

Supplementary Online Content

Gamble C, Krishan A, Stocken D, et al. Guidelines for the content of statistical analysis plans in clinical trials. *JAMA*. doi:10.1001/jama.2017.18556

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eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Identification of Existing Guidance on the Content of Statistical Analysis Plans

Error! Reference source not found. contains the list of funders and regulators who were contacted to identify existing guidance about the content of SAPs.

Index	Funder/Regulator	Type
1	Medicines & Healthcare Products Regulatory Agency (MHRA)	Regulator
2	European Medicines Agency (EMA)	Regulator
3	U.S. Food and Drug Administration (FDA)	Regulator
5	Health Technology Assessment (HTA)	Funder
6	Public Health Research (PHR)	Funder
7	Health Services and Delivery Research (HS&DR)	Funder
8	Efficacy and Mechanism Evaluation (EME)	Funder
9	Chief Scientist Office (CSO)	Funder
10	National Institute for Social Care and Health Research (NISCHR)	Funder
11	Medical Research Council (MRC)	Funder
12	European and Developing Countries Clinical Trials Partnership (EDCTP)	Funder
13	FP7 Health Research	Funder
14	Medical Council of Canada (MCC)	Funder
15	National Cancer Institute of Canada Clinical Trials Group (NCIC)	Funder
16	Experimental and Clinical Research Center (ECRC)	Funder
17	National Institute of Health (NIH)	Funder
18	Cancer Research UK	Charitable
19	Leukaemia & Lymphoma Research Trust	Charitable
20	Multiple Sclerosis Society	Charitable
21	Action Medical Research	Charitable
22	Age UK	Charitable
23	Alzheimer's Research UK	Charitable
24	Arthritis Research UK	Charitable
25	Asthma UK	Charitable
26	Breakthrough Breast Cancer	Charitable
27	Breast Cancer Campaign	Charitable
28	British Heart Foundation	Charitable
29	Bupa Foundation	Charitable
30	Cystic Fibrosis Trust	Charitable
31	Epilepsy Action	Charitable
32	Epilepsy Research UK	Charitable
33	Marie Curie Cancer Care	Charitable
34	Meningitis UK	Charitable
35	Roy Castle Lung Foundation, The	Charitable
36	SPARKS - The Children's Medical Research Charity	Charitable
37	Wellcome Trust, The	Charitable
38	European Organisation for Research and Treatment for Cancer (EORTC)	Charitable
39	Association of Medical Research Charities (AMRC)	Charitable

eTable 2. Consensus Criteria

Consensus classification	Description	Definition
Consensus in	Consensus that component should be included in the SAP Guidance Document	70% or more participants scoring as 7 to 9 AND <15% participants scoring as 1 to 3
Consensus out	Consensus that component should not be included in the SAP Guidance Document	70% or more participants scoring as 1 to 3 AND <15% of participants scoring as 7 to 9
No consensus	Uncertainty about importance of component	Anything else

eTable 3. Consensus Meeting Contributors and the Areas of Representation

Name	UK based Statisticians	Pharma industry Statistician	MRC HTMR network	US based Statisticians	Journal Editor	Regulator	Guidelines development
Douglas Altman	x				x		x
Jesse Berlin		x		x			x
Yolanda Barbachano						x	
Caroline Doré	x		x				x
Carrol Gamble	x		x				
Ed Juszczak	x						
Steff Lewis	x						
Elizabeth Loder					x		
Alan Montgomery	x						
Lim Pilar		x		x			
Deborah Stocken	x						
Paula Williamson	x		x				

eTable 4. Items That While Important When Implementing a SAP Do Not Necessarily Need to be Included

Index	Description
1	Summary of data cleaning carried out by the Statistician
2	Clear descriptions of how data cleaning will be performed and by whom
3	Summary of any complex checks carried out (e.g. checks conducted by the statistician as part of data cleaning)
4	Clear descriptions of specific complex checks to be performed and by whom (e.g. check missing randomisation numbers, check randomisation numbers are in chronological and sequential order)
5	Details of the location of the data to be analysed
6	Specification of how data will be merged and the unique parameters used for merging
7	List of any data importing and exporting to be carried out
8	Clear descriptions of how data importing and exporting will be done
9	Details of where data imported and exported will be stored
10	List and description of each primary and secondary outcome including details of any graphical representation of results
11	Dummy tables of all planned analyses (descriptive or comparative) presented in table format
12	Methods for handling outliers
13	Details of what data will be independently validated and quality checked e.g. source data verification
14	Details of how data validation and quality checking will be carried out
15	Method of how results will be validated (e.g. primary outcome, safety data and any unexpected results) and whether there will be independent programming of the primary outcome
16	Details of how final analysis datasets, programs and outputs will be archived at the end of the study analysis
17	Details of how final analysis datasets, programs and outputs will be shared with investigators at the end of the study analysis

eAppendix 1. Survey of UK Clinical Research Collaborative Registered Clinical Trials Units

CTU name: _____

Details of Stats Representative:

Name: _____

Email: _____

We ask for the above details for the sole reason of keeping a record of who has responded. We will not use any of the details for any analyses or reporting.

Section A: Current Practice

The following questions are about Statistical Analysis Plans (SAPs) and current practice within your CTU. To minimise variation in practice due to different study types and designs we ask that, unless otherwise specified, you base your answers on final analyses of RCTs for later phase studies. We would also be grateful if your responses could be made on behalf of your CTU, so it may help to discuss the survey with your colleagues before returning it.

1. Do you have a Standard Operating Procedure (SOP) that covers SAPs?

Yes No

1a. If no, reason why? *Please tick one.*

SOP is not required

-Please specify why _____

SOP under development

SOP required but development hasn't started

Other (*Please specify*) _____

2. Do you have a SAP template, or a set of specific instructions, that you use to write SAPs?

Yes No

3. Have you provided a copy of your:

SOP for SAPs Yes No

An example/template of a SAP Yes No

3a. If no, please send a copy to Ashma Krishan on (ashma.krishan@liv.ac.uk) or send an email to say why this is not possible.

4. What guidance documents have you referred to in developing your SAP template/instructions, or when writing your SAP? *Please tick all that apply.*

- ICH E3 Guidelines
- ICH E9 Guidelines
- MRC CT Toolkit
- SPIRIT Guidelines
- PSI Guidelines for Standard Operating Procedures for Good Statistical Practice in Clinical Research
- Guidelines produced by another CTU
- Other (*Please specify*) _____

5. Do you produce a SAP as standard practice for every later phase RCT?

- Yes No

5a. If no, for which types of later phase RCT, would you produce a SAP? (If you do not perform these types of later phase RCT at your CTU then please select N/A) *Please tick all that apply.*

	<i>SAP</i>	
	<i>produced</i>	<i>N/A</i>
CTIMP studies	<input type="checkbox"/>	<input type="checkbox"/>
Device studies	<input type="checkbox"/>	<input type="checkbox"/>
Surgical studies	<input type="checkbox"/>	<input type="checkbox"/>
Diagnostic test accuracy studies	<input type="checkbox"/>	<input type="checkbox"/>
Complex Intervention studies		
-Behavioural	<input type="checkbox"/>	<input type="checkbox"/>
-Educational	<input type="checkbox"/>	<input type="checkbox"/>
Other (<i>Please specify</i>) _____		

Comments _____

6. Other than later phase RCTs, for which of the following designs would you produce a SAP? (If you do not perform these studies at your CTU then please select N/A.) *Please tick all that apply.*

	<i>SAP</i>	
	<i>produced</i>	<i>N/A</i>
Feasibility studies	<input type="checkbox"/>	<input type="checkbox"/>
Randomised pilot studies	<input type="checkbox"/>	<input type="checkbox"/>
Non-randomised pilot studies	<input type="checkbox"/>	<input type="checkbox"/>
Early phase randomised studies	<input type="checkbox"/>	<input type="checkbox"/>
Early phase non-randomised studies	<input type="checkbox"/>	<input type="checkbox"/>
Other (<i>Please specify</i>) _____		

7. Which of the following tasks is the person termed the 'trial statistician' involved in?

- Producing the randomisation list
- Writing the statistical analysis section in the protocol
- Producing the open section of a DMC report
- Supervision of the open section of a DMC report
- Producing the closed section of a DMC report
- Supervision of the closed section of a DMC report
- Writing the SAP
- Producing the final analysis report
- Supervision of the final analysis report
- Membership of the TSC
- Other (*Please specify*) _____

8. Describe the characteristics of someone responsible for writing a SAP.

- (i) Seniority:
 - Junior Statistician
 - Senior Statistician
- (ii) Blinded to comparative analyses whilst working on the SAP:
 - Blinded
 - Unblinded
- (iii) Host Institution:
 - In the CTU
 - Outside the CTU

9. What is the role of the person responsible for writing a specific trial SAP? (*Our definition of 'responsible' is the person who produces the draft SAP and responds to comments*). Please tick all that apply.

- A statistician in the CTU not involved in the trial
- A statistician outside the CTU not involved in the trial
- A statistician in the CTU who sits on the TSC
- The statistician producing closed DMC reports
- The statistician in the CTU supervising production of the open DMC report
- The statistician in the CTU supervising production of the closed DMC report
- Other (*Please specify*) _____

10. Who else is involved in the development of the SAP? *Please tick all that apply.*

- A statistician in the CTU not involved in the trial
- A statistician outside the CTU not involved in the trial
- The statistician producing closed DMC reports
- A statistician in the CTU involved in the trial but blinded to treatment group comparisons
- The statistician in the CTU supervising production of the open DMC report
- The statistician in the CTU supervising production of the closed DMC report
- A statistician outside the CTU on the TSC/DMC
- Chief Investigator
- Member of Data Monitoring Committee
 - Please specify their role in the DMC _____
- Member of Trial Steering Committee
 - Please specify their role in the TSC _____
- Trial Co-ordinator/Manager
- Data/Database Manager
- Other (*Please specify*) _____

11. Who is responsible for approving and signing off the SAP? *Please tick all that apply.*

- A statistician in the CTU not involved in the trial
- A statistician outside the CTU not involved in the trial
- The statistician producing closed DMC reports
- A statistician in the CTU involved in the trial but blinded to treatment group comparisons
- The statistician in the CTU supervising production of the open DMC report
- The statistician in the CTU supervising production of the closed DMC report
- A statistician outside the CTU on the TSC/DMC
- Head of Statistics
- Chief Investigator
- Member of Data Monitoring Committee
 - Please specify their role in the DMC _____
- Member of Trial Steering Committee
 - Please specify their role in the TSC _____
- Trial Co-ordinator/Manager
- Data/Database Manager
- CTU Director
- Other (*Please specify*) _____

12. Who is the intended audience of the SAP? *Please tick all that apply.*

- Statisticians
- Chief Investigator
- Trial Management Group
- DMC/TSC Members
- Other (*Please specify*) _____

13. What timelines do you consider desirable for completing and signing off a SAP? *(Please indicate earliest time point applicable)*

- Prior to the first DMC meeting where allocation information is used to check the randomisation system or safety reporting
- Prior to any comparative outcome analyses carried out in DMC reports
- Prior to the database being locked and final analysis beginning
- Other *(Please specify)* _____

13a. In practice, what are your usual working timelines for completing and signing off a SAP? *(Please indicate earliest time point applicable)*

- Prior to the first DMC meeting where allocation information is used to check the randomisation system or safety reporting
- Prior to any comparative outcome analyses carried out in DMC reports
- Prior to the database being locked and final analysis beginning
- Other *(Please specify)* _____

Comments _____

In the following questions, our definition of someone blinded to the data is someone who has not seen any comparative results (e.g. using the intervention groups with allocation names or codes) but may be involved in the trial.

14. Do you think everyone involved in the preparation of the SAP should be blinded to the data whilst working on the SAP?

- Yes
- No
- Depends on experience
- Please specify _____
- Other *(Please specify)* _____

15. Do you ask for everyone involved in the development of the SAP to be blinded to the data whilst working on it?

- Yes
- No

16. According to the ICH E9 guidelines "The plan should be blind reviewed and possibly updated as a result of the blind review". Is this carried out at your CTU?

- Yes
- No

16a. If this is done in your CTU, who provides the blind review? *Please tick all that apply.*

- A statistician in the CTU not involved in the trial
- A statistician outside the CTU not involved in the trial
- A statistician in the CTU involved in the trial but blinded to comparative results
- Chief Investigator
- A statistician appointed as the independent member sitting on the DMC/TSC
- Head of Statistics

Other (Please specify) _____

16b. If no, reason why? _____

17. Do you produce a SAP that is used only for final analyses?

Yes No

17a. If yes, do you also write a separate SAP to cover interim analyses or other reporting timepoints?

Yes No

17b. If no, does the SAP also cover interim analyses?

Yes No

18. Do you version control your SAP?

Yes No

19. Do you:

(i) Document amendments

Yes No

(ii) Provide justification for amendments

Yes No

(iii) Explain timing of amendments in relation to unblinding of data

Yes No

20. In your SAP, do you include information on any of the following?

(i) Location of data and access details

Yes

No

Recorded elsewhere (Please specify) _____

(ii) How trial datasets will be merged

Yes

No

Recorded elsewhere (Please specify) _____

(iii) Data exports between trial database and statistical packages

Yes

No

Recorded elsewhere (Please specify) _____

(iv) Data manipulations/derivations
Yes
No
Recorded elsewhere (*Please specify*) _____

(v) Data cleaning/complex checks
Yes
No
Recorded elsewhere (*Please specify*) _____

(vi) Dummy or shell tables for presentation of results
Yes
No
Recorded elsewhere (*Please specify*) _____

21. Do you think information on the following should be captured within your SAP?

(i) Location of data and access details
Yes No
Comments

(ii) How trial datasets will be merged
Yes No
Comments

(iii) Data exports between trial database and statistical packages
Yes No
Comments

(iv) Data manipulations/derivations

Yes No

Comments

(v) Data cleaning/complex checks

Yes No

Comments

(vi) Dummy or shell tables for presentation of results

Yes No

Comments

22. How often are your SAPs publicly accessible?

Always
Sometimes
Made available if requested
Not currently but plan to in future
Never

22a. If "sometimes", how do you determine when to make your SAPs publicly accessible?

Only if CTIMP
Only if requested by publishing journal
Only in exceptional/unusual circumstances
Other (*Please specify*) _____

23. How do you make your SAPs publicly accessible?

On the CTU/trial specific website
In a journal
Not publicly accessible
Other (*Please specify*) _____

24. Please detail any difficulties/anxieties/ experiences you would like to share where the existence of a SAP has been helpful or unhelpful. *Please extend this section if needed.*

a) Helpful

b) Unhelpful

Any additional comments _____

—

Section B: Opinion on SAPs

The following questions are about opinions within your CTU about SAPs. We understand there might be varying opinions throughout your CTU, so please provide a consensus response on behalf of the CTU.

1. Would you find guidance on SOPs for SAPs useful?

Yes No

Please _____ explain:

2. Would you find guidance on the content of a SAP helpful?

Yes No

Please explain: _____

3. (i) Would you find a template on SOPs for SAPs useful?

Yes No

Please _____ explain:

(ii) Would you find a listing of what should be included in a SOP for SAPs useful?

Yes No

Please explain: _____

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Finally, would you be willing for us to visit your CTU to discuss your processes and experiences?

Yes

No

Any additional comments _____

—

Thank you so much for taking the time to complete this survey. Your CTU opinions and views are important for this project, and we are grateful for your support. (Please see over the page for details on returning the survey).

Listing of the UKCRC Registered Clinical Trials Units:

Barts and The London Pragmatic Clinical Trials Unit
Barts Clinical Trials Unit
Birmingham Clinical Trials Unit
Bristol Clinical Trials and Evaluation Unit
Bristol Randomised Trial Collaboration
Cambridge Clinical Trials Unit
Cancer Clinical Trials Unit Scotland (CaCTUS)-Glasgow and Edinburgh
Cancer Research UK and University College London Cancer Trials Centre (UCL CTC)
Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham
Centre for Healthcare Randomised Trials (CHaRT)
Diabetes Trials Unit (University of Oxford)
Edinburgh Clinical Trials Unit
Glasgow Clinical Trials Unit
Haematology Clinical Trials Unit (HCTU), Cardiff University
Imperial Clinical Trials Unit
Intensive Care National Audit & Research Centre (ICNARC)
Keele Primary Care Musculoskeletal Trials Unit
King's Clinical Trials Unit at King's Health Partners
Leeds Clinical Trials Research Unit
Leicester Clinical Trials Unit
Liverpool Trials Collaborative-Clinical Trials Research Centre
Liverpool Cancer Trials Unit
London School of Hygiene and Tropical Medicine CTU
Manchester Academic Health Science Centre - Trials Coordination Unit (MAHSC-CTU)
Medical Research Council Clinical Trials Unit at UCL
Newcastle Clinical Trials Unit (NCTU)
North Wales Organisation for Randomised Trials in Health (and Social Care) - NWORDH
Northern Ireland Clinical Research Support Centre
Nottingham Clinical Trials Unit
Norwich Clinical Trials Unit
NPEU Clinical Trials Unit (University of Oxford)
Oxford Clinical Trials Research Unit (OCTRU)
Oxford Cognitive Health and Neuroscience Clinical Trials Unit (OCHNCTU)
Oxford Primary Care and Vaccines Collaborative Clinical Trials Unit
Peninsula Clinical Trials Unit at Plymouth University
Primary Care Clinical Research and Trials Unit (PC-CRTU), University of Birmingham
PRIMENT Clinical Trials Unit
Sheffield Clinical Trials Research Unit
South East Wales Trials Unit
Tayside Clinical Trials Unit (TCTU)
The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU)
University of Oxford Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU)
University of Southampton Clinical Trials Unit
Wales Cancer Trials Unit

Warwick Clinical Trials Unit
York Trials Unit

eAppendix 2. Explanation and Elaboration of Essential Items

Section 1: Administrative information

Title and Trial registration

Item 1a: Descriptive title that matches the protocol, with ‘Statistical analysis plan’ either as a fore runner or sub title, and trial acronym (if applicable)

Explanation

The title provides vital information required for trial identification. The title should unambiguously state which trial the SAP relates to and should therefore be identical to the trial protocol with ‘Statistical analysis plan’ either as a fore runner or sub title. Ideally the title should identify the study design, population, interventions, and, if applicable, trial acronym.

Example

“Statistical analysis plan for the Stroke Oxygen Study (SO2S): a multi-center randomized controlled trial to assess whether routine oxygen supplementation in the first 72 hours after a stroke improves long-term outcome.”¹

Title and Trial registration

Item 1b: Trial registration number

Explanation

A trial registration number should be provided which uniquely identifies a clinical trial and its existence on a publicly-accessible registry. The International Committee of Medical Journal Editors (ICMJE) mandates the registration of clinical trials in a primary register of the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) or in ClinicalTrials.gov before recruitment of the first patient as a condition of consideration for publication². This identifier should be clearly listed in all relevant documentation including the protocol and the SAP.

Example

“Trial registration: ISRCTN50133740.”³

SAP Version

Item 2: SAP version number with dates

Explanation

Sequentially numbering and dating each SAP version avoids any confusion over which document is the most recent. Transparent tracking of version numbers and amendments facilitates trial conduct, review and oversight. The first final version of a document will be Version 1.0. It is recommended that subsequent final documents will have an increase of “1.0” in the version number (1.0, 2.0, etc.).⁴ While the document is under review, subsequent draft versions will increase by “0.1”, e.g., 1.1, 1.2, 1.3, etc. When the revised document is deemed final, the version will increase by “1.0” over the version being revised, e.g. the draft 1.3 will become a final 2.0.

Example

Version: 1.0 Date: July 3, 2014⁵

Protocol Version

Item 3: Reference to version of Protocol being used

Explanation

Referencing the version of the protocol being used is helpful as it links the SAP to the protocol and serves as a reminder that the SAP is not a standalone document and needs to be read in conjunction with the corresponding version of the protocol. This avoids the need for the author to duplicate information from the protocol in the SAP. If there have been protocol amendments after the SAP has been written then the SAP needs to be reviewed against the amendments, and updated where necessary. The information in Table 2 may be extended to record that the SAP has been reviewed in light of protocol amendments but no changes were required.

Example

This document has been written based on information contained in the study protocol version 5, dated 11 December 2012.⁶

SAP Revisions – revision history, with justification and timing

Item 4a/4b/4c: SAP Revision History

Justification for each SAP revision

Timing of SAP revisions in relation to interim analyses etc.

Explanation

A clear explanation of the changes made between each version of the SAP is essential, along with a justification for the revision and the date. This is important to maintain transparency. After the first version of the SAP is agreed and signed off, the SAP revision history should include the following

information: the previous version number, the SAP section changed, details of the change made along with justification for the revision, and date of revision. A justification for each SAP revision is necessary to document the reasons for changes. This ensures the external validity of the trial as it demonstrates that changes are not being made based on unblinded trial data. From a regulatory perspective when SAP revisions occur after unblinded interim analyses have been conducted the people involved in deciding, writing, or approving the SAP should ideally have no knowledge of unblinded data particularly if the trial will be used for a licence application. In other situations it may be sufficient for the justification to document the reason for the change is not based upon comparative data and for the approver to have no knowledge of unblinded data.

Table 2: Example of SAP revision history⁷:

Protocol version	Updated SAP version no.	Section number changed	Description of and reason for change	Date changed
1.0	2.0	Appendix D	Organisms added to the appendix	21/02/2014
2.0	2.0	No changes required	SAP reviewed against protocol amendments	31/07/2014

Roles and Responsibility – non-signatory names and contribution

Item 5: Names, affiliations, and roles of SAP contributors

Explanation

Individuals who contribute significantly to SAP development should have their contributions described. Listing the SAP contributors, their affiliations and their roles in the SAP development process provides due recognition, accountability, and transparency. Naming of authors and statements of author’s contributions is standard for SAPs published in journals such as *Trials*, but rare in unpublished SAPs. Contributors may be non-signatory members if only the statistician writing the SAP, supervising senior statistician and the chief investigator/clinical lead will sign and approve the SAP.

Roles and Responsibility – signatures

Item 6a: Signature of person writing the SAP

Explanation

The signature of the person writing the SAP is crucial as it identifies who is responsible for the SAP and that they have approved the SAP. In all circumstances this should be signed and dated. If an update has been made then the author of the update should sign the updated version.

Item 6b: Signature of senior statistician responsible

Explanation

The signature of the senior statistician responsible for overseeing the trial is important as it highlights that the SAP has been reviewed and approved by an experienced statistician. In some circumstances the senior statistician may be the person writing the SAP and such a dual role should be reflected in the signatories. The signature should always be dated.

Item 6c: Signature of chief investigator/clinical lead

Explanation

The signature of the chief investigator/clinical lead demonstrates that they have reviewed and approved the SAP. Once the final version has been approved and signed off it avoids any post-hoc changes being made without the justification and approval of all signatory members to maintain internal and external trial validity. The signature should always be dated.

Section 2: Introduction**Background and rationale** *(optional)*

Item 7: Synopsis of trial background and rationale including brief description of research question and brief justification for undertaking the trial

Explanation

The full rationale for undertaking the trial and trial background are explained in detail in the protocol so only a brief synopsis is necessary within a SAP to avoid duplication of information. The synopsis should include justification for undertaking the trial, why the trial is needed and description of the research question. This item would be regarded as essential if the SAP is to be accessible externally (e.g. published in a journal or on a website) but is optional if the SAP is an internal document only.

Example

“To be brief, chronic fatigue syndrome is characterised by chronic disabling fatigue in the absence of an alternative diagnosis, present in 0.2 to 2.6% of the population. The National Institute for Health and Clinical Excellence (NICE, UK) recommends two treatments: cognitive behaviour therapy (CBT) and graded exercise therapy (GET), but patient organisations recommend a third treatment: adaptive pacing therapy (APT). A definitive randomised trial was therefore needed to compare all three treatments with specialist medical care (SSMC) and to compare the established treatments (CBT, GET) against the new treatment (APT).”⁴

Objectives

Item 8: Description of specific objectives or hypotheses

Explanation

The trial objectives reflect the scientific questions to be answered by the trial, defining its rationale and scope. This information may be provided in sufficient detail within the protocol, in which case a reference would be sufficient. If the protocol contains insufficient detail as protocols usually target clinical rather than statistical readers, then additional detail may be required within the SAP. The trial hypotheses should be stated as these provide information on the framework (e.g. superiority, non inferiority) and regions of statistical testing (one or two-sided tests).

Example

Research hypothesis

The null hypothesis is that there is no difference in time to first blood stream infection between the standard and impregnated (antibiotic and heparin combined) groups. The alternative hypothesis is that there is a difference between the two groups.

Study objectives

The primary objective of this trial is to determine the effectiveness of heparin bonded or antibiotic impregnated CVCs (combined) compared with standard CVCs for preventing hospital acquired blood stream infection

Secondary objectives are:

- a. To determine the cost effectiveness of heparin bonded or antibiotic impregnated CVCs compared with standard CVCs, based on the primary outcome and costs of acute care from the perspective of the NHS.
- b. To determine the effectiveness of type of CVC in 3-way comparisons of heparin bonded versus antibiotic impregnated versus standard CVCs for preventing hospital acquired blood stream infection, based on culture, quantitative bacterial DNA, and clinical measures of infection.”⁷

Section 3: Trial Methods

Trial design – description of trial design

Item 9: Brief description of trial design including type of trial (e.g. parallel group, multiarm, crossover, factorial), allocation ratio and brief description of interventions

Explanation

Specify the type of trial design. This can influence many aspects such as methods used, risk of bias, trial conduct, costs, results and interpretation. For example, factorial or adaptive designs can involve more complex methods, analyses, and interpretations than parallel group superiority trials. Although most trials use equal randomisation (i.e. 1:1 for two groups), it is still important to provide the allocation ratio. For drug trials, specifying the phase of the trial (I-IV) may also be relevant.

Example

“The trial is a two centre, randomised, parallel-group, placebo-controlled trial. Treatment allocation is a 1:1 ratio. Patients are randomised to either gabapentin or matched placebo control.”⁶

Randomisation

Item 10: Randomisation details e.g. whether any dynamic allocation (e.g. minimisation) or stratification occurred (including stratifying factors used or the location of that information if not held within the SAP)

Explanation

Details regarding the randomisation process should be provided within the protocol. Additional detail such as the method of randomisation, e.g. minimisation or stratification, specific information relating to block sizes or specific factor levels used within minimisation or stratification should be stored in a restricted access area. Reference to where this information is stored should be provided in the SAP. This is to protect against predictability of the randomisation sequence by those providing clinical input to the SAP. This allows the statistician executing the SAP to identify stratification factors for use according to ICH E9.

Example

“Each randomisation is via minimisation incorporating a random element and incorporates the following factors: centre, WHO performance status (0 or 1 vs 2), prior oxaliplatin (yes vs no), prior bevacizumab (yes vs no), previous best response to therapy (PR/SD vs PD alone vs unknown) and dose reduction/delay/stop of therapy for toxicity during previous therapy (yes vs no).”⁸

Or

The randomisation process is described in full within the clinical trial protocol. Details of the randomisation method are held securely within the statistics master file.

Sample size

Item 11: Full details of the sample size calculation or alternatively reference to sample size calculation in protocol (instead of replication in SAP)

Explanation

The sample size calculation may be included in full in the SAP or a reference to the sample size calculation in the protocol or other document may be provided. The sample size calculation is an important piece of information for every trial as it determines how many patients are required in the primary analysis to ensure the trial is adequately powered to detect a clinically important difference. The size of that minimum clinically important difference may be used to interpret results. Justification of the sample size should be given including, if appropriate, the expected rate of attrition. All relevant information on which the calculation is based e.g., effect size, power, significance level etc., should be provided with any references to support parameter specifications together with details of any software used. Sufficient detail must be provided to enable another statistician to reproduce the calculation.

Example

“A sample size of 143 in each group will have 80% power to detect a difference in means of 0.50 assuming that the common standard deviation is 1.50 using a two group t-test with a 0.05 two-sided significance level. Allowing for 10% loss to follow up means we would need, a total of 316 participants (158 per group). The estimate used for the standard deviation in the sample size calculation was taken from an audit at Alder Hey Children’s NHS Foundation Trust based on children matching the inclusion criteria for this proposed study. A difference in HbA_{1c} of 0.5% is widely recognized as the threshold used by the Food and Drug Administration (FDA) and pharmaceutical industry to determine effectiveness of any new oral hypoglycaemic agents. Current national studies investigating therapeutic interventions in children with diabetes were powered using this effect size. An improvement of 0.61% was detected in adults in the meta-analysis of studies included in the 2004 HTA report suggesting that in addition to this estimate being the minimum clinically important it is also a realistic difference to detect.”

Framework

Item 12: Superiority, equivalence or non-inferiority trial hypothesis testing framework, and which comparisons will be presented on this basis

Explanation

Specifying the framework of a trial refers to its overall objective to test the superiority, equivalence or non-inferiority of one intervention from another. However, if for example the main objective is to determine equivalence of the primary outcome, secondary outcomes may be intended to demonstrate superiority. The SAP should clearly specify the framework for each outcome or provide a global statement.

Example

The SLEEPS trial protocol states the secondary objective is “to determine whether clonidine reduces side-effects and improves clinical outcomes due to its effects on reduction of sympathetic outflow, improved organ perfusion and protection in ischaemic reperfusion injury”. Therefore, the secondary outcomes are testing for superiority rather than equivalence like for the primary outcome.⁹

Statistical Interim analyses and stopping guidance

Item 13a: Information on Interim analyses specifying what interim analyses will be carried out and listing of time points

Explanation

Information needed to conduct interim analyses should be detailed including statistical methods to be used, who will perform the analyses, what interim analyses will be carried out and when they will be performed e.g. timing and frequency. If interim analyses are not planned then this should be stated for clarity. If details of interim analyses are included in the protocol, or another document e.g. DMC Charter, then depending on the level of detail given the appropriate document could be referenced to avoid duplication. If separate SAPs have been written for interim analyses then these should be referenced.

Example

“One formal statistical interim analysis is planned on the primary endpoint for the Ir vs IrCs comparison. This interim analysis was planned to take place when the study was at least 18 months into recruitment and at least half the number of patients required for the final analysis (as per the sample size calculation) were recruited (i.e. 375 patients).”⁸

Item 13b: Any planned adjustment of the significance level due to interim analysis

Explanation

If analyses are to be performed on the accruing data at multiple time points then methods must be used to control the type 1 error in order to avoid increasing the risk of a false positive result. Various statistical methods have been developed to control this inflated risk such as Haybittle-Peto or O'Brien-Fleming techniques and the chosen approach should be clearly specified, justified and referenced. The DMC Charter could also be referenced, if applicable.

Item 13c: Details of guidelines for stopping a trial early

Explanation

Details should be provided on the guidelines to be used for stopping a trial early. It should be clear whether a statistical method will be considered within the early stopping guideline.

Example

“For the planned interim analyses after one-third and two-thirds of the data collection, we will use a P of 0.00021 and 0.01189, respectively, to define early stopping criteria. We will use a group sequential α -spending function, calculated using the O'Brien–Fleming method, with two-sided symmetric bounds.”¹⁰

Or

“The Haybittle-Peto approach will be employed for interim analyses with 99.9% confidence intervals but importantly decisions around trial continuation will not be based on p-values alone.”⁷

Or

“Formal interim analyses of the accumulating data will be performed at regular intervals (at least annually) for review by an Independent Data Monitoring and Safety Committee (IDSMC). The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community.”¹¹

Timing of final analysis

Item 14: Timing of final analysis e.g. all outcomes analysed collectively or timing stratified by planned length of follow-up

Explanation

Information on the timing of final analyses should be included, if relevant. Information on timing of final analysis should explain whether all outcomes are analysed collectively or whether timing is stratified by length of follow-up required. Details should be provided on whether there are short-term and long-term outcomes and how they will be reported i.e. will all outcomes be analysed collectively or will the short-term outcomes be published earlier and the long-term outcomes reported at a later date.

Example

“Final analysis for the Ir vs. IrCs comparison is planned to take place in two separate stages, however if the PFS event rate and median follow-up of one year for the secondary endpoint of PFS is reached at the time of the first analysis (as is anticipated), analysis will take place in one stage: The first main report/publication of the trial will be prepared for the Ir/IrCs comparison when every patient has reached 12 weeks follow-up and data for the primary endpoint has been received and cleaned (anticipated to be November 2010). Longer-term endpoints for the Ir vs. IrCs comparison will be analysed when the required event rate of 273 PFS events across the Ir vs. IrCs arms, and median follow-up of one-year, has been reached (anticipated being November 2010).”⁸

Timing of outcome assessments

Item 15: Time points at which the outcomes are measured

Explanation

The time points at which outcomes are measured is helpful information that can be found in the protocol often in table format. The SAP should either refer to the relevant section of the protocol for details or include this information. If outcomes are required to be measured within a particular time window in relation to each planned visit in order to contribute to the analysis then this should also be specified.

Example

“The schedule of study procedures is given in the Table 8-1. The expected visit dates and visit windows are defined in Table 11.3-1. The start time for each calculation is the participants date of birth corrected for gestational age. Then additionally, 26 weeks, 52 weeks, 156 weeks and 260 weeks are added to determine the expected date for 6 months, 12 months, 3 years and 5 years follow up visits.”

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Section 4: Statistical Principles

Confidence intervals and p-values

Item 16: Level of statistical significance

Explanation

Where cut-off values are to be used to declare statistical significance then it is important for authors to document the significance level to be used including whether tests will be one- or two-sided. The significance level used for the primary outcome should be consistent with that used in the sample size calculation but secondary outcomes may use different levels.

Example

“All applicable statistical tests will be 2-sided and will be performed using a 5% significance level.”⁶

Item 17: Description of any planned adjustment for multiplicity, and if so, including how the type 1 error is to be controlled

Explanation

Authors should pre-define what methods will be used to conduct any adjustment for multiplicity as different methods can lead to different conclusions¹². The rationale for adjustment and method(s) chosen should be justified. If no adjustment for multiplicity is planned then an explicit statement should be included. Justification for the absence of multiplicity adjustments for secondary outcomes is probably unnecessary unless a claim is to be made on them, however for multiple testing on the primary outcome (e.g. different doses) justification should be given. If gatekeeping methods are to be used then authors should state the order of testing.

Item 18: Confidence intervals (CI) to be reported

Explanation

The CI is essential to the interpretation of statistical analyses reported for any of the primary or secondary outcomes. The level of CI to be reported should be decided at the design stage to avoid bias being introduced by modification based on trial data. The confidence levels used may be consistent across outcomes or vary by primary, secondary, exploratory and safety outcomes and this should be clearly specified.

Example

“All confidence intervals presented will be 95% and two-sided.”¹³

Adherence and Protocol Deviations

Item 19a: Definition of adherence to the intervention and how this is assessed including extent of exposure

Explanation

Authors should pre-specify their definition of adherence to the intervention. Non-adherence to the intervention can include not completing the intervention, (e.g. not consuming all prescribed drugs or consuming a lower dose than is prescribed). This may be reported to aid generalizability of results or may be linked to an analysis population specification.

Example

“Compliance is assessed based on the percent of subjects who have taken the scheduled number of pills. It is defined as:

$\% \text{ compliance} = (\text{number of pills taken} / \text{number of pills supposed to have been taken}) * 100\%$.

The number of pills supposed to have been taken will be calculated as the duration of treatment (end of study medication – start of study medication + 1) multiplied by 4. In this study 2 pills are taken in the morning and 2 pills in the evening.

Item 19b: Description of how adherence to the intervention will be presented

Explanation

Along with defining adherence to the intervention it is also crucial to describe how adherence to the intervention will be presented. This process avoids any bias being caused by adherence being defined after unblinding of data.

Example

“The number and % of participants taking more than 75% of the prescribed treatment will be presented in a table for i) randomisation to visit 3 and ii) visit 3 to visit 4. Results will be provided by treatment group” [summary of example 1 in 16a].

Or

“Descriptive statistics on the percent compliance (N, mean, SD, median, minimum, maximum) will be summarized by randomisation group.”

Item 19c: Definition of protocol deviation for the trial

Explanation

A protocol deviation is defined as a failure to adhere to the protocol such as the wrong intervention being administered, incorrect data being collected and documented, errors in applying inclusion/exclusion criteria or missed follow-up visits. A protocol deviation should be defined as major or minor. A deviation may be considered a serious breach if it affects efficacy, the safety, physical or mental integrity of the participants in the trial, or the scientific value of the trial. Protocol deviations should be defined prior to unblinding of data to avoid any bias being caused and due consideration given to inclusion of participants within analysis populations¹⁴. Protocol deviations may be defined in another document and referenced within the SAP.

Example

“The following are pre-defined major protocol violations with a direct bearing on the primary outcome:

- 1) Taking of rescue medication (loperamide) during the primary outcome assessment period i.e. weeks 11-12 of the treatment period.
- 2) Taking of antibiotics during the primary outcome assessment period i.e. weeks 11-12 of the treatment period.”¹⁵

Item 19d: Description of which protocol deviations will be summarised (may include details of whether deviation is major or minor and impact on analysis populations and approach to summarising protocol deviations e.g. number and type of protocol deviation, per group)

Explanation

A description should be provided on how protocol deviations will be summarised. Providing details of whether the deviation is major or minor is helpful if sensitivity analyses are to be conducted by removing patients with major deviations to assess impact on overall conclusions or to align with analysis populations. The approach to summarising the protocol deviation should also be made clear e.g. number and type of protocol deviations by intervention group or listing of all deviations.

Example

“Protocol deviations are classified prior to unblinding of treatment. The number (and percentage) of patients with major and minor protocol deviations will be summarised by treatment group with details of type of deviation provided. The patients that are included in the ITT analysis data set will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.”⁹

Analysis populations

Item 20: Definition of Analysis populations e.g. intention-to-treat (ITT), per-protocol, complete case, safety.

Explanation

The analysis populations should be specified in advance. This includes how the analysis populations will be defined and which outcomes will be analysed according to each analysis population. It is important to clearly define populations, even if terms are considered standard. For example, there is no consistent definition of ITT and the phrase has different meanings for different authors.¹⁶

Example

The intention-to-treat population will include all randomised patients, regardless of their eligibility, according to the treatment they were randomised to receive.

Or

A per-protocol population will be considered if >5% of the total number of patients in this comparison are major protocol violators. The per-protocol analysis set consists of subjects who were randomly assigned to treatment, have both a baseline and at least 1 post-baseline measurement on the primary efficacy variable, have a minimum exposure of 36 days to the double-blind treatment regimen, and have no major protocol violations such as violations of entry criteria, errors in treatment assignment and use of excluded medications.⁸

Or

The safety population will consist of all randomised patients in this comparison who have received at least one dose of study treatment. Patients will be analysed according to the treatment they actually received.

Section 4: Trial Population

Screening Data

Item 21: Reporting of screening data (if collected) to describe representativeness of trial sample

Explanation

If a trial collects screening data then it is important that the data are appropriately presented to describe the representativeness of the trial sample. This information is not only important for the trial but also important for future trials in the area. The process for screening patients e.g. how patients will be screened and what data will be collected, should be fully described within the trial protocol. According to the CONSORT guidelines¹⁷ as a minimum the number of patients who are assessed for eligibility should be provided with this information presented in a flow diagram, however, more detailed tabulations may be provided. The SAP should describe how this data will be summarised and presented.

Example

"The following summaries will be presented for all screened patients:

Enrolment: the number of days recruiting, the number of patients screened, the number of patients recruited, the number of patients recruited per day, the number of screened patients not recruited, and the reason for non-recruitment. This summary will be provided overall and by study centre."¹⁸

Or

"The total number of eligible babies was not collected during the conduct of this study as it was considered heavy on resources and would not be sufficiently reliable."¹⁹

Eligibility

Item 22: Summary of eligibility criteria

Explanation

The trial inclusion and exclusion criteria should be specified in the protocol. Details of how eligibility data will be summarised should be provided. Some CONSORT diagrams provide details of the

number of patients screened followed by a breakdown of how many patients were eligible and how many were excluded due to violating each inclusion/exclusion criteria.

Example

“The number of ineligible patients randomised, if any, will be reported, with reasons for ineligibility.”¹⁹

Recruitment

Item 23: Information to be included in the CONSORT flow diagram

Explanation

Information included within a CONSORT flow diagram displays the progress of all participants through the trial. The CONSORT guidelines say that “you must complete a flow diagram in order to be compliant with the CONSORT 2010 standard.”¹⁷ They provide a CONSORT flow diagram template that can be used and adapted to create a trial specific flow diagram. All necessary information that is displayed in a CONSORT flow diagram should be listed in the SAP so it is clear where the patient throughput will begin to be summarised and how, specific follow-up time points that will be presented along with information on withdrawals and loss to follow up. Alternatively, a study specific CONSORT flow diagram template can be included in the SAP highlighting the information that will be collected.

Example

“The “CONSORT” diagram comprising the number of people screened, eligible, consented, randomised, receiving their allocated treatment, withdrawing/lost to follow-up”²⁰

Or

“A CONSORT flow diagram (appendix A) will be used to summarise the number of patients who were:

- assessed for eligibility at screening
 - eligible at screening
 - ineligible at screening*
- eligible and randomised
- eligible but not randomised*
- received the randomised allocation
- did not receive the randomised allocation*
- lost to follow-up*
- discontinued the intervention*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

*reasons will be provided.”⁹

Withdrawal/Follow-up – level of withdrawal

Item 24a: Level of withdrawal e.g. from intervention and/or from follow up

Explanation

In this section, all the possible levels of withdrawal should be listed, which may differ from trial to trial. Participants may withdraw from the intervention but continue with follow-up; withdraw from follow-up but allow data collected to date to be used; withdraw from follow-up and withdraw consent for data collected to date to be used; or be lost to contact/follow-up. Some clarification within the SAP about how each level of withdrawal will be categorised and presented is important.

Example

“The level of consent withdrawal will be tabulated (classified as “consent to continue follow-up and data collection” “consent to continue data collection only”, “complete – no further follow-up or data collection”).”²¹

Item 24b: Timing of withdrawal/lost to follow up data

Explanation

Timing of withdrawals and lost to follow up is important information. This information allows you to see if there are any patterns in lost to follow up or withdrawals between the different time points and intervention groups. Timing of withdrawal from follow-up or lost to follow up data can be presented in a Kaplan-Meier graph, a table or incorporated into a CONSORT flow diagram. For each follow-up time point information on the number of withdrawals and reasons for withdrawal, number included in the analysis and the number died (if applicable) should be provided.

Example

“This will be presented in CONSORT diagram format rather than as a table, with numbers and reasons for withdrawal and/or exclusion from analysis given at each stage (delivery, 6 months, 1 year, 2 years.”²²

Item 24c: Reasons and details of how withdrawal/lost to follow up data will be presented

Explanation

Patients can withdraw and be lost to follow up for many different reasons e.g. moved home, unable to participate any longer, withdrawn by clinician reasons etc. It is useful for the trial team to attempt to ascertain reasons for all withdrawals and loss to follow up. According to ICH E6 “Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject’s rights”.²³ Details of how this data will be presented should be included in the SAP. This information may be presented by intervention arm within a CONSORT flow diagram or in a table.

Example

“The numbers (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the trial will be summarised by treatment arm.”¹⁵

Baseline patient characteristics

Item 25a: List of baseline characteristics to be summarised

Explanation

Presentation of baseline characteristics by trial arm is crucial for every trial as it allows the reader to see whether the characteristics are balanced across intervention groups. Details of which baseline

characteristics will be summarised in the final report should be specified. Any factors on which the randomisation has been stratified or minimised should be included so that balance across the randomised groups can be demonstrated.

Example

“Patients will be described with respect to age, gender, time since diagnosis, cancer type, performance status, the number of previous chemotherapies and presence of brain metastases at baseline, both overall and separately for the two randomised groups.”²⁴

Item 25b: Details of how baseline characteristics will be descriptively summarised

Explanation

It is important to describe how baseline characteristics will be summarised and presented in the final analysis report. Formal statistical comparisons of baseline data by randomised groups are not normally advocated^{25 26} but if such comparisons are planned these should be justified. It is recommended that prognostic baseline characteristics are presented for the analysis population included in the primary analysis of the primary outcome as well as for all randomised participants in order to assess whether attrition has introduced selection bias and/or upset the balance achieved at randomisation.

Example

“Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by mean, SD and range if data are normal and median, IQR and range if data are skewed. Minimum and maximum values will also be presented for continuous data. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted.”⁹

Section 5: Analysis

Outcome definitions

List and describe each primary and secondary outcome including details of:

Item 26a: Specification of outcomes and timings.

Item 26b: Specific measurement and units (e.g. glucose control hbA1c (mmol/mol or %))

Item 26c: Any calculation or transformation used to derive the outcome (e.g. change from baseline, quality of life (QoL) score, time to event, logarithm etc).

Explanation

The SAP should define each outcome explicitly clearly identifying primary and secondary variables. If multiple primary variables are used then the considerations outlined in ICH E9²⁷ (2.2.5 Multiple Primary Variables) should be explored with direction provided on interpretation. Consistency should be ensured with the chosen approach to adjust for multiplicity in item 17. If an outcome is recorded at multiple timepoints which of these timepoints are required for the specific outcome. Detailed explanations should be provided, for example for survival outcomes making it clear what the length of survival is (e.g. calculated from the time of randomisation or time of administration of intervention) and censoring information.

The SAP should identify the specific measurement variable and its units if applicable (e.g. overall survival in days) and provide descriptions and details of any data manipulations or derivations to be performed by the statistician. Detail needs to be provided on what data manipulations or derivations will be performed and how they will be carried out. This may be relevant when data collection units may vary, for example HbA1c measurement in % or mmol or quality of life scores. If the calculation of a score is more complex, but a validated algorithm is available, then providing a reference and a link to the algorithm is sufficient. Scoring, including handling of missing data, should follow that proposed by the instrument developers, unless there is good reason to use an alternative technique, which should be described and justified. Sufficient detail needs to be provided in order for the reader to understand how the scores or results are to be calculated for each outcome.

Example

“For the sleep outcomes calculated using sleep diaries and actigraphy, a minimum of 5 nights of data from the 7 days before the randomisation visit date and a minimum of 5 nights of data from day 77 to day 84 from the randomisation visit date are required.

Total night-time sleep calculated using sleep diaries

The total amount of sleep for 1 night will be calculated in minutes using the amount of time between the time that the child went to sleep and the time that the child woke up the following morning minus any night-time awakenings that the child has had. The baseline measurement will be calculated using the average total amount of sleep in the 7 days before randomisation and the post-treatment measurement will be the average total amount of sleep from day 77 to day 84 post randomisation (this corresponds to the final 7 days of treatment as patients received enough drug supply only for 84 days). A minimum of 5 nights of sleep from each time period is required for the data to contribute to the primary outcome. If a child has < 5 out of 7 nights completed the data will be regarded as missing and the remaining data will not be included in the primary analysis.”²⁸

Analysis methods

List and describe each primary and secondary outcome including details of:

Item 27a: - What analysis method will be used, and how the treatment effects will be presented

Explanation

Conclusions can be affected substantially by the analysis method(s) used, therefore it is extremely important to pre-specify the analysis method(s) so there is no possibility of the method being chosen because it gives the most positive results. If transformations are to be applied, then these should be specified along with the rationale for the transformation and the resulting interpretation.

For each outcome, the SAP should specify what analysis method(s) will be used for statistical comparisons and which trial participants will be included in this analysis if applicable. The SAP should also define what summary measures will be reported such as any descriptive statistics to be displayed, what the unit of each effect estimate will be and whether confidence intervals and p-values will be reported. If more than one method is to be used to analyse the primary outcome, e.g. adjusted and unadjusted for covariates, then the primary analysis method should be identified.

Example

“The number and percentage of deaths by 90 days after randomisation will be reported for each treatment group. The primary-effect estimate will be the relative risk of 90-day mortality, reported with a 95% CI. The absolute risk reduction and 95% CI will also be reported. Deaths by 90 days after randomisation will be compared between the treatment groups, unadjusted, using the Fisher exact test.”²⁹

Statistical Methods – adjustment for covariates

Item 27b: List and describe each primary and secondary outcome including details of:

- *any adjustment for covariates*

Explanation

For each analysis, the SAP should specify whether adjustment will be used, and if so, the covariates to be used (including the categories if applicable), and how these will be included in the model (e.g. as fixed effects, random effects etc.). For the primary outcome, it must be clear whether the adjusted or unadjusted analysis is the primary analysis as failing to pre-specify can lead to bias.

Example

“...adjusted for baseline variables, will also be conducted, using multilevel logistic regression. Baseline variables adjusted for in the multilevel logistic regression model will be the components of the MEDS score (age, metastatic cancer, nursing home residence, altered mental status, septic shock, respiratory difficulty, low platelet count and low neutrophil count) and a site-level random effect.”²⁹

Item 27c: List and describe each primary and secondary outcome including details of:

- *methods used for assumptions to be checked for statistical methods*

Explanation

All statistical tests require that a number of assumptions hold in order for the test to be valid and the conclusions drawn from the analysis to be correct. However, a two-stage analysis may lead to bias.³⁰⁻³³ If checks on the underlying assumptions are to be performed then it is important for these to be pre-specified.

Example

“The PH assumption will be checked by adding time-dependent covariates and graphing scaled Schoenfeld residuals against time (Therneau & Grambsch, 2000). If PH is found not to fit the data adequately, an AFT alternative will be fitted and the adequacy of its fit assessed using Q-Q plots (Bradburn et al. 2003).”²⁰

Item 27d: List and describe each primary and secondary outcome including details of:

- *alternative methods to be used if distributional assumptions (e.g. normality, proportional hazards etc) do not hold*

Explanation

Many distributional assumptions can be checked during blind data review²⁷ and the SAP updated accordingly. However, if assumptions can only be checked once the treatment allocations are known then the SAP should pre-specify the alternative methods to be used if the underlying assumptions do not hold. The approach taken should be considered carefully as bias may be introduced either by choosing the method of analysis based on the results of tests of assumptions³¹⁻³³ or from performing hypothesis tests in which the underlying assumptions are not upheld. Three possible approaches may be considered: i) pre-specify alternative analyses and how the statistician will choose between them in the SAP so that the process is transparent; ii) select a method of analysis that is robust to assumptions, e.g. survival analysis will be carried out using the restricted mean survival time (RMST)

method as this does not assume proportional hazards (PH); or iii) state the method of analysis to be used in the SAP and specify that a sensitivity analysis will be performed using an alternative set of assumptions and the results compared.

Example

“If PH is found not to fit the data adequately, an AFT alternative will be fitted and the adequacy of its fit assessed using Q-Q plots (Bradburn et al. 2003). If this too does not fit, a residual life analysis (Royston & Parmar 2011) will be used as the basis for summarising the treatment effect”²⁰

Statistical Methods – sensitivity analyses

Item 27e: List and describe each primary and secondary outcome including details of:

- *any planned sensitivity analyses for each outcome*

Explanation

For each outcome, where applicable, the SAP should specify whether any sensitivity analyses will be conducted, and what these analyses will be with the same level of detail as for the primary and secondary analyses. The SAP should also include details of the analysis population to be used for each sensitivity analysis. The SAP should state whether there is a minimum percentage of missing data required to trigger the need for sensitivity analyses.

Example

“A sensitivity analysis will be performed to include the patients that were not included in the primary analysis because they did not fully complete the loading dose and two hour maintenance period. They will be assumed to be not adequately sedated i.e. AS=0. The per-protocol analysis and sensitivity analyses will test the robustness of the primary complete-case analysis.”⁹

Statistical Methods – subgroup analyses

Item 27f: List and describe each primary and secondary outcome including details of:

- *any planned subgroup analyses for each outcome*

Explanation

All pre-planned subgroup analyses should clearly specify the baseline characteristics to be considered, the cut-offs for the subgroup categories, the statistical method that will be used

and how the results will be presented (e.g. in a forest plot). However while a large number of subgroup analyses should be avoided due to issues with multiplicity this may be appropriate for example when the aim is to demonstrate consistency across subgroups.

Example

“The following pre-specified subgroup analyses will be performed on the primary outcomes stratified by:

- whether randomised in the 1st or 2nd 24 hours after birth
- gestational age at birth as per minimisation: 23w, 24w, 25w, 26/27w, 28/29/30w.
- male versus female
- colonised versus not colonised at 2 weeks
- gestational age <28+0 versus ≥28+0

Results will be presented on forest plots with the interaction results alongside.”¹⁹

Missing data

Item 28: Missing data- reporting and assumptions/statistical methods to handle missing data (e.g. multiple imputation)

Explanation

The majority of trials will have some missing data³⁴, which can introduce bias depending on the type of “missingness” (e.g. missing completely at random, missing at random, missing not at random³⁵). Therefore, it is important that the SAP states how missing data will be handled and reported including details of any statistical methods and their assumptions, to be used to handle missing data. It should explain if there are any plans to impute missing outcome data, including a list of variables that will be used in the imputation process if multiple imputation (MI) is to be used. Using different statistical methods to handle missing data can lead to differing conclusions so it is crucial to pre-specify exactly what methods will be used under what circumstances, and which will be considered the primary analysis. It is highly recommended that sensitivity analyses are conducted to assess the robustness of trial results when using different methods to handle missing data³⁶ and these should be clearly described in the SAP.

Example

“Multiple imputation (MI) will be used to account for participants who have an observed outcome at 6 months, but are missing the outcome at 12 months, as well as participants who completed some, but not all, of the questions on the CPG disability score at 12 months. 20 imputations will be performed, and results will be combined using Rubin’s Rules. Only participants who will be included in the analysis will be included in the imputation model. Imputation will be performed separately within each treatment arm.

The imputation model will include the three questions which form the CPG disability score at baseline, 6 months, and 12 months, as well as site of recruitment, age, gender, the HADS depression score at baseline, and employment status (employed or in full time education vs not employed or in full time education) (14 variables in total). In the intervention arm, multilevel imputation will be performed, with 'course' included in the imputation model as a random effect. Missing data in any of the covariates to be adjusted for in the analysis (site of recruitment, age, gender, HADS depression score, CPG disability and baseline) will be accounted for using the same multiple imputation model as above. We will perform three sensitivity analyses for the primary outcome to assess the robustness of the results to other methods of account for missing data. The first sensitivity analysis involves specifying a different imputation model than that used in the primary analysis, and the last two sensitivity analyses involve re-analyse the primary outcome using two approaches which are not based on MI.”³⁷

Additional Analyses

Item 29: Details of any additional statistical analyses required e.g. complier-average causal effect (CACE) analysis³⁸

Explanation

Any additional analyses to be conducted should be specified with reasons these are required, a description of the additional analysis and how it will be conducted. This may include pre-specified exploratory analyses that are hypothesis generating or confirmatory of issues identified in other trials.

Example

“The delivery of a complex intervention may improve with time as those delivering the intervention gain experience and familiarity. Typically, such improvements will be more rapid at first and then tail off over time to reach a steady state; termed a “learning curve”. Modelling the learning curve enables estimation of the treatment effect for an experienced team. A site-level learning curve for patients randomly allocated to early, goal-directed, protocolised resuscitation (EGDPR) will be modelled by repeating the multilevel logistic regression on the primary outcome and including a power curve ($aX-b$) for the sequential observation number (X) for each EGDPR patient within each site.”²⁹

Or

“Complier Average Causal Effect (CACE) analysis: Instrumental variable regression will be used to investigate the effect of compliance to treatment dose, assuming linear dose-response relationship. The estimate of increased or decreased treatment effect with every 1% increase of compliance will be presented.”¹⁵

Harms

Item 30: Sufficient detail provided on summarising harms e.g. information on severity, expectedness and causality; details of how AE's are coded or categorised; how adverse events (AE's) data will be analysed, i.e. grade 3/4 only, incidence case analysis, intervention emergent analysis

Explanation

Consideration of safety data is key for every clinical trial. It is important that safety data is reviewed and details are provided in the SAP on how safety data will be summarised in the final analysis report including the analysis population to be used. Information may be provided on the severity, causality and expectedness of the adverse event, information on how the adverse events will be coded or categorised and by whom. The method of summarising the adverse event data should be described ensuring it is clear whether the descriptive summary will use number of events or number of patients and any analyses to be conducted (e.g. will the adverse events be compared descriptively or will formal statistical testing be undertaken.)

Example

“The number of treatment related serious adverse events (SAE), including treatment related deaths, are reported divided by their relationship as ‘definitely’, ‘probably’ and ‘possibly’ related to treatment. The proportions of patients with grade 3/4 toxicity or SAE will be compared descriptively across treatments and differences assessed for clinical significance.”³⁹

“The number (and percentage) of patients experiencing each AE/SAE will be presented for each treatment arm categorised by severity. For each patient, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of occurrences of each AE/SAE will also be presented for each treatment arm. No formal statistical testing will be undertaken.”⁷

Statistical Software

Item 31: Details of statistical packages to be used to carry out analyses (optional)

Explanation

Details of the statistical packages to be used to conduct the statistical analyses may be provided in the SAP. While version numbers of software may change during the lifetime of the trial and so should not be specified in the SAP they should be included within final reports.

Example

“The analysis will be carried out using Stata version 12. Other packages such as R, SAS, or REALCOM may be used if necessary.”²⁴

References

Item 32a: References to be provided for non-standard statistical methods

Explanation

References should be provided in a SAP for any non-standard statistical methods that will be used. If there is any doubt on whether a method is non-standard then it is better to include a reference.

Item 32b: Reference to Data Management Plan

Explanation

Reference should be made to the Data Management Plan (DMP) with the version number that was used when writing the SAP. This is important as both documents should be linked with information in the DMP that is also important for the final analysis report. If there is no DMP, then the location of this information (e.g. data handling and cleaning) should be provided.

Item 32c: Reference to the Trial Master File and Statistical Master File

Explanation

The Statistical Master File is part of the Trial Master File but is often held separately with restricted access. The Statistical Master File may hold details of the randomisation process or specific protocol deviations that the statistician needs to refer to when executing the statistical analysis plan. If a Statistical Master File is held separately to the Trial Master File then both should be referenced.

Item 32d: Reference to other Standard Operating Procedures or documents

Explanation

Reference should be made to any other Standard Operating Procedures (SOPs) or documents that are adhered to and followed when writing the SAP.

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