Clinical Epidemiology and Biostatistics Unit (CEBU)
STANDARD OPERATING PROCEDURE (SOP)

murdoch children's research institute **Version: 1.1**	**Title:** **Sample Size Estimation**

Murdoch Children's Research Institute

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Change History

20th October 2011: Initial version of guideline finalised – Version 1.0

16 April 2021: Initial version reviewed, cosmetic changes made – Version 1.1

Contents

1. PURPOSE

To describe the process to estimate the sample size required for a study.

2. APPLICABILITY

This procedure applies to all studies for which sample size estimation is performed by CEBU.

3. ROLES AND RESPONSIBILITIES

Statistician: responsible for the estimation of the sample size of a study.

Principal investigator (and/or the rest of the study team): helps the statistician by providing the clinical information required for the sample size calculation.

4. DEFINITIONS

nQuery Advisor: Power and Sample Size Calculation Software

ICH: International Conference on Harmonisation

CPMP: Committee for Proprietary Medicinal Products

5. INTRODUCTION

Sample size estimation activities for clinical trials should comply with the following:

- ICH E9 “Statistical principles for clinical trials”
- ICH E10 “The choice of control group in clinical trials”
- CPMP “Points to consider on the choice of non-inferiority margin”

6. PROCEDURE

6.1 Formal sample size

In order to carry out a sample size calculation the following information is required:

Study design: observational (cohort study, case-control study,...) or randomized controlled study (parallel groups, crossover,...), or single treatment group.

Sample size calculation type: hypothesis testing type or precision-based.

Main hypotheses to be tested /quantities to be estimated: superiority, equivalence, non inferiority if it is a comparison study; quantity to be estimated in case of a single group study

Number of groups and allocation/sample size ratio (for comparison studies)

Primary outcome variable: including variable type – continuous, proportion or time to event

On the basis of the research literature, previous studies and results provided by the Principal Investigator, the statistician needs to make assumptions, in conjunction with the research team, about the expected value of:

the primary outcome in the standard group (placebo or control group), the standard deviation of the primary outcome variable (continuous outcomes only), in an appropriate scale (usually the raw scale or log-transformed scale)

the expected dropout rate.

The statistician should establish statistical assumptions to perform the calculation, taking into account *ICH Statistical Guidelines*, *ICH Points to consider* and the study-specific phase of development. In particular:

Alpha level, as well as whether it will be a one-sided or two-sided test (for hypothesis testing studies), and if adjustments are to be applied for multiplicity (conventionally the overall alpha level is set at 5%, and a two-sided test is used)

If multiplicity is present, any adjustment to the Type I error rate should be specified. Multiplicity may arise, for example, from multiple primary variables, multiple comparisons of treatments, repeated evaluation over time and/or interim analyses.

Beta level or **statistical power** (hypothesis testing studies only; usually the beta level is set at 10% or 20%, equivalent to a statistical power of 90% or 80% respectively).

On the basis of the information above, the statistician applies the appropriate statistical formulas, usually by means of the nQuery Advisor program (latest available version) or Stata using the `sampsi` command.

If dropout is expected, the statistician should apply an adjustment to the number of patients according to the appropriate formula: $n^*=n / (1-\delta)$, where n^* is the adjusted sample size, n is the estimated size before adjustment and δ is the proportion of patients expected to drop out of the study before the collection of outcome data.

It is likely that there will be a range of sample sizes based on a range of assumptions used in the calculation. If this is the case, all scenarios should be presented and the findings should be discussed with the PI. The various calculations for the specific study should be documented using the "Sample Size Estimation Form".

Sample size calculation should be undertaken in conjunction with the PI and other members of the trial team where appropriate. The feasibility of the study should be discussed with the study team and if feasibility issues lead to constraints on the available sample size, the statistical limitations of the planned study should be made clear by the statistician.

Once the final estimated sample size is agreed upon, the statistician should write, or approve, the sample size section in the appropriate section of the study protocol, describing in detail all the statistical and clinical assumptions made to determine the sample size. Methods and estimates of any quantity used in the calculation should also be included, based on the information and literature provided by the PI, as well as details of where these estimates came from.

6.2 Informal sample size

In cases in which it is not possible to carry out a formal sample size calculation, for example pilot or exploratory studies, an informal justification of the sample size should be given (i.e. it may be estimated based on feasibility). However, the statistician should clearly explain the statistical limitations of the planned study.

The "Sample Size Estimation Form" should be used to provide justification for this informal sample size calculation discussed by the statistician and the PI, although a number of the fields on the form will be blank.

7. TIMING

Once the statistician receives the clinical information required for the sample size calculation from the PI, they can start the sample size estimation. Sample size calculation is an essential stage in the development of the study protocol and should be completed prior to study initiation. If no formal sample size calculation is carried out, the number of participants to be included in the study should be decided prior to the start of the study. In both cases the details of the sample size should be included in the final version of the study protocol.

8. REFERENCES

Sample Size Estimation Form

9. APPENDICES

N.A.