SOP 600 Statistical Analysis Plan

For Use in:	Research & Development
By:	All staff
For:	All staff involved in the conduct of research
Division responsible for document:	Research & Development
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SOP 600 v1.4

This Standard Operating Procedure (SOP) is available on the Research & Development pages on the NNUH website

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1. Contents

2. Definitions of Terms Used / Glossary

CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
ICH	International Conference for Harmonisation
NNUH	Norfolk and Norwich University Hospital
R&D	Research and Development
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedures
TMF	Trial Master File
UEA	University of East Anglia

3. Scope

This SOP defines the procedure for the production of Statistical Analysis Plan (SAP) for clinical trials where one is required. Whilst the detailed procedure of this SOP relates to clinical trials, the principles of this SOP may be adopted for non-clinical trials healthcare research by the member(s) of the research team with responsibility for statistical design and analysis.

4. Rules

Each trial should have an appropriately skilled and trained individual who has responsibility for the statistical aspects of the trial, acts as the 'trial statistician' and is appointed by the Sponsor or delegate.

The designated trial statistician should be named in the trial protocol.

5. Responsibilities

Some tasks may be delegated to other statisticians involved in the trial; however the designated trial statistician should check that these tasks are performed appropriately and accurately.

The trial statistician should interact closely with other members of the trial team including but not limited to the Chief and/or Principal Investigator, Clinical Trial Operations and Data Management staff.

6. Introduction to a Statistical Analysis Plan

There should always be pre-specified statistical methodology documented for analysis of a trial. This should be either in the protocol or in a separate document called a Statistical Analysis Plan (SAP).

A SAP may not be required where the trial protocol contains all necessary information including, for example, details such as adjusting for multiple testing and handling missing data. A statistical analysis plan is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary outcome variables and other data.

7. Producing a Statistical Analysis Plan

- An SAP should be written in collaboration between the trial statistician and the trial Chief Investigator
- Should be approved by the Trial Steering Committee, Independent Data Monitoring Committee, or both.
- Major revisions to the SAP should again be approved by the same bodies.
- No specific timing is suggested for the commencement of the writing of an SAP.
- However an agreed SAP should be produced before any formal efficacy data analyses, including formal interim efficacy analyses where pre-stated, are carried out.
- It is not necessary to produce a detailed SAP prior to the commencement of a study and it is recognised that in the light of data collected, or other considerations, amendments may be required.
- The SAP should, however, follow the general principles of analysis laid down in the statistical section of the study protocol (SOP 320)
- The SAP should be version-controlled during its production.
- SAPs should be included in the Trial Master File (TMF) in the section on Statistics and Data Management Methodology and included in the Statistics Master File
- Any analyses in the SAP that are not supported by the protocol should lead to an assessment by the Sponsor or delegate of whether a protocol amendment is required.
- Any changes to planned analyses following data release and unblinding, for example additional exploratory efficacy analyses, should be fully justified and communicated in the report of the results of the trial and a formal amendment of the SAP may be required.
- It should be noted that journals may require the final SAP to be submitted along with the protocol and draft manuscript to be considered as part of peer-review.

8. Statistical Analysis Plan Content

CONTENT

- The SAP should be a comprehensive and detailed description of the methods of analysis and presentation of data for the trial including main and formal interim efficacy analyses.
- The SAP should provide enough detail for a qualified statistician with no previous experience of the trial to perform the corresponding analysis.
- Any major discrepancies or changes between the analysis plan in the protocol and final SAP should be explained in the SAP and possibly any reports.
- Consideration should be given to the inclusion of the following, but recognising that not all need be included in all studies and that different studies may emphasise or detail different areas of analysis. These sections are consistent with guidance provided by Gamble et al (2017).

8.1 Authorship

This should include who prepared and who has approved the SAP, version and date.

8.2 Trial Background

A section should describe the background, (in brief) and objectives for the trial. This can be taken from the trial protocol. The ISRCTN or EUDRACT number should be provided.

8.3 Study Methods

A brief description of the trial type (e.g. superiority, parallel, multi-arm etc.) and what interventions are being used. The timing of outcome assessments should be stated. The sample size should be discussed and methods for participant allocation included. Any formal interim analyses should be included with stopping rules (including level of significance used) clearly stated.

8.4 Statistical Principles

This section should include broad statistical approaches including level of statistical significance used (with any adjustments due to multiple hypothesis testing stated) and confidence intervals used. A statement should be made of the analysis populations; e.g. the 'Intention-to-Treat' population, 'Per Protocol' etc. These should be clearly defined with respect to data collected (e.g. explicit definitions of adherence).

8.5 Trial Population

The reporting of screening data (if any) to describe the repetitiveness of the trial group should be included. There should be a summary of eligibility criteria (this can be lifted from the trial protocol). Further recruitment data, likely to be included in the CONSORT flow diagram should also be stated as should information on withdrawals to be included. A list of baseline characteristics to be descriptively summarized should be included.

8.6 Details of Analyses

The efficacy outcomes for the study should be clearly stated together with units and any calculations required (e.g. the ratio of two measures). This may need to include timings (e.g. events within a 6 month period). Primary and secondary outcomes should be distinguished and consistent with that stated in the protocol. Where there are multiple primary outcomes this should be elaborated upon to define what is considered a 'successful' trial outcome. Tertiary outcomes may also be defined.

A clear statement of the analysis methods, and what are primary analyses against secondary, should be stated, particularly in detail for the primary outcome(s). This should include model 'type', inclusion of co-variates and any model assumptions (e.g. any distributional assumptions). Methods for subgroup analysis should be included and any sensitivity analyses for any outcome variables. Methods to handle missing data should be included, together with any assumptions made.

Information regarding 'harms' to be reported should be stated. Details of adverse event coding should be included.

Statistical software to be used (including version) and any key references should be included.

8.7 Quality Assurance

Prior to finalization, the SAP must be reviewed by a suitable statistician who is not the primary author of the SAP and who is approved by the CI or PI. This will, most likely, be the independent statistician of the Trial Steering Committee or Data Monitoring Committee (or analogous groups where available). Compliance with this SOP will be assessed as part of routine monitoring, audits and inspections.

9. References

ICH Topic E 9 Statistical Principles for Clinical Trials: NOTE FOR GUIDANCE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIAL (CPMP/ICH/363/96)

Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA 2017;318(23):2337-234

10. Approval

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11. Reason for Update and Training Implication

This replaces SOP 600 v1.3

Update	Reason	Training Implication	Action
Changes made in order to bring the SOP in line with guidance published in JAMA 2017. Reformatted to new SOP template	Ensure current information is available and SOP is in a user friendly format	Yes	Review SOP and update training matrix