STANDARD OPERATING PROCEDURE FOR THE PREPARATION AND PEER REVIEW OF SAMPLE SIZE CALCULATION FOR CLINICAL RESEARCH

SOP NUMBER:	TASC SOP056 v6
AUTHOR:	Petra Rauchhaus
EFFECTIVE DATE:	07 April 2025
REVIEW DATE:	07 April 2027

1. PURPOSE

This document describes the procedure to prepare, and peer review a sample size calculation for clinical research studies in compliance with the principles of Good Clinical Practice.

2. SCOPE

This Standard Operating Procedure (SOP) applies to Clinical Trials of Investigational Medicinal Products (CTIMP) and clinical research sponsored or co-sponsored by the University of Dundee or NHS Tayside.

The document applies to statisticians, Chief Investigators (CI), Principal Investigators (PI) and all staff who are involved in clinical research studies.

The document covers initial sample size calculations for grant applications and protocol development, simple interim analyses and designs where sample size may be re-calculated during the study. The document can also be used to cover simple adaptive designs, for example, multi-arm trials with a common control, where all comparisons are powered and analysed independently. Other more complex adaptive designs are not covered by this SOP.

3. RESPONSIBILITIES

The number of participants in a clinical study, the sample size, should always be large enough to provide a reliable answer to the hypothesis being tested. This number is usually determined by the primary objective of the study and hence primary outcome. The method by which the sample size is calculated should be given in the protocol, together with the estimates of any quantities used in the calculations (such as variances, mean values, response rates, event rates, difference to be detected). The evidence for these estimates should also be given. It is important to investigate the sensitivity of the sample size estimate to a variety of deviations from these assumptions and this may be facilitated by providing a range of sample sizes appropriate for a reasonable range of deviations from assumptions.

Sample size calculations should refer to the number of participants required for the primary analysis and hence primary outcome. Consideration should be given to potential dropout rates, with sample size being defined as either 'full analysis set' (all randomised participants), intention to treat or modified intention to treat or the “per protocol set” (evaluable participants).

4. PROCEDURE

4.1 Sample Size estimation for study planning

4.1.1 At the planning stage of the study, prior to writing a protocol, the researcher can prepare their own sample size calculations or seek advice from a statistician in the Tayside Clinical Trials Unit (TCTU), Dundee Epidemiology and Biostatistics Unit (DEBU), a departmental statistician or an external statistician.

4.1.2 The researcher should have the following study specific information:

- The study design (e.g., Cross-over study, two group comparison, non-equivalence study).
- The primary outcome variable.
- The null hypothesis.
- The alternative ('working') hypothesis of the difference to be detected or rejected i.e., the minimal clinically important difference and its variability.
- The probability of erroneously rejecting the null hypothesis (the type I error).
- The probability of erroneously failing to reject the null hypothesis (the type II error) or power.
- The approach to dealing with treatment withdrawals and protocol violations.
- The evidence for the estimation of the Minimal Clinically Important Difference (MCID) and variation in the primary outcome (e.g., prior study results, literature review).

4.1.3 Where a novel approach to sample size estimation is proposed, a justification should be given why this method should be preferred over more standard methods. The justification should be supported by literature references.

4.1.4 The researcher or statistician will provide written, signed sample size calculations based on the information provided. This should include investigating the sensitivity of the sample size estimate to a variety of deviations from these assumptions and so provide a range of sample sizes appropriate for a reasonable range of deviations.

4.1.5 The relevant study specific information should be shared with an independent statistician who should calculate the sample size from these same assumptions independently. Both sample sizes should be compared to ensure the results match and any discrepancies resolved, the second independent sample size calculation and the comparison be documented, signed and dated (Doc Ref 114). If the study goes ahead, this document should be filed in the Trial Master File (TMF). If the researcher is the statistician, and does not have access to an independent statistician, the

researcher should re-check their calculations and sign and date that this has been done. Doc Ref 114 template can also be used for this purpose.

4.1.6 The sample size calculation, as well as the sensitivity sample size calculations, should be discussed between the researcher and the statistician where appropriate, to ensure that the study application uses an appropriate sample size.

4.2 Sample Size estimation for protocol writing

The original sample size calculation must be re-checked by the researcher and statistician where appropriate, before inclusion in the study protocol to ensure that the initial assumptions are still valid.

4.3 End of Study

All paper and electronic documentation created by the researcher and independent statistician where appropriate, relating to the original and revised sample size calculation will be retained with the TMF.

5. ABBREVIATIONS & DEFINITIONS

CI	Chief Investigator
CTIMP	Clinical Trial of Investigational Medicinal Product
DEBU	Dundee Epidemiology and Biostatistics Unit
MCID	Minimal Clinically Important Difference
PI	Principal Investigator
SOP	Standard Operating Procedure
TASC	Tayside Medical Science Centre
TCTU	Tayside Clinical Trials Unit
TMF	Trial Master File

6. ASSOCIATED DOCUMENTS & REFERENCES

Doc Ref 114: Sample Size Calculation

DOCUMENT HISTORY

History prior to 2021 is in the archived SOPs available from TASC Quality Assurance Dept.

Version Number:	Reviewed By (Job Title):	Effective Date:	Details of editions made:
3	Tracy Petrie (Quality Assurance Support Officer)	01/02/2021	Uploaded to new TASC SOP template which shows the new TASC website in the footer. Physical scan converted to electronic pdf as a requirement for upload to new TASC website.
4	Petra Rauchhaus (Clinical Trials Statistician)	05/04/2021	Scheduled review date. No changes made.
5	Petra Rauchhaus (Clinical Trials Statistician)	05/04/2023	Added a paragraph in section 4.1 regarding the use of novel

			approaches to sample size estimation.
6	Petra Rauchhaus (Clinical Trials Statistician)	07/04/2025	Added a paragraph in section 2 to include interim analyses and simple adaptive designs to the scope of the SOP.

8. APPROVALS

Approved by	**Date**
Dr Valerie Godfrey, TASC Quality Assurance Manager, on behalf of TASC Clinical Research Guidelines Committee	04 Apr 2025