



Strategies to Improve Understanding of Estimands and Analysis Section of Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

A well-written and comprehensive SAP ensures reproducibility, traceability, and adherence to regulatory guidelines. To achieve this, it's essential to consider the following key points when authoring or drafting SAP:

- Understand the Protocol Thoroughly
- Use a Template for Standardization
- Structure the SAP Clearly
- Incorporate Regulatory Guidance
- Focus on Clarity and Precision
- Anticipate and Plan for Possible Scenarios
- Ensure Stakeholder Review and Approval
- Ensure Reproducibility and Compliance
- Balance Detail with Brevity



ESTIMAND FRAMEWORK

Treatment

- Investigational product (IP) or comparator

Population

- Participants for whom IP is being studied

Variable

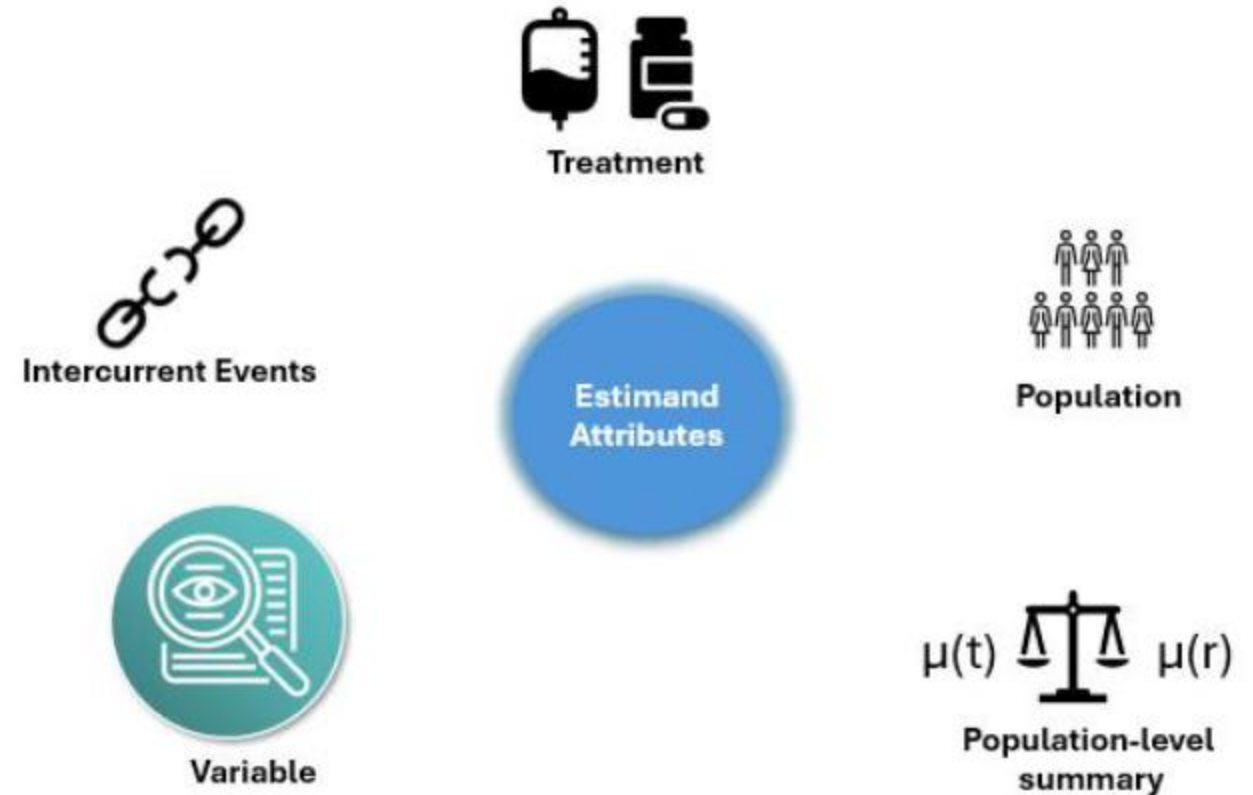
- The specific clinical variable or outcome being measured in the trial

Intercurrent Events (ICEs)

- ICEs are the events that can impact the interpretation of the treatment effect

Population-level summary

- In what way the treatment effect is summarized



ESTIMAND FRAMEWORK – EXAMPLES

Textual Approach

Treatment:

- Experimental:
 - Therapy for anaemia
- Control:
 - Placebo

Population:

- Adults (18 years or older) with chemotherapy induced anaemia

Variable:

- Change in haemoglobin concentration

Intercurrent Events (ICEs):

- Treatment discontinuation due to reason other than lack of efficacy or worsening of the adverse events. Data from all visits following the ICE will be marked as missing [Hypothetical Strategy]

Population-level summary:

- Difference in the haemoglobin concentration between Therapy for anaemia and placebo.

Tabular Approach

Treatment:	
Experimental:	
• Therapy for anaemia	
Control:	
• Placebo	
Population:	
• Adults (18 years or older) with chemotherapy induced anaemia	
Variable:	
• Change in haemoglobin concentration	
Intercurrent Events (ICEs):	Handling ICEs:
• Treatment discontinuation due to reason other than lack of efficacy or worsening of the adverse events.	• Data from all visits following the ICE will be marked as missing [Hypothetical Strategy]
Population-level Summary	
• Difference in the haemoglobin concentration between therapy for anaemia and placebo.	

OVERVIEW OF STRATEGIES FOR ADDRESSING INTERCURRENT EVENTS

Treatment Policy Strategy

The intercurrent event is disregarded, and the variable of interest is used regardless of its occurrence.

Hypothetical Strategies

The variable reflects the value it would take in a hypothetical scenario where the intercurrent event does not occur.

Composite Variable Strategies

The intercurrent event is informative of the patient's outcome and is incorporated into the variable definition.

While-on-Treatment Strategies

This strategy focuses on the treatment response before the intercurrent event, e.g., "while alive" for death as the event.

Principal Stratum Strategies

This focuses on the "principal stratum" where the intercurrent event either would or would not occur.

OVERVIEW OF STRATEGIES FOR ADDRESSING INTERCURRENT EVENTS - EXAMPLE

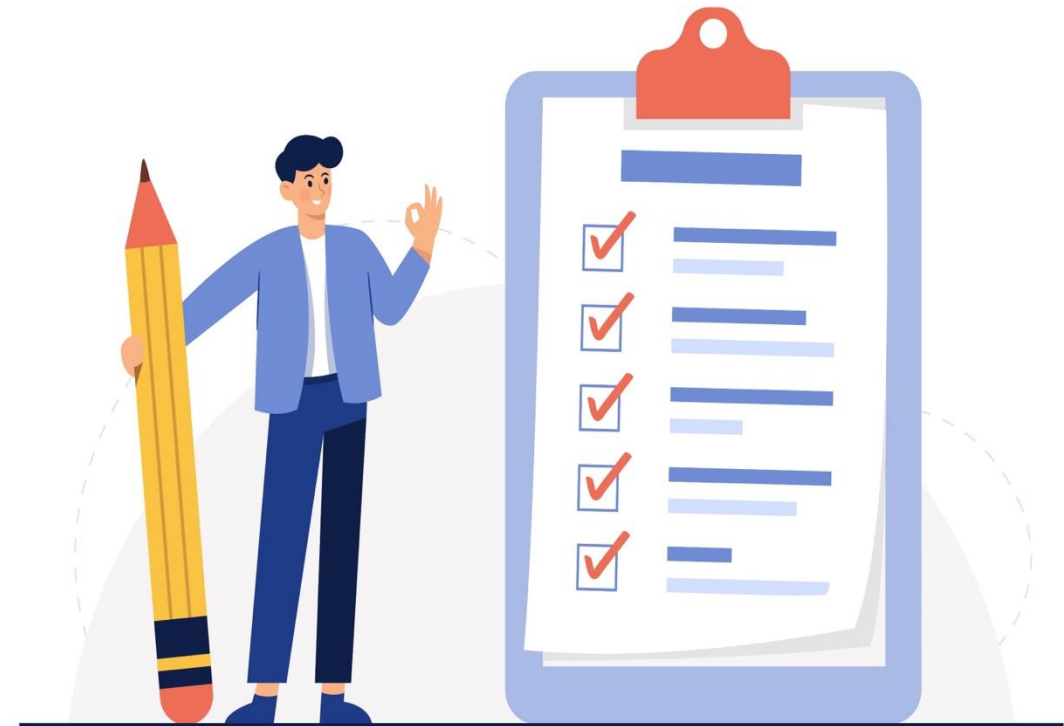
- **Treatment Policy Strategy:** Utilize data as observed
- **Hypothetical Strategies:** Set to missing from ICE point onwards
- **Composite Variable Strategies:** Set data to not achieving the endpoint or not having the expected observation value (actual or change)
- **While-on-Treatment Strategies:** Utilize data before ICE
- **Principal Stratum Strategies:** Utilizing data from a group of participants who will potentially experience the ICE (or group of participants who will not experience ICE)



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STRATEGIES FOR SAP AUTHORIZING

- Use Precise and Uniform Language
- Analysis Population
- Step-by-step Approach
- Estimand
- Time to Event
- Continuous Variables
- Categorical Variables
- Multiplicity
- Safety Assessments
- Missing or Partial Date/Time Handling
- SAP Training



STRATEGIES FOR SAP AUTHORIZING - USE PRECISE AND UNIFORM LANGUAGE

- Avoid vague or overly technical language
- Utilize standard statistical and clinical terminology
- Consistency throughout the SAP
- Clearly define the abbreviations
- Include definitions of the endpoints



STRATEGIES FOR SAP AUTHORIZING - ANALYSIS POPULATION

Population	Description	Criteria for Inclusion	Purpose
Full Analysis Set (FAS)	All randomized subjects.	All subjects who were randomized to a treatment group.	Primary efficacy analyses.
Per Protocol (PP)	Subset of FAS without major protocol deviations.	Randomized subjects who met key protocol criteria.	Supplementary analysis for efficacy, confirming robustness.
Safety Population	All subjects who received at least one dose of the study drug.	All treated subjects, regardless of adherence to the protocol.	Safety analyses (adverse events, serious adverse events).



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STRATEGIES FOR SAP AUTHORIZING – STEP BY STEP APPROACH

Adopt a step-by-step approach when defining the derivation of variables, enabling the programming team or biostatisticians to directly utilize this information for deriving variables at the ADaM level and writing the programs for statistical analysis



STRATEGIES FOR SAP AUTHORIZING - ESTIMAND

- Clearly outline the strategies
- Ordering of the Sections
- Anticipating and addressing all possible scenarios
- Handling of multiple ICEs



STRATEGIES FOR SAP AUTHORIZING - TIME TO EVENT

Deriving dates when multiple events are involved

Situation	Date of Progression or Censoring	Outcome
Tumour growth documented	Earliest tumour growth documented date	Event
Death (no prior progression)	Date of death	Event
No progression	Date of last assessment or Date of last available visit or early termination (whichever occurs earlier)	Censored
Unknown	Last known date	Censored



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STRATEGIES FOR SAP AUTHORIZING - CONTINUOUS VARIABLES

- Stating considerations for statistical analysis

Example: Descriptive statistics for continuous data will be presented as N, mean, standard deviation (SD), median, range (minimum and maximum), and interquartile range (IQR)

- For efficacy

Example: “After addressing the ICEs specified in the estimand section, missing data for the endpoint will be handled using a mixed model repeated measures (MMRM) approach under the assumption of missing at random (MAR).”

- For MMRM clearly state the variables included in the model

Example: Baseline variable, site, visit, treatment, and the interaction between visit and treatment

- Providing Pseudo code

STRATEGIES FOR SAP AUTHORIZING - CATEGORICAL VARIABLES

- Stating considerations for statistical analysis

Example: “Descriptive statistics for categorical data will be presented as counts and percentages.”

- For efficacy

Example: “After addressing the ICEs outlined in the estimand section, missing data will be imputed as not achieving the endpoint.”

- For statistical procedures clearly state the variables included into the considerations

Example: Cochran-Mantel-Haenszel (CMH) chi-square test should also be specified in relation to these stratification factors. For rare events, Fisher’s exact test will be used.

- Providing Pseudo code

STRATEGIES FOR SAP AUTHORIZING - MULTIPLICITY

- Stating Testing Procedure to be used

Example: hierarchical testing procedure - The primary endpoint will be tested first. If there are different doses, then the endpoint for dose 2 will be considered significant only if it is significant for dose 1. The secondary endpoint will be deemed significant only if the previous primary endpoint was significant.

- Clearly define the order



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STRATEGIES FOR SAP AUTHORIZING - SAFETY ASSESSMENTS

- Adverse Events
 - Presentation of TEAE
 - Sorting Order
 - Incident Rate
- Clinical Laboratory Tests:
 - Statistics to be presented for each parameter
 - Presentation of the Shifts
- Similar to the presentation of AE and laboratory test data mentioned above, the SAP should clearly define how to present safety assessments for vital signs, physical examinations, and other safety measures.



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STRATEGIES FOR SAP AUTHORIZING - MISSING OR PARTIAL DATE/TIME HANDLING

- Setting up missing or partial date or time

For example, birth date:

Set to missing if complete birthdate is missing

If only the day is missing, impute as the 15th

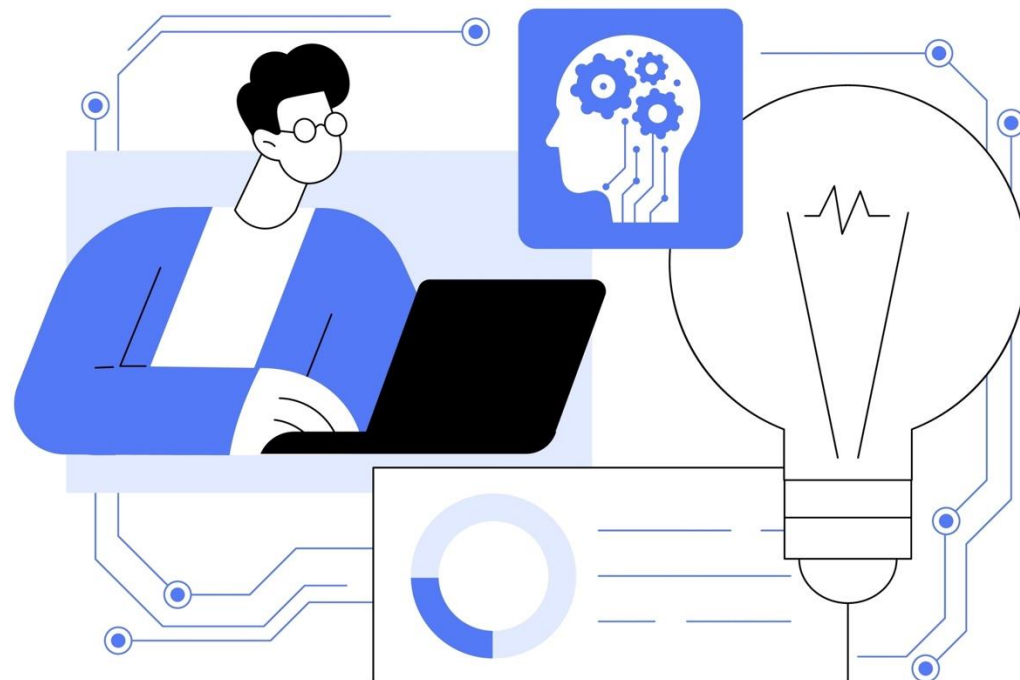
If only the month is missing, impute as June

If both the day and month are missing, impute as July 1st.

- Similarly, rule for missing or partial date or time for other datapoints such as AE should be defined clearly.

STRATEGIES FOR SAP AUTHORIZING - SAP TRAINING

- Once the SAP is finalized, it is beneficial to provide training to the Biometrics team members working on the study, explaining each section in detail.
- Training ensures that all team members, including biostatisticians, programmers, clinicians, and project managers, are aligned in their understanding and interpretation of the study's statistical analysis approach



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Q&A

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Thank You!

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