How to Develop a Statistical Analysis Plan for Clinical Trials

A statistical analysis plan (SAP) is a defined outline of the planned statistical analyses for a clinical trial, including basic and advanced methods. An SAP is crucial — it is one of the key regulatory confidential documents in the development of a clinical trial. It provides explicit guidance on statistical programming, as well as the presentation of results for a clinical trial. Depending on the organisation, statistical analysis plans might also be known as reporting and analysis plans or data analysis plans (DAP).

The most important thing to ensure while conducting a clinical trial is that it is executed with minimum bias. Therefore, each clinical trial needs to have a clear and detailed SAP to support reproducibility.

In clinical studies, the SAP is a critically important document. It ensures that the analyses used to evaluate all pre-planned study hypotheses are conducted in a scientifically valid manner and that all decisions are well documented. For best practice of clinical trials, reproducibility of research, and to avoid concerns of misuse of clinical research, a clear, detailed and very transparent SAP is crucial. In addition, the more comprehensive it is, the easier it will be for an SAS programmer to present in their analysis report later on.

However, producing a good quality SAP is a challenging task in clinical trial protocol development, which requires a strong command of statistical methodology, medical terminology and visualisation power.

There are four important types of SAP used in a clinical trial:

- Data monitoring committee SAPs
- Interim SAPs
- Integrated statistical SAPs
- SAPs for clinical studies

What Does an SAP Cover?

SAPs are mostly written as separate documents, but they can be included in the clinical study protocol as a standard operating procedure for dealing with the statistical part of the clinical study. The SAP must properly explain: the aims and primary objectives, secondary objective, exploratory objectives, primary/secondary/exploratory endpoints, trial population, design of the trial, sample size calculations with justifications/assumptions and the randomisation methods. Additionally, an SAP must describe in detail the statistical methodology, such as efficacy analysis, safety data analysis and reporting conventions. For example, the SAP must assure that the sample size is adequate for the nature of the tests used and the comparisons made.

There are three essential factors an SAP needs to maintain in a clinical trial:

- **Transparency:** Transparency concerning how the analysis will proceed, by specifying methodology that will be applied in advance
- **Communication:** Clear communication with everyone involved in the study on how to proceed
- **Replication:** Facilitates replication so that a future research team can follow the same steps to confirm the results on the same or a new sample

As per standard guidelines and best practice, it is important that the clinical trial project statistician/biostatistician prepares the study's SAP before the clinical trial starts, detailing all the planned analyses and study parameters, including analysis of set definitions and basic/advanced statistical methodology. The techniques must be chosen and defined in advance, to avoid the possibility of a particular method being selected because it results in the most positive results.

For example, if applying transformations, the thinking behind this should be explained clearly. The SAP can also specify what will be reported, using which unit of measurement, and whether this will include confidence intervals and p-values. Similarly, if multiple methods are being used to analyse the primary outcome, the SAP should specify which is the primary analysis method.

It is important to note the SAP is a working document, as the statistical analysis may depend on unpredictable factors or new statistical protocols may be established during the trial.

Who is Involved?

The clinical trial SAP should be started with an in-depth discussion between the study's principal investigators and a statistician. A medical statistician/biostatistician should then take charge of developing the SAP in coordination with the principal investigator of the study.

The statistician's roles and responsibilities include:

- Writing a research statement or hypothesis for the clinical trial study
- Determining the primary endpoints and secondary endpoint
- Establishing and developing a strategy to reduce bias
- Selecting a sample size for the clinical trial
- Defining all appropriate statistical methods for clinical trial data analysis

The document should be reviewed with special attention by a senior blinded biostatistician and finalised before it is submitted to the review board and regulatory authorities. If any protocol amendments are required, then the SAP will need to be amended as well. The importance of reviewing a statistical analysis plan is well documented, such as in the conference paper Ahrweiler *et al.* published in 2011.

As well as developing the SAP, another big contribution of the medical statistician/biostatistician is the designing, monitoring and analysing of clinical trial data.

For many clinical trials, developing a SAP requires the support of a freelance clinical statistician. This can either be for the

statistician producing the SAP, or as an impartial reviewer who was not involved in its development. With the help of an experienced freelance biostatistician, you can develop a thorough and error-free SAP, that will improve the quality of your clinical trials.

How Should the SAP be Developed?

When developing an SAP, the statistician will consider the details of the planned statistical analysis, the principal features of the technical analysis, the trial objectives, the data sources, the population studied, the study endpoints, the statistical methodology and sensitivity analysis and missing data.

Additionally, some other important considerations relating to the SAP in a clinical trial include:

1. Blinding the biostatistician to minimise bias
2. Documenting the SAP in such a way that all the data manipulations and analyses performed can be replicated
3. Maintaining a trial master file with all the relevant documentation

The SAP should guide the statistician to all necessary resources, such as The CONSORT Statement (and any extensions), the ICH E9 Statistical Principles for Clinical Trials PDF, the EQUATOR Network (a resource centre for good reporting of health research studies) and the National Institute for Health Research Trial Planning and Design Station.

In 2017, Gamble *et al.* published guidelines that recommend a minimum of 55 important items to be considered during the SAP, including title and registration (11), introduction (2), study methods (9), statistical principles (8), trial population (8) and analysis (17). Because there are so many factors to consider when designing an SAP, it can help to use a checklist.

Additional Guidelines to Follow

The most important guidelines include the FDA's Guidance for Industry: Statistical Principles for Clinical Trials. Additionally, to improve reproducibility, transparency and validity in clinical trials, the National Institutes of Health (NIH) published its "Rules for clinical trial studies registration and results information submission", which mandates trial registration, posting of clinical trial ongoing recruitment or results within ClinicalTrials.gov, and submission of the separate original document SAP along with the clinical trial research study protocol.

Additional important guidelines used in SAP development are the International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH E9) and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). Importantly, though these guidelines give us an idea of the body content of individual sections of the SAP, E3 and E9 do not specify specific statistical techniques. This is up to the statistician.

Because statistical methodology directly affects clinical trial decision-making, well-documented, confidential and transparent statistical conduct is essential. ICH E9 guidelines state that "the principal features of the eventual SAP of the data should be described in the statistical section of the protocol". However, SPIRIT guidelines refer to a separate SAP.

Because the SAP is such an essential document, it needs to be reported to regulatory authorities like the Food and Drug Administration (FDA) or European Medicines Agency (EMA).

Standard guidelines suggest that the SAP needs to be stored confidentially in the clinical trial master file — it can then be used during regulatory authority audits to check if statistical documents have followed standard guidelines exactly.

Further points to remember include:

- The SAP is not a standalone document. It should be read in conjunction with the clinical trial protocol
- The clinical trial protocol should be consistent with the principles of the SPIRIT 2013 Statement
- The SAP is to be applied to a clean or validated data set for analysis

Detailed guidelines are also available from funders, regulatory authorities, journals, industry representatives and UK Clinical Research Collaboration registered Clinical Trial Units (UKCRC CTUs). Additionally, the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials in-depth details are described in JAMA. An elaboration document is also available to provide a more in-depth detailed explanation of each checklist item. Finally, you can view the SAP statement in the EQUATOR Network and the MRC-NIHR Trials methodology research partnership.

REFERENCES

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5. MRC-NIHR Trials Methodology Research Partnership (TMRP)
6. UK Clinical Research Collaboration registered Clinical Trial Units

Rudra Patel

Rudra Patel is a freelance medical writer and biostatistician at Kolabtree, providing scientific and regulatory writing services as well as end-to-end statistical services. He is a clinical operations manager at SymGet Technologies, a contract research organisation (CRO) that focuses on advanced project management, clinical operations, medical writing, statistical analysis, staffing and training. He has over 15 years of clinical research experience working with pharmaceutical companies, CROs and the medical device and healthcare industry.