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# Practical and methodological considerations in using external comparators for clinical trials from real-world data sources

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# To ensure a timely pathway patient access, RCTs may be too slow or even unethical in specific circumstances

- **Randomization is the gold standard for experimental design**
  - Balances both measured and unmeasured confounders
- **However, randomized controlled trials (RCTs) may not be possible in cases of:**
  - Rare disease
  - Severe disease where no good treatment is available



**Examples: Oncology trials for rare or previously untreatable disease**

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**A proposed solution:**

**Use of external comparators using real-world data (RWD)**

# Use of RWD as external comparators provides fresh opportunities, but also new complications

## Why real-world data?

- There has been the rapid growth in the availability and use of routine health care data to explore effectiveness and safety.
- RWD more often reflect the typical use of treatments in the clinical setting and tend to encompass patients with widely varying characteristics and co-morbidities (external validity).
- Use of **RWD in post-authorization safety studies (PASS)** has become standard practice.

### Real-world data includes:

Routine health care data captured in electronic health records (EHR), registries, claims data, and chart review studies.

# Use of RWD as external comparators provides fresh opportunities, but also new complications

## Opportunities:

- The FDA has shown increasing support for the use of RWD in general and recently, RWD as external comparators specifically.
- The EMA remains skeptical, but has shown a willingness to consider external comparators given strong evidence.

## What is needed?

# Use of RWD as external comparators provides fresh opportunities, but also new complications

## Opportunities:

- The FDA has shown interest in RWD in general and recently in external comparators specifically.
- The EMA remains skeptical but may consider external comparators in the future.



## Drugs approved by the EMA using external comparator studies to support:

### Zalmoxis, 2016 (MolMed)

Genetically modified T-cells for reduction in graft versus host disease in stem cell transplants for blood cancers.

- Area of high unmet need
- Declared 'orphan medicine' in 2003 due to rareness of the disease
- Administered only in high-risk blood cancer cases

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## Challenges:

- Use of RWD data in trials re-introduces biases common to observational studies.
- Routine healthcare data is not collected for the primary purpose of research; data may be missing or collected with a different rigor from clinical trials.

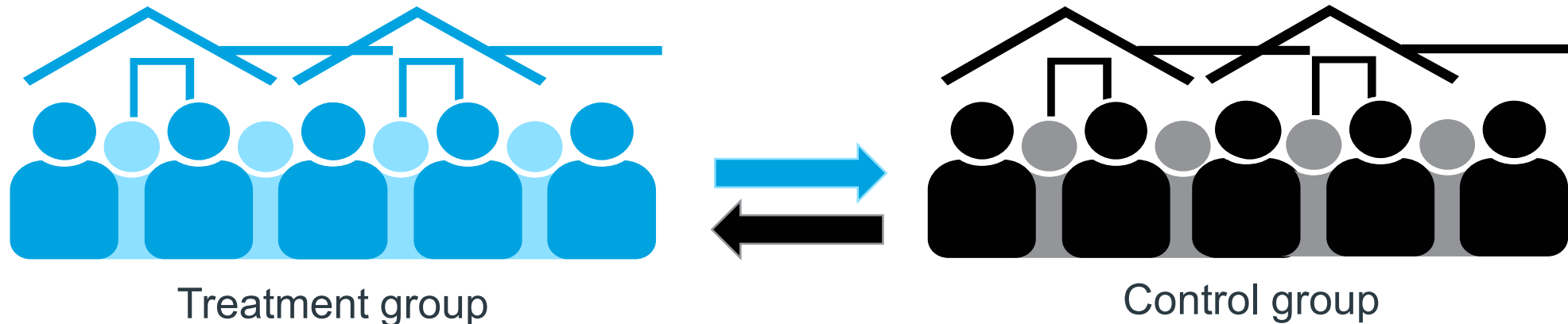
## What is needed?

**A framework by which trials using external comparators can be evaluated**

# Implementation of Pocock's 6 Criteria of Exchangeability [1] to ensure an internally valid comparison

For an internally valid comparison, the two populations (trial and external) should be perfectly exchangeable with one another.

**Exchangeability:** if the treatment status were exchanged, the value observed for the outcome in absence of the treatment would be the same [2].



# Implementation of Pocock's 6 Criteria of Exchangeability [1] ensure an internally valid comparison

For an internally valid comparison, the two populations (trial and external) should be perfectly exchangeable with one another at a minimum with regard to:

1. Eligibility criteria
2. Patient characteristics/confounders
3. Mode of treatment
4. Outcome measure
5. Time period
6. Setting

However, RWD external comparator patients are not going to be perfectly exchangeable with trial participants.

## Ways in which RWD is often different from trial data:

- Active vs passive reporting
- Use of proxies for determining an event
- Use of alternative diagnostic instruments
- Setting is routine care and not a clinical trial



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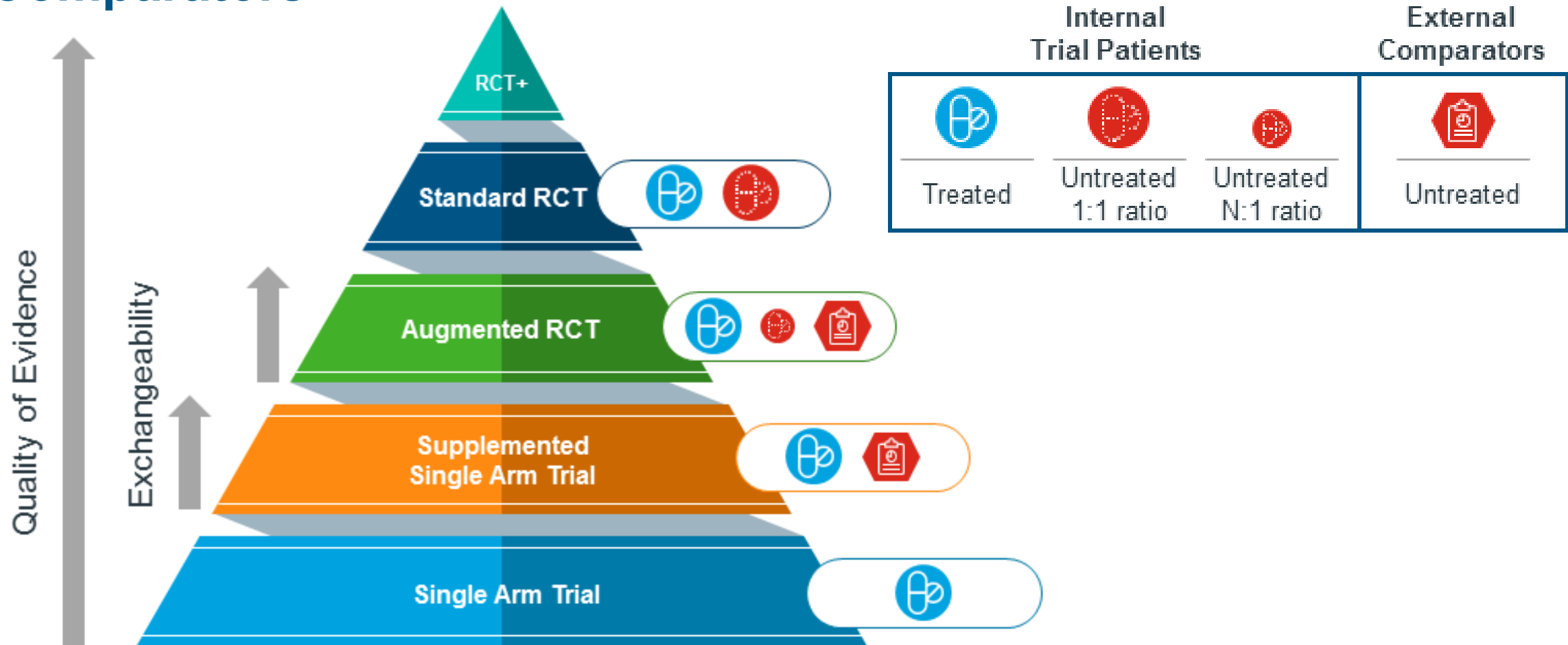
However, RWD external comparator patients are not going to be perfectly exchangeable with trial participants. **Accepting this...**

## Research aims:

How can we use exchangeability to evaluate the strength of the evidence of these trials?

What aspects of study design and analysis are necessary to maximize the strength of the evidence?

# Study Designs: Hierarchy of Evidence with RWD External Comparators



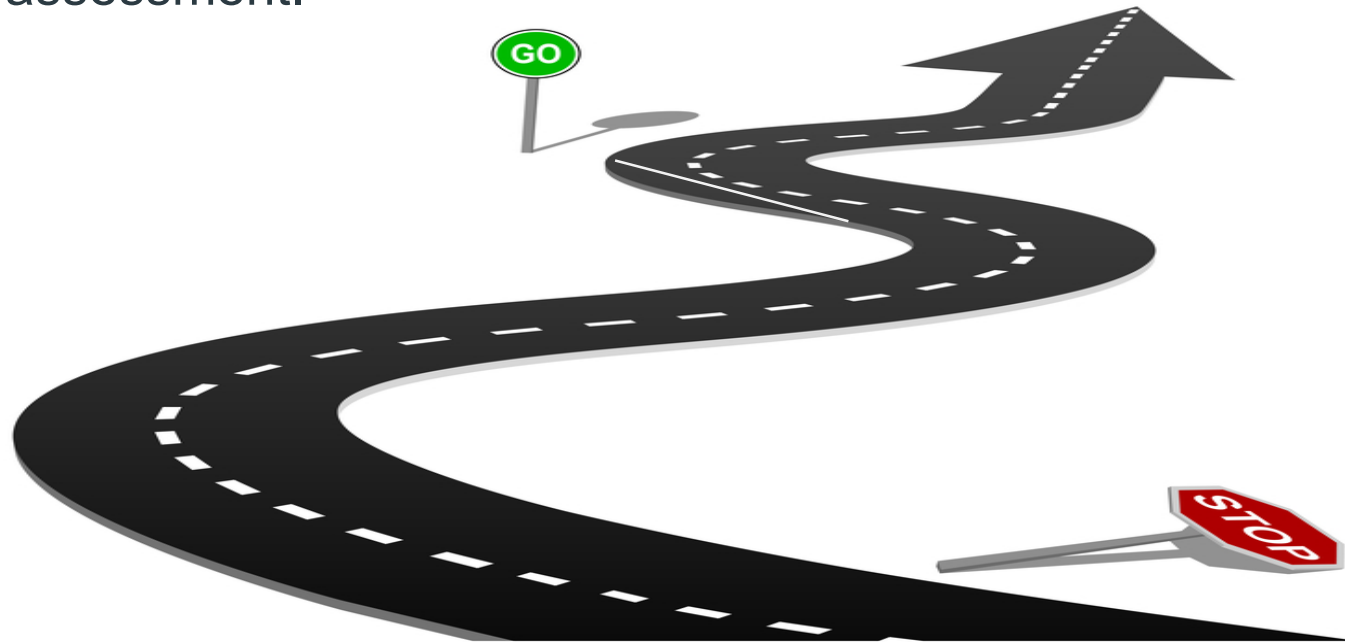
The quality of evidence is expected to increase as one goes from a single arm trial to an RCT; similarly, within the designs for a trials using RWD external comparators, the quality of evidence is expected to increase as the exchangeability between the trial participants and the external comparators is increased.

# Our 4-step process for analyzing studies using RWD external comparators to maximize quality of evidence



# Step 1: Assess feasibility of data source and study design

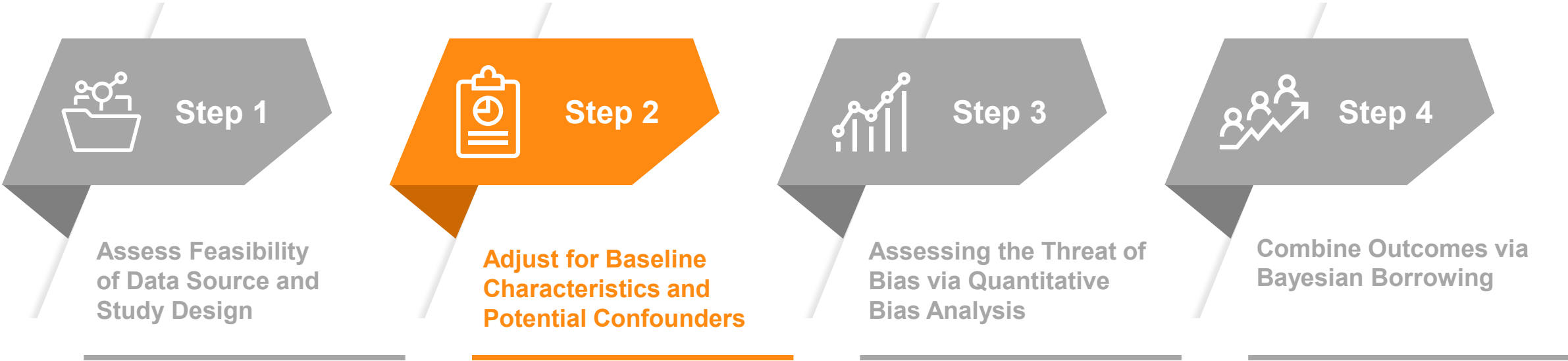
- A) Identify all important variables associated with selection, confounders, outcome measure, etc.
- B) Maximize exchangeability in the study design where possible.
- C) Identify sources of non-exchangeability for later bias assessment.



Example:

- GO Fully available
- ? Available, partially missing  
→ Assess bias
- ? Available, proxy used  
→ Assess bias
- X Not available  
→ Go/No-go?  
→ Assess bias

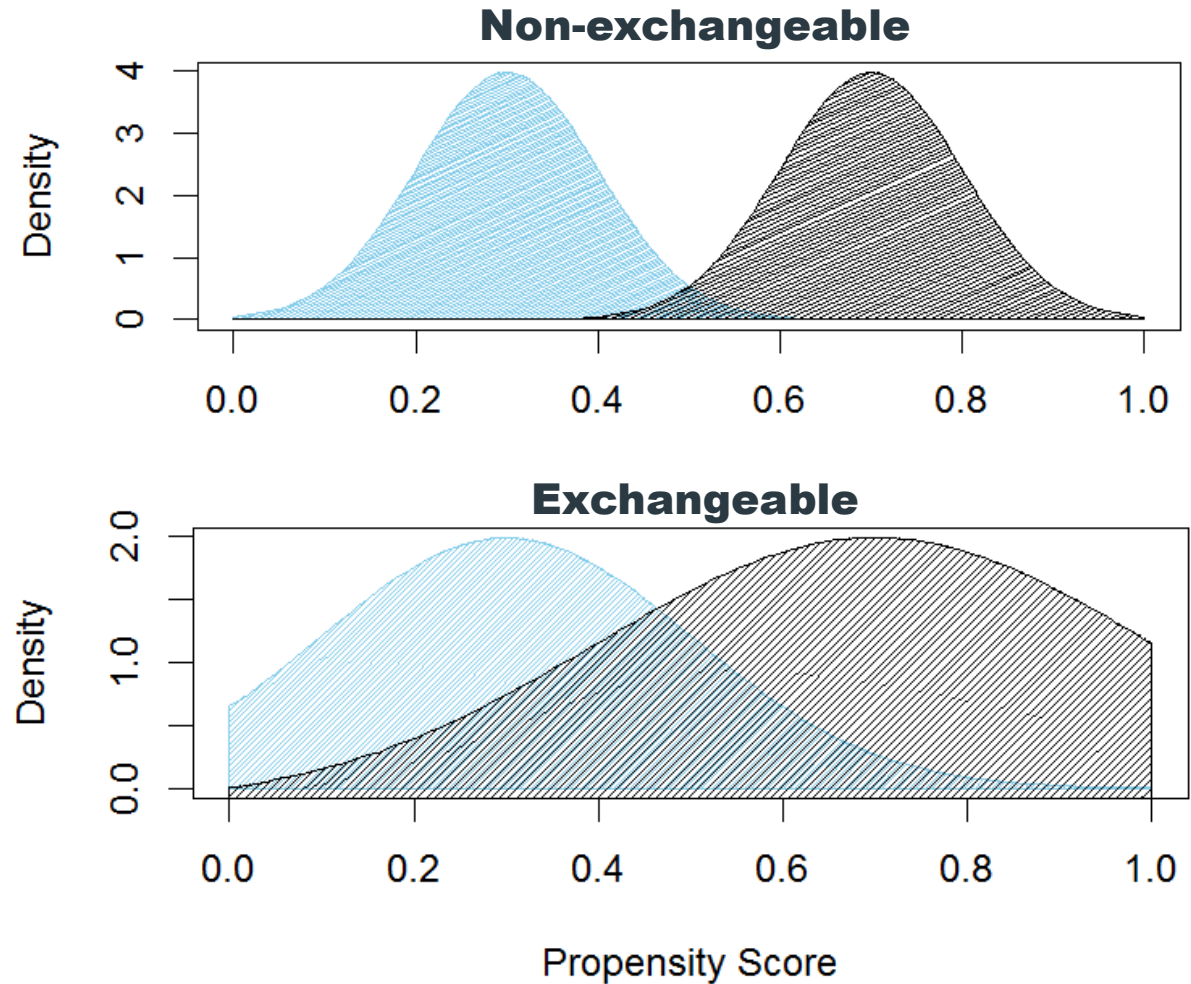
# Our 4-step process for analyzing studies using RWD external comparators to maximize quality of evidence



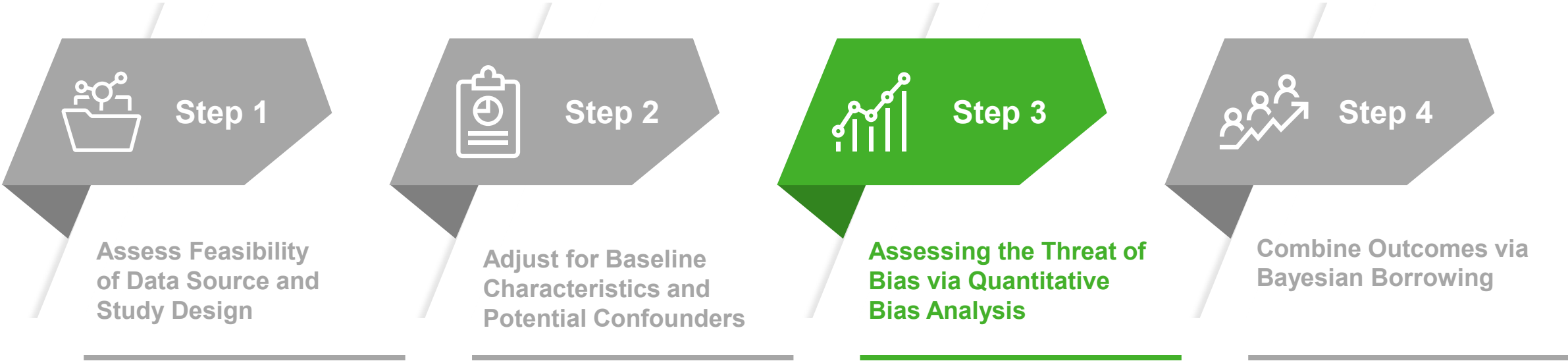
## Step 2: Adjust for baseline characteristics and potential confounders

Wherever characteristics/confounders are measured, they can be adjusted for through the statistical means typically employed for observational studies, propensity score methods or covariate adjustment (as appropriate).

- Propensity score analysis can also be used to illustrate and assess the exchangeability of the populations [5-6].



# Our 4-step process for analyzing studies using RWD external comparators to maximize quality of evidence



## Step 3:

## Assess the Threat of Bias via Quantitative Bias Analysis

**While we cannot usually correct for the effects of unmeasured factors, we can estimate the impact of specific threats of bias based on prior or external knowledge.**

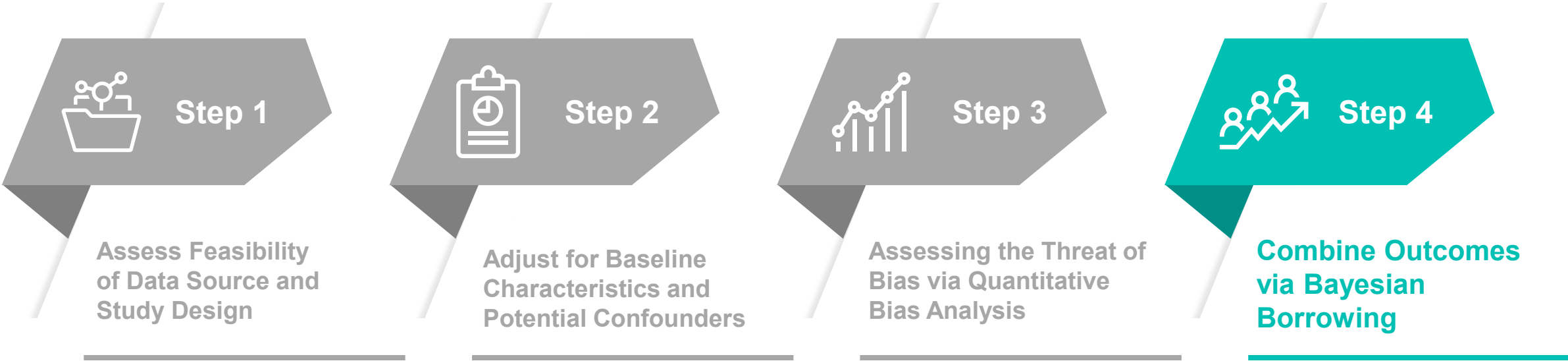
- **Quantitative bias analysis** is any bias modelling using deterministic or probabilistic models [7-8].
- Sources of bias identified in our roadmap in **Step 1**.
- Each source of bias may be considered and modelled separately, but joint modelling of sources of bias is preferred where possible.
- Alternatively, one may estimate how large a bias is necessary to change the inference of the study.

### Common sources of bias:

- Selection bias
- Misclassification error
- Measurement error
- Missingness
- Uncontrolled confounding



# Our 4-step process for analyzing studies using RWD external comparators to maximize quality of evidence



## Step 4: Combine outcomes via Bayesian borrowing

Completely exchangeable

=

Pool data

Reality somewhere in between

=

Bayesian borrowing

Completely non-exchangeable

=

Discard external data

Bayesian borrowing, or Bayesian discount functions, can be applied in order to combine outcomes from different sources.

### Examples [9]:

Power prior [10-12]:

$$(\pi(\theta) * L(\theta|D_{Ext})^w) * L(\theta|D_{Int})$$

Hierarchical models

Commensurate methods [13]

## Step 4: Combine outcomes via Bayesian borrowing

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Reality somewhere in between  
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**Bayesian borrowing, or Bayesian discount functions, can be applied in order to combine outcomes from different sources.**

- The difficulty is in knowing how much credibility to give to the external outcomes.
- We suggest drawing on Steps 1-3 and expert knowledge to quantify the amount of non-exchangeability as weighting or prior distribution.
- Assess sensitivity of the inference to choice of prior and weights
- Methods that make use of covariates in addition to the outcomes are preferable, but underresearched.

# Conclusions

- What we lose in rigor of design must be re-gained in rigor of analysis.
- Given recent regulatory support for external controls, having an appropriate **framework for evaluating clinical trials** using RWD external controls is of urgent importance.
- The **strength of the evidence** stemming from a trial performed with RWD external comparators may be evaluated in terms of study design (Augmented RCT or Supplemented Single Arm Trial) and in terms of non-exchangeability between the external and trial population.
- Use of a **feasibility assessment** before onset of data collection and of a **quantitative bias analysis** after accounting for measured confounders can strengthen the quality of evidence.
- **Bayesian borrowing** may be used to combine outcomes from RWD external comparators and the internal comparator arm of an RCT (in an Augmented RCT), but should be informed by the assessment of exchangeability.



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# Questions?

