**Guidelines for the content of statistical analysis plans in clinical trials (SAPIT)**

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## Abstract

**Importance:** While guidance on statistical principles for clinical trials exists there is an absence of guidance covering the required content of statistical analysis plans to support transparency and reproducibility.

**Objective:** To develop recommendations for a minimum set of items that should be addressed in statistical analysis plans for clinical trials, developed with input from statisticians, previous guideline authors, journal editors, regulators and funders.

**Design:** Funders and regulators (N=39) of randomized trials were contacted and the literature was searched to identify existing guidance; a survey of current practice was conducted across the network of UK Clinical Research Collaboration registered trials units (N=46, 1 unit had 2 responders) and a Delphi survey (N=73 invited) was conducted to establish consensus on statistical analysis plans. The Delphi survey was sent to statisticians in trials unit who completed the survey of current practice (N=46), CONSORT and SPIRIT guideline authors (N=16), pharmaceutical industry statisticians (N=5), journal editors (N=7), and regulators (N=2) (3 participants were included in 2 groups each), culminating in a consensus meeting attended by experts (N=12) with representatives from each group. The guidance subsequently underwent critical review by statisticians from the surveyed trials units and members of the expert panel of the consensus meeting (N=51) , followed by piloting of the guidance document in the statistical analysis plans of 5 trials.

**Findings**: No existing guidance was identified. The registered trials unit survey (46 responses) highlighted diversity in current practice and confirmed support for developing guidance. The Delphi survey (54 of 73, 74% participants completing both rounds) reached consensus on 42% (N=46) of 110 items. The expert panel (N=12) agreed that 63 items should be included in the guidance with an additional 17 items identified as important but may be referenced elsewhere. Following critical review and piloting some overlapping items were combined leaving 55 items.

**Conclusions and relevance:** Recommendations are provided for a minimum set of items that should be addressed and included in statistical analysis plans for clinical trials.

## Background

Transparency has been described as a fundamental value of society and initiatives to increase transparency in relation to clinical trial data have been launched.1 Given the influence of statistical decisions on trial conclusions, well documented and transparent statistical conduct is essential. This is relevant given concerns regarding research reproducibility .2

The contribution of the statistician to the design and analysis of clinical trials is acknowledged to be essential.3 Guidance on statistical principles for clinical trials (ICH E9)4 state “the principal features of the eventual statistical analysis of the data should be described in the statistical section of the clinical trial protocol”. However, ICH E94 and SPIRIT guidelines on protocol content5 refer to a separate statistical analysis plan (SAP). The level of detail appropriate for a SAP exceeds that of a protocol. According to ICH E94 a SAP “contains a more technical and detailed elaboration of the principal features stated in the protocol and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data”. While guidance exists on the content of clinical trial protocols5 and reporting standards for clinical trials6, both of which require a summary of the statistical analyses, there is no guidance on SAP content. Consequently, there is marked variation in practice.

This Special Communication provides recommendations for a minimum set of items that should be addressed and describes the methods used to develop this list. The recommendations are intended to aid the drafting of SAPs for clinical trials and improve their completeness.

## Methods

The need to develop guidance on SAPs was raised during discussion by statisticians attending a UK Clinical Research Collaboration (UKCRC) Registered CTU (Clinical Trials Unit) Statisticians’ Operational Group meeting in November 2012. This group included 46 senior statisticians, each representing their CTU within the network. This wider group was engaged throughout the development process as well as user-testing and piloting. The members of the CTU network, based in the UK, conduct clinical trials funded by governmental agencies, foundations, and global pharmaceutical companies under the remit of the European Medicines Agency, the UK Medicines & Healthcare Products Regulatory Agency (MHRA), and the US Food and Drug Administration. An application for funding was developed and submitted to the MRC Network of Hubs for Trials Methodology Research in December 2013 and the project started in May 2014.The SAP guidance document was developed with the primary intention of being applicable to the final analyses of later-phase randomized clinical trials (RCTs) addressing the minimum recommended content of a SAP within the context of the following assumptions:

1. The SAP is not a standalone document and should be read in conjunction with the clinical trial protocol;
2. The clinical trial protocol should be consistent with the principles of the SPIRIT 2013 Statement5; and
3. The SAP is to be applied to a clean or validated dataset for analysis.

This guidance document summarizes the findings of a comprehensive search to identify existing SAP guidance; a survey of current practice of statisticians within UKCRC registered CTUs; and a Delphi survey to establish consensus. Consistent with advice received from the Central Office of Research Ethics, the UK Health Research Authority Decision Tool7 indicated ethical approval was not required for the surveys and consent to take part was indicated by survey participation.

### Identification of Guidance

Major randomized clinical trial (RCT) funding bodies and regulators were identified from responses to a previous survey8 which had generated a list of funders actively supporting clinical trials across at least two CTUs within the last five years. The full list is contained in supplemental table 1, and includes the European and Developing Countries Clinical trials Partnership (EDCTP), FP7 Health research, Medical Council of Canada, National Cancer Institute of Canada Clinical Trials Group, European Organisation for Research and Treatment for Cancer, National Institutes for Health, and the National Institute for Health Research. The list, which was reviewed by the project team (May 2014), was extended to include regulators (FDA, EMA, MHRA).

All funders and regulators were contacted by email (June 2014). If a response was not received, up to two further reminder emails were sent. If no response was received, the organization was contacted by phone and the study team discussed whether alternative contacts within the organization could be approached to participate.

Journals were contacted in parallel to funders and regulators, and included Journal of the American Medical Association (JAMA), the British Medical Journal (BMJ), the New England Journal of Medicine (NEJM) and the Lancet as the leading medical journals publishing clinical trials. Journals identified via a PubMed search (June 2014) publishing SAPs as standalone publications were also contacted (Trials, Critical Care and Resuscitation, and International Journal of Stroke). The goal was to identify whether the journals had any internal guidance or recommendations on SAPs, if they followed any externally available guidance on SAPs, whether and how they used SAPs within the peer review process, and any policies on the publications of SAPs. Each journal website was searched for information relating to SAPs within their support for authors and reviewers prior to contacting a journal editor.

### Survey of current practice

The aim of the survey was to identify current practice and opinions about SAPs. A list of the 45 registered CTUs was accessed from the UKCRC website (June 2014). One CTU reported being split across two sites with each using separate Standard Operating Procedures (SOPs) and requested that each site complete the survey separately. The survey was developed by AK, CG and DS and adapted in response to comments from the project team. To reduce the number of survey questions copies of Standard Operational Procedures for SAPs and templates or examples of SAPs were also requested. In addition the survey was piloted during July 2014 by statisticians from the CTUs of the study project team prior to distribution.

A senior statistician at each CTU, identified as the network’s nominated statistics contact, was asked to complete the survey to reflect practices and majority opinion within the statistician’s CTU (Aug 2014). For networks in which there was no nominated statistics contact, the survey was sent to the CTU Director who was asked to delegate completion on behalf of the unit. Two reminder emails were sent to encourage responses. Survey completion was highlighted at network events at which non-responders were approached to discuss completion. A copy of the survey and the participating CTUs is provided in supplementary table 2.

### The Delphi survey

**Participants**

The aim of the Delphi survey was to establish consensus among a broad range of stakeholders. The initial list of participants was sent to the project team for review and amendment (Jan 2015). The UKCRC registered CTU participants were identified from the survey of current practice(N=46). CONSORT and SPIRIT guideline authors were identified from relevant publications and websites (N=16). Pharmaceutical industry contributors were selected from recommendations from the project team and aimed to have both industry and academic experience (N=5). The journal editors contacted to identify existing guidance were also contacted to participate in the Delphi (N=7). Regulators from the EMA and the MHRA were included (N=2). Contacts with the FDA were unsuccessful in identifying a participant in the Delphi. Three participants contributed to multiple categories, for example guideline author and journal editor.

**Delphi contents**

A comprehensive list of items that should or could be included within a SAP was derived after reviewing suggested guidance identified from contacting funders and regulators, considering the responses to the survey of current practice and review of the copies of Standard Operational Procedures for SAPs and examples of SAPs provided with the survey responses or identified in the literature search. Items were listed individually but grouped under relevant domains.

The list was reviewed by the project team for completeness, comprehension, and suitability of the domains (Jan 2015). The Delphi was completed during Feb 2015 with each round lasting two weeks. During round one, Delphi participants could suggest additional items for inclusion in round 2. Round 2 included all items from round 1 as well as the additional items suggested by participants. Suggestions were reviewed by the project team and checked for duplication prior to inclusion in round 2.

**Scoring process**

Participants were asked to score the importance of each item when writing, following, or reviewing a SAP. The scale was presented with 1 to 3 labelled ‘not important’, 4 to 6 labelled ‘important but not critical’ and 7 to 9 labelled ‘critical’. 9

All individual participants who completed round 1 were emailed and asked to complete round two. In round two, for each item participants were presented with the number and percentage of participants who chose each score. Participants were shown their score from round 1, and provided with an option to revise their score for each of the items or keep it the same as their score in round 1.

**Consensus meeting**

The definition of consensus was predefined and is presented in supplementary table 3. Briefly consensus-in was determined by 70% or more of participants scoring the item as ‘critical’ and <15% of participants scoring as ‘not important’, with consensus-out having 70% or more of participants scoring as ‘not important’ and <15% of participants scoring as ‘critical’.

Following round two of the Delphi process, a consensus meeting was held (March 2015) with expert representation from each group : CTU senior statisticians, regulators (MHRA), statisticians in the pharmaceutical industry, and journal editors. The 12 expert panel members are listed in supplementary table 4.

All items included in the Delphi were reviewed at the consensus meeting. Items on which consensus had been reached were highlighted but not discussed further. The expert panel members were asked to discuss each item for which consensus had not been reached and following discussion to make a recommendation regarding its inclusion with consensus-in items within the minimum set of items that should be addressed and included in statistical analysis plans for clinical trials.

### Critical review and piloting

The aim of the critical review and piloting was to ensure the Guidance produced was fit for purpose, appropriate to the needs of statisticians authoring and implementing SAPs and to identify any items requiring clarification. The first draft of the guidance underwent critical review by attendees at the UKCRC registered CTU Statistics Operational Group meeting in April 2015. Meeting attendees were able to provide additional comments based on further discussions with the statistics team within their CTU until September 2015. Following incorporation of comments the guidance was sent to the expert panel involved in the Delphi consensus meeting prior to being piloted by senior statisticians across five trials in January 2016.

## Results

Of the 39 funding bodies or regulators that were contacted and asked about their requirements or guidance for SAPs, 28 responded (72%). Four responders referred to ICH E94, three to the UK MRC website or ICH GCP guidance3, and 21 indicated an absence of guidance or recommendations relevant to SAPs. A comprehensive search of the literature and references of published SAPs did not identify any publications relevant to the content of statistical analysis plans.

The survey to establish current practice was distributed by email to each of the 45 UKCRC registered CTUs (46 respondents), with a 100% response rate. Responses demonstrated variability in current practice around the processes of producing statistical analysis plans and their content. The production of guidance on SAP content was supported by 85% (n=39) of responders.

Of the 73 invited participants 56 (77%) completed round 1 and 54 (73%) round 2. Those completing round 2 included: CTU statisticians=40/46 (87%), Editors=3/7 (43%), Guidelines=8/16 (50%), Industry=5/5 (100%), Regulator=1/2 (50%), 3 responders contributed to two groups each). Thirty percent of the responders were from outside the UK and included Canada, Germany, Ireland, Denmark, Australia, and the USA.

Round 1 contained 89 items , consensus-in was reached on 28 items, and an additional 21 items were suggested by responders. Round 2 contained 110 items (89 pre-populated items from round 1 and the 21 suggested items) and at the end of round 2, a total of 46 items were consensus-in with 1 item consensus-out.

At the end of the consensus meeting there were: consensus-in on 63 items, consensus-out on 30 items, and 17 items that the expert panel felt are important but do not necessarily need to be included (see supplementary Table 5). These 17 items may be found in other trial documents but the SAP should incorporate references to where details of these items can be found.

The critical review meeting, held in London, was attended by 51 statisticians from 37 CTUs (April 2015). Participants were asked to consider the ordering and clarity of the descriptions of each of the 63 items, and to highlight any concerns. To ensure discussion and complete coverage of the items within the meeting, attendees were split into groups with each group allocated one of the six sections to review and feedback on as a priority. Meeting attendees were also encouraged to discuss the draft guidance with other statisticians within their CTUs and return any additional collective responses. Additional responses were received from eight CTUs.

Two issues were raised: the first was whether the sample size calculation should be replicated from the protocol in full or referenced; the second was concerning the use of a two-stage analysis in which the assumptions of the analysis approach are tested and then the analysis determined by whether the assumptions are met or not. The sample size statement was amended to support an individual statistician’s preference to replicate or reference the protocol. The issue surrounding the two stage-analysis was more controversial and in response to discussions the guidance was amended to ensure that this was highlighted in the discussion of that item. During critical review of the 63 items some items were found to overlap and were combined, leaving 55 items or sub items. Table 1 displays the essential items and their subitems. There are six sections: Title and Trial Regiatration (11 items/sub items); Introduction (2 items); Study Methods (9 items/sub items); Statistical Principles (8 items/sub items); Trial Population (8 items/sub items); and Analysis (17 items/sub items).

An open request for five volunteers to undertake piloting of the recommendations in the guidance document was made at the critical review meeting. Twelve statisticians expressed an interest and were invited to participate; five were selected to cover CTUs with varying experience in Wales, England, and Scotland, each of whom applied the guidance document to trials in adults and children, and included pharmaceutical and non pharmaceutical interventions including devices and physiotherapy. The piloting feedback did not require any changes to the guidance and the comments received supported its content and usability.

Similar to other reporting guidelines5 6 10 an elaboration and explanation of each item is included within supplementary table 6. Examples are provided to illustrate each item, along with an explanation of the rationale and detailed description of the issues to be addressed. Examples for each item are based on real SAPs either published in journals, or provided by responders to the CTU survey, or contained within National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Monographs.

## Discussion

It is important that every clinical trial has a clear and comprehensive SAP to support reproducibility. Leading organizations and funding bodies openly support data sharing as best practice for clinical trials.11 Such support will undoubtedly increase the availability of data from original research resulting in an increase of attempts to replicate results. To support the reproducibility of research and allay concerns of misconduct and fraud in clinical research, a clear comprehensive and transparent account of pre-planned statistical analyses must be available.12 The aim of this Guidance is to establish the minimum set of essential items required for a SAP for a clinical trial , and is intended to lead to improvements in the integrity of trial conduct and reporting by facilitating their critical appraisal, execution, replication, and identification of any deviations from the pre-specified methods.

This SAP guidance was developed following established transparent methodology and involving a diverse range of stakeholders involved in the design, funding, conduct, review, and publication of clinical trials. The guidance has been piloted by a number of statisticians. Although the guidance was developed with a focus on the regulatory requirements of trials of medicinal products, and in particular later phase trials, many aspects are transferable to studies of other types of interventions, phases, and designs.

This guidance document does not cover when a SAP should be written but early authoring of SAPs, before any data have been collected or analyzed should be encouraged. The final opportunity to amend the SAP is in response to the blind review, defined as the checking and assessment of data during the period of time between trial completion and the breaking of the blind.4 Following this point, deviations from the SAP and additional analyses should be clearly indicated as such within all reports and publications.4 In the UK the Health Research Authority have developed a protocol template13 to improve consistency in the way that the items covered by SPIRIT are included within a protocol and a similar template may be beneficial for SAPs.

The guidance assumes that the SAP is not a standalone document, and therefore it is not necessary to replicate large portions of the protocol which should instead be clearly referenced. The SAP should contain a statement that it is consistent with the principal features of the statistical methods described in the protocol or a section detailing which analyses are different to those planned in the protocol and why. Any abbreviations used should be spelled out in full.

The practice of making SAPs publicly available should be supported.14 A major step towards public availability of SAPs is the requirements of the US National Institutes of Health Final Rule for Clinical Trials Registration and Results Information Submission,15 which in addition to posting of results within ClinicalTrials.gov also requires posting of the SAP if not contained within the protocol. In the discussion of public comments relating to the Final Rule15 it was noted that many of the benefits of the protocol that were cited by commenters were derived from the information regarding the statistical analyses. This represents acknowledgment that SAPs have an important role in reducing the occurrence of, and facilitating the detection of, bias particularly in relation to selective analysis and reporting. 16 17 Some journals, including JAMA, require the SAP to be submitted alongside the report of a clinical trial for use within the peer review process. The SAP may be made available as supplementary material or published as a stand alone article. While this is encouraging, and increases public availability of SAPs, there is no guidance on how the SAP should be used or evaluated. Similar to protocols, the ability of a SAP to provide transparency is dependent on its content.

Any guidance needs to be responsive to relevant information from future projects and initiatives, and changes in legislation. Key initiatives that may influence SAP content include the addendum to ICH E9 on estimands and sensitivity analyses18, data sharing initiatives,19 and mandatory requirements to post clinical trial results in the European Clinical Trials Database (EudraCT) and ClinicalTrials.gov .15 20 21 Future revisions of this document will be made available periodically and extensions to other study designs including observational studies22 and studies with adaptive designs and Bayesian analyses should be considered.

Conclusion:

Recommendations are provided for a minimum set of items that should be addressed and included in statistical analysis plans for clinical trials.

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**Table 1**: SAP Guidance Document: recommended items to address in a clinical trial SAP

|  |  |  |
| --- | --- | --- |
| **Section/Item** | **Index** | **Description** |
| **Section 1: Administrative Information** |  |
| Title and Trial registration | 1a | Descriptive title that matches the protocol, with ‘Statistical analysis plan’ either as a fore runner or sub title, and trial acronym ( if applicable) |
|   | 1b | Trial registration number |
| SAP Version | 2 | SAP version number with dates |
| Protocol Version | 3 | Reference to version of Protocol being used |
| SAP Revisions | 4a | SAP revision history |
|   | 4b | Justification for each SAP revision |
|   | 4c | Timing of SAP revisions in relation to interim analyses etc. |
| Roles and Responsibility | 5 | Names, affiliations, and roles of SAP contributors |
|  Signatures of:  | 6a | - Person writing the SAP |
|   | 6b | - Senior statistician responsible  |
|   | 6c | - Chief investigator/clinical lead |
| **Section 2: Introduction** |  |  |
| Background and rationale | 7 | Synopsis of trial background and rationale including a brief description of research question and brief justification for undertaking the trial |
| Objectives | 8 | Description of specific objectives or hypotheses  |
| **Section 3: Study Methods** |   |   |
| Trial design | 9 | Brief description of trial design including type of trial (e.g. parallel group, multiarm, crossover, factorial) and allocation ratio and may include brief description of interventions |
| Randomization | 10 | Randomization details e.g. whether any minimization or stratification occurred (including stratifying factors used or the location of that information if it is not held within the SAP) |
| Sample size | 11 | Full sample size calculation or reference to sample size calculation in protocol (instead of replication in SAP) |
|  Framework | 12 | Superiority, equivalence or non-inferiority hypothesis testing framework, including which comparisons will be presented on this basis |
| Statistical Interim analyses and stopping guidance | 13a | Information on interim analyses specifying what interim analyses will be carried out and listing of time points |
|   | 13b | Any planned adjustment of the significance level due to interim analysis |
|  | 13c | Details of guidelines for stopping the trial early |
| Timing of final analysis | 14 | Timing of final analysis e.g. all outcomes analyzed collectively or timing stratified by planned length of follow-up |
| Timing of outcome assessments | 15 | Time points at which the outcomes are measured including visit ‘windows’ |
|  |  |  |
| **Section 4: Statistical Principles** |
| Confidence intervals and p-values  | 16 | Level of statistical significance  |
|   | 17 | Description and rationale for any adjustment for multiplicity, and if so, detailing how the type 1 error is to be controlled  |
|  | 18 | Confidence intervals (CI) to be reported |
|  Adherence and Protocol Deviations | 19a | Definition of adherence to the intervention and how this is assessed including extent of exposure |
| 19b | Description of how adherence to the intervention will be presented |
|   | 19c | Definition of protocol deviations for the trial |
|   | 19d | Description of which protocol deviations will be summarized  |
|  Analysis populations | 20 | Definition of analysis populations e.g. Intention to treat, Per protocol, complete case, safety |
| **Section 5:Trial Population** |  |  |
| Screening data | 21 | Reporting of screening data (if collected) to describe representativeness of trial sample  |
| Eligibility | 22 | Summary of eligibility criteria |
| Recruitment | 23 | Information to be included in the CONSORT flow diagram |
| Withdrawal/Follow up | 24a | Level of withdrawal e.g. from intervention and/or from follow-up |
|   | 24b | Timing of withdrawal/lost to follow up data |
|  | 24c | Reasons and details of how withdrawal/lost to follow up data will be presented |
| Baseline patient characteristics  | 25a | List of baseline characteristics to be summarized  |
| 25b | Details of how baseline characteristics will be descriptively summarized  |
|  **Section 6: Analysis** |  |  |
| Outcome definitions |   | **List and describe each primary and secondary outcome including details of:**  |
|   | 26a | - specification of outcomes and timings. If applicable include the order of importance of primary or key secondary endpoints (e.g. order in which they will be tested) |
|   | 26b | - specific measurement and units (e.g. glucose control hbA1c (mmol/mol or %))  |
|   | 26c |  - any calculation or transformation used to derive the outcome (e.g. change from baseline, QoL score, time to event, logarithm etc)  |
|  Analysis methods | 27a | - what analysis method will be used, and how the treatment effects will be presented |
|   | 27b | - any adjustment for covariates |
|   | 27c | - methods used for assumptions to be checked for statistical methods |
|   | 27d | -   details of alternative methods to be used if distributional assumptions do not hold e.g. normality, proportional hazards etc |
|   | 27e | - any planned sensitivity analyses for each outcome where applicable |
|   | 27f | - any planned subgroup analyses for each outcome including how subgroups are defined |
| Missing data | 28 | Reporting and assumptions/statistical methods to handle missing data (e.g. multiple imputation) |
| Additional analyses | 29 | Details of any additional statistical analyses required e.g. Complier-average causal effect (CACE23) analysis |
| Harms | 30 | Sufficient detail on summarizing safety data e.g. information on severity, expectedness and causality; details of how adverse events (AE's) are coded or categorized; how AE data will be analyzed, i.e. grade 3/4 only, incidence case analysis, intervention emergent analysis  |
| Statistical Software | 31 | Details of statistical packages to be used to carry out analyses |
| References | 32a | References to be provided for non-standard statistical methods |
|   | 32b | Reference to Data Management Plan |
|   | 32c | Reference to the Trial Master File and Statistical Master File |
|   | 32d | Reference to other standard operating procedures ( SOPs) or documents to be adhered to. |