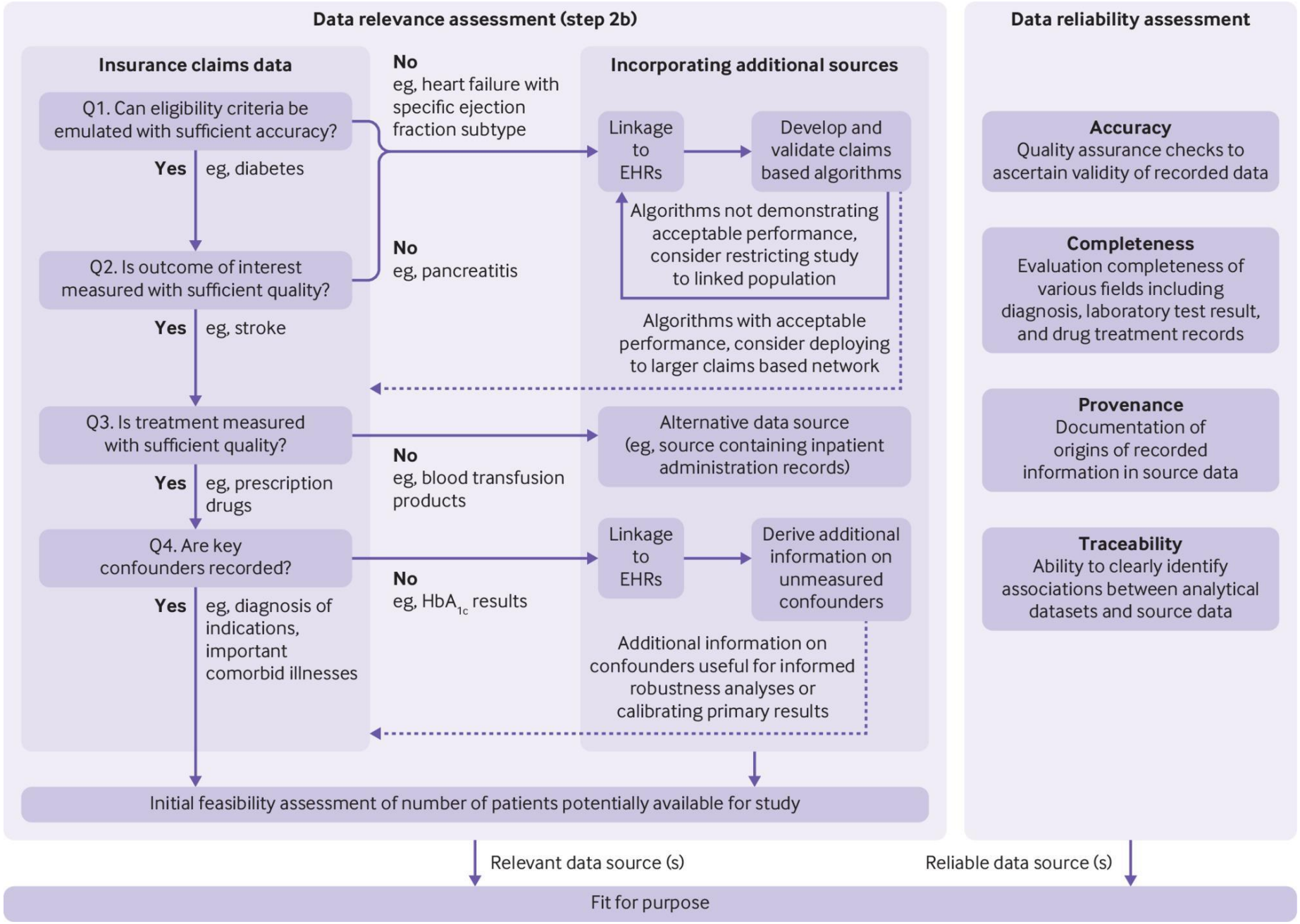
Accepted: 10 December 2020

In alignment with the International Council of Harmonization's strategic goals, a public-private consortium has developed a structured template for planning and reporting on the implementation of real world evidence (RWE) studies of the safety and effectiveness of treatments. The template serves as a guiding tool for designing and conducting reproducible RWE studies; set clear expectations for transparent communication of RWE methods; reduce misinterpretation of prose that lacks specificity; allow reviewers to quickly orient and find key information; and facilitate reproducibility, validity assessment, and evidence synthesis. The template is intended for use with studies of the effectiveness and safety of medical products and is compatible with multiple study designs, data sources, reporting guidelines, checklists, and bias assessment tools.

Real world evidence (RWE) generated from sources of real world data via the application of principled database epidemiology increasingly informs important decisions about the clinical effectiveness of medical products and interventions.[1-5] Unlike clinical trials, which can leverage the power of randomisation, or non-randomised studies with prospective data collection for a specific research purpose, most RWE studies make secondary use of electronic data collected as part of routine healthcare processes (eg, administrative claims and electronic health records). Generating high quality evidence when analysing data not collected for research purposes requires decision making about many complex design and analytical parameters to handle temporality, measurement, confounding, and other potential sources of bias. Compared with trials and non-experimental studies that prospectively collect data for a research question, RWE studies have greater variability in design and analysis options. Owing to the current lack of structure in study reporting, assessment of RWE studies often

Wang et al. *BMJ.* 2021;372:m4856

Step 2b: Identify fit-for-purpose data



Data relevance assessment

Insurance claims data

Q1. Can the eligibility criteria be emulated with sufficient accuracy?

Yes (T2DM- PPV of 96% in a previous validation study)[1]

Q2. Is the outcome of interest measured with sufficient quality?

Yes (genital infections- PPV of 90% in a previous validation study)[2]

Q3. Is the treatment measured with sufficient quality?

Yes (SGLT2i and DPP4i from part D claims)

Q4. Are key confounders recorded?

Yes (comorbid conditions, other antidiabetic treatments, demographics)

No (diabetes control i.e HbA1c results, major risk factor for infections)[3]

Incorporating additional sources

Linkage to EHRs

Derive additional information on unmeasured confounders

Additional information on confounders useful for informed robustness analyses

Initial feasibility assessment of number of patients potentially available for the study
(24,961 users of SGLT2i or DPP4i in Medicare claims linked to MGB EHRs)

Data reliability assessment

Accuracy
Raw data converted to Sentinel CDM, validity of the recorded data assessed upon conversion

Completeness
Raw data converted to Sentinel CDM, completeness of the recorded data assessed upon conversion

Provenance
Origins of the recorded information in the source data, which include insurance claims and EHRs, are recorded

Traceability
Relationships between the analytic datasets and source data clearly identified

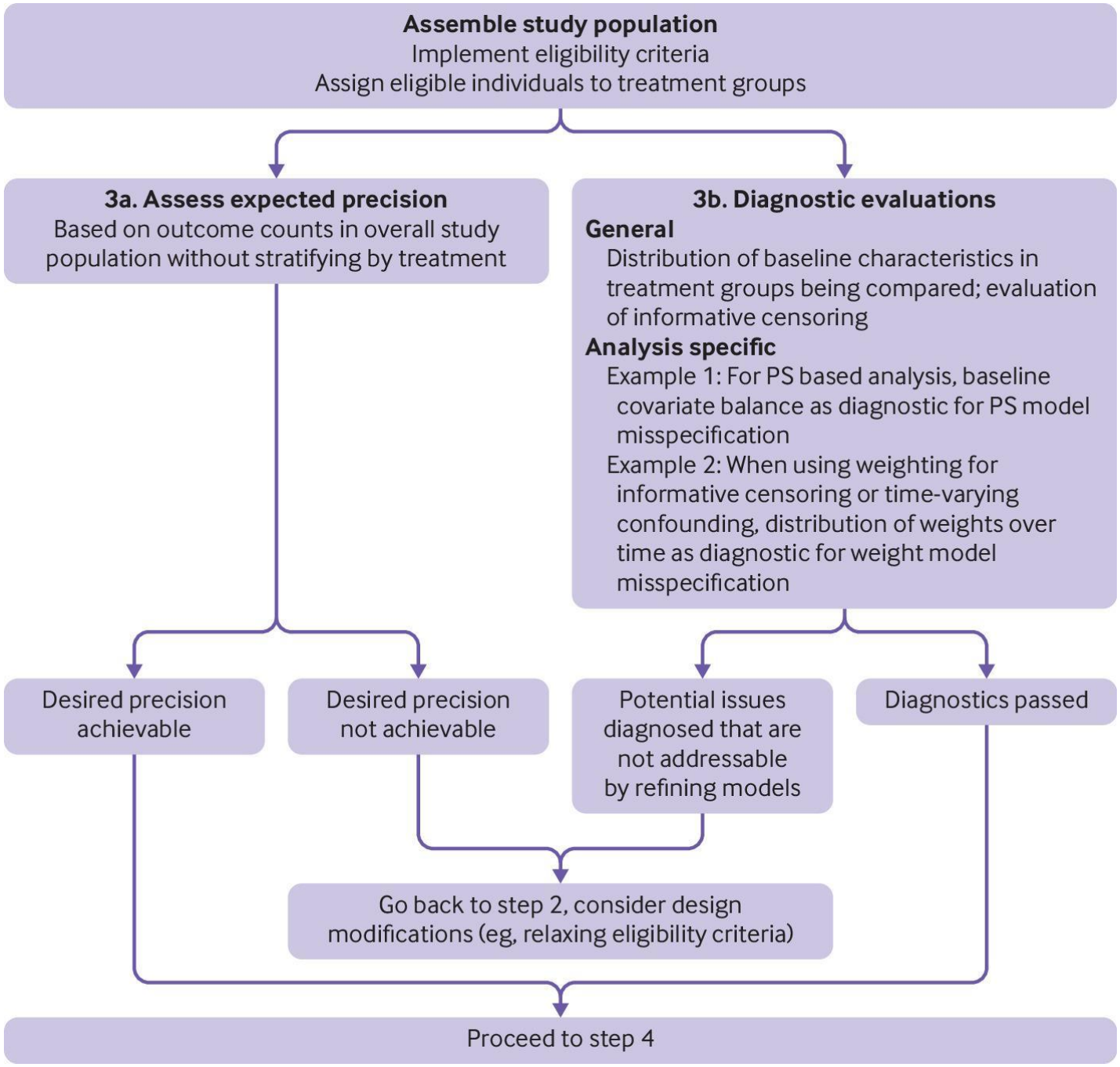
Relevant data source(s)

Reliable data source(s)

Fit for purpose

1. Solberg et al. Am J Med Qual 2006
2. Smith et al. Multiple Sclerosis and Related Disorders 2022
3. Mor et al. AJE 2017

Step 3: Expected precision and diagnostics



Step 3: Expected precision and diagnostics (case-example)

Assemble study population
Implement eligibility criteria
Assign eligible individuals to treatment groups

3a. Assess expected precision

- Outcome counts in the overall study population without stratifying by treatment = 40 (2.7%)
- Estimated 95% confidence interval under an assumed null treatment effect based on the outcome counts and sizes of two treatment groups = (0.35-1.65)

Desired precision not achievable

Go back to Step 2, consider design modifications (e.g. relaxing eligibility criteria)

Study medication users in Medicare (2013 to 2019) — N= 24,961

Continuous 6-month enrollment in Medicare parts A, B, D — *n*= 20,335

New users of study medications with recorded DM — *n*= 13, 676

Aged 65 or older, no history of ESRD or HIV based on ICD codes or procedure codes for dialysis pre-exposure, no history of genital infections — *n*= 9,339

HbA1c test results available from EHRs — *n*= 1,498

Exposure group assignment — DPP4i= 1,004, SGLT2i = 494

Step 3: Expected precision and diagnostics (case-example)

Assemble study population

Implement eligibility criteria

Assign eligible individuals to treatment groups

Study medication users in Medicare (2013 to 2019) — N= 24,961

Continuous 6-month enrollment in Medicare parts A, B, D — *n*= 20,335

New users of study medications with recorded DM — *n*= 13, 676

Aged 65 or older, no history of ESRD or HIV based on ICD codes or procedure codes for dialysis pre-exposure, no history of genital infections — *n*= 9,339

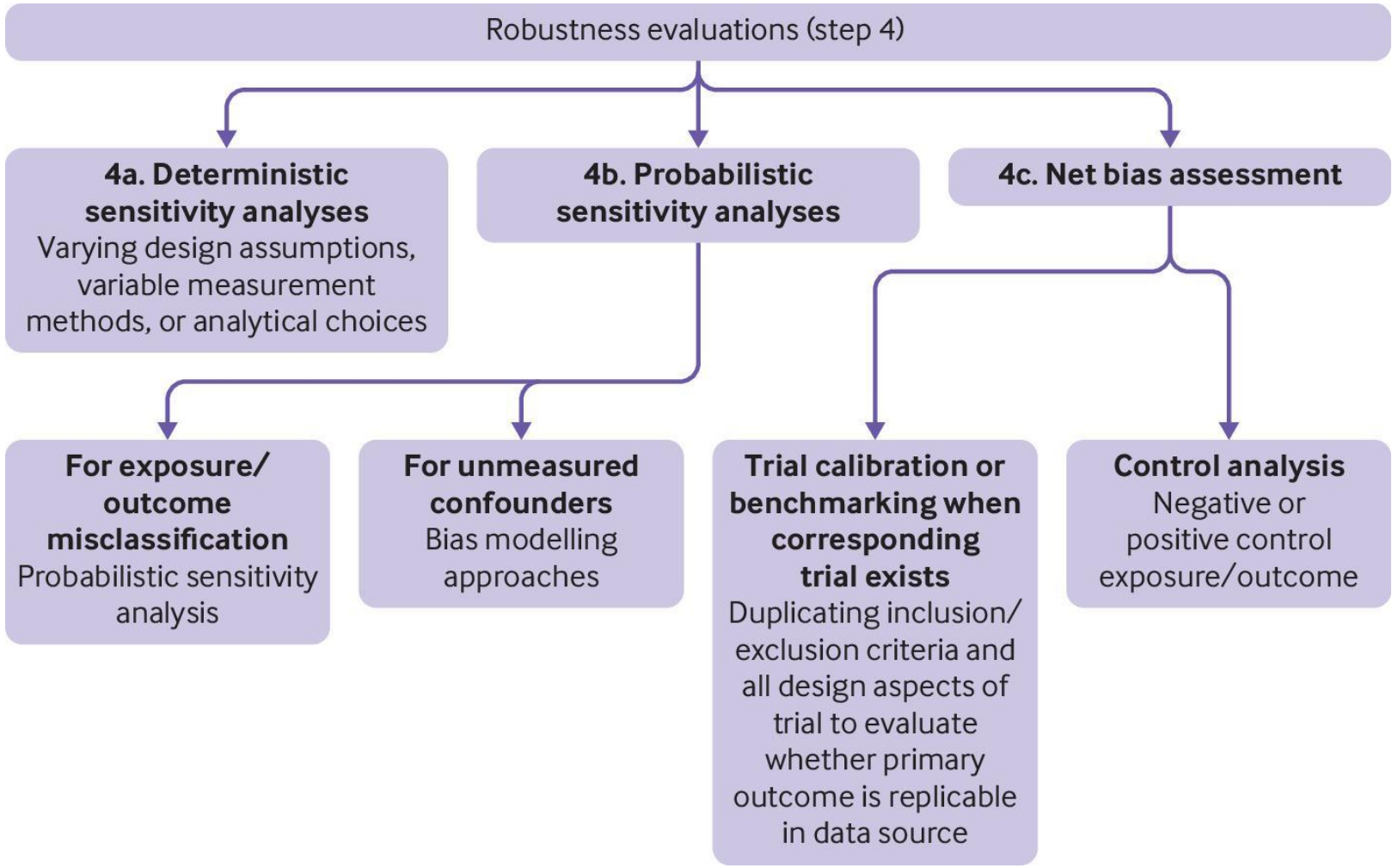
3a. Assess expected precision

- Outcome counts in the overall study population without stratifying by treatment = 293 (3.1%)
- Estimated 95% confidence interval under an assumed null treatment effect based on the outcome counts and sizes of two treatment groups = (0.73-1.27)

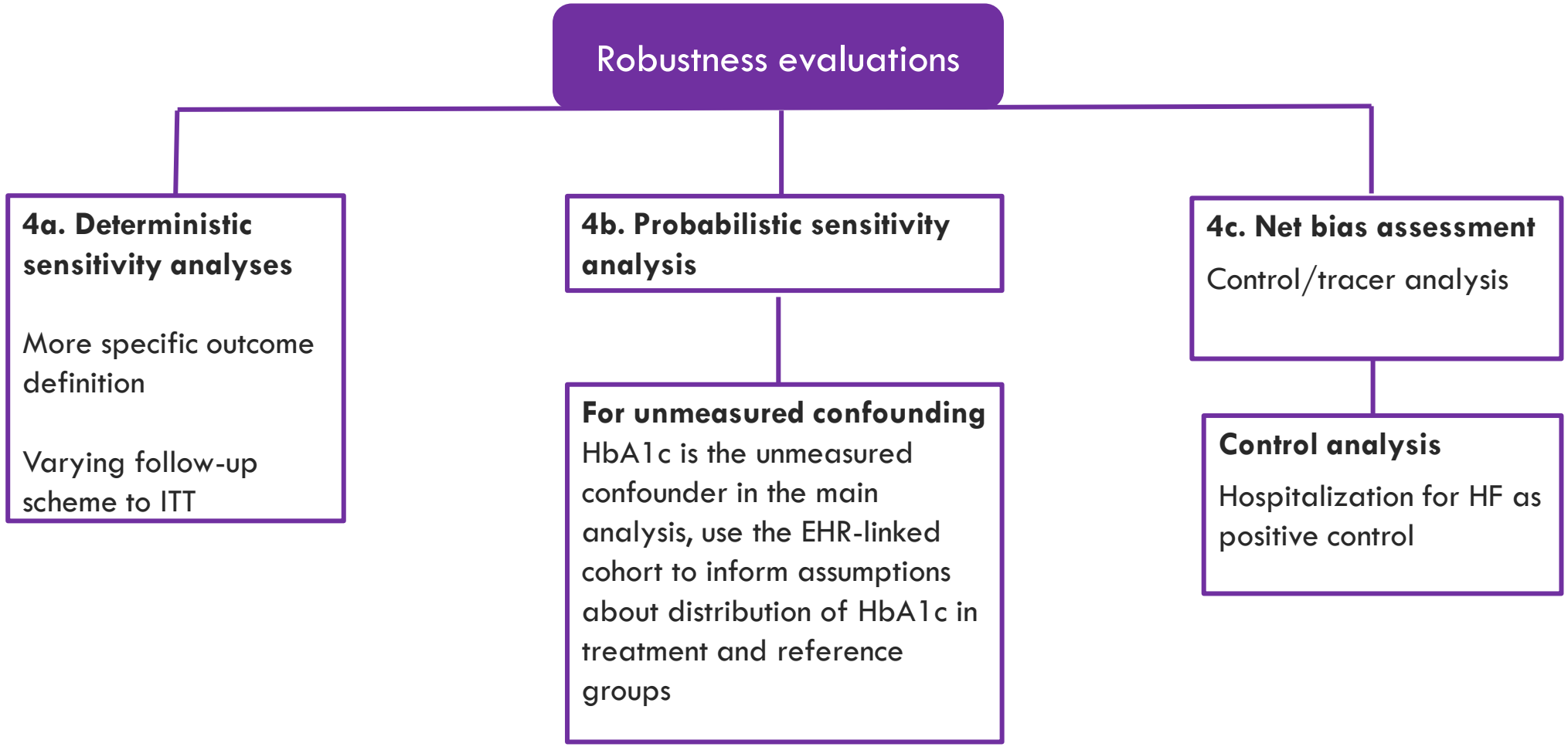
Desired precision achievable

Proceed to Step 4

Step 4: Robustness evaluations



Step 4: Robustness evaluations (case-example)



Step 5: Inferential analysis

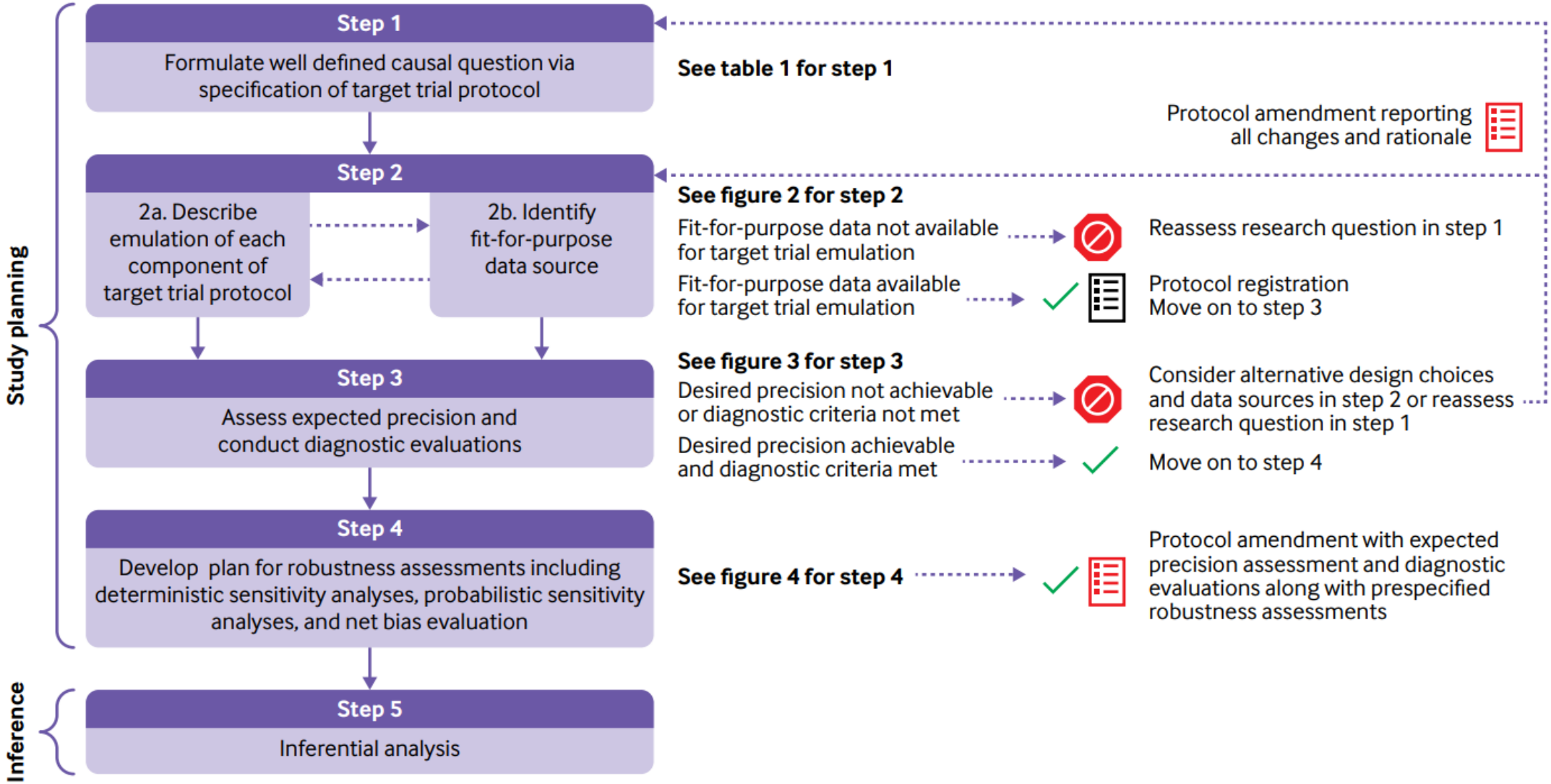
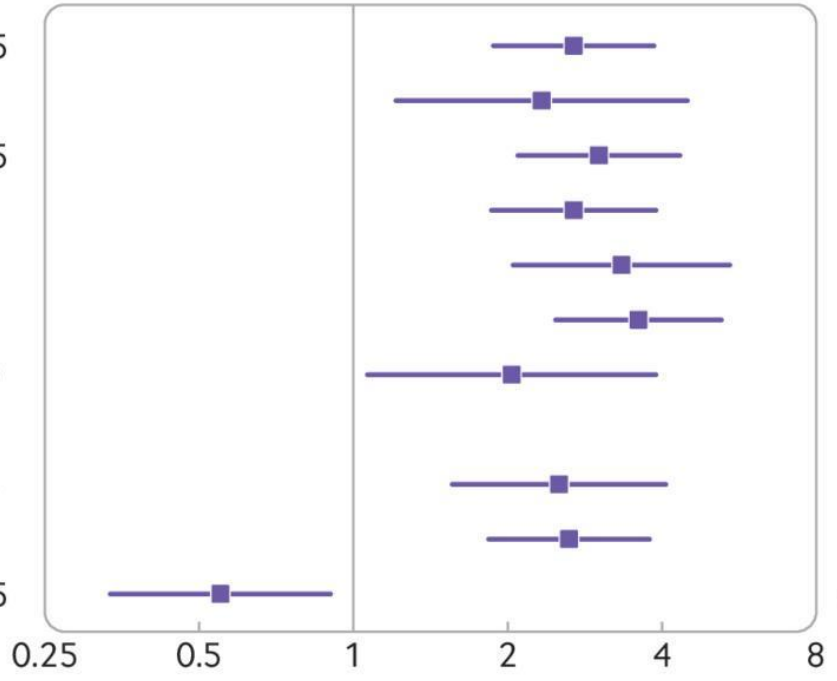


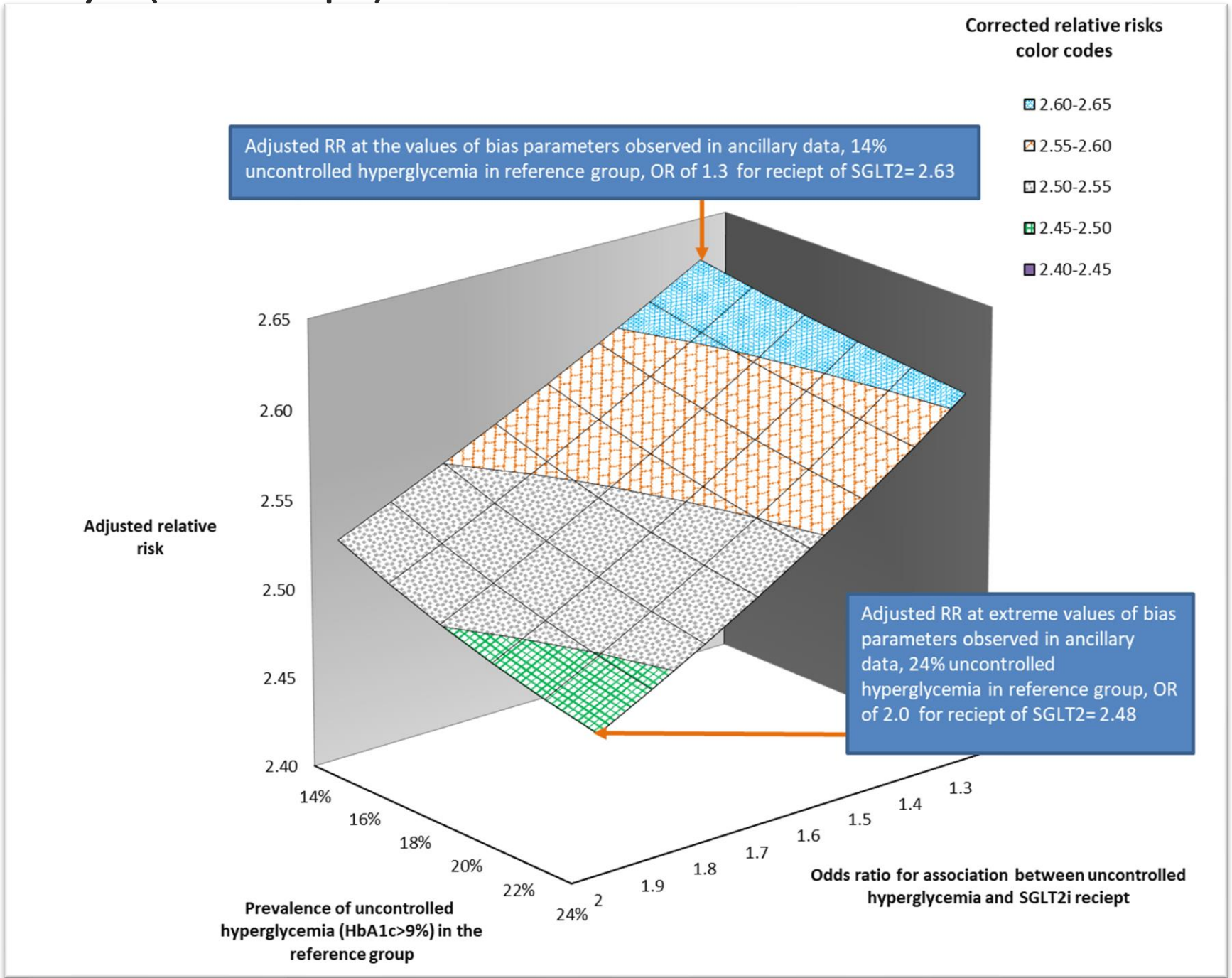
Fig 1 | Overview of the process guide for inferential studies using healthcare data from routine clinical practice

Step 5: Inferential analysis (case-example)

Variable	Events/person years: SGLT-2 inhibitors	Events/person years: DPP-4 inhibitors	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Primary analysis				
Full cohort	123/1553	170/5785		2.68 (1.86 to 3.86)
Male sex	41/912	54/2781		2.32 (1.21 to 4.46)
Female sex	82/620	134/3055		3.00 (2.08 to 4.32)
Age <75 years	77/1026	77/2755		2.69 (1.84 to 3.93)
Age ≥75 years	44/500	81/3068		3.32 (2.04 to 5.41)
With history of infection risk factors	67/655	80/2821		3.60 (2.48 to 5.23)
Without history of infection risk factors	56/886	90/2910		2.04 (1.07 to 3.91)
Robustness evaluations				
Sensitivity analysis: more specific outcome definition	47/1596	68/5826		2.51 (1.54 to 4.11)
QBA: correcting for unmeasured HbA_{1c}	-	-		2.63 (1.82 to 3.78)
Positive control outcome: heart failure hospital admission	23/1612	149/5785		0.55 (0.34 to 0.91)



Step 5: Inferential analysis (case-example)



Summary

- We introduced a stepwise process that systematically considers key decision nodes for evaluating causal effects of treatments using healthcare data

- The process outlined in this framework can facilitate transparent communications between various stakeholders and motivate critical considerations for the clinical research community

Thank You

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