DEVELOPMENT OF GUIDANCE FOR STATISTICAL ANALYSIS PLANS FOR CLINICAL TRIALS

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Introduction

- SAPs topic discussed at Nov 2012 UKCRC Stats Meeting
  - Lack of guidance
    - ICH E3- Clinical Study Report
    - ICH E9- Statistical Principles
  - Variation in practice
  - Resource constraints
- International Stakeholders Group on Reporting Biases role of SAPs in reducing such bias
- Aim-produce comprehensive guidance for SAPs
  - increase efficiency & quality of SAPs to reduce selective reporting of analyses

Project components

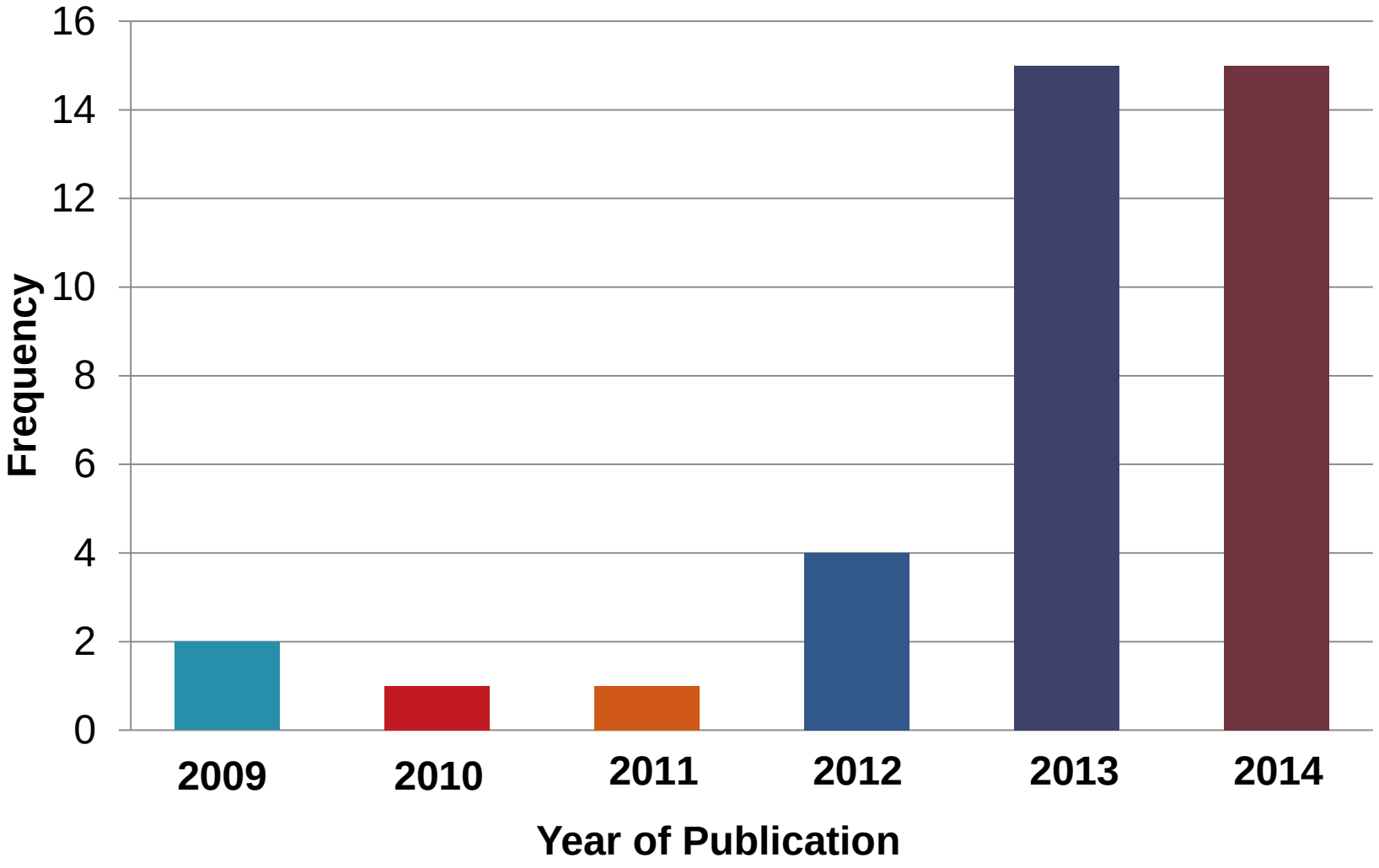
- Identification of existing Guidance
- Survey of current practice across registered CTUs
- Delphi Survey
  - Consensus meeting
- Development of Guidance
- Critical Review by registered CTUs
- Piloting the guidance

-funded by the MRC Hubs Network

Identification of existing guidance

- Contacted all major RCT funding bodies, regulators, charitable organisations
- Contacted 39 and 28 responses received (Response rate 72%)
- No guidelines on SAPs other than ICH E9

Standalone Publication of SAPs



Publication of SAPs

- Move to publication of SAPs
  - Question what are journals using to assess quality of SAPs?

Publication Journal	Publish SAPs	Submission	Guidance
Trials	✓	✗	✗
JAMA	✗	✓	✗
BMJ	✗	✗	✗
NEJM	✓	✓/✗	✗
Lancet	✗	✗	✗

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No information on website but response from Trials: “We encourage publication of study protocols and SAP is generally considered a part of this. We ask that sufficient detail is given in the SAP so an independent researcher is able to rerun the analyses; however, this is enforced through the peer review process, rather than through specifying set items.”

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"All manuscripts reporting clinical trials must include a copy of the trial protocol including the complete statistical analysis plan"

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No information on website but response from BMJ: “We don't have any specific advice on reporting statistical analysis plans, but I can see that this would be useful.”

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"The protocol of a clinical trial should be submitted as a separate PDF file. A statistical analysis plan may be included with the protocol"

Review HTA Monographs

- HTA guidance requests SAPs to be included
- 155 published in total only 10% (16/155) included SAPs
  - 25% (39/155) mention SAP but do not include
  - HTA not enforcing their request for SAP publication

Survey of UKCRC Registered CTUs

- Aim: identify current practice & opinions
- Survey development:
  - SAP SOP/ template requested to reduce number of questions.
  - piloted amongst co-applicants
- 100% response rate (46/46)

Questions

- Are UKCRC CTUs writing SAPs?
- Who is the intended audience of a SAP?
- When should it be written?
- Who should be involved in writing it?
- Who should approve it?
- Which analyses should you write a SAP for? Should it cover interim analyses as well as final analyses?
- Should it cover data manipulations, merges, QC……..

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100% write a SAP for later phase RCTs

93% have a SOP for SAP
- –2 under development
- –1 not required

87% have a SAP template or set of instructions that they use when writing SAP

Questions

- Are UKCRC CTUs writing SAPs?
- Who is the intended audience of a SAP?
- When s
- W
- Sh

Audience	Number of CTUs % (N)
Statisticians	96% (44)
Chief Investigator	78% (36)
Trial Management Group	78% (36)
DMC/TSC Members	65% (30)

When should a SAP be written?

Timelines for completing and signing off a SAP:

Desirable timelines for completing and signing off a SAP

- 48% - ‘Prior to any comparative outcome analyses carried out in DMC reports’

Actual timelines for completing and signing off a SAP

- 50% - ‘Prior to the database being locked and final analysis beginning’.

Trade off: writing SAP earlier limits knowledge of data how it behaves compared to writing SAP before database lock and having detailed SAP.

Who should be involved in writing it?

Characteristics	Responsibility	Number of CTUs % (N)
Seniority	Junior Statistician	15% (7)
	Senior Statistician	33% (15)
	Both	52% (24)
Blinded to comparative analyses whilst working on the SAP	Blinded	65% (30)
	Unblinded	15% (7)
	Both	17% (8)
	Missing/NA	2% (1)

- Blinding:

Should everyone involved in the prep. of SAP be blinded?	Do you ask everyone involved in development of SAP to be blinded to data % (N)	
	Yes	No
Yes	77% (24)	23% (7)
No	0% (0)	100% (10)
Depends on Experience	33% (1)	67% (2)
N/A/Other	0% (0)	100% (2)

  - ICH E9 Guidelines: “The plan should be blind reviewed and possibly updated as a result of the blind review” 63% of CTUs undertake blind review.

Who should approve the SAP and sign-off the SAP?

Role of person responsible for approving & signing off the SAP	Number of CTUs % (N)
Chief Investigator	87% (40)
The statistician in the CTU supervising production of the open DMC report	39% (18)
A statistician in the CTU involved in the trial but blinded to treatment group comparisons	37% (17)
The statistician in the CTU supervising production of the closed DMC report	37% (17)
Member of TSC	35% (16)
Head of Statistics	30% (14)
A statistician outside the CTU on the TSC/DMC	24% (11)
Member of DMC	24% (11)
The statistician producing closed DMC reports	22% (10)
CTU Director	20% (9)
A statistician in the CTU not involved in the trial	11% (5)
Trial Co-ordinator/Manager	11% (5)
Data/Database Manager	7% (3)
A statistician outside the CTU not involved in the trial	4% (2)

Which analyses should you write a SAP for?

Produce SAP only for final analyses	Number of CTUs % (N)
Yes	41% (19)
If yes, do you write a separate SAP to cover interim analyses or other reporting time points?	
Yes	74% (14)
No	26% (5)
No	59% (27)
If no, does the SAP also cover interim analyses?	
Yes	100% (27)
No	0% (0)

Delphi Survey

- Aim - to establish consensus on content of SAPs.
- 73 Participants-
  - CTUs,
  - contributors to CONSORT and SPIRIT guidelines,
  - methodologists,
  - pharmaceutical industry statisticians,
  - journal editors
  - regulators.
- List of components identified using copies of SOPS for SAPS and SAPs returned in response to survey
- Listing sent to co-applicants to review
- Comprehensive list of 89 components to consider for inclusion within SAP

Delphi survey

- Two rounds
- Round 1- list of 89 items each person asked to score between 1 and 9
  - Opportunity to add items
- Summarise scores- show responders their scores against other responders
- Round 2 - ask to rescore and score new items

Definition of Consensus

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

Delphi Survey – Round 1

- Response rate – 77% (56/73)
  - CTUs – 87% (40/46)
  - Non-CTUs – 48% (16/33)
- Results:
  - Consensus In – 32% (28/89)
  - Consensus Out – 0%
  - Borderline Consensus – 11% (10/89)
  - No Consensus – 57% (51/89)
- Additional Components suggested - 21

Delphi Survey – Round 2

- Response rate – 96% (54/56)
  - CTUs – 71% (40/56)
  - Non-CTUs – 25% (14/56)
  - Missing – 4% (2/56)
    - Reasons: illness and on A/L
- Results:
  - Consensus In – 42% (46/110)
  - Consensus Out – 1% (1/110)
  - No Consensus – 47% (52/110)
  - Borderline Consensus In – 8% (9/110)
  - Borderline Consensus Out – 2% (2/110)

Consensus Meeting

- Consensus Meeting members
  - co-applicants
  - representation from MHRA,
  - pharmaceutical industry statisticians
  - journal editors

- Meeting focused on components that achieved borderline consensus in, borderline consensus out and no consensus

- Provided expert panel with copies of results from round 2 and asked them to discuss results and following discussion make a recommendation

Consensus Meeting Results

- Consensus In:
  - 61 Items
- Consensus Out:
  - 29 Items
- Related to SAP and important to document but elsewhere:
  - 17 Items

Guidance context

- Protocol is compliant with the SPIRIT
- The SAP applies to a clean/validated dataset
- The SAP is not a standalone document
  - Should be read in conjunction with the protocol
  - Avoid replicating large chunks of the protocol referencing it instead

Consensus Out

- Description of interventions
- Randomisation details
  - List generation; how treatment allocation is concealed; blinding
- Inclusion/Exclusion Criteria
- Statistical Methods section of protocol- (statement of compliance instead)
- Listing of follow-up assessments
- Listing of measurements taken at each follow-up assessment
- Methods of measurement of outcomes
- Descriptions of what would be defined as an AE, AR, SUSAR and SAE etc.
- Details on PharmacoVigilance
- Listing of abbreviations used in document
- Details on data quality to be performed by the Statistician i.e. completeness of data.
- Blank trial specific CONSORT flow diagram

Consensus Out Cont'd

- Method of model building e.g. forwards, backwards etc
- List and describe each primary and secondary outcome including definitions of outcomes with details on:
    - order of analyses described e.g. descriptive, univariate, multivariate etc
- Details on any other analyses to be conducted by others e.g. Health Economics etc
- Results on Interim analyses e.g. where can the results be found and any consequences or decisions made following the results
- Actual results of Interim analyses
- Details of what statistical programs will be validated and quality checked
- References to any relevant Standard Operating Procedures (SOPs) with version number
- Reference to Monitoring Plan
- Signatures of:
    - Person who will execute the SAP; Senior Statistician responsible for supervision of person executing SAP; Head of Statistics; Chair of TSC;
    - Chair of DMC; Health Economist

Guidance Document

- Guidance document intended for later phase RCTs
- Recommendations provided address minimum content to be included within SAP
- Appendix section includes items that are important to SAP and in particular a RCT but do not necessarily need to be included in SAP

  - SPIRIT guidelines mention in relation to data management for example that there should be reference to where these items are found if not in protocol and we feel that applies to SAP too.
- Did not want a checklist approach
- Did want item, description, example

SAP Guidance

Section/Item	Index	Description
Section 1: Administrative Information		
Title and Trial registration	1a	Descriptive title identifying the study design, population, interventions, and, if applicable trial acronym
	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 of SAP revisions
	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 leader

Section 2: Introduction		
Background and rationale	7	Short synopsis of trial background and rationale including brief description of research question and brief justification for undertaking the trial
Objectives	8	Specific objectives or hypotheses

Section 3: Study Methods		
Trial design	9a	Brief description of trial design including type of trial (e.g. parallel group, crossover, factorial, single group) and allocation ratio and may include brief description of interventions
Randomisation	10	Randomisation details e.g. whether any minimisation or stratification occurred (including 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	9b	Superiority, equivalence or non-inferiority study, and which comparisons will be presented on this basis
Statistical Interim analyses and stopping guidance	15a	Information on Interim analyses e.g. what interim analyses will be carried out and listing of time points
	15b	Any planned adjustment of p-values due to interim analysis
	15c	Details of guidelines for stopping a trial early
Timing of final analysis	18b	Timing of final analysis e.g. all outcomes analysed collectively or timing stratified by planned length of follow-up
Timing of outcome assessments	18a	Time points at which the outcomes are measured including visit windows

Section 4: Statistical Principles		
Levels of confidence intervals and p-values	12	Level of Confidence Intervals (CI)
	13	Level of Statistical Significance
	14	Any adjustment for multiplicity including how the type 1 error is controlled across multiple treatments or endpoints (if applicable)
Adherence and Protocol Deviations	15a	Definition of adherence to the intervention and how this is assessed including extent of exposure
	15b	Description of how adherence to the intervention will be presented
	15c	Definition of protocol deviations for the trial
	15d	Description of which protocol deviations for the trial will be summarised (may include details on whether level of 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)
Analysis populations	16	Analysis populations e.g. Intention to treat, Per protocol, complete case

Section 5: Study Population		
Screening data	17	Reporting of screening data to describe representativeness of study sample to be presented
Eligibility	18	Summary of eligibility data to be presented
Recruitment	19	Information for CONSORT flow diagram
Withdrawal/Follow up	20a	Level of withdrawal e.g. from intervention and/or from follow-up
	20b	Timing of withdrawal/lost to follow up data
	20c	Reasons and details on how withdrawal/lost to follow up data will be presented
Baseline patient characteristics	21a	List of baseline characteristics to be summarised
	21b	Details on how baseline characteristics will be descriptively summarised e.g. categorical data will be presented using counts and percentages, continuous data will be presented using number of patients, mean, median, SD, minimum, maximum and IQR

Section 6: Analysis		
Outcome definitions		List and describe each primary and secondary outcome including details on:
	22a	- specification of outcomes and timings. If applicable include the order of importance of major or key secondary endpoints (e.g. order in which they will be tested)
	22b	- specific measurement and units (e.g. glucose control hbA1c (mmol/mol or %))
	22c	- any calculation used to derive the outcome (e.g. change from baseline, QoL score, time to event etc)
Analysis methods	23a	- what analysis method will be used, and how the treatment effects will be presented
	23b	- any adjustment for covariates
	23c	- methods used for assumptions to be checked for statistical methods
	23d	- details on alternative methods to be used if distributional assumptions do not hold e.g. normality, PH etc
	23e	- any planned sensitivity analyses for each outcome where applicable
	23f	- any planned subgroup analyses for each outcome including how subgroups are defined where applicable
Missing data	24	Missing data- reporting and assumptions/statistical methods to handle missing data (e.g. multiple imputation)
Additional analyses	25	Details on any additional statistical analyses required e.g. Complier-average causal effect (CACE) analysis
Harms	26	Sufficient detail provided on summarising safety data e.g. information on severity, expectedness and causality; details on how AE's are coded or categorised; how AE data will be analysed, i.e. grade 3 out of 4 only, incidence case analysis, intervention emergent analysis

Statistical Software	**27**	**Details on statistical packages to be used to carry out analyses**
References	28a	References to be provided for non-standard statistical methods
	28b	Reference to Data Management Plan
	28c	Reference to the Trial Master File and Statistical Master File
	28d	Reference to other SOPs or documents to be adhered to

Challenges

- Developing survey
  - Response rates
  - Who are you surveying? E.g. Trial statistician
- Delphi survey
  - Response rate outside of the network lower
- Balance of detail and confidentiality
- Finding good examples to illustrate items
- Feedback
  - Critical review and expert panel
  - Building in flexibility e.g. whether or not to test for assumptions, full replication of sample size calculations
  - Did/didn’t want a template
- Allowance for variation in statistical resource

Where are we now?

- Second round of expert comments
- Piloting identified
- Expect to finalise before end of year at which point go to for endorsement
- Endorsement
  - UKCRC reg CTU exec group
  - NIHR- SAPs published on HTA trial web pages along with protocols
  - Shift in time frame
- Kept engagement with CTUs throughout
  - Update after 12 months of use/feedback