ECTU Central Office SOP ECTU_ST_04: Statistical Analysis Plans

Version No:	7.0
Issue Date:	02 Oct 2023
Effective Date:	16 Oct 2023

Authorship and Approval			
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Document Revision History		
Version No.	Effective Date	Summary of Revisions
(ACCORD)	29th Jun 2009	Last version held within ACCORD
1.0	6th Aug 2012	Moved to ECTU format.
2.0	23rd Mar 2015	Updated following detailed review
3.0	26th June 2017	Updates after scheduled review. Reference to ECTCU_WPD_ST_W4, SAP Template and weblinks to ICH guidance and ACCORD SOP added to Section 4.
4.0	26th Aug 2019	Updated at scheduled review. Document moved to new SOP template.
5.0	25 March 2021	Updated following review. Changes to sections 3.1 to 3.15, including substantial edits to sections 3.11, 3.13, and 3.14, to clarify blinding.
6.0	7th May 2021	Minor changes to 3.11, 3.13 and 3.14 to establish database lock as the fixed time point before which the SAP should be finalised.

7.0	16 Oct 2023	Major changes at scheduled review. The SOP now focuses on the processes to generate and/or update a SAP. In contrast, the working practice document (WPD) focusses on what to put in a SAP. Many items that were previously in the WPD have been moved to the SOP. The SOP has been updated to use the current SOP template.

1.0 PURPOSE

The purpose of this SOP is to define the procedures for the production, review and approval of the Statistical Analysis Plan (SAP) for research studies.

2.0 SCOPE

This SOP applies to all CTIMP trials (regardless of randomisation status) with statistical support provided through ECTU. It is recommended that this SOP is also followed for non-CTIMP trials.

3.0 RESPONSIBILITIES

The SAP is the responsibility of the trial statistician (or designee).

4.0 PROCEDURE

4.1 The study protocol and the SAP

4.1.1 The statistical methods to be used for the analysis of the trial data should be included in the protocol.

4.1.2 It is not essential for every study to have a SAP if all relevant information is contained in the protocol.

4.1.3 The SAP might include additional detail of the analyses described in the protocol, or describe additional secondary analyses or exploratory analyses.

4.1.4 The SAP and protocol should not contradict one another. In particular, the outcome measures to be analysed and analysis populations that are mentioned in the protocol's Statistical Methods section must be matched in the SAP.

4.1.5 If there are any differences between the type of methods described in the protocol and the type of methods described in the SAP, then these should be explained in the SAP. If there are major differences, then a protocol amendment should be submitted.

4.2 First draft of the SAP

4.2.1 Following approval of the protocol, case report form (CRF), and any other applicable study specific documents, and before study database lock or formal interim analysis (if applicable), the trial statistician or designee should write the SAP, using the latest version of

the ST004 - SAP Template, and with reference to ECTU Central Office WPD ECTU_ST_W4: Additional Guidance on the Contents of a Statistical Analysis Plan (SAP).

4.2.2 The SAP should be a comprehensive and detailed description of the data analysis methods proposed for a study, to avoid post hoc decisions that may affect the interpretation of the statistical analysis.

4.2.3 The SAP may be written solely by the trial statistician (or designee) or it may be jointly written with other ECTU personnel. The writers are considered to be the authors of the SAP.

4.2.4 To help with preparing the first draft, the SAP authors may consult the Chief Investigator and, if necessary, any other relevant study collaborators.

4.3 Review of first draft

4.3.1 On completion of the first draft, the SAP should be circulated for review and comment to the Chief Investigator and any other statisticians working on the trial (unless they are unblinded to the study data). In some cases it may also be appropriate to send the SAP to other members of the trial team e.g. the trial manager. The authors will then, if appropriate, update the SAP based on any comments or suggestions they receive. This procedure will need to be repeated until the SAP content is agreed.

4.3.2 Where there is a formal interim analysis, it is recommended that the group who will formally review the interim analysis results (usually the independent Data Monitoring Committee (DMC) members) review a draft of the statistical analysis plan and agree to the planned analyses in advance of any formal interim analysis reporting, and before the DMC members have seen unblinded data from the trial.

4.4 Completion and approval

When the SAP authors, the trial statistician (or designee), the CI, and any other appropriate members of the trial team are satisfied that the SAP is complete, then the last updated draft version of the SAP is deemed the final version. It will then need to be approved by the signatories detailed in the “SAP Approval Signatures” table in the SAP.

4.5 Timing of SAP approval

4.5.1 If a study requires a formal interim analysis, then the SAP must be finalised and approved before the formal interim analysis begins.

4.5.2 If a study does not have a formal interim analysis, then the SAP *must* be finalised and approved before database lock for the final analysis.

4.5.3 Although not essential, it is recommended that the SAP is finalised and approved at least 6 months before database lock to allow time for any protocol amendments to be completed in the case that the statistical analysis methods proposed in the SAP begin to diverge from what is written in the study protocol. This could happen for example in the case that the Chief Investigator changes their mind about how the final analysis results should be summarised or

presented; or if new methodological research is published (external to the trial) which suggests a different statistical approach should be undertaken.

4.6 Blinding

4.6.1 The SAP should not be written by anyone with unblinded access to the data to avoid bias. Specifically, in blinded trials, the SAP should not be written by anyone unblinded to treatment arm.

4.6.2 If the SAP is written by someone who is initially blinded to the data but later becomes unblinded during the trial, then this person cannot continue to write the SAP after they have become unblinded. In this case, authorship must be transferred to someone who is blinded.

4.6.3 Before the SAP is finalised, an unblinded statistician could, if appropriate, conduct a sense check from what they know of the blinded data (e.g. assess whether a variable that was expected to be normally distributed is actually highly skewed).

4.7 Changes to a finalised SAP

4.7.1 Changes pre-database lock: Any pre-database lock changes to the statistical analyses should be documented as a new version of the SAP. The creation, review, and approval procedures for a new version of the SAP are specified in sections 4.2 to 4.4 of this SOP.

4.7.2 Changes post database lock: Any changes of the SAP after database lock or after the first formal interim analysis (if applicable) should be justified and fully documented in the statistical report. If there have been substantial changes to the SAP, such as using a completely different primary analysis approach to the one originally planned, a new version of the SAP should be written, making it clear that this was written after database lock or after the first formal interim analysis.

4.8 General instructions

4.8.1 The latest version of ST004 SAP Template should be used when writing a new statistical SAP document or when updating an old one.

4.8.2 The authorship of the SAP, version and date should be clear.

4.8.3 The SAP authors should ensure they are using the current version of the protocol when writing or updating the SAP, paying particular attention to this when the Trial Master File is stored outside ECTU.

4.8.4 The SAP authors should review the data collection forms to ensure that the proposed analyses are feasible from the data collected, and if necessary, will update the SAP to reflect changes to the forms and protocol during the conduct of the trial.

5.0 RELEVANT DOCUMENTS AND REFERENCES

ECTU Central Office WPD ECTU_ST_W4: Additional Guidance on the Contents of a Statistical Analysis Plan (SAP) (on shared drive):
ECT Unit/SOPs/Finalised SOP and WPD/ST/WPD/Current PDF versions for use/

ST004 - SAP Template (on shared drive)
ECT Unit/SOPs/Finalised SOP and WPD/ST/Supporting Document and Templates/Current/

ACCORD SOP CR007 Study Documents, CR007 T-01 CTIMP Protocol Template (on ACCORD website)
http://www.accord.scot/research-access/resources-researchers/sop

ICH E9, Statistical principles for clinical trials, 1998 (CPMP/ICH/363/96)
https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials-scientific-guideline