Clinical Epidemiology and Biostatistics Unit (CEBU)

STANDARD OPERATING PROCEDURE (SOP)

murdoch children's research institute **Version: 1.1**	**Title:** **Statistical Analysis Plan (SAP) for Interim Reports**

Murdoch Children's Research Institute

Prepared by: Katherine Lee and Francesca Orsini

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Authorised by: Katherine Lee

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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 for developing, reviewing and approving the Statistical Analysis Plan (SAP) for the interim report of a study.

2. APPLICABILITY

This procedure applies to all studies for which the SAP for the interim analysis is delegated to CEBU.

3. ROLES AND RESPONSIBILITIES

Statistician: responsible for the development of a detailed document regarding the methods of statistical data analysis proposed for the study.

Review team: responsible for the approval of the SAP. This should include the principal investigator, the staff involved in the study conduct and the Sponsor's reference person (in the case of commercially sponsored studies).

4. DEFINITIONS

Unblinding: when a member of the study team requests to know the treatment allocation of one more participant in the study.

5. INTRODUCTION

The SAP for an interim analysis is a document that contains a technical and detailed description of the interim analysis planned in the protocol, and includes detailed procedures for executing the statistical analysis of the data for the interim analysis. Number, methods and consequences of interim analyses should be carefully planned in advance and described in the protocol. This document should elaborate on the protocol providing details of exactly what should be presented in the interim report and details of statistical analysis (where relevant). Special circumstances may dictate the need for an interim analysis (for example at the request of the data monitoring committee, DMC) that was not defined at the start of a trial. In this case, a protocol amendment describing the additional interim analysis should be completed.

There are two distinct types of interim analysis:

- The first type of monitoring concerns the oversight of the quality of the study. For the purpose of overseeing the quality of the study the interim report may include details of whether the protocol is being followed, the acceptability of data being accrued, the success of planned accrual targets, the appropriateness of the design assumptions, success in keeping patients in the trial, etc. This type of monitoring does not require access to information on comparative treatment effects, nor unblinding of data and therefore has no impact on the Type I error of the final study results.
- The second form of interim report is to assess safety of a study. Such monitoring involves breaking the blind to enable the committee to make treatment comparisons. Interim analysis requires unblinded access to treatment group assignment and comparative treatment group summary information. In some cases this may involve safety data only so that the committee can make a judgement about whether there are more harmful effects in one arm of the study than the other. In other cases the committee may wish to

look at outcome data and in particular the primary outcome. If the primary outcome is to be compared between the treatment groups this necessitates that the protocol contains statistical plans for the interim analysis to maintain the Type I error probability of the study.

When an interim analysis is planned with the intention of deciding whether or not to terminate a trial, this is usually accomplished by the use of a group sequential design. The goal of such an interim analysis is to stop the trial early if the superiority of the group under study is clearly established, if the demonstration of a relevant group difference has become unlikely, or if unacceptable adverse effects are apparent in one or more arms of the study.

Any interim analysis that is not planned appropriately (with or without the consequences of stopping the trial early) may flaw the results of a trial and possibly weaken confidence in the conclusions drawn at the end of the study. Therefore, such analyses should be avoided. If unplanned interim analysis is conducted, the clinical study report (if required) should explain why it was necessary, the degree to which blindness had to be broken, provide an assessment of the potential magnitude of bias introduced, and the impact on the interpretation of the results.

Guidance is provided in ICH E9 "Statistical Principles for clinical trials" and ICH Point to consider documents. The contents of the SAP should clarify all the items relevant for the analysis and interpretation of interim data, in particular including details of the statistical method required.

6. PROCEDURE

FLOW CHART OF ACTIVITIES

In due time according to timelines foreseen for the interim analysis, the statistician starts developing the SAP on the basis of the appropriate template.

The SAP for the interim analysis should contain:

- The considerations which will govern the interim analysis
- The interim analysis objectives
- A detailed description of the variables involved in the interim analysis
- Details of early stopping rules (where required).

(for details see *General Principles* section)

The statistician sends the first version of the SAP to the review team. The review team reviews the first version of the SAP documentation and returns any comment to the statistician for clarification. The statistician addresses the review comments and discusses any conflicting and outstanding issues with the SAP review team. Once the review comments have been incorporated and all the outstanding issues have been addressed, forwards the SAP documentation to the review team for approval (approval via e-mail is acceptable).

The PI should keep a copy of the SAP for the interim analysis with the rest of the study documents, ideally an electronic copy in a dedicated file within the study directory.

GENERAL PRINCIPLES

Early stopping rules

If the interim analysis intends to compare treatment arms with respect to efficacy or safety at any time prior to formal completion of a study it should be carefully planned in advance and described in the SAP. In

particular, if the analysis intends to make official comparisons between treatment groups with the aim of looking for treatment differences in the outcome measures, details should include the number of times the data will be compared, the method used for comparison and details of any stopping rules which should be applied where necessary. When an interim analysis is planned with the intention of deciding whether or not to terminate a trial, boundaries for monitoring efficacy require more evidence to terminate a trial early (i.e. they are more conservative) than boundaries for monitoring safety. In either case it is important to specify the boundary which should be adopted, noting that the boundary should be used as a guideline rather than a rule. When the trial design and monitoring objective involve multiple endpoints then this aspect of multiplicity may also need to be taken into account. The SAP should describe the schedule of interim analyses and the early stopping rules.

Unblinding issues

All staff involved in the conduct of the trial should remain blind to the results of such analyses, because of the possibility that their attitudes to the trial will be modified and cause changes in the characteristics of patients to be recruited or biases in treatment comparisons. This principle may be applied to all investigator staff except for those who are directly involved in the execution of the interim analysis. Investigators should only be informed about the recommendation to continue or to discontinue the trial, or to implement modifications to trial procedures as required. In some cases the DMC may wish the trial statistician to remain blinded as well, in which case they may need to get an independent statistician to generate the report or else report the results by treatment groups A and B with an independent person (often the person who generated the randomisations) telling them what A and B represent.

7. TIMING

The SAP for an interim analysis must be developed after the protocol has been finalised and before any database lock. It must be approved before the interim analysis itself is undertaken.

8. REFERENCES

SAP Template interim analysis

9. APPENDICES

N.A.