Statistical Analysis Plan

This template is a general guideline to develop a statistical analysis plan (SAP) in the context of a randomised controlled trial (RCT). Not all aspects of this template will be used in a single RCT, therefore, the selection of suitable sections will be decided by the trial statistician and the trial leader. For more information, see the paper "Guidelines for the Content of Statistical Analysis Plans in Clinical Trials" by Carrol Gamble, Ashma Krishan, Deborah Stocken et al (JAMA. 2017;318(23):2337-2343). https://jamanetwork.com/journals/jama/fullarticle/2666509

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1 Trial Identifications

Refer to CCTU SOP023 Statistical Analysis Plan for the key requirements of a statistical analysis plan (SAP). The key document for regulatory requirements is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines E9-Statistical Principles for Clinical Trials. Depending on the study, some sections may be not applicable in which case they may be deleted. Example text is provided in *italics.*

TRIAL FULL TITLE	
EUDRACT NUMBER[1]	
SAP VERSION	
ISRCTN NUMBER[2]	

SAP VERSION DATE	
TRIAL STATISTICIAN	
TRIAL CHIEF INVESTIGATOR	
SAP AUTHOR	

Delete this section before circulating any draft or final version of a SAP.

[1]https://eudract.ema.europa.eu/

[2]http://www.isrctn.com/

2 Abbreviations and Definitions

List all abbreviations and acronyms alphabetically. Spell all abbreviated terms in the main text at first appearance and give abbreviation in parenthesis.

AE	*Adverse Event*
CRF	*Case Report Form*
IMP	*Investigational Medical Product*
SAP	*Statistical Analysis Plan*

3 Introduction

3.1 Preface

Include a brief summary of background information copied directly from the protocol. Do not be re-write it.

3.2 Purpose of the analyses

For example:

These analyses will assess the efficacy and safety of [IMP] in comparison with the [standard] and will be included in the clinical study report.

4 Study Objectives and Endpoints

4.1 Study Objectives

(ICH E3; 8.)

Describe the overall purpose of the study. Additional elaboration may be helpful.

4.2 Endpoints

(ICH E9; 2.2.2)

List separately the primary, secondary and exploratory endpoints.

4.3 Derived variables

Endpoints that are derived variables, i.e. not in case report form (CRF), should be clearly defined, for example: a binary variable indicating if another variable has increased from baseline.

5 Study Methods

5.1 General Study Design and Plan

(ICH E3;9)

- Experimental design (x-period cross-over, longitudinal, 2x2 factorial, observational, cohort, other)
- Type of control(s) (placebo, no treatment, active drug, different dose or administration, historical)
- Blinding (unblinded, single-blinded, double-blind, other)
- Randomisation with/without stratification or minimisation
- Randomisation timing relative to treatments, events and study periods
- Study periods (screening, baseline, active treatment, follow-up)

A flow-chart may represent the last two points.

5.2 Equivalence or Non-Inferiority Studies

(ICH E3; 9.2, 9.7.1, 11.4.2.7. ICH E9; 3.3.2)

- In non-inferiority studies, the null hypothesis is the new treatment is worse but acceptably similar to the standard treatment (acceptable means it provides other benefits, e.g. safety, toxicity, cost).

- In equivalence studies, treatment differences must lie within predefined equivalence bounds (small ± differences).
- In non-inferiority studies, the difference between new and old treaments must be positive, or the ratio>1 (non-inferiority bound).

The equivalence or non-inferiority bound(s) must be pre-specified.

Regulatory bodies may provide advice on the choice of bound(s).

If previous studies resulted in licensing approvals, their bounds can be used as guidelines.

Otherwise, bounds can be chosen to reflect differences between current treatments.

5.3 Inclusion-Exclusion Criteria and General Study Population

(ICH E3;9.3. ICH E9;2.2.1)

The SAP may include:

- list of all inclusion/exclusion criteria copied from the protocol, or
- description of diagnostic or disease related criteria (e.g. *a history of chronic back pain for over 10 years*)

It is distinct from the Analysis Population (section 7.2). There, the aim is identifying sub-populations for analysis purposes.

5.4 Randomisation and Blinding

(ICH E3; 9.4.3, 9.4.6. ICH E9; 2.3.1, 2.3.2)

Describe details of randomisation and blinding to enable reproduction.

Include any minimisation, stratification or blocking used to avoid or minimise bias.

Document any software packages used to perform the randomisation.

Exception: in a double-blind study, details may be given only in the final report and not the SAP.

5.5 Study Variables

(ICH E3; 9.5.1. ICH E9; 2.2.2)

Describe the frequency and timing of all the relevant variable observations or assessments. A table or flow chart may be appropriate for example

	Baseline	Day 1 of every 3 week treatment cycle	Every 9 weeks on treatment	At 18 weeks or on stopping chemotherapy	Follow-up visits at 6 and 12 weeks post treatment, then at least every 12 weeks
History and examination	x	x		x	x
Weight	x	x		x	x
Vital signs	x			x	x
Haematology	x	x		x	x
Biochemistry	x	x		x	x
Urinary pregnancy test	x				
Tumour response	x		x	x	x (and every 12 weeks until progression)
Blood samples for predictive markers[$]	x		x (week 9 only)		
Concomitant medication	x	x		x	x
Administer chemotherapy		x			
QOL	x		x	x	x (12 weeks

questionnaire					only)
Adverse event monitoring		x		x	x

Define time-windows to convert dates into visit numbers, e.g. *assessments collected 26-30 days post-randomisation are identified as the 4-week visit*.

Which rules will classify measurements outside scheduled assessment times?

Further description of important variables:

- Ranges of numeric endpoints and their corresponding text descriptors, e.g.:
  - *Visual analogue scale (VAS) measured as 0-100 (0=no pain, 100=worst pain)*
  - *1-4 ordered categorical scale (1=no pain, 2= slight pain, 3=moderate pain, 4=extreme pain)*
- *Additional methods (e.g. carrying forward values into missing observations, transformation of values, combining multiple variables into a single value such as EQ-5D Quality of Life questionnaire)*

Create subsections for numerous variables as in the protocol (e.g. efficacy, safety) and sections 8-12 of this document.

6 Sample Size

(ICH E3; 9.7.2. ICH E9; 3.5)

Copy from protocol

Amendments should be explained here

Use section 10.1 to explain how to adjust the primary analysis for sample size if required.

Name software or libraries used in calculating sample size

7 General Considerations

7.1 Timing of Analyses

When, or under what criteria, the final analyses will be performed.

Data cleaning and locking processes to comply with SOP, e.g.:

- *The final analysis will be performed after XXX progressions have been observed*
- *The final analysis will be performed when XXX subjects have completed visit Y or dropped out prior to visit Y.*
- *The final analysis will be performed on data transferred to the file XXX, having been documented as meeting the cleaning and approval requirements of SOPZZZ and after the finalisation and approval of this SAP document.*

7.2 Analysis Populations

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 5.2)

Identify sub-populations with a formal title (e.g. Full Analysis, Per Protocol, Safety)

Describe inclusion criteria.

N.B. "intention to treat" refers to how subjects are assigned to a treatment group for the purposes of analysis (i.e. the treatment they are randomised to but not necessarily the one received); it can be used within *any* analysis population and thus is not a suitable description for a population itself.

Examples:

7.2.1 Full Analysis Population

- *All subjects who received any study drug*
- *All subjects who received any study drug and who participated in at least one post-baseline assessment*
- *All subjects who were randomised*

7.2.2 Per Protocol Population

- *All subjects who adhere to the major criteria in the protocol (e.g. all subjects who completed at least two efficacy analyses, whose study drug compliance was between 75% and 125% and who did not take any rescue medication)*

- *All subjects who did not substantially deviate from the protocol as to be determined on a per-subject basis at the trial steering committee immediately before data base lock.*

7.2.3 Safety Population

- *All subjects who received any study treatment (including control) but excluding subjects who drop out prior to receiving any treatment.*
- *All subjects who received any study treatment (including control) and are confirmed as providing complete follow-up regarding adverse event information.*

Discuss each of the following

- Specification of the primary efficacy population
- Specification of the population to be used for each type of data (e.g. background, safety, efficacy, health-economic).

If the primary analysis is based on a reduced subset of the subjects with data (e.g. subjects who complete the active phase of the study) and if the trial is intended to establish efficacy, there should be additional analyses that use all the randomised subjects with any on-treatment data.

Assign each subject's inclusion/exclusion status with regard to each analysis population prior to breaking the blind.

The exact process for assigning the statuses will be defined and documented prior to breaking the blind along with any predefined reasons for eliminating a subject from a particular population.

7.3 Covariates and Subgroups

(ICH E3; 9.7.1, 11.4.2.1. ICH E9; 5.7)

- Identify covariates (continuous or categorical, including subgroups) expected to affect specific endpoints, e.g. demographics or baseline, concomitant therapy, etc.

- Document any model selection procedures, e.g. forward stepwise selection, manual likelihood ratio tests, etc.

- Stratification/minimisation variables should be included in the primary analysis; otherwise specify why not, e.g. *omitted because it introduced too many categories*.
- List important demographic or baseline variables to be included in the main analyses, e.g. age, gender, ethnic group, prognosis, prior treatment, etc. It need not be exhaustive.
- Recommended: note any *a priori* hypothesis of subgroup differences.
- Recommended: note any potential exploratory analysis.
- Subgroup analyses should focus on detecting interactions. N.B. It is flawed to present an analysis that provides two p-values, one for each of the two subgroups, and then report that only one subgroup showed a statistically significant difference.
- Where applicable, discuss the impact of the sample size on the power of subgroup analyses or reference section 6 if discussed there.

7.4 Missing Data

(ICH E3; 9.7.1, 11.4.2.2. ICH E9;5.3. EMA Guideline on Missing Data in Confirmatory Clinical Trials)

- Missing data will be quantified per variable (%).
- Describe missing data patterns, e.g. permanent, transient, monotonous, etc.
- Suggests methods to handle missing data, e.g. multiple imputation methods such as chained equations, random effects models or complete case analyses. Discuss possible biases of chosen method and underlying assumptions, e.g. Missing At Random.
- Variable-specific information for imputing missing data, where appropriate, will be documented in section 5.5; analytical methods may be further detailed in section 8.

7.5 Interim Analyses and Data Monitoring

(ICH E3; 9.7.1, 11.4.2.3. ICH E9; 4.1, FDA Feb 2010 "Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics")

7.5.1 Purpose of Interim Analyses

- Typical reasons for using interim analyses are:
    - uncertainty about some aspect(s) of the treatment(s) (safety, termination for futility of efficacy) and,
    - help to re-design the study at Data Monitoring Committees, e.g. changing doses, endpoints, treatment arms, randomisation weighting and/or subgroup enrichment.

7.5.2 Planned Schedule of Interim Analyses

- Identify timing of interim analyses.
- What scope of decisions will be taken at future interim analyses.

N.B. Technically, details of the interim analysis beyond the next interim can be left open to be decided sequentially at each interim, under the proviso that rules for the analysis to combine the future data at each stage are defined and the scope for adaptations is not enlarged. However, it is recommended to plan as much as possible in advance and give a full predicted schedule of all interim analyses.

7.5.3 Scope of Adaptations

- Broadly describe which aspects of the trial may be revised at an interim analysis.
- Document any formal rules governing these adaptations.
- What analyses, summaries or figures will be used to inform the choice of adaptations?

7.5.4 Stopping Rules

- Document any formal stopping rules for futility, efficacy or lack of power.
- If possible, the probability of each possible eventuality under the null and alternative hypothesis should be documented, e.g. the probability of stopping for futility or efficacy, or continuing to the next stage.

7.5.5 Analysis Methods to Minimise Bias

Beware of biases if a general "naïve" analysis pooling all data at the end, e.g. as in a fixed design.

Examples of biases:

- In group sequential designs, the estimate of treatment effects will be biased away from the stopping region
- For sample sizes that are revised to reflect the estimated treatment effect at the first interim, the naïve pooled estimate will be biased away from the null.
- Whenever possible, any known bias must be discussed, and methods proposed to correct them must be documented.
- To prevent conflicting conclusions, the primary analysis should be chosen in advance.

7.5.6 Adjustment of Confidence Intervals and p-values

- In interim analyses, stopping early for efficacy rules will adjust for multiple testing so that the actual overall significance level is equal to the nominal chosen before the trial, e.g. Pocock (1982) or O'Brien and Flemming (1979) are seminal works in sequential testing that could be implemented.

- In interim analyses, stopping early for futility preserves the overall significance level, so nominal confidence interval and p-value at the end of the trial can be used. If substantial trial adjustments are envisaged, it is recommended to revisit power calculations.

7.5.7 Interim Analysis for Sample Size Adjustment

- Specify rules for adjusting samples sizes in interim analyses, e.g. conditional power calculations.
- Different weights can be given to different waves of data collection. If so, the final analysis must specify how these weightings will be used, see section 7.5.5.

7.5.8 Practical Measures to Minimise Bias

- Uncontrolled reporting of interim analyses to investigators could lead to bias, e.g. they may stop recruiting.
- The final analyses could be biased by knowledge of interim results by the analyst.
- Inappropriately revealing interim results could induce the "Hawthorne effect".
- Any level of unblinding, either of individual subjects or of treatment estimates, could induce biases.
- Therefore, it is important to establish and control who will have access to what information at each stage of the trial.
- The following should be explicitly documented:
    - who will perform any interim analysis?
    - who will see any data or analyses at the interim and make decisions?
    - what information will be publically available following an interim analysis?
    - what information will be provide to the sponsor and investigators?
    - who will be unblinded at any point in the trial?
    - who will perform any final analyses and remain blinded?
    - Will any safety monitoring decision remain isolated from efficacy information?

7.5.9 Documentation of Interim Analyses

- Snapshots of the data available at each interim analysis should be preserved, as should all documentation of analysis plans, programming code and reporting provided at each interim. It should be possible to recreate the decision process from the trial archive.
- Record what documents will be created and stored thus.

7.6 Multi-centre Studies

(ICH E3;9.7.1, 11.4.2.4. ICH E9; 3.2)

It can be copied from the protocol.

Where a multi-centre study is intended to be analysed as a whole, describe the following:

- Procedures to combine individual centre results into more usable pseudo-centres with greater numbers of subjects
- Rationale for the combining of centres and the decision rule for whether or not the grouping will be necessary
- Methods to test for qualitative or quantitative treatment-by-centre interactions
- Analyses of treatment comparisons that will allow for centre differences with respect to response
- Centre effects should be considered exploratory in analyses of studies that have not been explicitly designed with enough power to detect centre effects.
- Some thought should be put into whether centres may have fixed or random effects.

The general discussion about the analysis of subgroups in section 7.3 is applicable to centre effects.

7.7 Multiple Testing

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 2.2.5)

- It can be copied from the protocol.
- If multiple testing is required, the nominal significance level should be preserved. Common statistical techniques are Bonferroni's correction or false positive discovery rate (FDR).

N.B. In a confirmatory trial, there is usually one primary outcome. However, if multiple primary outcomes exist, they should either be deterministically combined or significance level maintained through Bonferroni or FDR or other methods. If the trial is focused on hypotheses generation, the preservation of the overall significance level is of lesser importance. However, it is recommended to reflect this in a statistical discussion, and present confidence intervals rather than p-values.

Identical issues arise if there are:

- more than two treatment groups,
- subset analyses,
- multiple time points,
- multiple methods of analysis,
- sensitivity analyses for missing data.

8 Summary of Study Data

The following are broad guidelines. Alternative summaries may be required in specific situations.

Specify:

- How data will be ordered
- How summary tables will be structured (e.g. columns for each treatment and overall in the order: Placebo, Experimental Low Dose, Experimental High Dose, All Subjects.)
- Descriptive or summary statistics that will be displayed for continuous data and for categorical data.
- The analysis populations upon which the tables and figures will be based.

Example:

> *All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment in the order (Control, Experimental) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.*

Only deviations from the general overview will be noted in the subsequent sub-sections within section 8. However, all variables to be summarised need to be documented below.

8.1 Subject Disposition

- Specify which variables from the CRF will be used to establish how many subjects reached the various stages of the trial, how many dropped out and for what reasons (death, toxicity, treatment failure, withdrew consent). For example *the number screened, randomised, reached visit 1, study close, follow-up visits …*
- An overview of the time-dependent rates of recruitment should be provided.
- Establish how to resolve ambiguities from multiple sources of visit date, e.g. decide which will be the most trusted source.
- This section should determine how the population membership and population size for each treatment (to be used in most table headers) will be determined.
- A skeleton CONSORT diagram should be provided in this section that provides an explicit statement of what statistics are to be provided.
- If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

8.2 Protocol Deviations

- Define the specific protocol deviations that could impact the analysis (e.g. major deviations and a definition of a major deviation) and specify the methods used to describe and analyse them. Clearly define which deviations will exclude a subject from each of the analysis populations defined in section 7.2.
- If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

8.3 Demographic and Baseline Variables

- Identify all demographic or baseline variables, i.e. those recorded at, or shortly before, randomisation or first treatment administration.
- Define any transformation required, e.g. log transformation of right-skewed variables.

- It may be appropriate to summarise these data by centre.
- If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

8.4 Concurrent Illnesses and Medical Conditions

- Include which coding system, if any, was used, e.g. MedDRA, WHO drug dictionary.
- If appropriate, use standard text: 'The summary statistics will be produced in accordance with section 8.'

8.5 Prior and Concurrent Medications

- Distinguish between prior and concurrent medication.
- Include a description of which, if any, coding system was used (e.g. MedDRA, WHO drug dictionary).
- If appropriate, use standard text: 'The summary statistics will be produced in accordance with section 8.'

8.6 Treatment Compliance

Examples of the assessment of treatment compliance include: remaining pill count, diary records of medication. Any method for calculating a measure of treatment compliance should be defined clearly here. The variables used to assess treatment compliance should be identified.

If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

9 Efficacy Analyses

These are broad guidelines that should be applicable to most variables. In some cases, it may be more appropriate to clarify items that do not conform to the general methods in individual sections below. All the variables being considered should be mentioned explicitly in the subsections below even if they are mentioned in this section.

- Specify the method of summarising and formally analysing the efficacy data.
- Clarify if any item needs to be handled differently from the norm.
- The following should be specified in this section:
    - Sort order of the data listings.
    - Grouping of summary table information, e.g. by treatment group and in what order, possibly adding a combined "all subjects" column.
    - Summary statistics that will be produced for continuous and categorical data.
    - Analysis populations that will be used and identification of the primary population.
- Include the following details as required. Place them either in section **Error! Reference source not found.**, if broadly applicable across most analyses, or in the relevant subsections below:
    - The statistical model underlying the analysis including, strata, covariates, baseline values and interaction terms.
    - A statement of the clinical objective rephrased in precise statistical terms (null and alternative hypotheses).
    - The nature of the hypothesis: descriptive, exploratory or confirmatory.
    - The methods used to obtain parameter estimates, confidence intervals and, if required, p-values.
    - Methods used to check any assumptions behind the analyses (histograms, box plots) and approaches to be taken if the data do not meet the assumptions.
    - The rationale for the choice of statistical procedures.
    - The test statistics, the sampling distribution of the test statistic under the null hypothesis, significance level, alternative hypothesis, whether the test is 1 (justify) or 2 sided.
    - If Bayesian techniques are to be used, specify and justify which prior distributions will be considered, or how the prior(s) will be obtained.
    - Any procedures for removing non-significant covariates from the model or model selection procedures in general.

- Methods for handling longitudinal data or missing data.

- Examples:

All efficacy variables will be listed by subject within study centre. Data will be summarised by treatment group. N, Mean, Standard Deviation, Minimum and Maximum will summarise continuous efficacy variables, whereas number and percent will summarise categorical efficacy variables.

All analyses of the continuous efficacy variables (e.g. VAS pain score) will be performed as analysis of variance with treatment group adjusting for study centre and surgical category. Treatment groups will be tested at the 2-sided 5% significance level.

All assumptions for regression models will be assessed by viewing plots of the residual values

All analyses of categorical efficacy measures will be performed using logistic regression with treatment group and adjustments for study centre.

9.1 Primary Efficacy Analysis

- Define the primary analysis (singular) that will provide the main result of the trial in this section.
- This section of the document should be structured in parallel with 4.2 in terms of the ordering of endpoints considered.
- If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

9.2 Secondary Efficacy Analyses

- Include all secondary efficacy analyses. There may be secondary analyses of the primary endpoint including subgroup analyses and sensitivity analyses, which will be included in this section.
- If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

9.3 Exploratory Efficacy Analyses

- Further analysis of exploratory endpoints used for hypothesis generation and exploration should be included here.
- If appropriate, use standard text: 'The summary statistics will be produced in accordance with section 8.'

10 Safety Analyses

This section includes general descriptions of the safety data analysis methods. If any of the items require a unique approach then this should be noted in the appropriate subsection below.

Specify:

- Sort order of any listings
- Grouping of summary information (e.g. by preferred terms and treatment group, including an "All Subjects" column)
- Descriptive statistics that will be displayed for continuous data and for categorical data.
- Analysis populations on which the descriptions will be based.
- How repeat events will be handled when producing summary statistics. For example: *"When calculating the incidence of adverse events, or any sub-classification thereof by treatment, time period, severity, etc., each subject will only be counted once and any repetitions will be ignored; the denominator will be the total population size."*

Only deviations from the aforementioned analytical and summary approaches will be noted in the subsequent subsections of section 10.

Variables being summarised should be listed in the subsections below.

10.1 Extent of Exposure

If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

10.2 Adverse Events

- If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

- It is useful to include an identification of the components of the numerator and denominator that will be used to calculate incidence rates and percentages. For example: *"When calculating the incidence of adverse events, or any sub-classification thereof by treatment, time period, severity, etc., each subject will only be counted once and any repetitions of adverse events will be ignored; the denominator will be the total population size."*

- Be certain to specify those adverse events that will be included in the summary and analysis. For example, treatment emergent adverse events are those events that occur after the baseline assessment, and some definitions also include those adverse events that worsen post-treatment.

- It may be appropriate only to report the incidence of specific AEs of interest, in which case document these specific AEs. Or it may be appropriate only to report the incidence of AEs that are judged to be related to the treatment.

10.3 Deaths, Serious Adverse Events and other Significant Adverse Events

If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

10.4 Pregnancies

- If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

- If the study did not perform any pregnancy tests or pregnancies are impossible, for example if it was limited to male or post-menopausal subjects only, then explain this succinctly.

10.5 Clinical Laboratory Evaluations

If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

Address the issues of:

- Normal ranges that differ between study centres. Explicitly tabulating the normal ranges when producing the SAP may be useful and timely to ensure the normal ranges have been provided by all centres.
- How to handle duplicate laboratory test within study periods. Normally summaries are only provided over scheduled laboratory tests. Any unscheduled follow-up tests performed for medical or safety concerns, are normally only listed.

Laboratory tests are often summarised using shift tables. Shift tables may show the change in laboratory values from baseline to either each subsequent visit, the final visit, or the most extreme post-baseline value.

An alternative may be a figure showing a scatter plot of the baseline value on the horizontal axis versus the subsequent values, as considered above, with different plotting symbols used to distinguish different treatment groups.

10.6 Other Safety Measures

- If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

- Vital signs might be appropriately included in this subsection. Many of the points made regarding laboratory tests in section 10.5 are relevant to vital signs.

11 Pharmacokinetics

- Describe pharmacokinetic and pharmacodynamic parameters to be analysed and the approach to the data summaries and analyses.

- Include pharmacodynamic data in section 111 only if it is not considered as efficacy data included in section 9. If there are no such data collected then this section may be deleted.

- If appropriate use standard text: 'The summary statistics will be produced in accordance with section 8.'

- If there are a number of variables observed then it may be necessary to generate subsections below. All variables being summarised must be explicitly mentioned.

12 Other Analyses

Variables that cannot be easily included in the preceding sections should have their own section here. Replace the heading "Other Analyses" with more appropriate text. Some examples of such data are: health economic data, quality of life data, patient satisfaction data.

All the comments from section 8 onwards may be relevant.

13 Figures

Figures are an excellent method to communicate both summary statistics and formal analyses. They also provide an effective means to check assumptions (e.g. assuming a symmetric distribution to justify the use of an arithmetic mean).

They should be used generously and always considered as alternatives or supplements to tabulation for all analyses detailed in sections 3 to 16. In some cases, tabulations are required simply to check the integrity of the study (e.g. baseline variables), are of little direct scientific interest and thus may not benefit from a graphical display. However primary and secondary analyses, along with summaries of primary and secondary endpoints should routinely be considered as candidates for graphical displays.

14 Reporting Conventions

Describe reporting conventions, for example the precision used for reporting p-values and other numeric values.

Example:

> *P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place*

greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

15 Technical Details

Include a brief statement of: study-specific documents used, including version numbers; which software package or packages used; and the directory/file paths used to store data, code and output documents.

Describe what quality assurance measures are in place to monitor the quality of any coding. Document who will review which pieces of code, and to what level of detail. For example:

A second review statistician will independently reproduce the primary analyses and summary statistics table X, Y, Z. The reviewing statistician will have an overview of the entire analyses and will explicitly check the code producing tables A, B & C (selected at random) as well as any other pieces of code as desired.

16 Summary of Changes to the Protocol

If the statistical analysis plan proposes changes to the statistical approach described in the protocol then summarise those changes in this section. Analyses are usually faithful to those specified in the protocol, but occasionally different, or supplemental, analyses are needed. Explain the reason for such changes. You may choose to identify those analyses that are not from the protocol in the relevant sections above. However, documenting the changes here greatly aids clarity.

Other important, non-statistical changes to the protocol should also be noted in this section, for example the introduction of an additional treatment group.

17 References

Provide references for any citations in the main body of the SAP.

For example:

- Pocock SJ (1982) Interim Analyses for Randomized Clinical trials: The Group Sequential Approach. *Biometrics* **38**: 153–162
- O'Brien PC, Fleming TR (1979) A Multiple Testing Procedure for Clinical Trials. *Biometrics* **35**: 549–556

18 Listing of Tables, Listings and Figures

This section is to give precise details for each table, listing or figure to be produced. As a minimum it will be a tabulation of the following aspects unique to each table or listing.

- Title
- Footnotes
- Numbering
- Population
- Endpoint(s)
- Time Points or details of how to conglomerate multiple observations
- Covariates or Subgroups used to break down summary statistics
- Which summary statistics will be calculated
- Or, what formal analysis will be used

Such a table should be derived from an accompanying data set or spreadsheet that will be used to automate some of the aesthetic aspects of table production.

For figures the equivalent information is:

- Title
- Footnotes
- Numbering

- Population
- Type of figure (or combination thereof): scatter plot, box plot, line-graph, bar chart …
- Endpoint(s), and which is used for horizontal and vertical co-ordinates
- Statistic(s) used in calculating co-ordinate values used in the figure
- Covariates used within the figure used to determine colours or symbols
- Covariates used to define facets or sub-plots

The aim of producing such detailed information is to encapsulate as much routine decision making early on in the process of reporting a trial. It should be done in a way to avoid repetition of the same work later. A secondary purpose is to avoid ambiguity if the work of producing the tables is transferred to someone other than the author of the SAP.

If possible, it is recommended to supplement the above with examples from previous trials, or bespoke mock tables specifically created for the trial.

These detailed specifications can have *minor* revisions during the production phase without needing to revise the SAP, providing that the specifications in the main body of the SAP sections 3 to 16 are met.

The following is a partially complete example of a listing of tables. It was created originally as an excel file and then pasted into word.

Table Title	Number	Population	Endpoint	Time Points or how to	Covariates or	Summary Statistics	Formal Analysis	Foot Notes

				conglomerate	Subgroups		
Disposition	1.1	NA	Disposition	Baseline-week21	Treatment	count	NA
Summary of Baseline Variable	1.2	Full Analysis	Age	Baseline	Treatment	n, mean, SD, Median, min, max	NA
			Cancer Type	Baseline	Treatment	p% (x/n)	NA
			ECOG Status	Baseline	Treatment	p% (x/n)	NA
			Centre	Baseline	Treatment	p% (x/n)	NA
			Height	Baseline	Treatment	n, mean, SD, Median, min, max	NA
			Weight	Baseline	Treatment	n, mean, SD, Median, min, max	NA
			Surface Area	Baseline	Treatment	n, mean, SD, Median, min, max	NA
			Pulse Rate	Baseline	Treatment	n, mean, SD, Median, min, max	NA
			Blood Pressure	Baseline	Treatment	n, mean, SD, Median, min, max	NA
Incidence of Dose	2.1	Full	Dose	weeks 3-24	Treatment	p% (x/n)	NA

modification		Analysis	Modification				
GEE Logistic Regression Analysis of the Incidence of Dose Modifications	2.2	Full Analysis	Dose Modification	Observations clustered by Subject across all weeks	Treatment	NA	GEE logistic regression
Kaplan-Meier Estimates/Ratios of time to first dose modification: 12 weeks	2.3	Full Analysis	time to dose modification	estimate at 12 weeks	Treatment	NA	KM estimates
Cox PH Regression for Time to First Dose Modification	2.4	Full Analysis	time to dose modification	NA	Treatment	NA	Cox Proportional hazards
Summary of the Incidence of Dose Modifications by Week	2.5	Full Analysis	dose modifications	NA	Treatment and Cancer Type	p% (x/n)	NA
Summary of the Incidence of Dose Modifications by Centre	2.7	Full Analysis	dose modification	up to week 12	Treatment and Centre	p% (x/n)	NA

Mock Tables.docx

The corresponding Mock Tables are here

The following is an example of a listing of figures. It was created originally as an excel file and then pasted into word.

Title	Number	Population	Type of graph	Horizontal Variables	Vertical Variables	Groupings	Statistics	Facets
Boxplot of percentage change in tumour diameter	6.1	Full Analysis	Boxplot	Treatment	Tumour diameter		Mean, Median, IQR, 5th, 95th percentile	NA
Progression Free Survival	6.2	Full Analysis	KM	time	probability	Treatment	Survival Estimates	NA
Overall Survival	6.3	Full Analysis	KM	time	probability	Treatment	Survival Estimates	NA
Probability of Dose Modifications	6.4	Full Analysis	KM	time	probability	Treatment	Survival Estimates	NA

Mock Figures.docx

The corresponding Mock Figures are here

Having reached the end you should edit the headers and footers to add in the correct study title, change the version number, the date you finalised the current version (do not use the automatic “today’s date” as this will change each time you open the

document). Also check the accuracy of the table at the top of the document. Update the table of contents. Leave in this reminder paragraph until the final version is confirmed.