Paper AS01

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

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ABSTRACT

Typically, a Statistical Analysis Plan (SAP) comprehensively delineates data analysis and data handling strategies for a clinical study. The Biometrics team relies on details and instructions provided in SAP to generate essential outputs such as tables, listings, and figures (TLFs). Hence, it's imperative to draft SAP in a manner that facilitates understanding and adherence, ensuring seamless data handling and analysis. Misinterpretation of details from SAP could result in misapplication of rules, necessitating rework leading to missed deadlines and impacting overall timeline of the study deliverables. This paper will focus on the estimands and analysis sections (includes four attributes, the population, variable, intercurrent events, and population-level summary) of SAP, addressing strategies to prevent confusion and conflicts in statements.

INTRODUCTION

SAP is a key document in any clinical trial. While each organization may have its own template, the purpose of the SAP remains the same i.e. to describe how the clinical study data will be analyzed and presented. Although the formats may vary, the essential components are consistent. The SAP not only outlines estimands and the statistical methods used, but also covers aspects such as:

- Imputation of missing dates
- Windowing for unscheduled visits
- Additional analyses not specified in the protocol

Given its importance, the SAP must be drafted clearly and thoroughly, ensuring that anyone reviewing it can easily understand and follow the steps needed for deriving variables and performing the analysis.

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 a SAP:

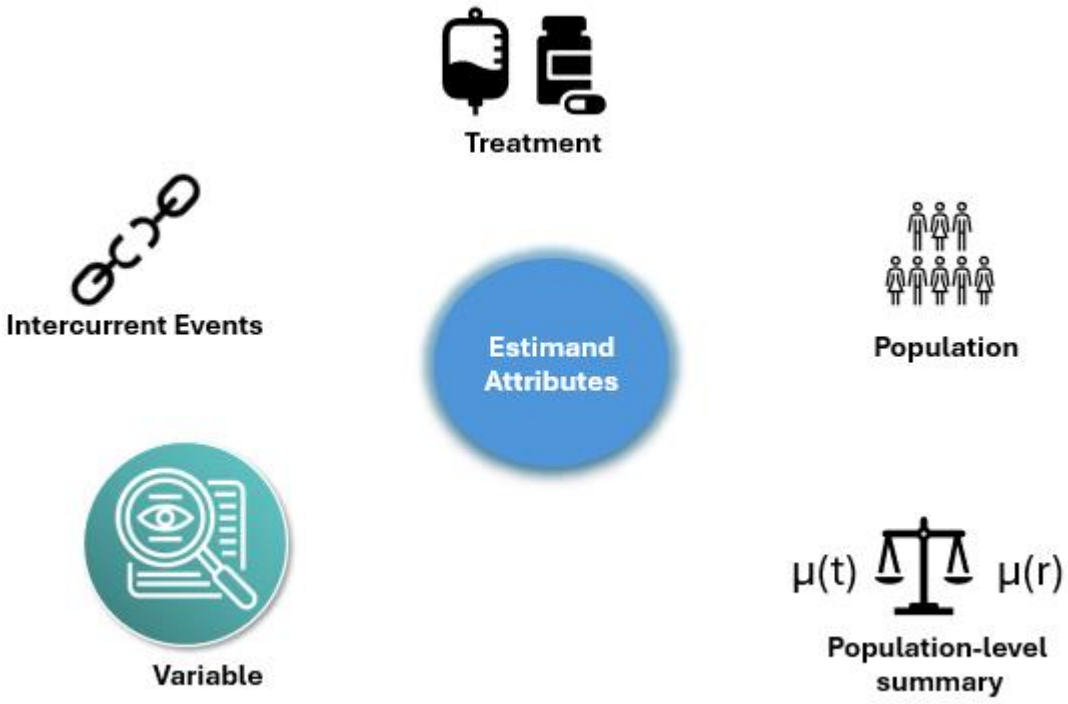
- Understand the Protocol Thoroughly
- Use a Template for Standardization
- Structure the SAP Clearly
- Incorporate Regulatory Guidance
- Focus on Clarity and Precision
- Anticipate and Plan for Possible Scenarios
- Ensure Stakeholder Review and Approval
- Ensure Reproducibility and Compliance
- Balance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

ESTIMAND FRAMEWORK

An estimand offers a clear and precise description of the treatment effect being evaluated in a clinical trial. It addresses the fundamental question i.e. treatment effect are we aiming to estimate. Introduced by the ICH E9 (R1) addendum in 2019, the concept enhances the transparency of clinical trial outcomes by explicitly aligning the study's objective with data analysis and interpretation. While the use of the estimand framework is not mandatory for all trials, regulatory authorities strongly recommend its adoption to improve clarity and ensure alignment between trial objectives and data analysis.

Although the approach to writing the estimand section may vary across organizations, its core purpose remains the same: to provide a clear and accurate description of the treatment effect without causing confusion.

Figure 1: Estimand Attributes



Following are the two examples of defining the estimand section in SAP:

1) Textual Approach

Treatment:

- Investigational product (IP) or comparator
- Example:
  - Experimental:
    - Therapy for anaemia
  - Control:
    - Placebo

Population:

- Participants for whom IP is being studied
- Example:
  - Adults (18 years or older) with chemotherapy induced anaemia

Variable:

- The specific clinical variable or outcome being measured in the trial
- Example:
  - Change in haemoglobin concentration

Intercurrent Events (ICEs):

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

- In what way the treatment effect is summarized
- Example:
  - Difference in the haemoglobin concentration between Therapy for anaemia and placebo.

2) Tabular Approach: Above can be utilised as tabular form

Table 1: Estimand

<table>
<tr><td colspan="2">Treatment: Investigational product (IP) or comparator.

Example:
Experimental:
• Therapy for anaemia
Control:
• Placebo</td></tr>
<tr><td colspan="2">Population: Participants for whom IP is being studied.

Example:
• Adults (18 years or older) with chemotherapy induced anaemia</td></tr>
<tr><td colspan="2">Variable: The specific clinical variable or outcome being measured in the trial.

Example:
• Change in haemoglobin concentration</td></tr>
<tr><td>Intercurrent Events (ICEs): ICEs are the events that can impact the interpretation of the treatment effect.

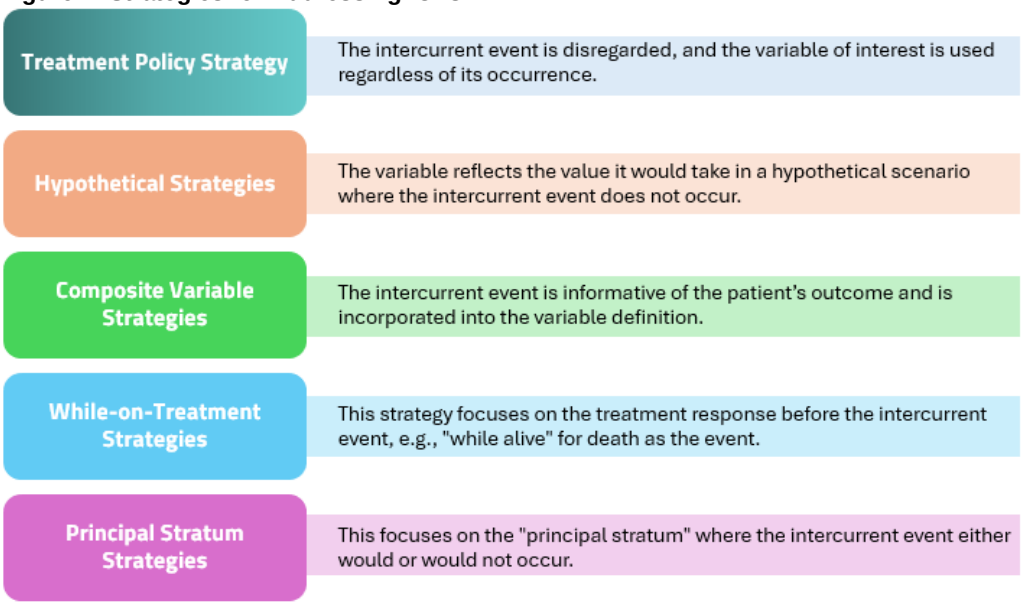
Example:
1. Treatment discontinuation due to reason other than lack of efficacy or worsening of the adverse events.</td><td>Handling ICEs: Strategies to handle ICE

Example:
1. Data from all visits following the ICE will be marked as missing [Hypothetical Strategy]</td></tr>
<tr><td colspan="2">Population-level Summary: In what way the treatment effect is summarized

Example:
• Difference in the haemoglobin concentration between therapy for anaemia and placebo.</td></tr>
</table>

OVERVIEW OF STRATEGIES FOR ADDRESSING INTERCURRENT EVENTS:

Figure 2: Strategies for Addressing ICEs



Following example illustrates how ICE can be handled using different strategies:

- 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)

STRATEGIES FOR SAP AUTHORING

Writing SAP that is easily understood by team members, including biostatisticians and SAS programmers, requires clear, concise, and well-organized communication.

Here are a few key points to consider before and during the drafting of the SAP:

USE PRECISE AND UNIFORM LANGUAGE

We should avoid vague or overly technical language and instead utilize standard statistical and clinical terminology. Consistency throughout the SAP is essential, and any abbreviations or specific terms should be clearly defined in the list of abbreviations at the start of the document. Additionally, including definitions of the endpoints would enhance clarity and understanding.

ANALYSIS POPULATION

The definition of each population and a statement regarding the use of the analysis population in each analysis section should be clearly articulated.

Table 2: Analysis Set (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).

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.

ESTIMAND

To help programmers and biostatisticians grasp the estimand framework and the strategy for handling ICEs, it's essential to clearly outline the strategies to be adopted for each ICE in the SAP. Simply defining the estimands framework is not enough; the placement of the statements is equally important. Specifically, the statistical methods must be in the following order (if applicable based on SAP template):

- Primary Hypothesis
- Primary Efficacy Endpoints
- Primary Estimands (Estimand 1)
- Analysis Methods (Primary, Sensitivity, Supplementary, etc.)

Arranging the SAP sections in this order helps programmers and biostatisticians understand the sequence in which analyses (Primary, Secondary, Exploratory, etc.) will be conducted after addressing the ICEs. For instance, once the

estimands framework is established, the beginning of the Analyses section should be “After handling ICEs,” and then we should continue stating about the methods. A crucial aspect of writing the SAP is anticipating and addressing all possible scenarios to avoid conflicts, queries, and amendments. In the context of estimands, one such scenario involves subjects with multiple ICEs before the visit of interest. In this case, it’s important to clearly specify how multiple ICEs will be managed, such as: “For subjects with multiple ICEs, the ICE with the most significant impact on clinical interpretation will take precedence over the handling strategies for any other ICE”.

TIME TO EVENT

To conduct a time-to-event analysis, we need to derive the duration variable using a start date, typically the randomization date, and an analysis date, which may be either the event date or the censoring date. The event dates will vary for each parameter. If there is only one event linked to the analysis date, the process is straightforward; however, it becomes more complex when multiple events are involved. In these situations, we must specify all relevant events to establish the analysis date for each parameter, with the earliest event date after randomization being used. A few examples are provided below:

Table 3: Progression-free Survival (PFS) – Situation, Date and Outcome

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

For example, when deriving the duration for a parameter such as progression-free survival (PFS), it should be stated that PFS is defined as the time (in days, weeks, months, or years) from the date of randomization until the date of progression (relapse) or death from any cause, plus one day. Additionally, clear instructions must be provided for handling censoring, including guidance on selecting the appropriate censoring date when the event has not occurred. The details of the methods to be employed for analyzing time-to-event data, such as the log-rank test, must be clearly defined along with any relevant stratification factors.

CONTINUOUS VARIABLES

In general, the considerations for statistical analysis should clearly specify how descriptive statistics will be presented. For example, it should state: “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, if the estimand framework is defined in the SAP, it should be addressed in the efficacy analysis section. For instance, if we have longitudinal data (such as change from baseline) and are assessing differences between treatment groups, we can specify this in the Analysis Method section. It might read: “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).”

When utilizing MMRM, it is important to clearly state the variables included in the model, such as baseline variable, site, visit, treatment, and the interaction between visit and treatment. Additionally, define the covariance matrix for repeated measures within subjects, along with the approximation for the degrees of freedom. It is beneficial to specify the order of the covariance matrix to mitigate convergence issues during MMRM execution. Lastly, include the statistics that will be presented in the output, such as Least Squares (LS) means, Confidence Intervals (CIs), and p-values.

Providing pseudo code in the appendix section of the SAP can also aid in understanding the code to be implemented for generating the outputs. Pseudo code example for MMRM:

```
proc mixed data=_datasetname_ method=reml;
class trt01pn usubjid avisitn site sex;
model chag = trt01pn avisitn site sex trt01pn*avisitn base / ddfm=kr;
repeated / subject=usubjid (trt01pn) type=un;
lsmeans trt01pn*avisitn / cl pdiff;
 estimate 'treatment T - R on week 2' trt01pn -1 1
```

```
 trt01pn*avisitn -1 0 1 / cl lower lowertailed;
 estimate 'treatment T - R on week 4' trt01pn -1 1
 trt01pn*avisitn 0 -1 1 / cl lower lowertailed;
run;
```

Including pseudo code in the appendix of the SAP is particularly beneficial when dealing with complex methods and analyses, such as Multiple Imputation (MI), tipping point analysis, and trimmed means. These analyses often require several intricate steps, each of which must be executed with precision to ensure accurate results.

When presenting these methodologies, even if each step is clearly defined in the main text, the complexity involved can still create opportunities for confusion. For instance, programmers and biostatisticians may misinterpret the intended logic or overlook critical nuances in the procedures, leading to potential errors in coding. Such mistakes can have significant repercussions, resulting in missing data, incorrect statistical calculations, or flawed interpretations of results

CATEGORICAL VARIABLES

Considerations for statistical analysis should clearly specify how descriptive statistics will be presented “Descriptive statistics for categorical data will be presented as counts and percentages.”

For efficacy analysis, if the estimand framework is defined in the SAP, it should be addressed in this section. For example, if we have binary data (such as response or remission) and are assessing differences between treatment groups (for response or remission), this can be specified in the analysis method section, stating: “After addressing the ICEs outlined in the estimand section, missing data will be imputed as not achieving the endpoint.”

Additionally, the statistical procedures to be employed, such as the chi-square test, should be clearly defined, particularly if there are stratification factors to consider in our analysis then test such as Cochran-Mantel-Haenszel (CMH) chi-square test should also be specified in relation to these stratification factors. Pseudo code example for CMH:

```
proc freq data=dataset;
 tables site*sex*trt01pn*var/cmh
 alpha=0.1 ;
 weight count;
run;
```

where var is the response variable.

In cases where events are sparse, we should define alternative procedures, stating, “For rare events, Fisher’s exact test will be used.” Finally, it is essential to specify the statistics that will be included in the output, such as counts, percentages, and p-values.

MULTIPLICITY

If any testing procedures are employed to control Type I error, they should be clearly stated. For example, if a hierarchical testing procedure is used, this section should provide detailed information about the hierarchy established to control Type I error. This might include statements such as: “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.” and in the case of two doses, this statement will be modified to indicate that the secondary endpoint will be considered significant only if both dose 1 and dose 2 are significant. If co-primary endpoints exist, please adjust the wording accordingly.

For multiple secondary endpoints, we should clearly define the order in which the secondary endpoints will be tested, and state that the next secondary endpoint will be considered significant only if the previous secondary endpoint was significant.

SAFETY ASSESSMENTS

There are several analyses defined in the protocol under safety and these safety analyses should be defined in the SAP clearly. Some of the examples of safety assessment are:

Adverse Events: For Adverse Event (AE) summaries, Treatment-Emergent Adverse Events (TEAEs) are typically the focus, and all relevant summaries must be clearly defined and outlined in the SAP. It is important to explicitly state how TEAEs will be presented, such as summarizing by System Organ Class (SOC) and Preferred Term (PT), along with additional details like severity, relationship to treatment, and other relevant attributes. Additionally, the SAP should specify how deaths will be reported, including details on the cause of death and the scenarios under which these will be presented. The sorting of frequencies should also be specified to ensure that the generated output table is clear and well-organized

Clinical Laboratory Tests: All laboratory tests to be included in the reports, such as hematology and chemistry parameters, must be clearly defined in the SAP. Additionally, the specific statistics to be presented for each parameter, along with the corresponding visit or time point, should be explicitly stated. If the objective includes identifying patterns or shifts in laboratory values, the SAP should clearly define how shifts from baseline to post-baseline visit ranges will be presented in the reports, ensuring clarity in the interpretation of the data.

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.

MISSING OR PARTIAL DATE/TIME HANDLING

When working with data that involves dates, such as defining an event as a treatment-emergent adverse event (AE) or calculating age using the date of birth and the date the informed consent form (ICF) was signed, there is a significant likelihood of encountering missing or partial dates and times. We need to impute these missing or incomplete dates or times. The challenge arises in defining how to handle these missing or partial dates and times, as different dates require distinct handling rules, and these should be handled in an appropriate manner.

For example, when handling missing or partial date/time data, we can use the following approach: If the complete birth date is missing, it will not be imputed. However, for partial dates, if only the day is missing, it will be imputed as the 15th. If only the month is missing, it will be imputed as June. If both the day and month are missing, the date will be imputed as July 1st.

Missing dates are most common in adverse event (AE) datasets, making it crucial to address each scenario. For AE start date, we should consider cases where both the date and time are missing, only the time is missing, or other variations. Similarly, for the AE end date, we need to account for situations where the complete end date is missing, both the day and month are missing, only the day is missing, or only the time is missing.

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. This 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.

CONCLUSION

To conclude, enhancing the understanding of estimands and the analysis section while drafting the SAP can be achieved by considering the following key points:

- Avoid vague or overly technical language and ensure consistency throughout the document.
- Clearly define the analysis population.
- Adopt a stepwise approach when defining the derivation of variables.
- Organize the sections logically.
- Establish strategies for addressing intercurrent events and managing multiple intercurrent events (ICEs).
- Clearly define the derivation, imputation, and analysis methods for efficacy outputs.
- Provide a clear description of how safety data will be performed and presented.
- Ensure accurate handling of partial or completely missing dates.
- Conduct a dedicated SAP meeting to facilitate discussion and clarification.

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