



Framework for Incorporating Estimands within the Statistical Analysis Plan

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Introduction – A Fundamental Shift

What was the problem with historical clinical trials?

Ambiguity in handling post-randomization events and missing data led to difficult-to-interpret results.

What is the solution?

The ICH E9(R1) Addendum.

What is the key concept?

Separating the "What" (the treatment effect/estimand) from the "How" (the statistical method/estimator).

What is the SAP's role?

The Statistical Analysis Plan is the primary document where these abstract concepts become actionable procedures.



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Overview of the Five Attributes



Variable

The clinical outcome being measured.



Population

The target subjects in the study.



Treatment

Investigational product compared to a comparator.



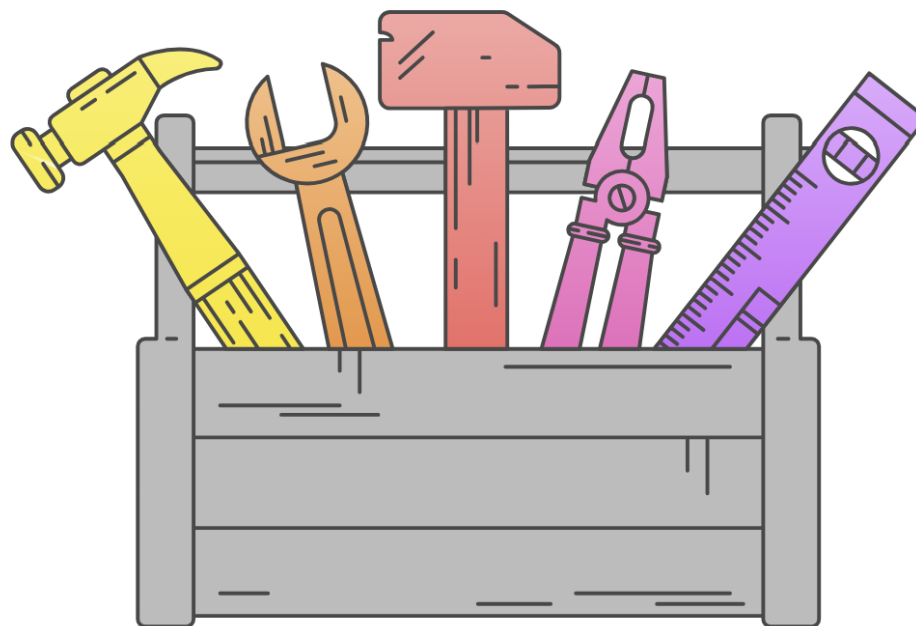
Intercurrent Events

Post-randomization events that may occur.



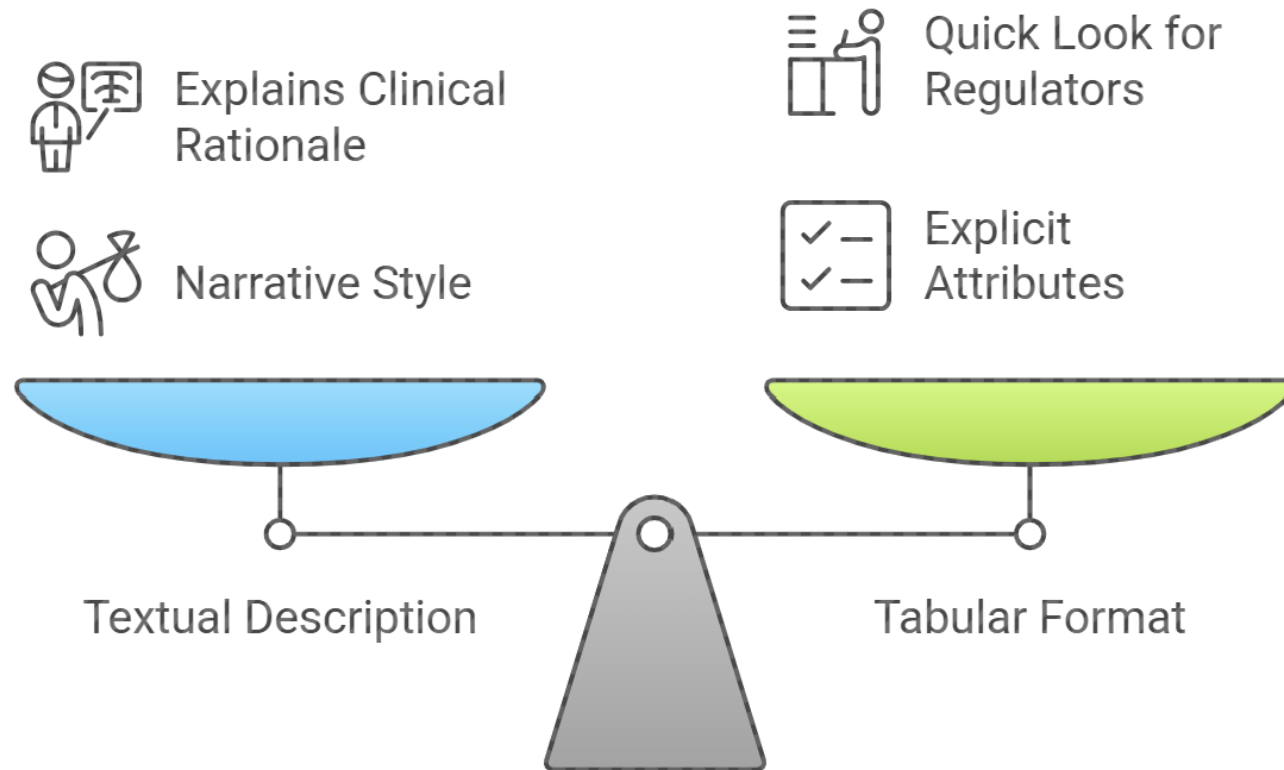
Summary Measure

Population-level effect of the treatment.



Defining Estimands in the SAP – Two Approaches

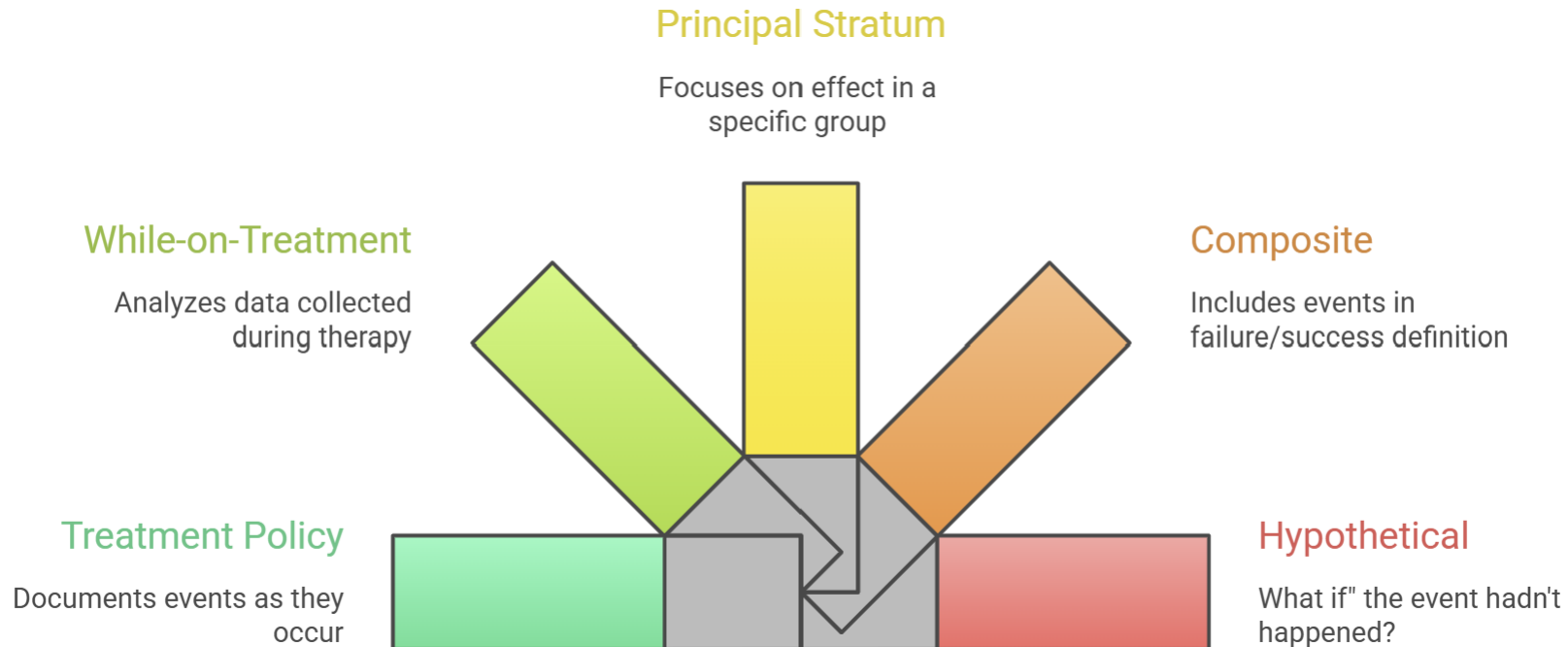
The SAP should make estimands accessible to both clinicians and programmers.



Handling Intercurrent Events (ICEs)

ICEs occur after treatment and "intercurrent" with the endpoint.

Strategies to Document in the SAP:



Missing Data – Property of the Estimator

- **Important Distinction:** Missing data is **not** an ICE.
- **Estimand Influence:** The strategy chosen (e.g., Treatment Policy) dictates what data is considered "missing" vs. "relevant."
- **Mechanisms to Specify:**
 - **MCAR:** Unrelated to data.
 - **MAR (Missing at Random):** Explained by observed variables (commonly handled by MMRM).
 - **MNAR (Missing Not at Random):** Depends on unobserved data (requires sensitivity analysis).

Primary Analysis Implementation

- **Likelihood-based Models (MMRM):** Standard for MAR; handles missingness implicitly.
- **Multiple Imputation (MI):** Reflects uncertainty by creating multiple datasets.
- **ADaM Considerations:**
 - Datasets should include one record per visit.
 - Traceability to **ADICE** (Analysis Dataset for Intercurrent Events) is crucial for justifying assumptions.

Sensitivity vs. Supplementary Analyses

Characteristic	Sensitivity Analysis	Supplementary Estimands
«» Purpose	Tests robustness of primary estimand	Addresses different clinical questions
⌕ Assumptions	Varies assumptions, keeps question same	Addresses different clinical questions
≡ Examples	Tipping Point Analysis, Jump-to-Reference (J2R)	Primary = Treatment Policy, Supplementary = While-on-Treatment

Sensitivity Case Study: Tipping Point Analysis

- **Goal:** To see how extreme the "badness" of missing data must be to overturn a study's success.
- **In the SAP:**
 - Define incremental "deltas" (shifts) applied to the treatment arm.
 - Identify the "Tipping Point" where $p\text{-value} > 0.05$.
 - **Reporting:** Use tables and graphical displays to show results across a range of delta values.

Cross-Functional Collaboration & Conclusion

- Collaboration:** Estimands are not just for statisticians. Clinicians define the "What," and Programmers ensure the data supports the "How."
- Key Takeaways:**
 - Traceability from Protocol to SAP to ADaM is mandatory.
 - The SAP is the "Single Source of Truth."
 - Clear estimand definitions reduce regulatory risk and improve trial interpretability.



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Intuitively

Thank You!

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