Robustness of external control arm: When to use them

Prepared For: ISPOR 2021

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Conflict of interest: All authors are consultants working at Evidera PPD
April 7th, 2021

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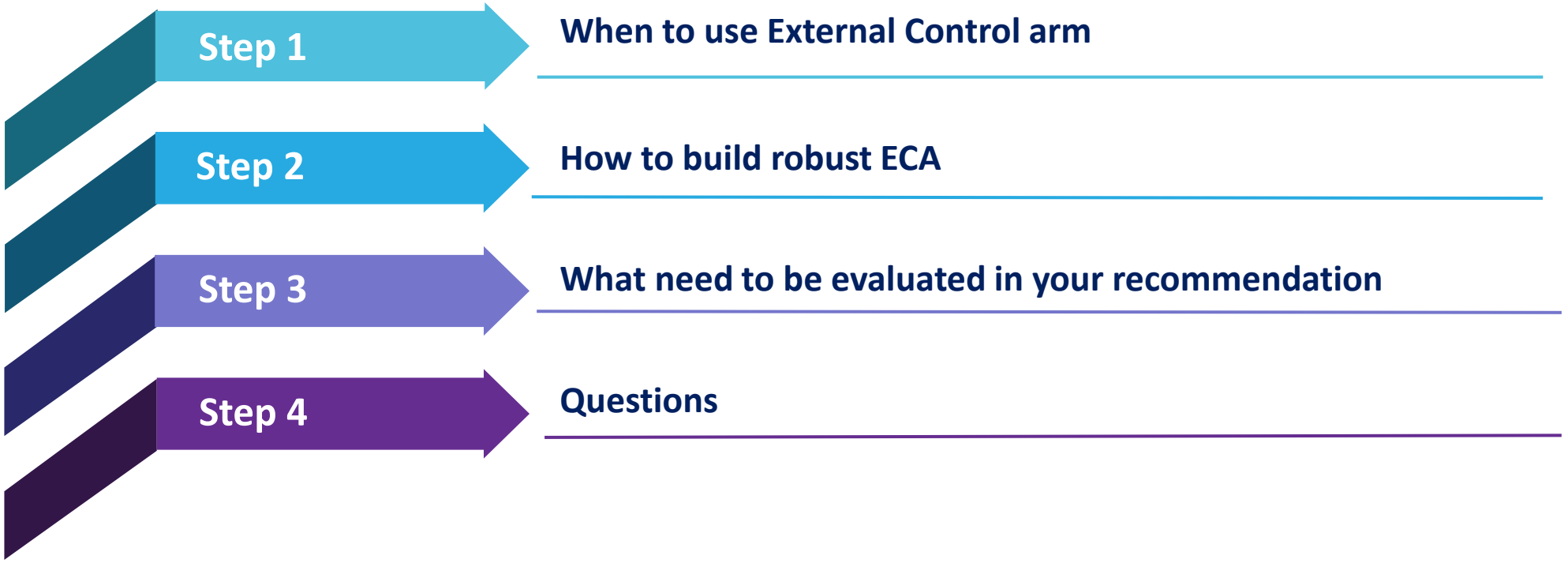
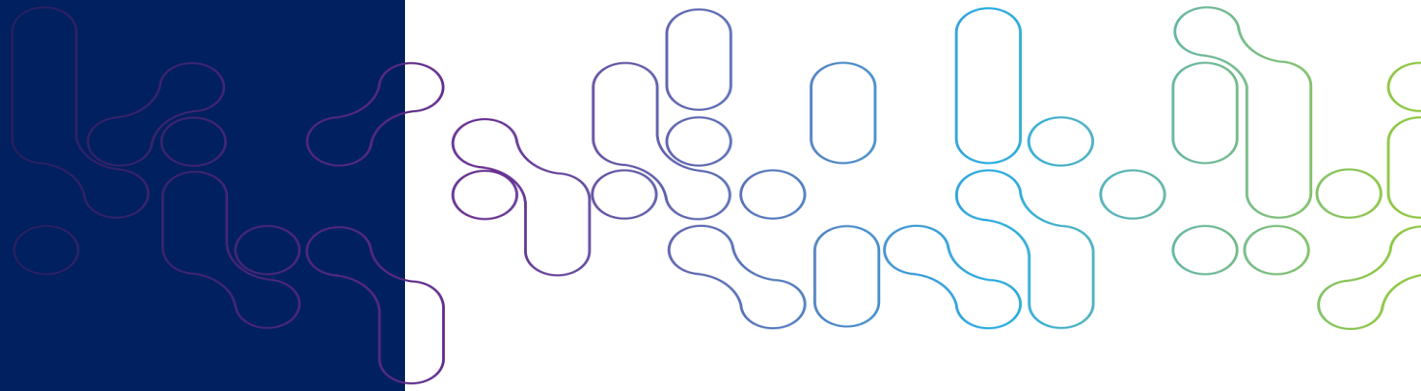
Outline


Step 1
When to use External Control arm
Step 2
How to build robust ECA
Step 3
What need to be evaluated in your recommendation
Step 4
Questions

Context: When to use ECA



Context

- Randomized clinical trials (RCT) can be challenging or unethical and single-arm trials are preferred
  - Rare indications with high unmet need,
  - Therapies with high benefit versus risk
- These trials do provide evidence of efficacy and safety
- Regulators, payers, and other stakeholders are still interested in comparative results versus a control population.
- Strong support for efficacy and safety can emerge from single-arm trials with ECA
  - The natural history of a disease is well defined,
  - The standard of care is well defined and not changing over time,
  - An external control population can be identified that is very similar to that of the treatment group,
  - The results provide a compelling contrast to observed changes in outcomes of the trial (large treatment effect).

FDA Open to Using Real-world Data for ECAs in Certain Circumstances

"At FDA, we're committed to advancing ways that data leveraged from these streams – typically called **real-world data** – is transformed into evidence using transparent data standards that can give all stakeholders confidence in the data's provenance, so that more of this data can be used to generate the evidence that the agency needs to improve regulatory decision making."

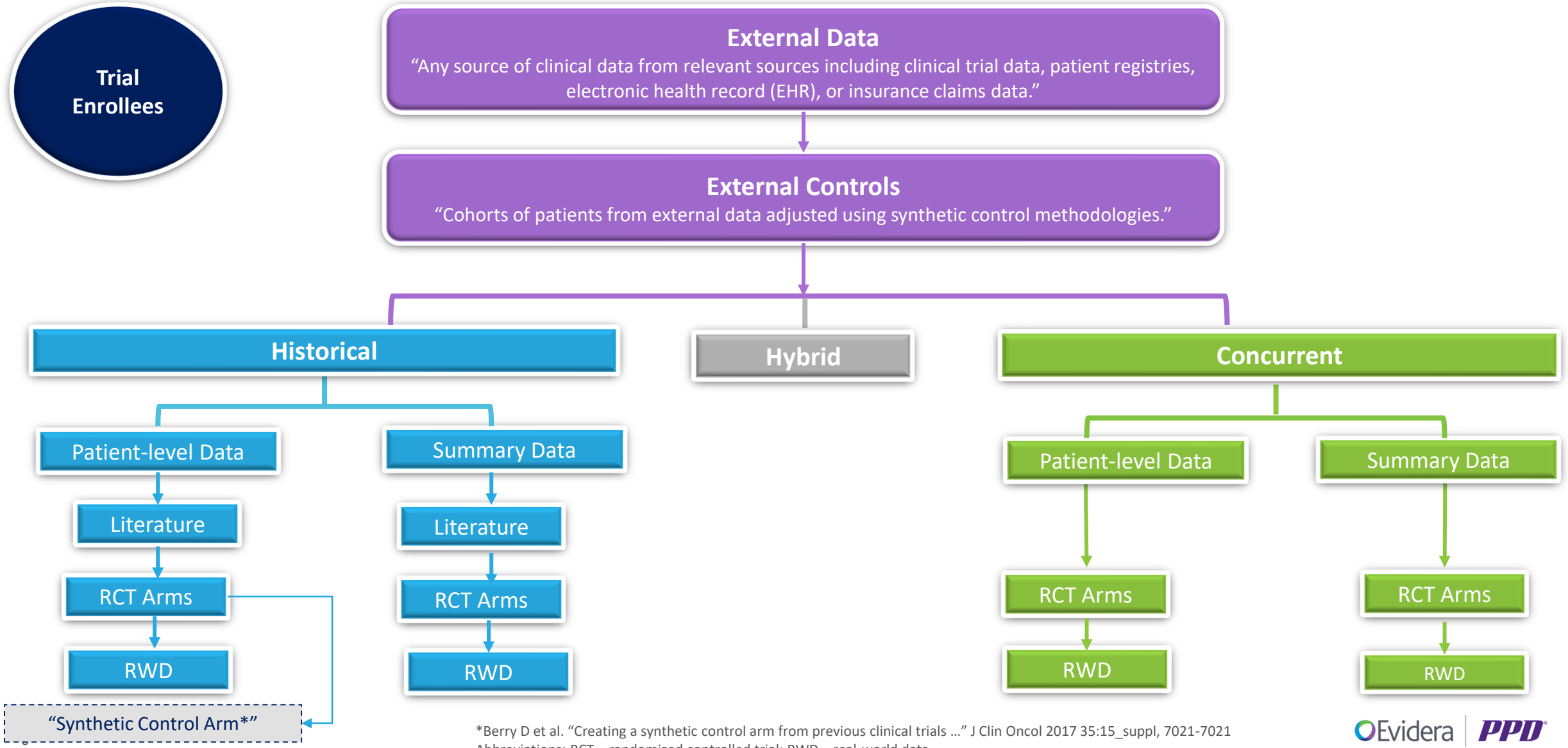
—US FDA*

Circumstances that may prompt the use of ECAs

- **Rare indication with high need/urgency, poor outcomes**
- **Therapy with large benefit vs. risk**
- **RCT unethical/unfeasible, significantly delays to patient access**
- Pandemic
- **Scientific concerns about treatment switching/cross-over**

ECA Applications	Examples
Accelerating Research	Medidata Synthetic Control Arm® received FDA approval for the use of an ECA in phase III registrational trial in recurrent glioblastoma (rGBM), an aggressive form of brain cancer. The Medidata ECA combined historical trials data from more than 22,000 clinical trials studies with randomized patients and helped overcome high patients drop out rates.
Evaluating Efficacy	Pfizer and Merck KGaA used an ECA from patient medical chart review to assess the efficacy of Bavencio (avelumab), a PD-L1 inhibitor, for treating Merkel cell carcinoma. EHR data from community and academic hospitals were used to create the ECA which helped overcome difficulties in recruiting a prospective control due to short patient survival time.
Accelerating Approval	ECA has led to the approval of remdesivir for COVID-19. Gilead Sciences, a longtime PPD partner, presented an urgent request to initiate global clinical trials of remdesivir, its then-investigational COVID-19 therapy, under an extremely aggressive timeline
Label expansion	Amgen's leukemia drug Blincyto (blinatumomab) received label expansion based on evidence of a single-intervention group trial that compared response rate in the trial with historical RWD from 694 comparable patients from US and EU EHR.

External Control Arm



*Berry D et al. "Creating a synthetic control arm from previous clinical trials …" J Clin Oncol 2017 35:15_suppl, 7021-7021
Abbreviations: RCT = randomized controlled trial; RWD = real-world data

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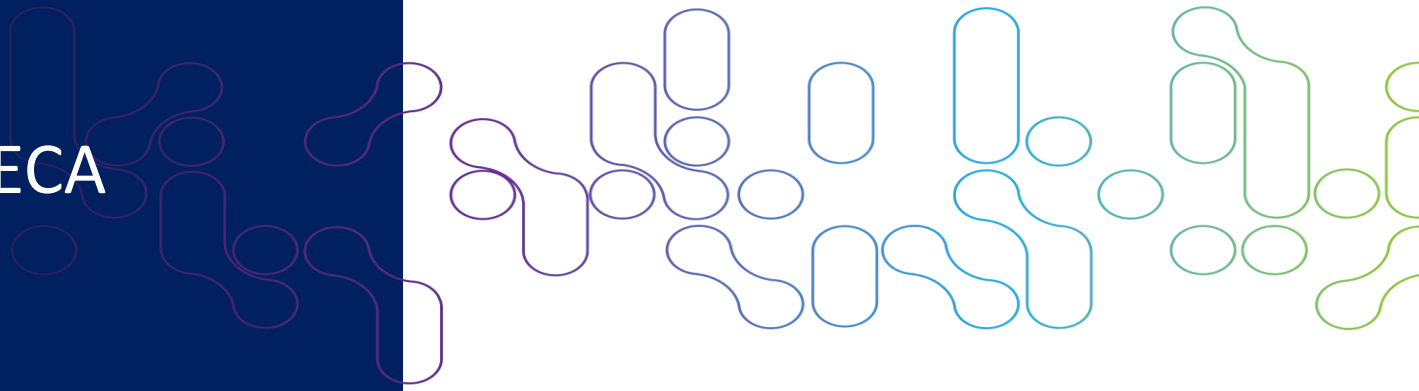
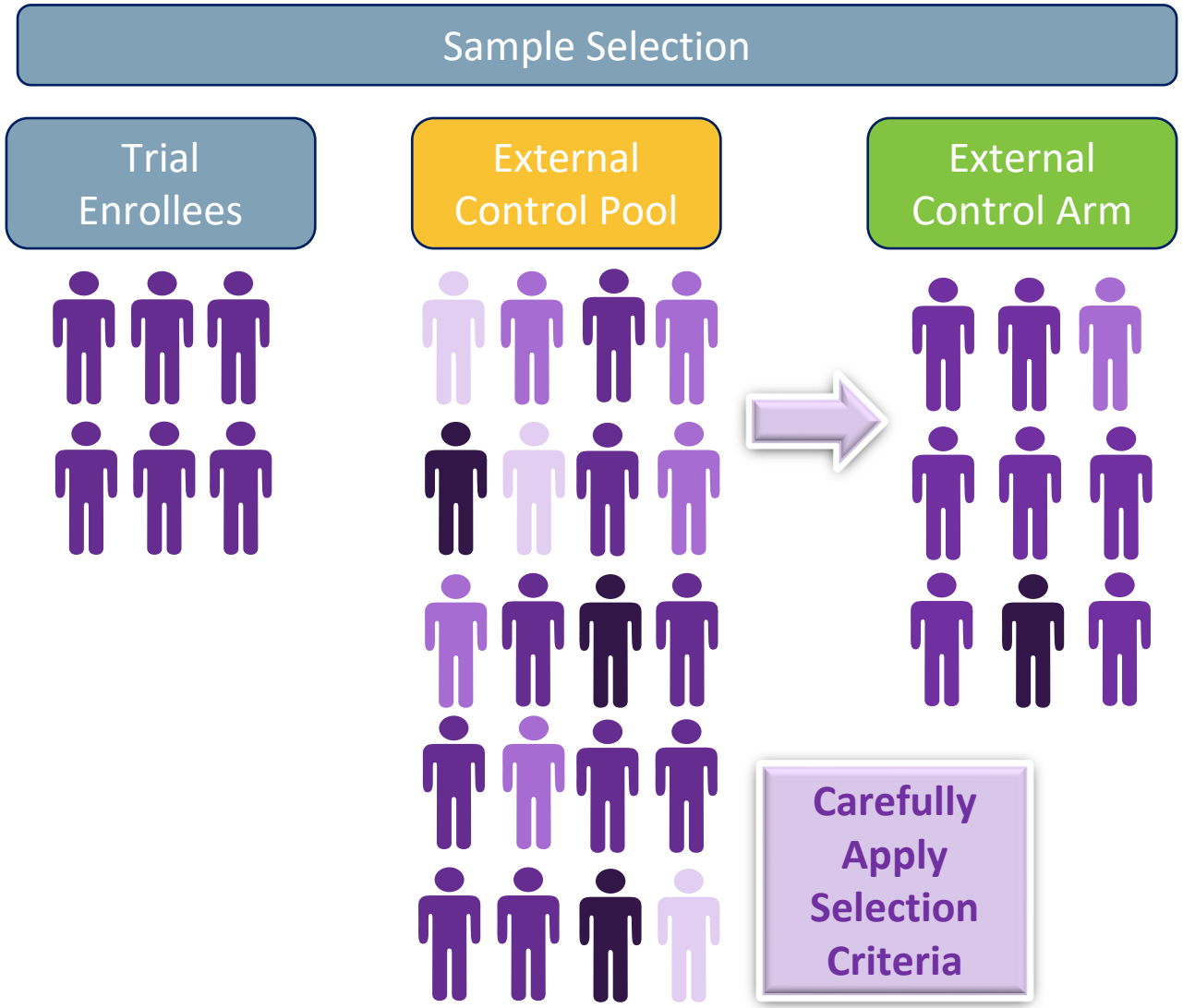
Process: How to Design a Strong ECA



Visual Concept- Constructing a Control Arm From External Data Sources



Additional Analytic Considerations
Exact matching
Propensity score matching
Inverse probability of treatment weighting
Propensity score weighting by odds
Outcome regression models
Simulation

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Emulate Target Trial Protocol

- Eligibility criteria
- Treatment strategies
- Randomized assignments
- Start/End follow-up
- Outcomes
- Causal contrast
- Analysis plan

e.g., Single arm trial protocol can be seen as the target trial

Control cohort will be constructed from RWD emulating the target trial protocol

- **Multiple potential data sources**
  - **Data from other RCTs (e.g., placebo arms)**
  - **Published literature**
  - **Real-world data**
    - **Existing EMR augmented with relevant measures via chart review**
    - **Electronic health record (EHR) extraction**
    - **Chart reviews**
    - **Physician panels**

Three Key Requirements to select right sources of data

Granularity

Contemporary data

Large sample size

Deviations from target trial are sources of bias in observation studies, a bad ECA is easy to build!

How Will We Get There: Thinking Through a Quality ECA Design

Team Science: Clinical, Statistical, Operational, Scientific, Design Specialist, Regulator Expert and More

Purpose of ECA

- Hypothesis testing
- Context / Benchmarking
- Regulatory approval?
  - Primary
  - Label change
  - PMR
- HTA / market access

Research Question

- Is it a causal question?
- Specify in detail

Study Design

- Single arm
- Hybrid
- Retrospective
- Prospective

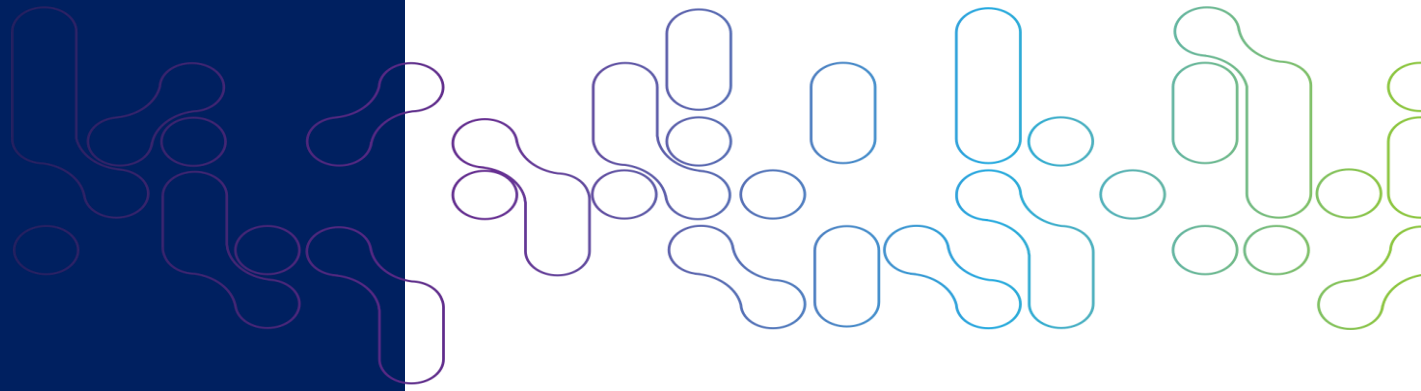
Data Fit-for-Use Evaluation

- Data reliability
- Conformance
- Completeness
- Plausibility
- QC, QA, verification, validation
- Data relevancy
- Sufficient N
- Representative
- Granularity & longitudinal availability of key measures

Description of the ECA

- Target trial context
- Appropriate I/E
- Time element
- Historical
- Concurrent
- Outcomes
- Analysis plan

What need to be evaluated



When it comes to regulatory submission

Understanding Agency

- It is not common to use ECA for regulatory submission
- An ECA should not replace a randomized trial when it is possible to perform one
- According to the FDA, non-randomized, single-arm trials with real-world data (RWD) external controls (e.g., historical controls) are a possible type of control arm in an adequate and well-controlled study.
- Typically, the ECA uses data from past traditional clinical trials, but in some cases, RWD have been used as the basis for external controls.

Being prepared and realistic

- The decision to use an ECA for regulatory submission need to either be
  - Suggested by the agency
  - Discussed in advance and transparently with the agency
- Avoid surprise to the agency

Dealbreaker elements

- The use of external controls has limitations, including difficulties in reliably selecting a comparable population due to:
  - Potential changes in medical practice
  - Lack of standardized diagnostic criteria
  - Lack of equivalent outcome measures
  - Variability in follow-up procedures
  - Quality of data
  - Lack of sufficient data to match I-E of the trial

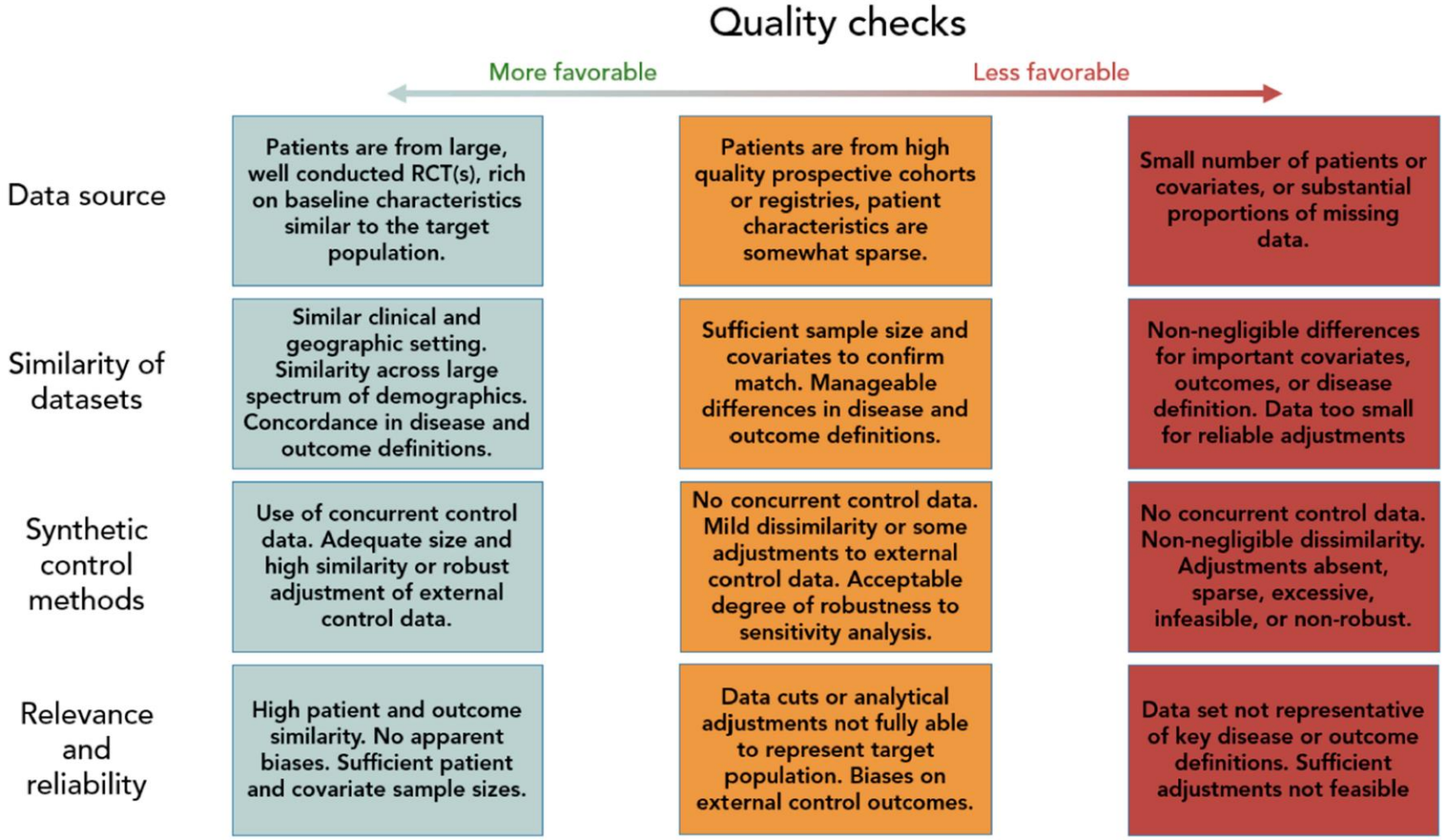
Limit biases through:

- Clear research question (understand why you need the ECA)
- Design
  - Emulate a clinical trial using RWD
  - Eligibility period
  - Time zero
- Data
  - Quality
  - Completeness
  - Validity
- Analytics
  - IPW
  - Matching
  - Simulations

Decision Matrix: ECA Data Sources vs Objectives

	Data Sources	Objectives		
		Accelerating drug development	Evaluating Efficacy	Regulatory Approvals
Prospective Cohort Design	Registries/Natural History	• Eligibility criteria • Outcome definition • Assessment schedule • Patient characteristics • Follow-up timeframe	• Eligibility criteria • Outcome definition • Assessment schedule • Patient characteristics • Follow-up timeframe	• Eligibility criteria • Outcome definition • Assessment schedule • Patient characteristics • Follow-up timeframe • Safety outcomes
Retrospective Cohort Design	Chart Review	• Outcome definition • Follow-up timeframe	• Outcome definition • Eligibility criteria	• Assessment schedule • Safety outcomes
	Electronic Healthcare Databases	• Safety outcomes • Sample size	• Sample size	• Safety outcomes • Patient characteristics • Eligibility criteria • Time zero • Assessment schedule
	Clinical Trial data	• Patient population (eligibility criteria) • Outcome definition • Assessment schedule	• Patient population (eligibility criteria) • Outcome definition • Assessment schedule	• Patient population (eligibility criteria) • Outcome definition • Assessment schedule • Safety outcomes

ECA Quality Check Process



Thorlund, Kristian et al. “Synthetic and External Controls in Clinical Trials - A Primer for Researchers.” Clinical epidemiology vol. 12 457-467. 8 May. 2020, doi:10.2147/CLEP.S242097

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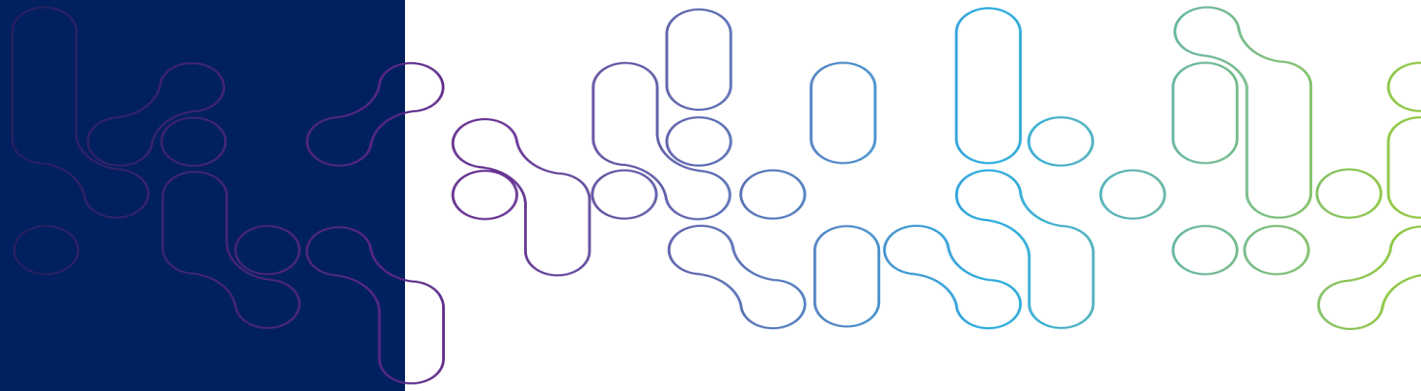
Conclusion slide



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Summary of ECA construction key points

Representativeness of external comparator arm

- Same patient pool in the single-arm trial
- Drawn from population(s) that are similar to the population from which single-arm trial patients were selected and enrolled (source population)

Prioritization of key criteria for selection is critical for efficiency

- Not all criteria applied in single-arm trial available; insure against immortal time bias
- Consistency with analytic strategy
- Ensure representation matches all important questions (e.g., sufficient data on important subgroups)

Importance of endpoint collection methods and endpoint definitions

- Collect the data to a high degree of completeness and accuracy
- Document clearly and transparently
- Validation studies

Importance of transparency, reproducibility, and robustness of findings

- Detailed scientific protocol, clear objectives, I/E, endpoints, SAP
- Sensitivity analyses

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