Australian Clinical Trials Alliance

ACTA STInG Statistical Analysis Plan Template

June 2020

ACTA gratefully acknowledges operational funding from the Australian Government's Medical Research Future Fund

PURPOSE OF DOCUMENT

This document provides a template for statistical analysis plans and will enable the user to develop a detailed and structured plan pre-specifying the analysis of a clinical trial.

ROLE OF ACTA IN DEVELOPING STATISTICAL ANALYSIS PLAN

ACTA supports the Statisticians Interest Group (STInG) to promote professional standards of statistics in trials and where possible harmonise the practice of statistics in clinical trials settings within Australia. The generic advice provided by ACTA STInG should be considered while taking into account the specific individual circumstances and needs of the particular trial.

ACKNOWLEDGEMENTS

We acknowledge the contributions of ACTA members and members of ACTA's Statisticians Interest Group and Innovative Trial Design Reference Group in the preparation, development and review of this document. In particular, we would like to acknowledge the contribution by A/Prof Laurent Billot in the development of this template.

DISCLAIMER

The information in this document is for general guidance only. ACTA does not make any representations or warranties (expressed or implied) as to the accuracy, currency or authenticity of the information provided.

INSTRUCTIONS

The template includes instructions in red font (for example: "Instructions: "Some studies may have multiple authors included on the analysis plan; however, only those who substantially contributed to the plan should be considered for formal approval. These would typically include the principal investigator, the study statistician and the project manager") which are meant to be deleted before finalising the analysis plan. Text included between inequality signs (for example: <text>) is meant to be replaced with relevant information.

DOCUMENT HISTORY

Version	Date	Changes made to document	Authors
1.0	7 July 2020	First version	A/Prof Laurent Billot, with input from ACTA Innovative Trial Design Reference Group Leadership

<Study logo>

<STUDY NAME>

Statistical Analysis Plan

<version>

<date>

Authors:

Instructions: List authors and their affiliations, consider including ORCID identifiers.

<Author 1>

<Author 2>

<Author 3>

<Author 4>

<etc.>

Study identifiers:

Instructions: Include relevant identifiers

<NHMRC Application ID: APPxxxxx>

<ANZCTR: include ID with hyperlink>

STATISTICS IN TRIALS INTEREST GROUP

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Instructions: include list and definition of abbreviations used throughout the analysis plan.

1 ADMINISTRATIVE INFORMATION

1.1 STUDY IDENTIFIERS

Instructions: include relevant study identifiers such as the details of the protocol version used as reference as well as registration details (e.g. ANZCTR registry, WHO UTN or ClinicalTrials.gov). Please also include the funding details (e.g. NHMRC application number). Please add/delete bullet points below as needed.

- Protocol: <number>, <version>, <date>
- World Health Organization Universal Trial Number: <identifier>.
- ClinicalTrials.gov register Identifier: <identifier>.

1.2 REVISION HISTORY

Version	Date	Changes made to document	Authors
1.0 (draft)			

1.3 CONTRIBUTORS TO THE STATISTICAL ANALYSIS PLAN

1.3.1 ROLES AND RESPONSIBILITIES

Name and ORCID	Affiliation	Role on study	SAP contribution

1.3.2 APPROVALS

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and, in particular, confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention(s) being assessed).

<author name>

<signature> <date>

<author name>

<signature> <date>

<author name>

<signature> <date>

Instructions: Some studies may have multiple authors included on the analysis plan; however, only those who substantially contributed to the plan should be considered for formal approval. These would typically include the principal investigator, the study statistician and the project manager.

2 STUDY SYNOPSIS

Instructions: Start with one paragraph summarising the study using the PICO (population, intervention, control, outcome) framework and outlining the design of the study (e.g. the XXX Study is a parallel two-arm randomised control trial looking at the effect of XXXX vs XXXX in patients with XXXX). Consider including a diagram of the study design.

2.1 STUDY OBJECTIVES

2.1.1 PRIMARY OBJECTIVE

Instructions: Clearly state the primary objective including the statistical hypothesis being tested.

2.1.2 SECONDARY OBJECTIVES

Instructions: If relevant, include secondary objectives together with the associated statistical hypotheses.

2.2 PATIENT POPULATION

2.2.1 INCLUSION CRITERIA

- <criterion>
- <criterion>
- <criterion>
- <criterion>
- <criterion>
- <criterion>

2.2.2 EXCLUSION CRITERIA

- <criterion>
- <criterion>
- <criterion>
- <criterion>
- <criterion>
- <criterion>

2.3 OUTCOMES

Instructions: list all pre-specified outcomes using a clear hierarchy for the primary and secondary outcomes, including detailed definitions. Details of the timepoints that the outcome is measured should also be included. Make sure there is consistency with the protocol or document departures from the protocol in Section 3.1.

2.3.1 PRIMARY OUTCOME

- <outcome>

2.3.2 SECONDARY OUTCOMES

- <outcome>
- <outcome>
- <outcome>
- <outcome>
- <outcome>
- <outcome>

2.3.3 SAFETY OUTCOMES

- <outcome>
- <outcome>
- <outcome>

2.3.4 <TERTIARY/EXPLORATORY> OUTCOMES

- <outcome>
- <outcome>
- <outcome>

2.4 INTERVENTION

Instructions: describe the details of each intervention being assessed including any potential control/treatment as usual arm.

2.5 RANDOMISATION AND BLINDING

Instructions: Describe randomisation and blinding procedure including stratification variables, balancing method as well as details of who has been unblinded during the trial conduct.

2.6 SAMPLE SIZE

Instructions: Describe the sample size/power calculations with enough details to allow an independent person to reproduce the calculation.

3 STATISTICAL ANALYSIS

3.1 GENERAL PRINCIPLES

Instructions: Use this section to provide general information about the analysis plan. This includes, but is not limited to, the following items:

- Summary of changes compared to the protocol or public registries
- Scope of this analysis plan (e.g. if only applicable to some of the data collected)
- Detail of statistical software that will be used for the analyses.
- Reporting conventions
- Data cleaning approach
- Data definitions/derivations including, but not limited to, visit windows definitions
- Method for validating the results (e.g. double-programming).

This section can be broken down into subheadings as appropriate.

3.2 INTERIM ANALYSES

Instructions: Describe any interim analyses (to be) conducted including stopping rules and their impact on the final type-I error rate if applicable.

3.3 MULTIPLICITY ADJUSTMENT

Instructions: Describe strategy for handling multiplicity of testing and control the final type-I error rate.

3.4 BLIND REVIEW

Instructions: If a blind review was conducted or is being planned, consider including details and relevant findings and/or what analyses are conditioned by the results of a future blind review.

3.5 DATA SETS TO BE ANALYSED

Instructions: Clearly define analysis population(s), (e.g. intention to treat, per-protocol, safety and to which analyses each population will apply). If planning per-protocol analyses, it is important to include details about what compliance level and/or protocol deviations will be used to define the per-protocol population.

3.6 SUBJECT DISPOSITION

Instructions: explain how the status of subjects will be reported. This should at least include a CONSORT flowchart. Where relevant, consider including a separate flowchart/plot describing withdrawals and losses to follow-up in details.

3.7 PATIENT CHARACTERISTICS AND BASELINE COMPARISONS

Instructions: explain how baseline characteristics will be summarised. Consider including a list of all relevant variables and their definitions.

3.8 COMPLIANCE TO STUDY INTERVENTION(S)

Instructions: include a list of variables that will be used to define compliance together with their exact definition and the way they will be analysed and compared across randomised arms. Variables can include, but are not limited to, time between randomisation and start of the intervention, cumulative exposure to the intervention (dose or duration), average individual compliance, and reasons for lack of compliance.

3.9 CONCOMITANT THERAPIES

Instructions: Explain how concomitant interventions will be summarised and compared across randomised arms.

3.10 ANALYSIS OF THE PRIMARY OUTCOME

Instructions: Consider starting with a paragraph outlining the general principles governing the analysis of the primary outcome.

3.10.1 MAIN ANALYSIS

Instructions: include all the details about the primary analysis including the exact definition of the primary endpoint, the statistical test or model to be used, the statistical assumptions being made by the test/model in question, the estimand of interest, any covariate adjustments, handling of correlations within the data (i.e. in a longitudinal or clustered design), handling of missing data, etc. Consider including tests that will be used to assess the validity of underlying assumptions (e.g. proportional hazard assumptions). Variations from this main analysis such as different ways of handling missing data or adjusting for covariates can be described in the following sections.

3.10.2 ADJUSTED ANALYSES

Instructions: Include details of any additional adjusted analyses that will be conducted if relevant. The list and definition of all variables to be adjusted for should be included together with any variable selection method to be used. Given adjusted analyses can potentially apply to other outcomes, an alternative option is to include a section about adjusted analyses higher up in the SAP.

3.10.3 SUBGROUP ANALYSES

Instructions: Include a list of pre-specified subgroups and how the categories will be defined where relevant (e.g. three age categories: <40, 40-<60, 60+). Also explain how the effect of the subgroup variable will be estimated (e.g. by adding an interaction term to the main model). Given adjusted analyses can potentially apply to other outcomes, an alternative option is to include a section about adjusted analyses higher up in the SAP.

3.10.4 TREATMENT OF MISSING DATA

Instructions: Include rules that will determine how the missing data will be handled (e.g. If more than 5% of patients from the intention to treat population are missing the primary outcome). This should include details of what kind of imputation will be performed if relevant. If using multiple imputation, details should also be provided on which variables will be included in the imputation model and how many sets of imputed data will be created. Given adjusted analyses can potentially apply to other outcomes, an alternative option is to include a section about adjusted analyses higher up in the SAP.

3.10.5 OTHER SENSITIVITY ANALYSES

Instructions: Describe any pre-planned additional sensitivity analyses of the primary outcome. For example, these could include additional covariate adjustments, causal or mediation analyses, additional methods for handling missing data (e.g. best/worst case imputations, tipping point analyses), using a different censoring method, using a generalized linear model instead of a random effect model, etc. Please note that this is not an exhaustive list.

3.11 ANALYSIS OF SECONDARY OUTCOMES

Instructions: For each secondary outcome or type of secondary outcomes (e.g. all survival secondary outcomes), include a section describing the planned analyses. This should include details about any potential adjustments, subgroup analyses, treatment of missing data and any sensitivity analyses planned.

3.11.1 <SECONDARY OUTCOME 1>

<add details here>

3.11.2 <SECONDARY OUTCOME 2>

<add details here>

3.11.3 <SECONDARY OUTCOME 3>

<add details here>

3.12 ANALYSIS OF SAFETY OUTCOMES

Instructions: This section should provide details about how the safety data from the study will be analysed, including the summaries to be presented and details of any formal comparisons between intervention groups to be made.

3.12.1 ADVERSE EVENTS

<add details here>

3.12.2 LABORATORY DATA AND VITAL SIGNS

<add details here>

3.13 ANALYSIS OF <OTHER/TERTIARY/EXPLORATORY> OUTCOMES

Instructions: This section should provide details about how other outcomes such as tertiary or exploratory outcomes, if present, will be analysed. As for other outcomes, it should include details about any potential adjustments, subgroup analyses, treatment of missing data and any sensitivity analyses planned.

4 REFERENCES

Instructions: include reference to the published protocol if available as well as for non-standard statistical methods.

1. <reference 1>
2. <reference 2>
3. Etc.

APPENDIX 1: PROPOSED TABLES AND FIGURES

Instructions: It can be very useful to include dummy tables to provide a clear guide for how the results will be presented. Below is a list of common tables, figures and listings typically produced in a randomised clinical trial; however, they are neither exhaustive nor applicable to every trial. When designing dummy tables, a good principle is to be as specific as possible to remove possible interpretation errors. Ways to do so include adding footnotes to the tables, direct clarifying notes to the programmer/statistician who will be responsible for the analysis as well as providing statistical code.

For examples of dummy tables, please refer to the library located on the ACTA STInG webpage.

Figure 1: Consort flowchart
Table 1: Baseline characteristics
Table 2: Baseline medical history
Table 3: Compliance to intervention
Table 4: Reasons for discontinuing intervention
Table 5: Protocol deviations
Table 6: Concomitant therapies
Table 7: Physiological and laboratory values during the study period
Figure 2: Longitudinal mean plot of <variable>
Table 8: Analysis of primary outcome
Figure 3: Forest plot for subgroup analysis of primary outcome
Figure 4: Kaplan-Meier plot of time to <endpoint>
Table 9: Continuous and binary secondary outcomes
Table 10: Adverse events
Listing 1: Protocol deviations
Listing 2: Adverse drug reactions

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