Externally Controlled Trials in Oncology

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ECT Overview

Guidance

Challenges

Examples

ECT Rationale

Context for use

- Feasibility Challenges
- Ethical Concerns
- Questionable Equipoise

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Potential Applications

- Pediatrics
- Rare Diseases
- Significant unmet medical need
- Molecular subgroups
- Under-represented populations

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Recently Released FDA RWE Guidances

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products
Draft Guidance for Industry, September 2021

Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry
Guidance for Industry, December 2023

Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products
Guidance for Industry, August 2023

Data Standards for Drug and Biological Product Submissions Containing Real-World Data
Guidance for Industry, December 2023

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products
Guidance for Industry, September 2022

Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products
Draft Guidance for Industry February 2023

Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products
Draft Guidance for Industry , March 2024

RWD Source

Submissions

Design

Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products *Draft* Guidance for Industry

Definition: An externally controlled trial (ECT) measures outcomes in participants receiving the investigational treatment according to a protocol compared to outcomes in a group of people external to the trial who did not receive the same treatment.

Appropriateness: The suitability of an externally controlled trial design depends on the clinical setting. Consult the relevant FDA review division early in drug development to determine if an externally controlled trial is reasonable.

ECT Rationale

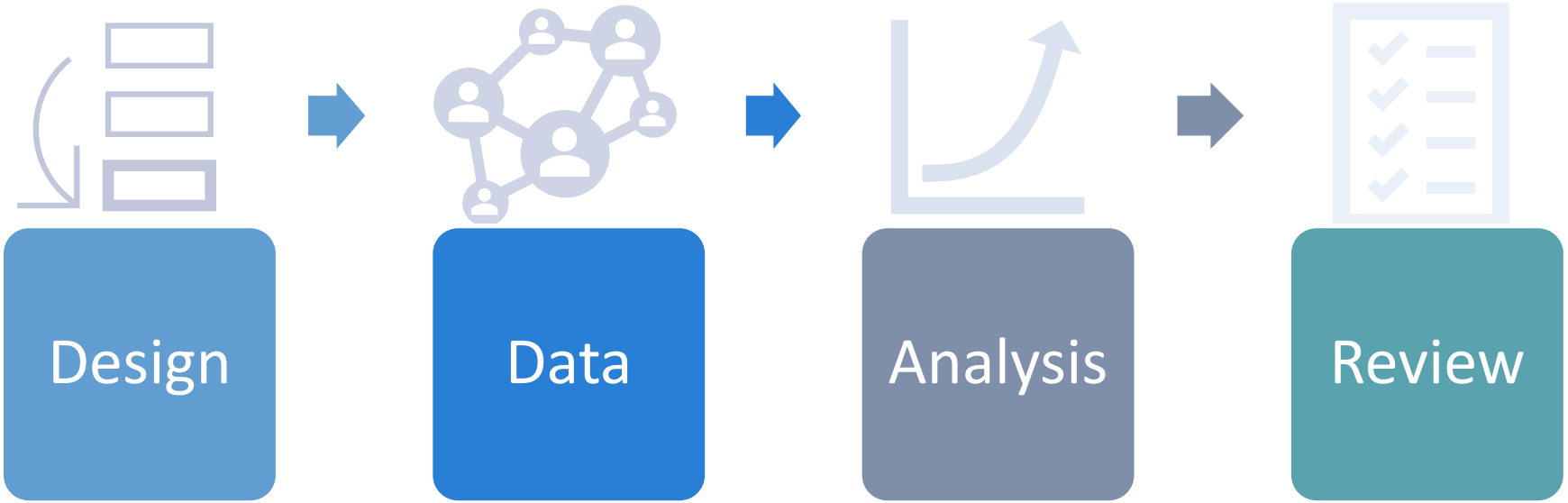
Before selecting an ECT Design

- consider the likelihood that such a **non-randomized** design would be able to distinguish the effect of a drug
- in many situations, the likelihood of credibly demonstrating the effectiveness of a drug of interest with an external control is low

Factors affecting suitability of an externally controlled trial

- heterogeneity of the disease
- preliminary evidence regarding the drug product under investigation
- approach to ascertaining the outcome of interest
- whether the goal of the trial is to show superiority or non-inferiority

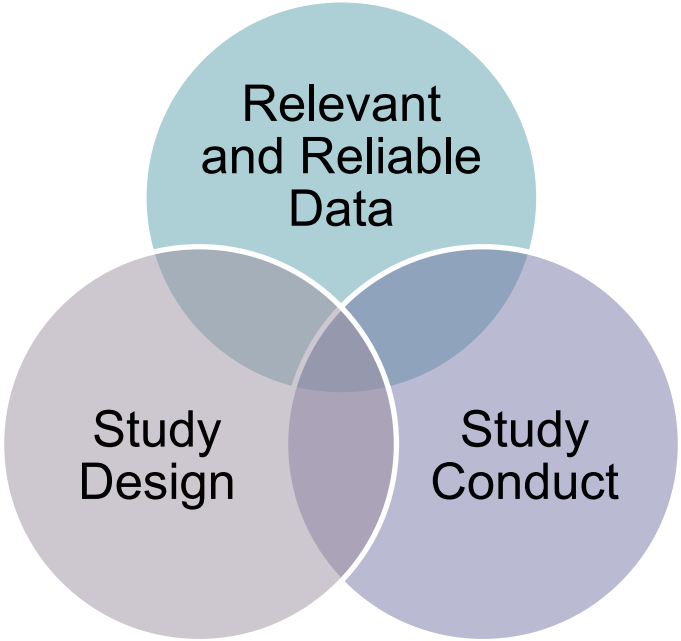
ECT Considerations



Regulatory Objective

What is the level of evidence needed to demonstrate effectiveness?

- As benchmark, baseline, or natural history study [**epidemiology**]
- As individual patient-level matched data for formal comparative study [**effectiveness**]



Considerations for Assessing Data Comparability

Time Periods • Standard of care • Supportive care	**Geographic Region** • Access to care	**Diagnosis** • Expected variation	**Prognostic Factors** • Availability • Similarity	**Treatment** • Dose and duration • Line of therapy • Concurrent regimen
Index Date	**Loss to Follow-up**	**Intercurrent events**	**Outcome** • Frequency • Ascertainment	**Missing Data**

Consult with the relevant review division

Early and Often

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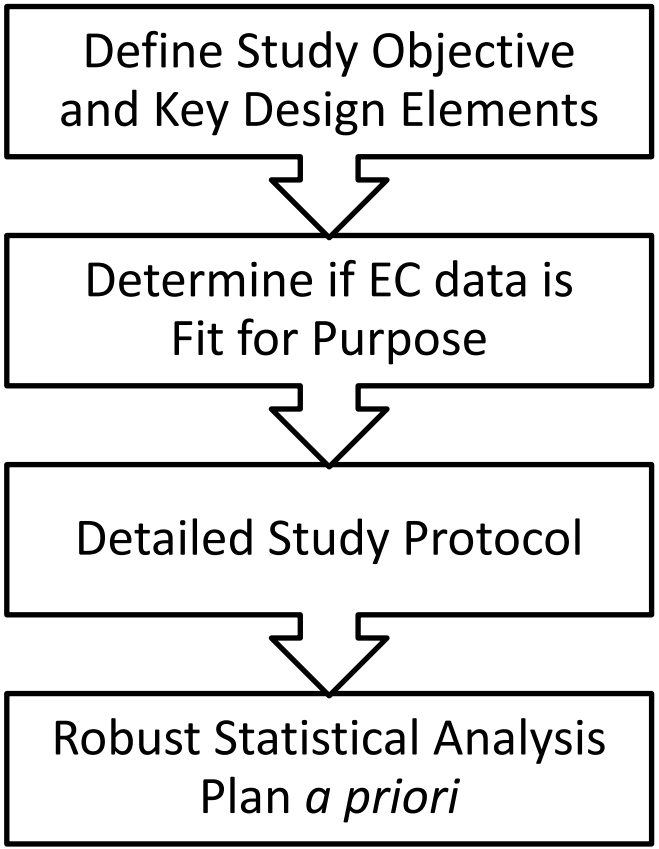
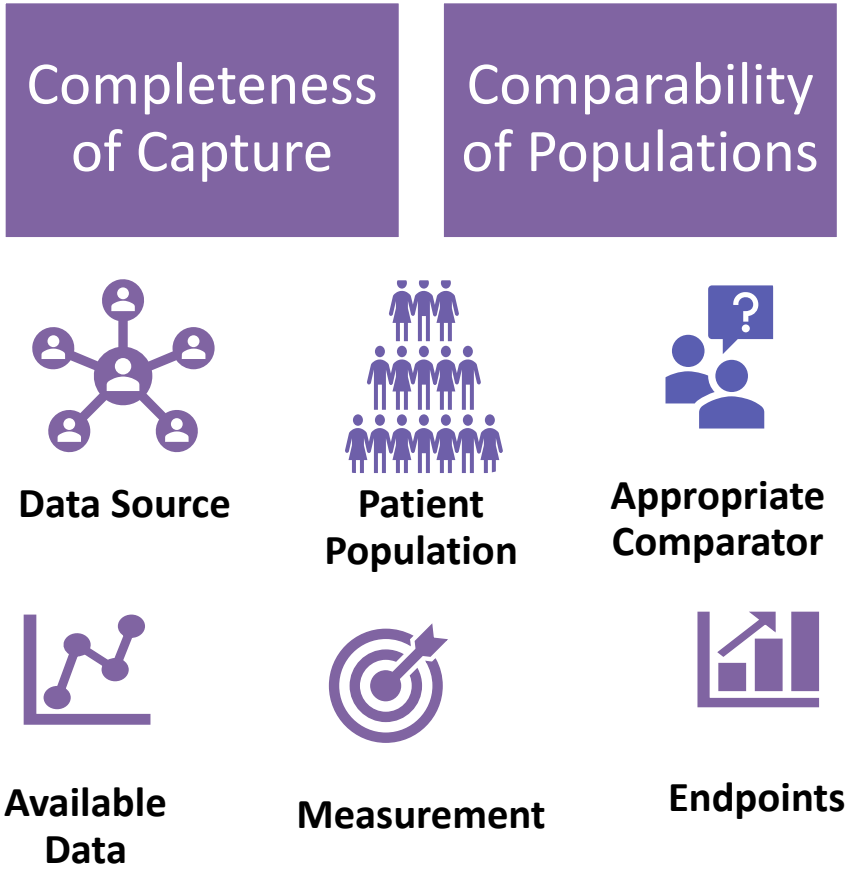
Study Conceptualization Review





Externally Controlled Designs

Clinical Scenario: Limited or no randomized studies available

Use of External Controls: Often limited to providing important clinical context; has been used in various applications and considered supportive only

Common Limitations

- **Lack of pre-specified protocol** to ensure the selection of a comparable patient population; selection bias concerns
- **Lack of formal statistical comparisons** or statistical methodology not established *a priori*
- **Data Source Appropriateness**
  - **Covariate Ascertainment**: Limited information on patient demographic or clinical characteristics
  - **Outcome Ascertainment**: Variance in follow up; outcome misclassification
- **Confounding:** Concerns with measured, unmeasured, and residual confounding
- **Index Date Selection and Immortal Time Bias**

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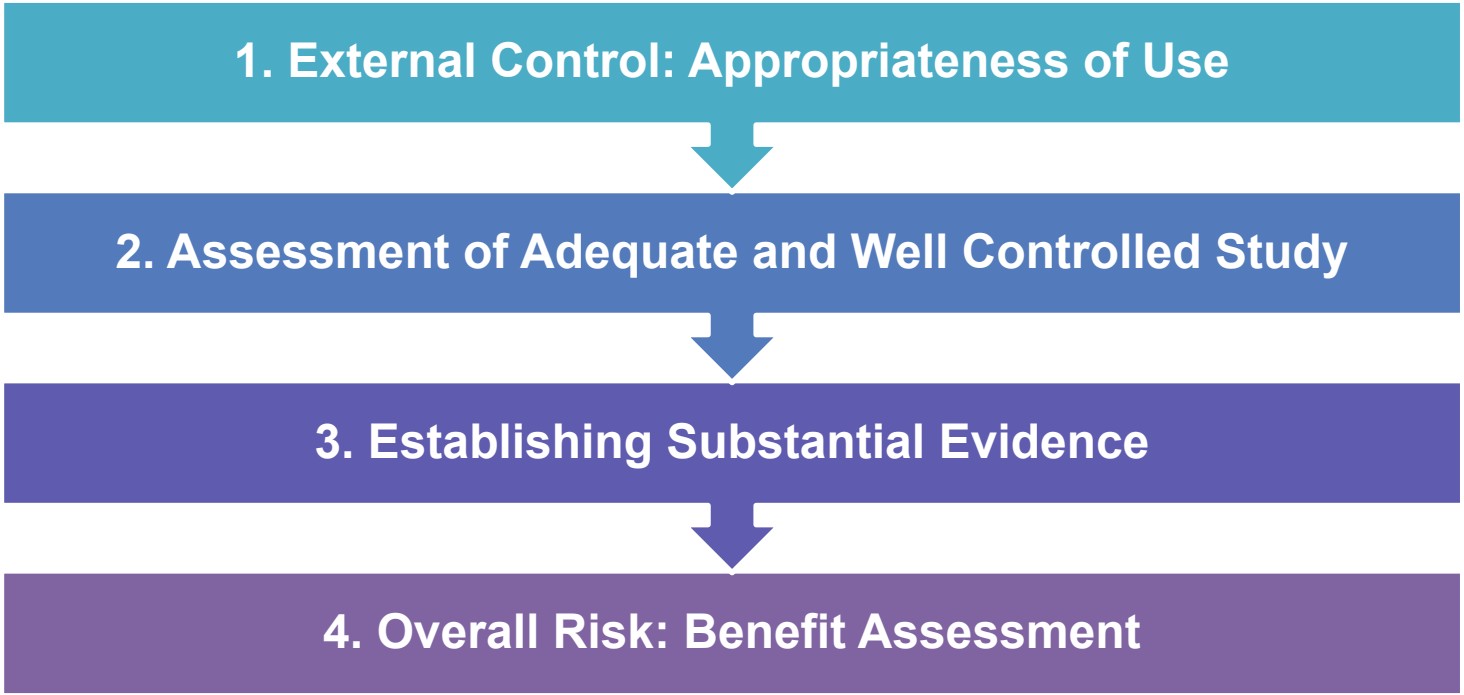
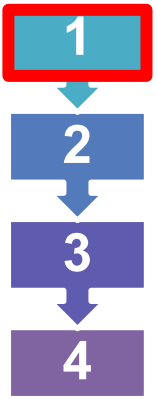
Approach to Regulatory Review of ECTs





Evaluation of an External Control

Selected characteristics of the disease setting that should be met for EC use

1. The natural history of disease is **well defined**
2. EC population is **very similar** to treatment group
3. Concomitant treatments that affect the primary endpoint are **not substantially** different
4. Evidence of change in the established progression of disease (e.g. **tumor shrinkage**)

Data must be Fit-for-Purpose

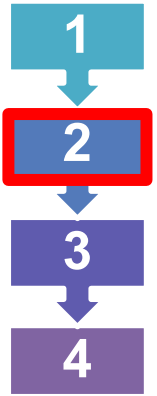
Relevance

includes the availability of key ***data elements*** (exposure, outcomes, covariates) and sufficient numbers of representative patients

Reliability

includes data ***accuracy***, **completeness. provenance,** and ***traceability***

FDA guidance for industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,* (2019) and *Rare Diseases: Common Issues in Drug Development* (2019)

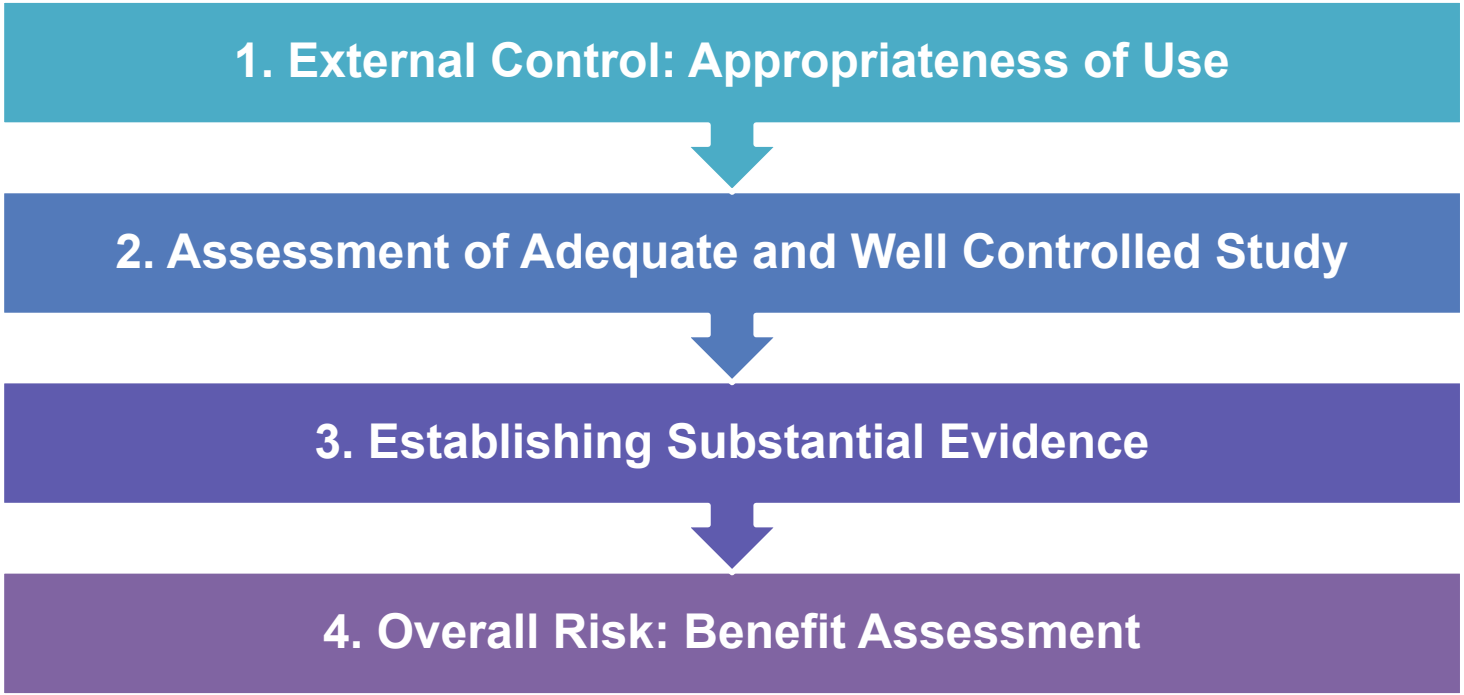


Adequate and Well Controlled Studies

*Reports of **adequate and well-controlled investigations** provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs*[21 CFR 314.126]

Adequate and Well Controlled Studies	
1. Clear Statement of Objectives	• Includes prespecified analyses
2. Study Design	• Permits valid comparison to a control
3. Patients are Selected Appropriately	• Adequate assurance patients have the disease or condition being studied
4. Minimizes Bias	• Treatment Assignment: Comparability of groups (e.g. randomization) • Procedures should be described (e.g. blinding) to minimize patients, observer, and data analyst bias
5. Reliable Assessments and Analysis to Assess Drug Effect	• Protocol (well-defined variables, methods, criteria) • Appropriate use of statistical methods and assessment of bias

Approach to Regulatory Review of ECTs



Eflornithine (DFMO)

Regular Approval on December 13, 2023

Indication To reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.

Context High unmet need in a rare, life-threatening disease

Clinical Evidence Single-arm clinical trial with clinical trial data derived EC and confirmatory evidence

Investigational Arm: single-arm trial (Study 3(b), Stratum 1) of 90 treated patients most of whom were previously enrolled on ANBL0032

External Control Arm: National Cancer Institute/Children's Oncology Group-sponsored clinical trial (Study ANBL0032) of 270 patients propensity-score matched to DFMO-treated patients on 11 demographic and clinical characteristics

Strong mechanistic non-clinical data

Outcomes

Event-Free Survival	HR=0.48 (95% CI: 0.27, 0.85)
Overall Survival	HR=0.32 (95% CI: 0.15, 0.70)

ODAC Discussion Summary

Given the primary evidence of efficacy was from an ECT and available confirmatory data was from non-clinical studies, an ODAC was held in 2023 to discuss eflornithine (DFMO)

Uncertainties

- Potential biases due to non-randomized study design
- Limitations of animal models

Strengths

- Large effect size
- Robust statistical analyses
- Strong preclinical models

Discussion: highlighted challenges of application, feasibility of RCT

Committee voted (16 Yes – 4 No) that there was sufficient evidence to establish efficacy

DFMO Regulatory Context

- 1st oncology approval relying on an **externally controlled trial** as primary clinical data to support substantial evidence of effectiveness

Clinical Context

- Rare, life-threatening cancer with high unmet need
- Feasibility concerns regarding successfully conducting new RCT

Evidentiary package unique and each component was essential for approval

- High-quality external control arm in a comparable population (matched on >10 clinical characteristics)
- Consistent estimation of the treatment effect through numerous sensitivity and supportive analyses
- Manageable safety profile for oncology product
- Strong nonclinical mechanistic data

- **RCTs remain strongly preferred** development approach to demonstrate effect on a time-to-event endpoint, even in rare cancers

Regulatory Insights

- With **rare exception**, RCTs are required to assess the effect of a drug on a time-to-event endpoint (e.g., EFS, OS)
    - Randomization balances known and unknown prognostic factors
- Often the likelihood of credibly demonstrating the effectiveness of a drug with an ECT is low and sponsors should choose more suitable designs
- Fit-for-use data can be a rate limiting factor
    - Establishing that data for an external control is appropriate for formal comparison is a first step often not reached in drug development programs considering ECTs
- When reliable objective responses are not expected, development plans should move quickly to a randomized trial

Acknowledgements

Oncology RWE Program

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TEAM FoRWD comprises FDA scientists with expertise in pharmacoepidemiology, hematology and oncology, epidemiology, biostatistics, and regulatory science to evaluate opportunities for RWD in regulatory contexts that can complement our understanding of medication risks and benefits for patients.

OCE Leadership

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FDA

Project 5 in 5

Crowdsource oncology community to identify **5** clinically-relevant questions in oncology using FDA-approved therapies that can be answered through pragmatic trials over **5** years – open May 5 – July 5, 2024!