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External Controls: What does it take to Get Real?

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BACKGROUND

- Randomised controlled trials (RCTs) are the gold standard for evaluating treatment efficacy and safety. However, in certain situations—such as rare diseases or urgent therapeutic needs—RCTs may be impractical or unethical. In these cases, single-arm trials (SATs) are often used, but their lack of a control group limits the ability to make causal inferences.
- External control (EC) studies using real-world data (RWD), particularly individual patient-level data (IPD), may offer a solution to construct comparator cohorts. EC studies are increasingly used to support regulatory and health technology assessment (HTA) submissions, especially in oncology and rare diseases. Yet, methodological variability and inconsistent expectations across healthcare decision makers have led to mixed acceptance [1,2].
- To address this, the GetReal Institute members developed a framework, reviewing RWD-based EC methodologies and stakeholder guidance. This framework aimed to consolidate and summarise methodological guidance and expectations to improve the concordance and clarity of methodological guidance for EC studies using RWD. The framework will be updated over time as updated guidance is issued from healthcare decision-makers

METHODS

- The framework was developed to help researchers guide the design and execution of RWD-based EC studies supporting regulatory and HTA submissions at the point of study planning. The process was iterative and multi-sourced, integrating regulatory and HTA guidance, academic literature, and stakeholder input. The process took a four phased approach:
- **Guidance Collation:** Review of 37 published documents from Regulatory and HTA sources, and screening of 38 peer-reviewed publications (2018–2024) sourced from PubMed, Embase, Google Scholar, with the key words, “external control arms,” “real-world evidence,” “HTA,” and related terms, validated and supplemented by GetReal working group members
- **Framework Design:** Development of a Suitability Decision Tree, 7-Step Operational Process and Stakeholder Expectations Table
- **Stakeholder Engagement:** Facilitation of 3 workshops with a range of international attendees (n= 20–25) representing regulators, HTA bodies, academia, industry, patients. Discussions focused on scoped topics for inclusion in the framework including suitability, data sources, and bias mitigation.
- **Validation & Refinement:** Confirmation of framework within expert focus group (n=6-8) and final validation review conducted by the GetReal Institute members on distribution of the final draft

LIMITATIONS

- The existing guidance used to inform the framework was identified through a pragmatic literature search, with no systematic review conducted. The framework had limited direct input from Regulators, with HTA representatives acting as the main contributors to the development.

RESULTS: The Framework is structured around 3 pillars

Pillar 1: EC Study Suitability

- **International Council for Harmonisation guidance** recommends EC studies when:
  - Treatment effects are expected to be large.
  - Disease course is highly predictable.
  - Endpoints are objective.
  - Impact of baseline/treatment variables is well-characterised.
- **Published guidance is variable and inconsistent** on when EC studies are appropriate; this framework introduces a structured decision-tree to support early-stage evaluation of feasibility.
- **Decision-tree developed** to help rule out more suitable study types (e.g., RCTs, head-to-head observational studies, and MAICs) before considering EC studies.
- **Healthcare decision-makers vary in evidentiary expectations**; the decision-tree is agnostic to regulatory vs. HTA use cases.
- **Data availability matters**: Preference for individual patient-level data (IPD) over aggregate data should be considered based on feasibility and evidentiary needs.

Pillar 2: Decision-maker Requirements

- **Healthcare decision-maker expectations** vary across regulators and HTA bodies; sponsors must align study design with evidentiary needs early in the planning. Phase.
- **Comparative table mapping guidance** from major authorities (FDA, EMA, NICE, HAS, CDA-AMC, PMDA, etc.) across core EC dimensions:

1. Data Quality

- Data sources should be fit-for-purpose, representative of the target population, and contain key variables.

2. Data Logistics

- Ensure data governance complies with local laws and protocols are made publicly available.

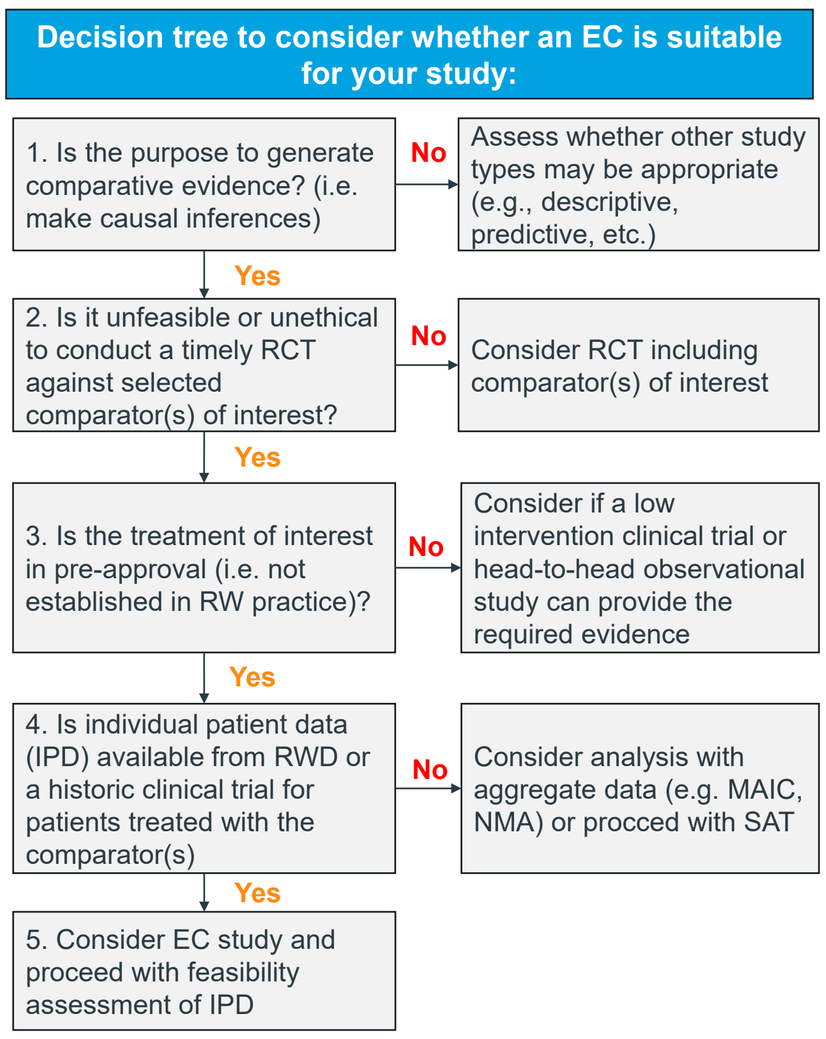
3. Design and Analytical Approach

- Emulate target trials and clearly define research questions and corresponding estimands (e.g. ICH estimand framework), with a clear, prespecified statistical analysis plan (SAP)

4. Engagement Strategy

- Early engagement with regulators and HTA bodies is critical to align on EC justification and study design.

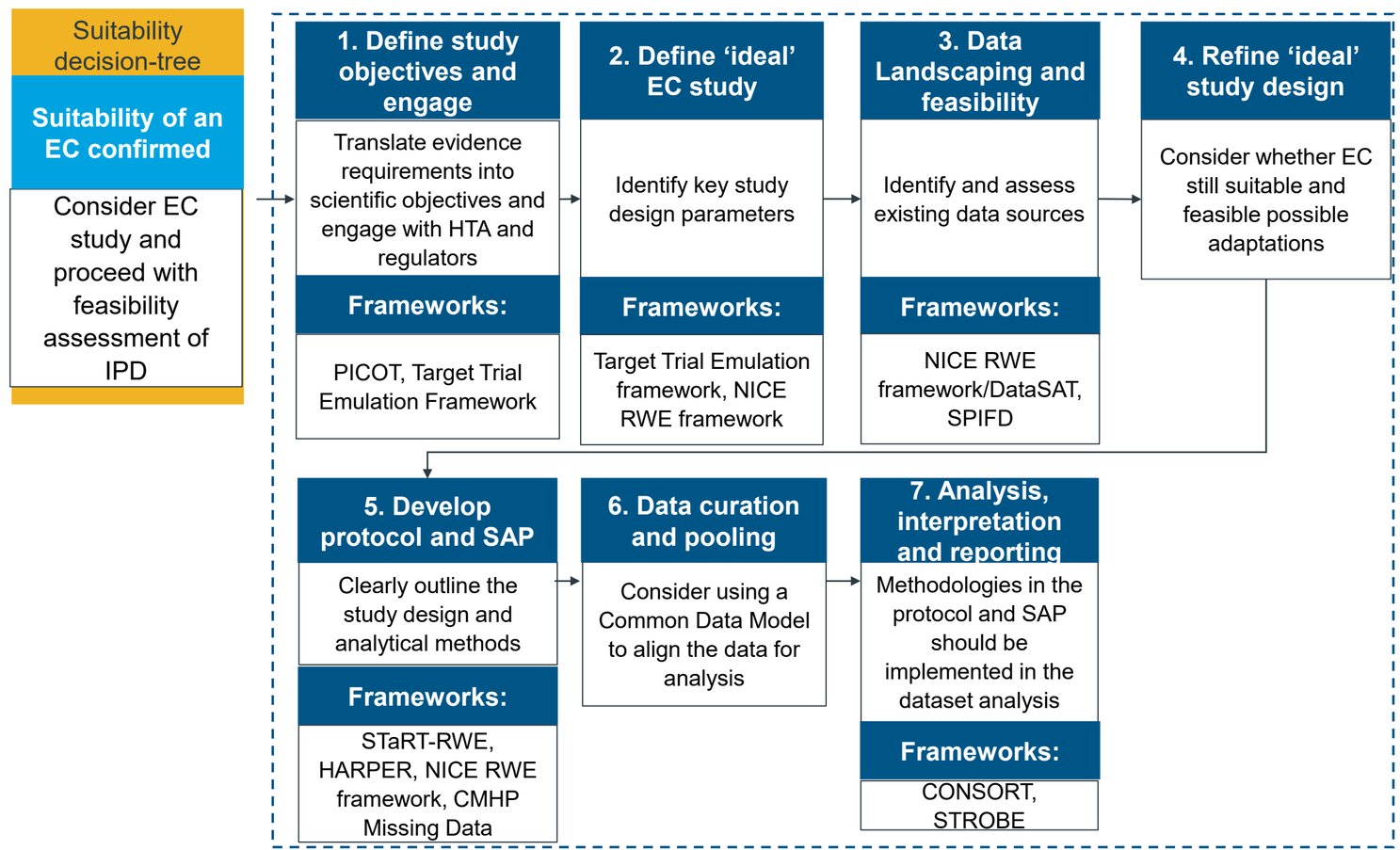
Decision tree to consider whether an EC is suitable for your study:



Pillar 3: Design and Data Principles

- When an EC is considered, appropriate attention to design and conduct may help reduce bias.
- **Step 1: Define objectives and engage with healthcare decision makers** to specify key elements like target population, comparators, and endpoints. Use frameworks like PICOT to clarify objectives.
- **Step 2: Define ‘ideal’ target trial and identify key study design parameters** using the target trial emulation framework.
- **Step 3: Conduct data landscaping and feasibility assessment** to identify suitable data sources, ensuring statistical robustness and alignment with healthcare decision makers.
- **Step 4: Refine ‘ideal’ target trial** and objectives following assessment of data sources, identify feasible adaptations, and evaluate trade-offs to capture key variables.
- **Step 5: Develop a comprehensive study protocol and SAP,** detailing how bias, confounding, and missing data will be addressed, with clear documentation and transparency.
- **Step 6: Ensure high-quality RW data,** use a common data model, document processes, and consider linkage for enhanced analysis.
- **Step 7: Analyse data securely, document decisions, leveraging guidelines, where available.** Tailor reports for healthcare decision makers.

Design and data principles: Implementation of an EC



1. *Effectively Leveraging RWD for External Controls: A Systematic Literature Review of Regulatory and HTA Decisions.* **Sola-Morales O, Curtis LH, Heidt J, Walsh L, Casso D, Oliveria S, Saunders-Hastings P, Song Y, Mercado T, Zusterzeel R, Mastey V, Harnett J, Quek RGW.** 2, s.l. : Clin Pharmacol Ther, 2023, Vol. 114.; *2. Analytical Methods for Comparing Uncontrolled Trials With External Controls From Real-World Data: A Systematic Literature Review and Comparison With European Regulatory and Health Technology Assessment Practice.* **Hogervorst MA, Soman KV, Gardarsdottir H, Goettsch WG, Bloem LT.** 1, s.l. : Value Health, 2025, Vol. 28

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