Worldwide Clinical Trials

Estimand Strategies in Early Phase Clinical Research

A Case Study in Type 2 Diabetes

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Estimand strategies have become a cornerstone of modern clinical research, providing a structured framework to clearly define the treatment effect of interest by aligning study objectives with trial design, conduct, and analysis. Introduced formally in the ICH E9(R1) addendum, estimands help address complexities such as intercurrent events (i.e., events occurring after randomization or dosing, such as treatment discontinuation, rescue medication use) by clarifying how researchers should handle these events in estimating treatment effects. This approach enhances trial results' transparency, interpretability, and relevance for different stakeholders, including regulators, clinicians, and patients. While initially emphasized for confirmatory Phase III trials, estimand strategies are increasingly implemented in early phase (Phase I and Phase II) trials, where they can improve decision-making, optimize dose selection, and better characterize early treatment effects in varied clinical scenarios.

The Five Estimand Strategies Explained

Strategy	Clinical Question	Intercurrent Events	Key Use Case
Treatment Policy	What happens when the drug is prescribed in practice?	Ignore (i.e., include all data)	Real-world effectiveness
Hypothetical	What is the drug's effect if no rescue therapy is needed?	Model outcome as if the event did not occur	Regulatory / mechanistic effect
Composite	Does the drug help reach the desired outcome without rescue therapy?	Redefine the event as part of outcome	Clinically important events as outcomes
While on Treatment	What is the effect on the drug alone?	Censor at event occurrence	Effect during treatment
Principal Stratum	What is the drug's effect in patients who would do well without rescue medication?	Analyze subgroup based on event potential	Specific subpopulations

Advantages & Limitations of Estimands in Phase I-II Research

Estimands can assist in Phase I-II clinical development by:	However, an estimand strategy may not be advisable if:
⊕ Pre-defining trial objectives and desired outcomes (e.g., biological vs. practical effect)	⊖ The trial is hypothesis-generating
⊕ Assisting in endpoint selection and prioritization	⊖ Intercurrent events of interest are unknown, of uncertain relevance, or of inestimable frequency
⊕ Informing dose selection and trial progression (e.g., hypothetical estimand strategy to model dose-response)	⊖ Sample sizes do not allow for statistical modeling and subgroup analyses for complex strategies (e.g., hypothetical and principal stratum methods)
⊕ Identifying drug sensitivities to patient behavior, adherence, or concomitant / rescue medications	⊖ Treatment duration requires surrogate endpoints (vs. direct endpoints)
⊕ Establishing continuity for study design and interpretation for future pivotal studies	⊖ Study adaptability (e.g., individual dose titration) is prioritized
⊕ Providing conventional interpretations of variable intercurrent events within small sample sizes	

Estimand in Action

A sponsor is designing a parallel group, active-controlled Phase II study examining a novel agent (DRUG) in type 2 diabetes. The primary endpoint is change in HbA1c at 24 weeks. The sponsor will prescribe a rescue medication (e.g., SGLT2i) if DRUG (or active control) does not improve HbA1c to a prespecified threshold (e.g., ≤ 7%) at a 12-week intermediate endpoint. The example below suggests the direction for an estimand strategy aligned with the sponsor's research.

Strategy	Clinical Question	Approach	Favorable Interpretation
Treatment Policy	What is the effect of DRUG on HbA1c (24 w), regardless of SGLT2i use?	Analyze all patient data regardless of SGT2i use	At 24 w, DRUG lowered HbA1c regardless of SGLT2i use
Hypothetical	What would be the effect of DRUG on HbA1c (24 w) if a patient does not require concomitant SGLT2i?	Any patient taking SGLT2i is modeled as if they had not been taking SGLT2i	At 24 w, DRUG would have lowered HbA1c without SGLT2i therapy

Composite	What is the effect of DRUG on treatment outcomes at (24 w)?	Define treatment failure as (1) HbA1c ≥ 7% OR (2) new SGT2i use by 24 w	At 24 w, DRUG improved treatment outcomes: lowered HbA1c and did not require new SGLT2i therapy
While on Treatment	What is the effect of DRUG monotherapy?	A patient who initiates SGLT2i therapy at 12 w only has their HbA1c data up to 12 w included in analysis; later data is censored	At 24 w and/or prior intermediate endpoints to be identified in analysis, DRUG lowered HbA1c in patients without SGLT2i therapy
Principal Stratum	Among patients who were predicted to be 'favorable responders', what is the effect of DRUG?	Define a specific subgroup of patients for analysis (e.g., favorable responders) based on baseline characteristics	At 24 w, DRUG lowered HbA1c in patients who were not expected to require SGLT2i therapy

Takeaways

In early phase clinical research, estimand strategies enhance the clarity and relevance of study outcomes by explicitly aligning trial objectives with handling intercurrent events. This structured approach supports more informed decision-making in dose selection, go/no-go decisions, and the design of later-phase trials. As early phase studies grow in complexity and strategic importance, the integration of estimand thinking ensures greater scientific rigor and regulatory alignment from the outset of drug development.

Feature	Early Phase (Phase I, II)	Late Phase (Phase III)
Main Goal	Understand mechanism, dose, early signal	Demonstrate efficacy, support labeling
Estimand Focus	Often hypothetical or while on treatment	Often treatment policy or composite
Value of Estimand	Improves trial design and downstream decisions	Clarifies trial interpretation for regulators/payers
Intercurrent Events	Less frequent, but still relevant (e.g., dropouts)	More common, must be pre-specified
Regulatory Expectation	Encouraged	Required under ICH E9 (R1)

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