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Single Day Event

Navigating Real-World Evidence in Regulatory Submissions for Externally Controlled Trials (ECTs)

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Life Sciences & Healthcare Consulting

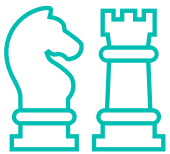
Engineering R&D Services | Quality & Regulatory Affairs | Market Access | HEOR & RWE | CROs | Pharmaceuticals | Medical devices & Biotechs

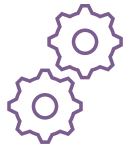
Navigating RWE for ECTs

Motivating the design choice

Why externally controlled trials matter when randomization is infeasible or unethical ?

What regulators expect ?
Pre-specification, Comparability, Transparency





How to operationalize:
Objective endpoints, Data fitness, Bias controls

What case studies reveal:
Omblastys, Vijoice, Prograf
-Patterns and pitfalls

Why ECTs, why now ?

Motivate the design choice

When randomization is infeasible/unethical; contexts: rare disease, oncology, severe unmet need

ECT as a prespecified use of RWE (from EHR, claims, registries, prior trials)

Regulatory stance: acceptable case-by-case; rigor must approximate randomized trials

FDA framing and expectations

Translate guidance into a sponsor checklist

1/ **Prespecify protocol and SAP before data lock**

2/ **Define time zero; align follow-up windows; prevent immortal time bias**

3/ **Predefine confounders; plan comparability assessment; sensitivity analyses required**

4/ **Commit to patient-level data and code for replication; ensure data rights**

Appropriateness: When ECTs work

Suitability signal vs red flags

Favorable:

- Stable natural history
- Objective endpoints
- Large expected effect
- Consistent SOC

Caution:

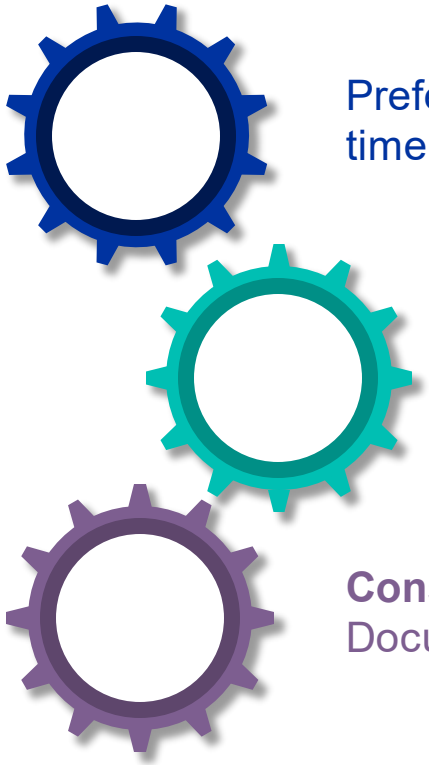
- Heterogeneous disease
- Evolving diagnostics
- Subjective outcomes

Strategic tip:

Superiority framing is more credible than non-inferiority

Endpoint strategy: Single arm context

Make “objective endpoints first” actionable



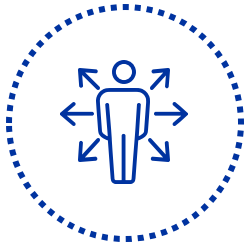
Prefer objective response rate (ORR), mortality, hospitalization over time to event when observation timing varies

Endpoint harmonization matrix: Definitions, Assessment windows, Adjudication approach

Consistency: Code systems harmonized; Provenance/audit trail; Documented inclusion/exclusion of data sources

Building the external arm: Data fitness

What “fit-for-purpose” really means



Reliability:

- Completeness
- Accuracy
- Timeliness of exposures
- Outcomes
- confounders

Relevance:

- Captures prognostics
- Prior therapies
- Performance status
- Biomarkers, concomitants

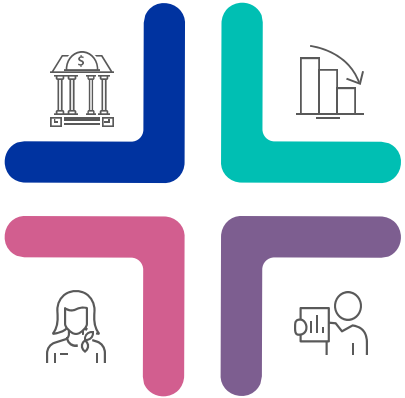
Consistency:

- Code systems harmonized
- Provenance/audit trail
- Documented inclusion/exclusion of data sources

Comparability and bias mitigation

Make comparability measurable and auditable

Design: restriction, eligibility mapping, aligned index date



Analytics: exact/PS matching, IPTW/overlap weights, prognostic scores

Diagnostics: standardized differences plots; overlap/positivity checks

Robustness: negative controls; quantitative bias analysis; tipping point thresholds

From protocol to SAP: Pre-specification blueprint

Protocol-Must haves

- Sources and feasibility screens;
- Inclusion/exclusion mappings;
- Exposure windows
- Index date
- Endpoints
- Confounders

SAP Must haves

- Primary model
- Balance criteria
- Missingness plan
- Misclassification checks
- Sensitivity menu
- Subgroup plans

Source-selection audit trail

- Accessed sources
- Feasibility results
- Inclusion/exclusion justifications

What case studies reveal ?

Aspect	Omblastys (hypothetical anti-oncology biologic)	Vijoice (alpelisib)	Prograf (tacrolimus)
Therapeutic area / indication	• Relapsed or refractory solid tumors with oncogenic **ABL-fusion** • Ultra-rare population; single-arm Phase II pivotal study	• PIK3CA-Related Overgrowth Spectrum (PROS) • First targeted therapy in this congenital overgrowth disorder	• Prevention & treatment of organ-transplant rejection • Broad post-marketing life-cycle management (kidney, liver, heart)
Why ECTs were needed	• Ethical & operational infeasibility of randomization due to disease rarity and urgency • No approved comparators	• Heterogeneous phenotype; small, geographically dispersed population • Placebo deemed unacceptable by regulators & patient advocates	• Long-term outcomes are influenced by surgical techniques and evolving SOC; historical RCT data often outdated • Pragmatic evaluation of regimen changes (e.g., dose minimization)
Key RWE data sources leveraged	• Global oncology registries capturing molecular profile & survival • Electronic health records (EHRs) curated via common data model (CDM)	• Natural-history consortium datasets (NIH, European PROS registry) • Patient-reported outcome (PRO) mobile app feeding into EHR	• US & EU transplant registries (e.g., UNOS, ELTR) • Integrated hospital pharmacy databases for tacrolimus exposure
External control construction	• Propensity-score–matched cohort from pooled registries (n≈120) matched 1:1 on ECOG, tumor burden, prior lines	• Bayesian dynamic borrowing of natural-history controls (n≈90) with hierarchical model updating as trial data accrued	• Synthetic control arm drawn from UNOS database; inverse probability of treatment weighting (IPTW) to balance donor and recipient risk factors

What case studies reveal ?

Aspect	Omblastys (hypothetical anti-oncology biologic)	Vijoice (alpelisib)	Prograf (tacrolimus)
Primary endpoints & statistical methodology	• Overall response rate (ORR) & duration of response (DoR) evaluated by Blinded IRC • Doubly robust estimator used after matching	• Percent change in lesion volume at 24 wks • Bayesian posterior probability threshold prespecified for regulatory success	• 5-year graft survival & renal function (eGFR slope) • Marginal structural models to handle time-varying tacrolimus exposure
Bias-mitigation strategies	• Harmonized RECIST imaging read across datasets • Sensitivity analyses for unmeasured confounding via tipping-point approach	• Centralized radiological adjudication of natural-history scans • Multiple-imputation for missing growth-curve data	• Calendar-time stratification to account for improvements in peri-operative care • Instrumental-variable analysis leveraging HLA-mismatch tiers
Regulatory interactions & outcomes	• FDA Type C meeting endorsed external control concept; accelerated approval granted with post-marketing confirmatory RCT commitment	• EMA PRIME & FDA Breakthrough designations dependent on robustness of natural-history control; full approval with RWE as primary evidence	• Supplemental NDAs supported by RWE accepted by FDA & PMDA to extend dosing guidance; ECT framework cited in label change
Lessons for future ECT submissions	• Early alignment with regulators on covariate selection & analytic plan • Ensure traceability of source data and audit readiness	• Engage patient foundations to enrich natural-history datasets • Bayesian frameworks can optimize evidence borrowing while controlling type I error	• Legacy registries are valuable but require data-quality upgrade (linkage, standardized outcomes) • Continuous real-world monitoring can replace repeated RCTs for mature products
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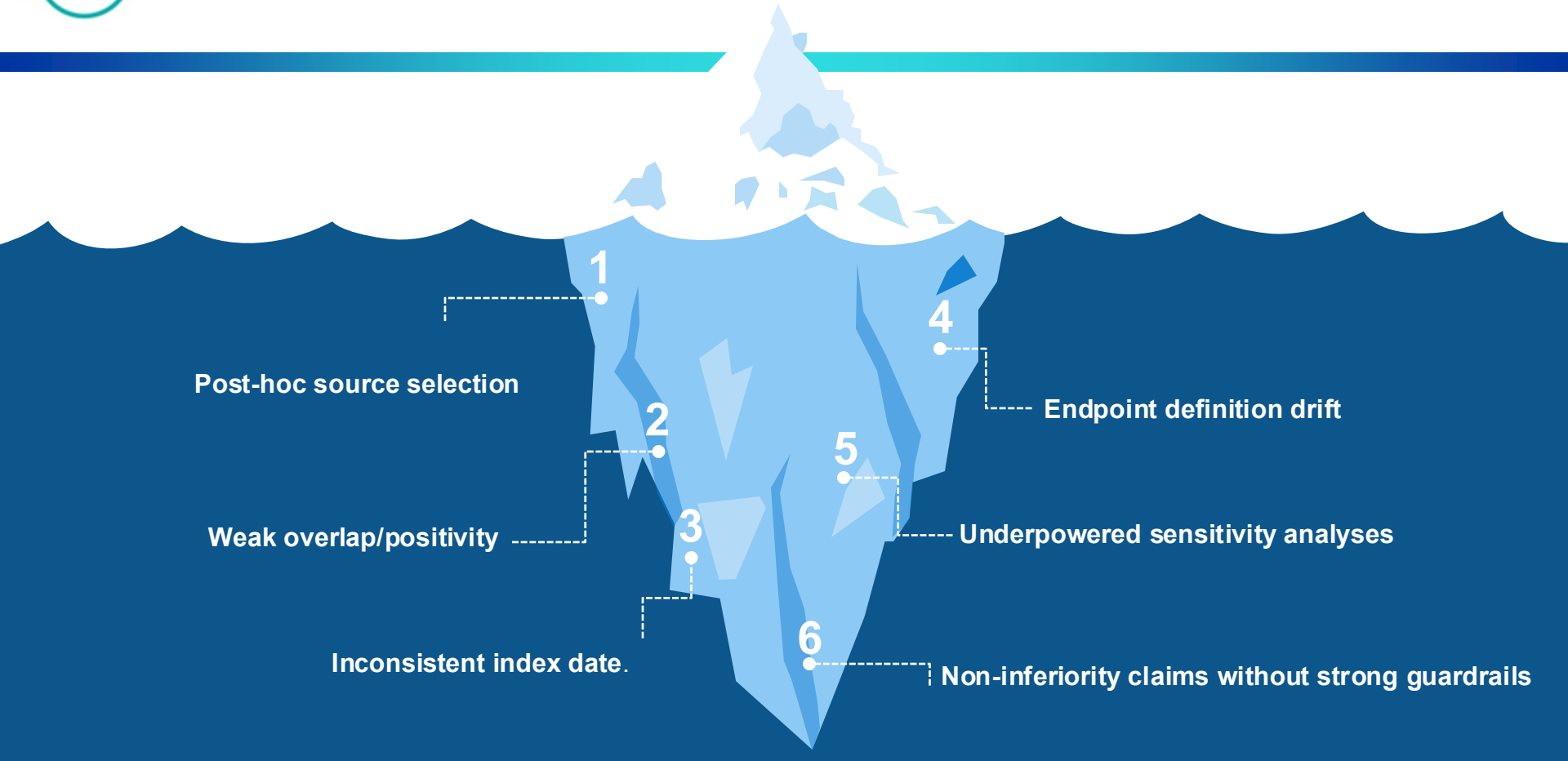
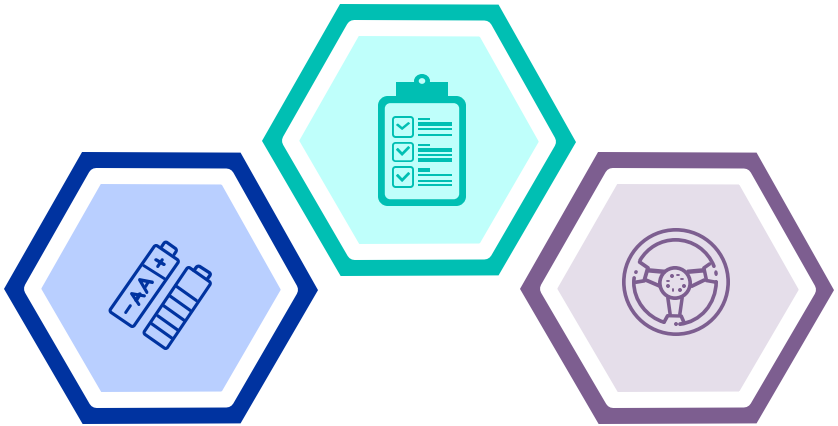
Pitfalls and how to avoid them



Submission mechanics and reviewer experience

eCTD placement:
- Modules 2 summaries
- Module 5 reports and programs
- Reviewer roadmap linking artifacts

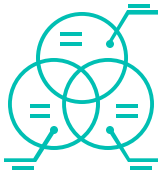
- Patient level data (both arms)
- Execution code
- Code lists
- Data dictionaries
- Readme
- Provenance logs



Early meetings:
- Align on ECT suitability
- Endpoints, and analysis
- Document decisions and trace changes

Fin!

Prespecify design and analysis end to end, including data source audit trails



Prioritize objective endpoints and rigorous time alignment to cut bias at its root

Submit patient level, reproducible packages; negotiate data rights early

Thank you

The Global Healthcare Data Science Community

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