PHUSE APAC CONNECT 2026

RE05: External Comparator Studies in the Era of Real-World Data

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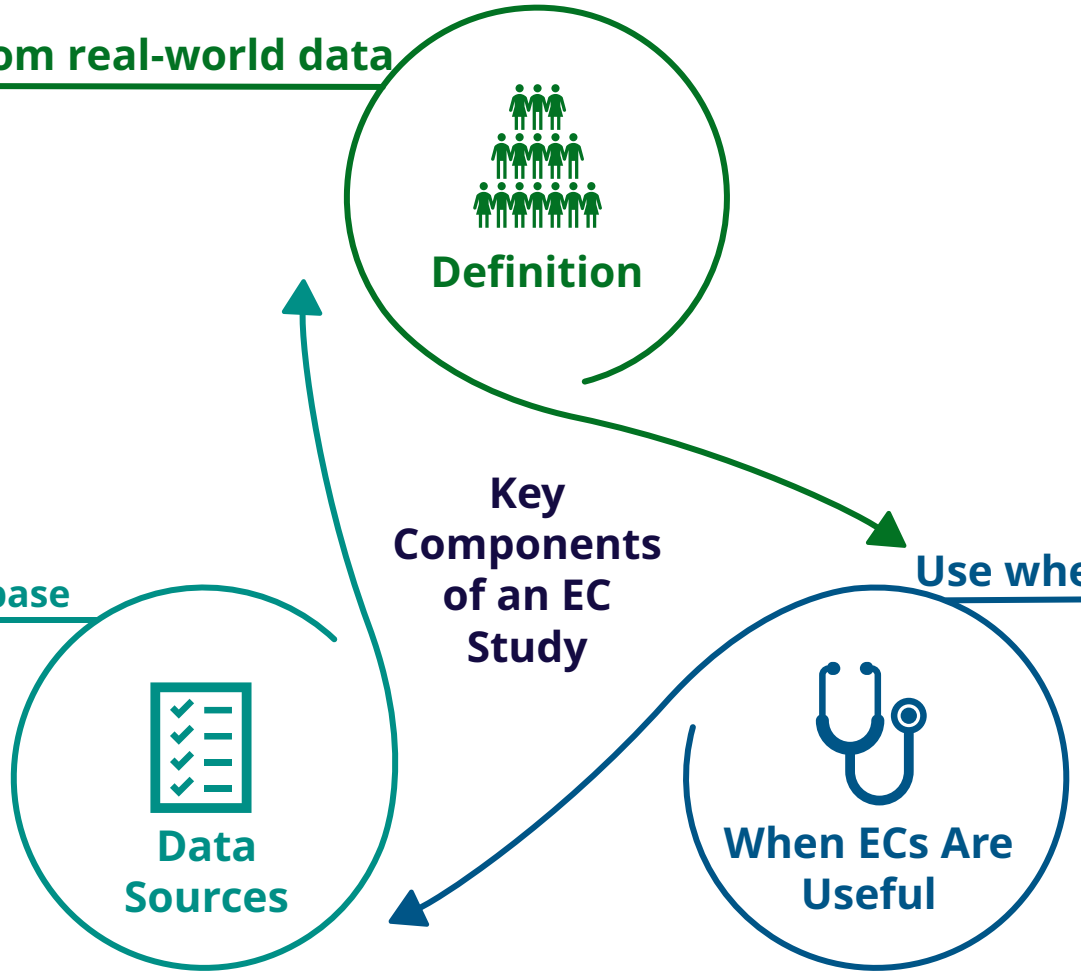
Agenda

+ Introduction
+ Data Sources & Curation
+ EC Design Frameworks (Estimand + Target Trial Emulation)
+ Marginal Estimator Choices
+ Bias Reduction Strategies
+ Sensitivity & Supplemental Analyses
+ End-to-End Methodology
+ Regulatory Perspective
+ Key Takeaways
+ Questions & Discussion

What is an External Comparator (EC) Study?

Comparator cohort constructed from real-world data

EHR, disease registries, claims database



⚠️ ***While EC studies are valuable, RCTs remain the gold standard and should be conducted when feasible!***

Why EC Studies Are Increasingly Adopted

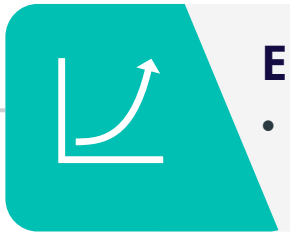
Bridge RCT Gaps

Feasibility Challenges

- RCTs infeasible, unethical, or impractical (e.g. rare diseases, oncology, public health emergencies)

A large anticipated treatment effect can make an RCT unethical

- E.g., randomizing a CAR-T treatment against chemotherapy



EC studies advantage

- Instead of of having a single-arm trial (SAT) with no control group, added value by constructing a comparator population

Regulatory

- Growing regulatory openness especially for rare diseases and oncology

Data Sources & Curation

Fit-for-purpose data

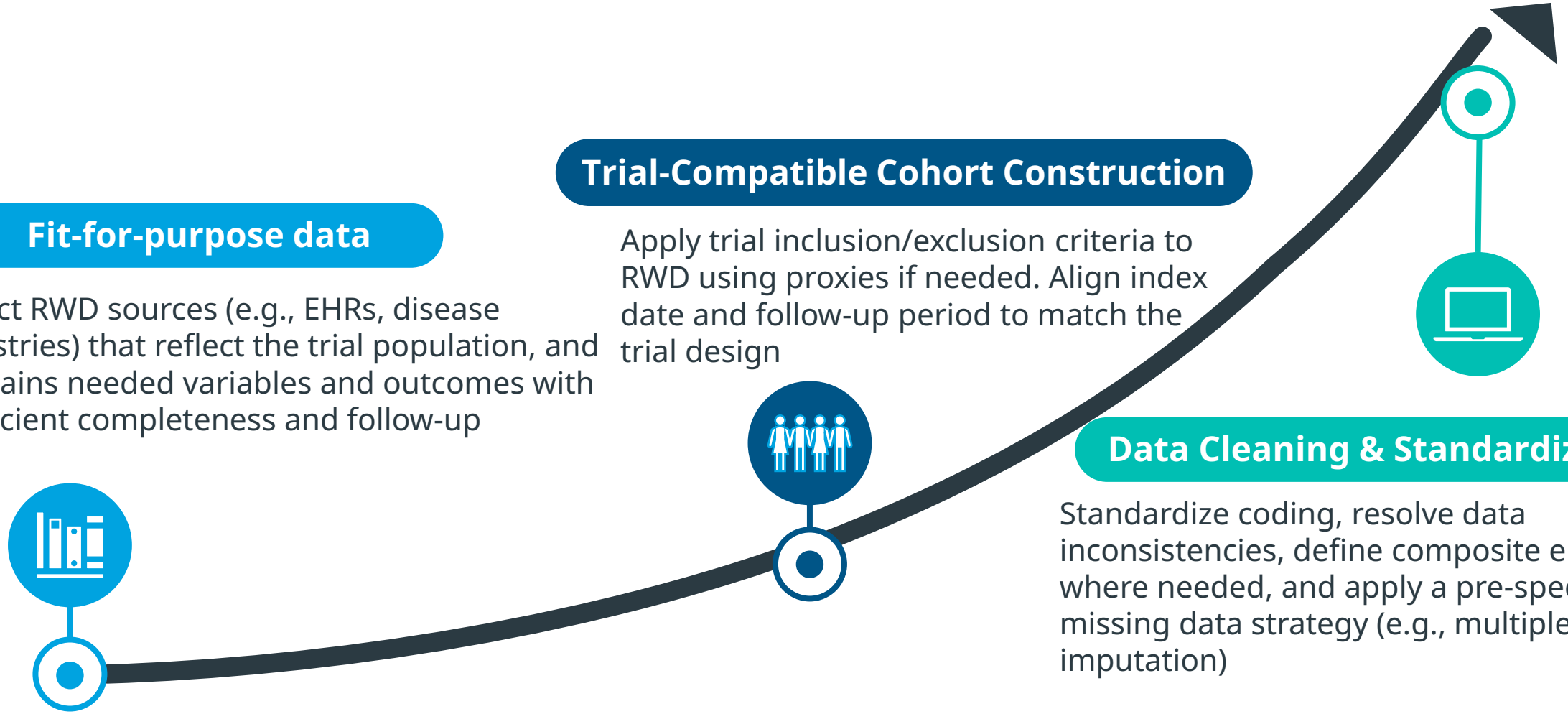
Select RWD sources (e.g., EHRs, disease registries) that reflect the trial population, and contains needed variables and outcomes with sufficient completeness and follow-up

Trial-Compatible Cohort Construction

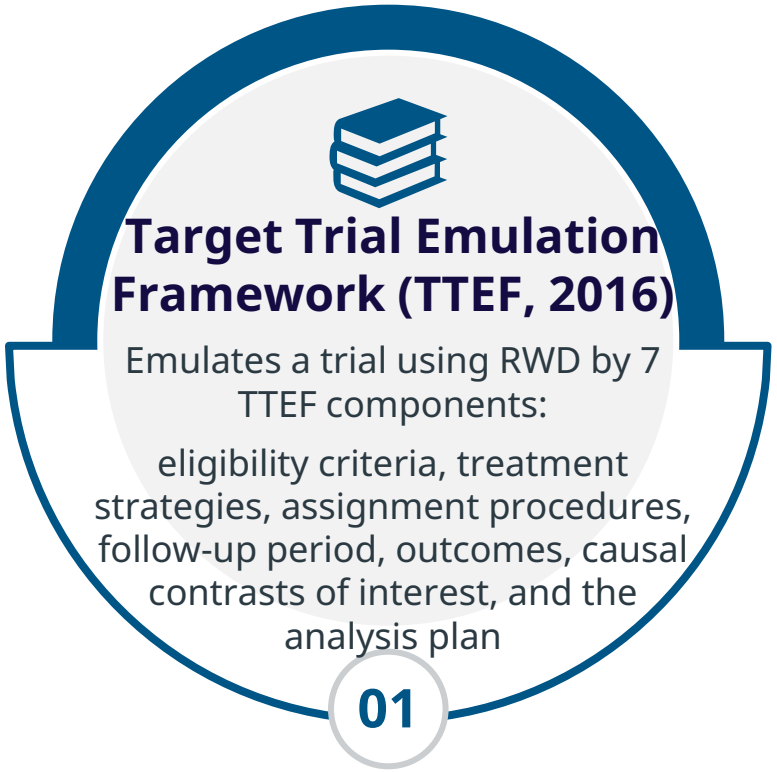
Apply trial inclusion/exclusion criteria to RWD using proxies if needed. Align index date and follow-up period to match the trial design

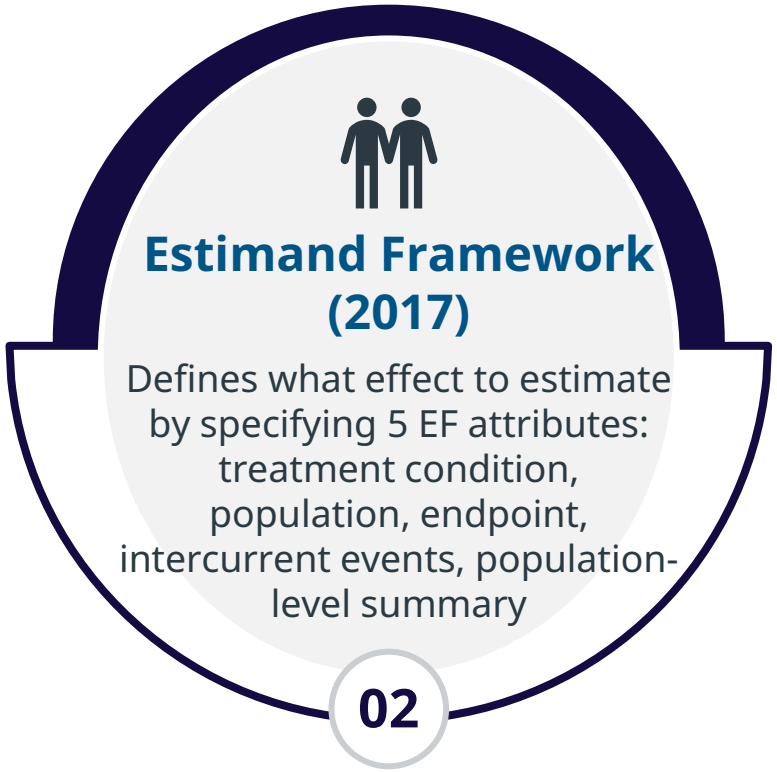
Data Cleaning & Standardization

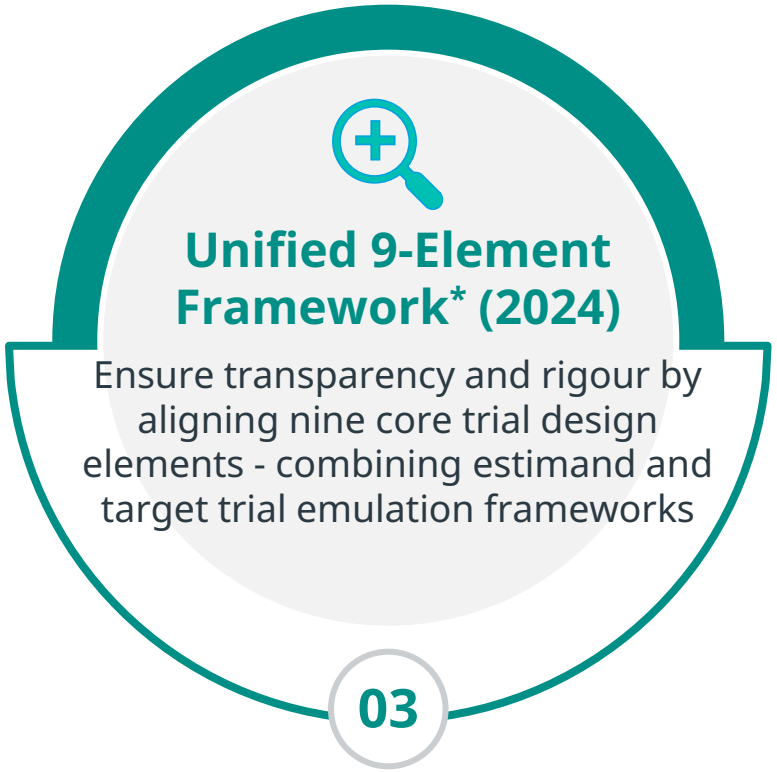
Standardize coding, resolve data inconsistencies, define composite endpoints where needed, and apply a pre-specified missing data strategy (e.g., multiple imputation)



Core Design Framework for EC Studies







*: Rippin G, Sanz H. External comparator studies and the joint application of the estimand and target trial emulation frameworks. Front Drug Saf. Regul. 2024;4:1409102. https://doi.org/10.3389/fdsfr.2024.1409102.

Marginal Estimator Choices

ATT

Estimates the treatment effect based on the baseline values of the treated (trial) population

- 👍 Applies the logic of counterfactuals
- 👎 The approach is anchored on the artificial RCT population (many exclusion criteria, too healthy subjects compared to practice)

ATE

Effect as expected in the pooled population (treated and untreated)

- 👍 Estimates a more realistic effect than the ATT for the treatment application after approval.
- 👎 Pooled population is still not a completely realistic target population

ATU

Effect as expected in the untreated (comparator) population

- 👍 Best for HTA and informative for regulatory decisions (potentially as a supplementary analysis).
- 👍 Works best for some statistical methods*

ATO

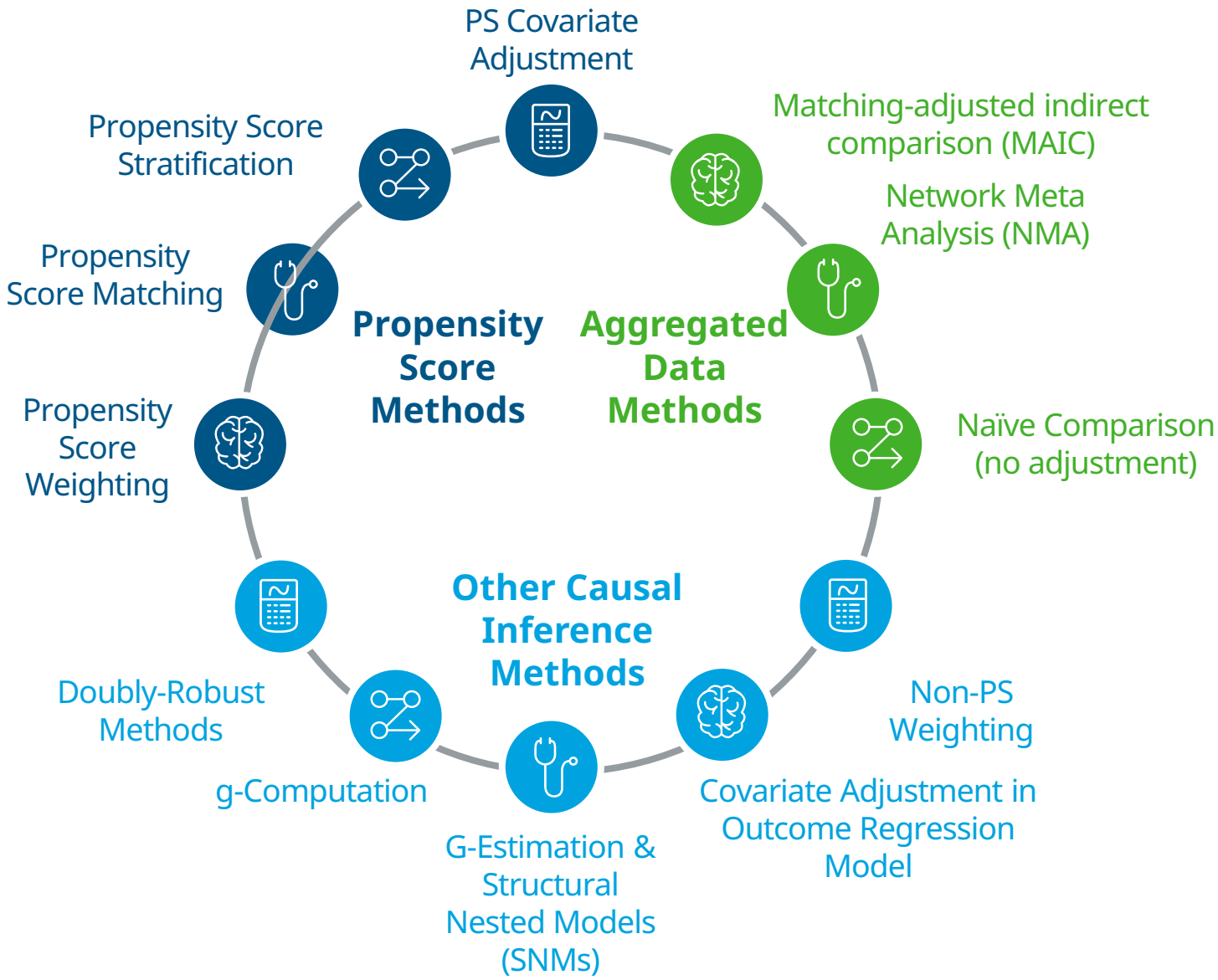
Effect in the population closest to a hypothetical RCT

- 👍 Highest internal validity
- 👎 Interpretation more complex than ATT, ATE and ATU

*: Rippin et al. External Comparator Studies: Performance of Four Missing Data-Handling Approaches, Stratified by Four Different Marginal Estimators. Drug Safety 2025;48 https://doi.org/10.1007/s40264-025-01586-x

Choose the primary estimator in alignment with regulatory/HTA and present all marginal estimators at least for the primary endpoint

Confounding-Adjustment Approaches



Propensity Score Methods

Bias Reduction

PS Matching

Pair treated and control patients with similar PS values. Estimates typically the ATT, but can be modified to estimate also the ATE, ATU or ATO, e.g., by adding a weighting step after matching. Typically reduces the sample size, which may be problematic dependent on the number of available comparator patients.

PS Weighting

Applies weighting to balance baseline factors across cohorts. Retains the full sample. Need to check for high weights.

Stratification

Group patients into PS strata (e.g. quintiles) to compare outcomes within strata. Simple and transparent, but does not remove all bias

Outcome regression with PS

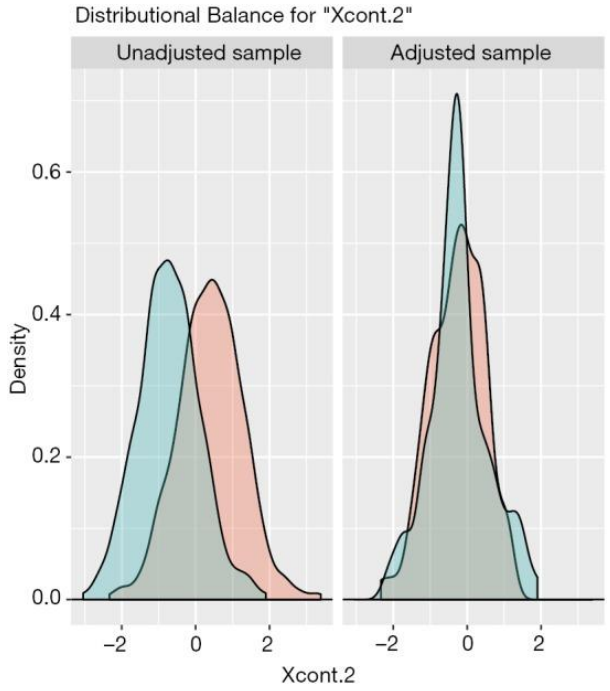
Include PS in outcome model. Does not estimate a marginal treatment effect and introduces regression model dependency.

Note: Each method may target different marginal estimators (ATT, ATE, ATU, ATO)

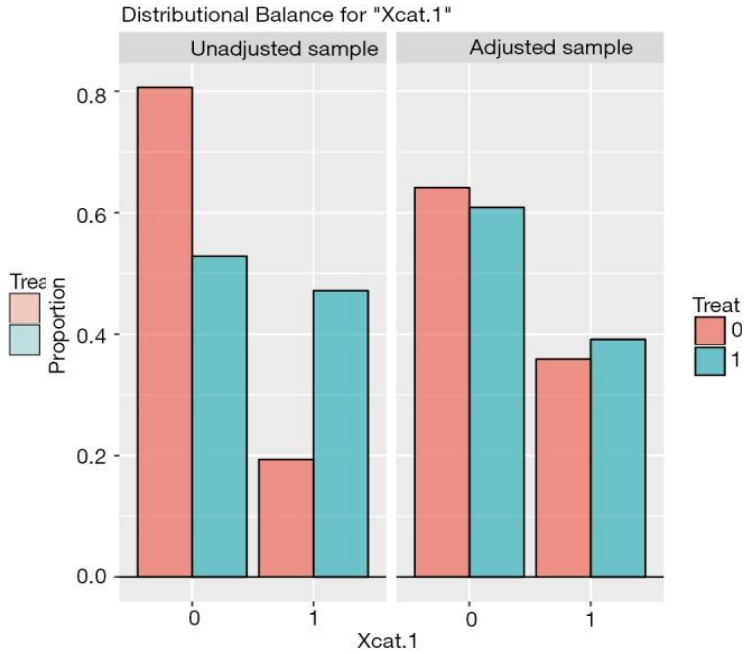
Propensity Score: Balance Diagnostics

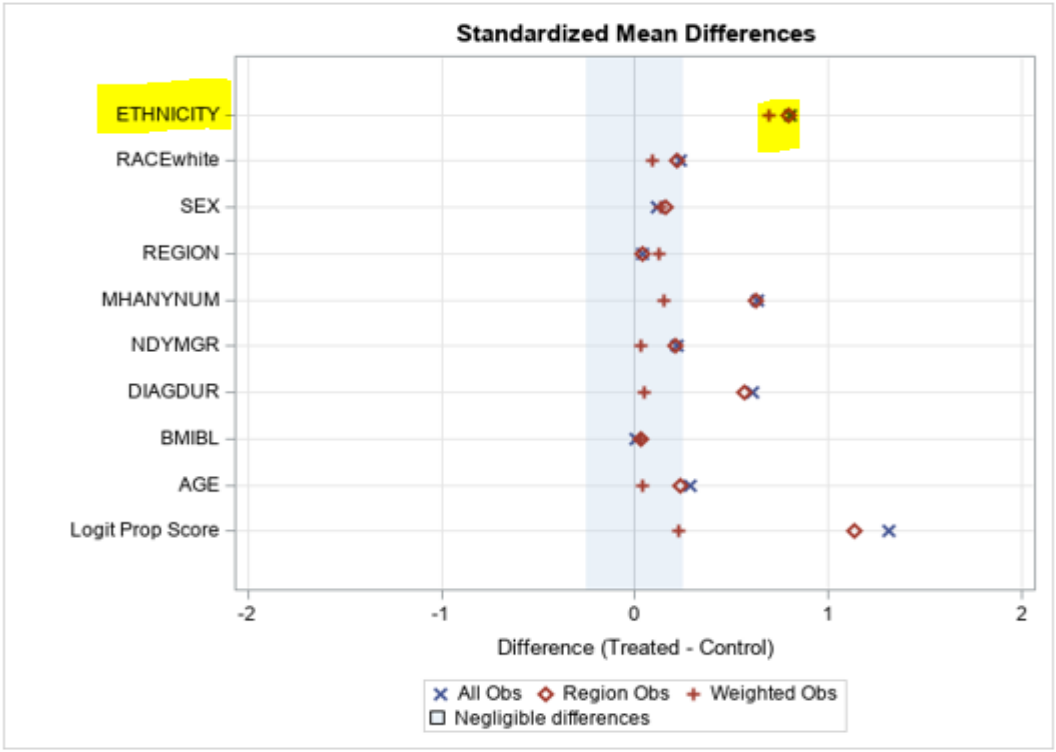
- Calculate Standardised Mean Differences (SMD) for key covariates
- Target SMD < 0.10 for acceptable balance
- Investigate imbalance (e.g. outliers, poor overlap) and refine PS model if needed
- Balance checks confirm comparability between trial and external cohorts
- Follow pre-specified plans for model refinement to maintain transparency

Continuous covariate



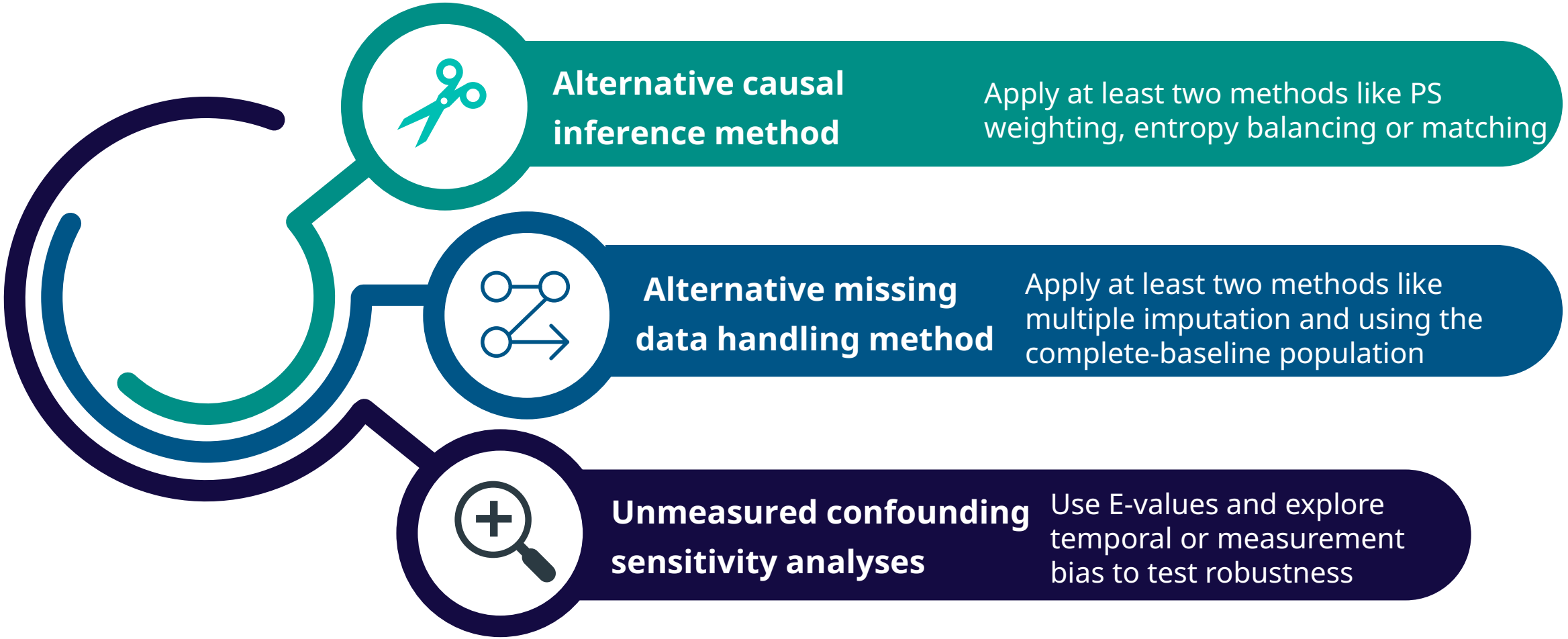
Categorical covariate





Zhang et. al. Balance diagnostics after propensity score matching. Ann Transl Med. 2019 Jan;7(1):16. doi: 10.21037/atm.2018.12.10.
Stuart E.A. Matching Methods for Causal Inference: A Review and a Look Forward. Statist. Sci. 25 (1) 1 - 21, February 2010.

Sensitivity & Supplemental Analyses



Alternative causal inference method

Apply at least two methods like PS weighting, entropy balancing or matching

Alternative missing data handling method

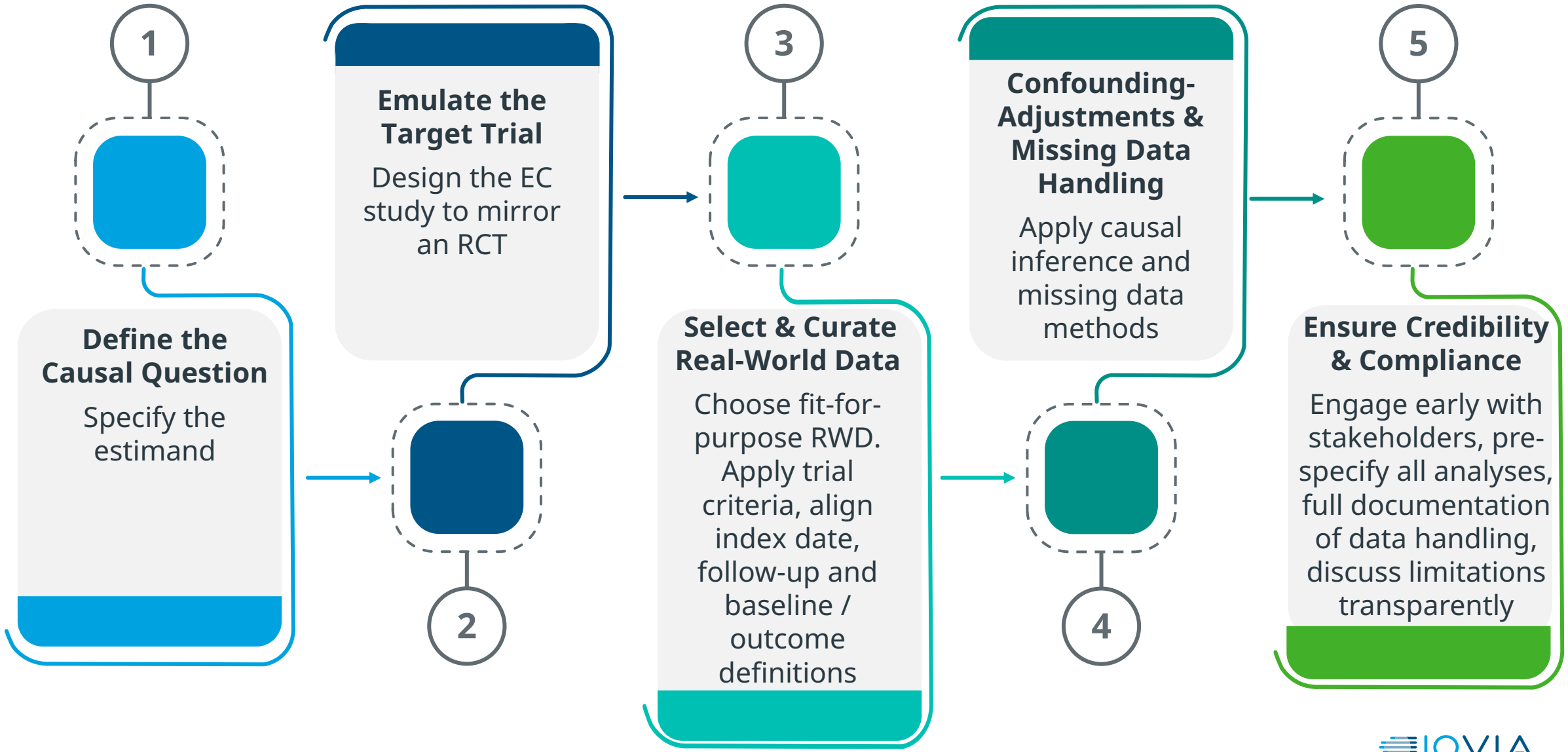
Apply at least two methods like multiple imputation and using the complete-baseline population

Unmeasured confounding sensitivity analyses

Use E-values and explore temporal or measurement bias to test robustness

Further sensitivity analyses may include usage of different index dates and other study-specific critical assumptions / definitions. All supplementary/sensitivity analyses should be pre-specified in protocol /SAP to ensure transparency and credibility

End-to-End Methodology for EC Studies



Regulatory Perspective

Pre-Specification & Transparency

Define the estimand, emulate a target trial, engage early with stakeholders, detailed SAP, document assumptions, proxies, data inconsistencies, and discuss limitations

Population & Endpoint Alignment

Map trial criteria to RWD (justify any proxies), ensure cohort comparability, align time-zero, baseline, endpoints

Data Fitness & Provenance

Data relevance & reliability

Bias Control & Robustness

Demonstrate robustness of results which includes showing covariate balance (e.g. SMD < 0.10), conducting many sensitivity and supplementary analyses, and assessing the impact of any potential unmeasured confounding (e.g. E-value)

Summary of Key Takeaways

01 Design Discipline

02 Data Rigour

03 Analytical Strength

04 Regulatory Alignment

Questions & Discussion

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