MRC-NIHR Trials Methodology Research Partnership: Webinar recording

An early phase clinical trials extension to the guidelines for the content of Statistical Analysis Plans

Presented by Victoria Homer (University of Birmingham)

17 February 2022

On behalf of the UKCRC Registered CTU Network

The slides are also available below.

For any queries, please contact uktmn@nottingham.ac.uk

https://www.youtube.com/watch?v=5jw-ELuJQgY

An Early Phase Clinical Trials Extension to the Guidelines for the Content of Statistical Analysis Plans

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Definition

For the purpose of this project, we are defining early phase clinical trials as trials which aim:

- To determine safe doses and dosing schedules for a treatment/intervention (phase I),
- To establish whether there is any signal of efficacy (phase I/II or II).

To include single-arm or randomised phase I trials and single-arm phase II trials.

Background

The design, conduct and analysis of early phase trials does not solely impact that specific study, but has implications on all related subsequent trials.

This project aims to address one component of running a successful early phase trial by providing guidance in the generation of trial Statistical Analysis Plans (SAPs).

Guidelines for the Content of Statistical Analysis Plans in Clinical Trials

Carrol Gamble, PhD[1]; Ashma Krishan, BSc[2]; Deborah Stocken, PhD[3,4]; et al

» Author Affiliations | Article Information

JAMA. 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556

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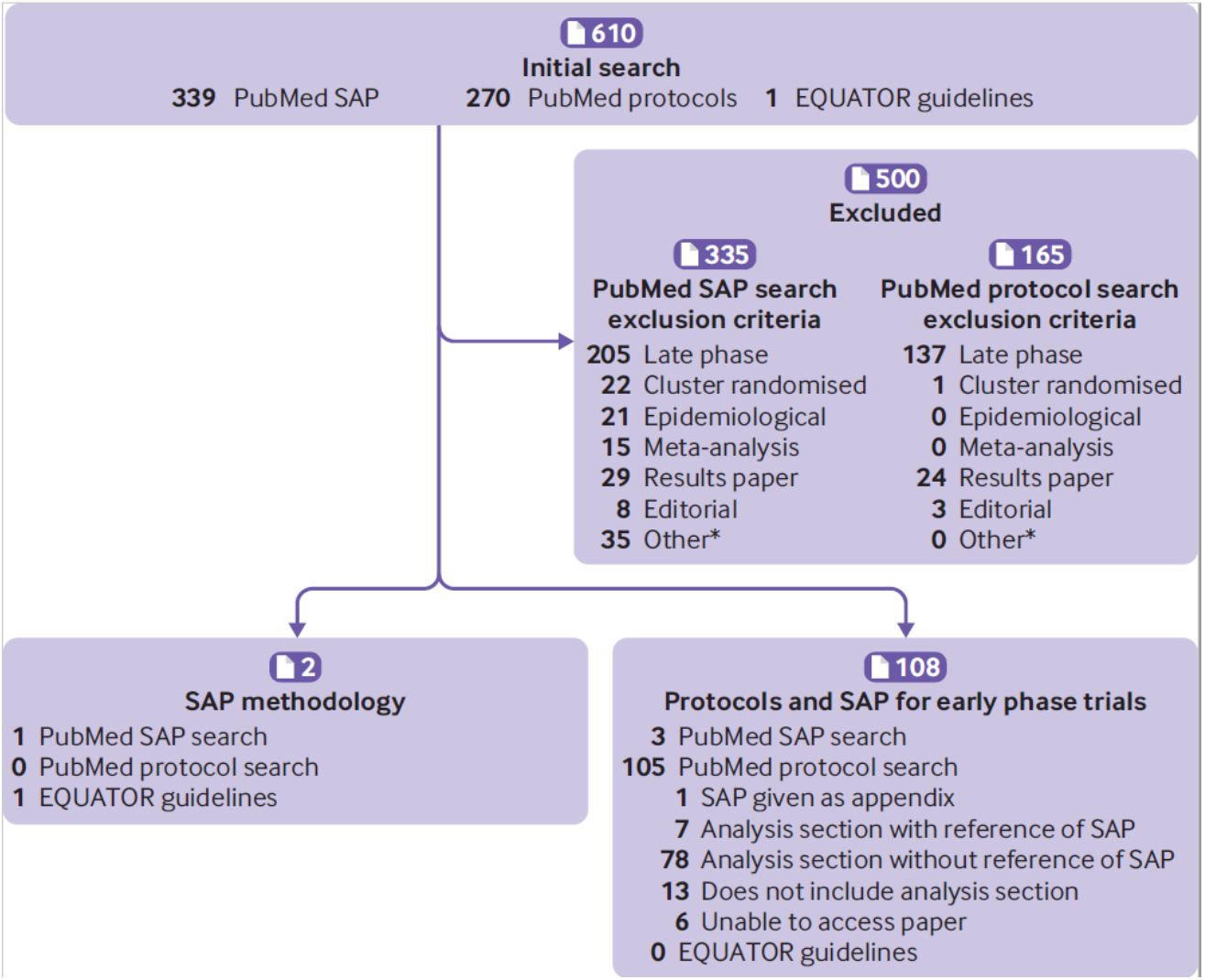
Literature Review Results



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Requirements of Funders and Regulators

- Dose-escalation decisions are often poorly documented potentially resulting in ambiguously and non-robust decisions to escalate.
- When model-based approaches are used, the choice of model should be clearly justified, the risk of overdosing must quantified and justified to be acceptable, supported by simulation where applicable.
- The strategy for evaluating model adequacy should be pre-specified.
- Explicit and detailed stopping criteria, interim go/no-go rules and dose escalation rules.
- The programming codes for novel modelling should be made available in the SAP.

Guideline Development – CTU Survey

Survey of UK CTUs:

- Circulated to the UKCRC network in May 2020
- 40 CTUs responded.
- 21 indicated conducting early phase trials.
- Current authoring practice and content of SAPs was gauged.
  - Practice and content of early phase SAPs varied (e.g. some units would not produce SAPs for rule based phase I trials as sufficient information would be contained within the protocol).
  - Most common that units had templates/instructions covering all trials but some had bespoke early phase template.

Guideline Development – Expert Review Meeting

Expert Review Meeting:

- Held 26th October 2020.
- 16 UK and US academic & NHS statisticians, pharmaceutical statisticians, and regulators.
- Reviewed draft guidelines, discussed some of the larger proposed amendments and ‘contentious’ issues.
- Comments received from those who couldn’t make the meeting

Guideline Development – Piloting

Piloting:

- Guidelines piloted on early phase trials at 6 UK CTUs.
- Piloting occurred on new and existing phase I and II trials in differing therapeutic areas
- Guidelines updated for a final time following these reviews.

Proposed Guidelines

Of the original 55 items proposed in Gamble *et al.*, 30 items have remained unchanged, 25 have been modified to better reflect early phase trials, and a further 11 new items have been proposed.

Each item is supplemented by:

- An extended description,
- Examples covering different trial designs and therapeutic areas.

Proposed Guidelines – Example Update

Objectives

Item 8:

Description of specific question, objectives or hypotheses. It should be made clear what the key objectives are (for example primary and secondary objectives that encompasses toxicity, efficacy, PK, PD, or some combination).

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, then additional detail may be required within the SAP. From the trial objectives or hypotheses, it should be clear whether the final trial conclusions (and where appropriate, the dose to be taken forward), are to be based on toxicity, efficacy, PK, PD or some combination of the aforementioned. In the scenario where the design is jointly assessing toxicity and efficacy, it should be clear which one is to take precedent in the scenario where they draw different conclusions.

Example:

"ADaPT aims to establish a dose of the treatment sufficient to raise circulating DHEA levels in severely injured trauma and hip fracture patients with rule-based escalation supplemented by Bayesian hierarchical models." [8]

"CLARITY aims to assess the eradication of detectable minimal residual disease (MRD) using the drug combination." [9]

Proposed Guidelines – Unchanged Items

Things which have stayed the same:

- Administration information
- Timing of final analysis and outcome assessments
- Adherence and protocol deviations
- Statistical software
- References

Proposed Guidelines – Minor Alterations

Minor alterations include:

- Amendments to items and descriptions to ensure pertinence to early phase clinical trials
- Details regarding what the key objectives are and whether they encompass toxicity, efficacy, PK, or PD
- Amendments to wording to reflect that while they can occur, randomisation and formal hypothesis testing in early phase clinical trials are rare, and therefore sections on these details may not be required.
- Greater details regarding analysis population (and how they will be referred to) to reflect that patients may enter the trial in cohorts.

Proposed Guidelines – Significant Alterations

Significant alterations include:

- Increased details regarding trial design methodology, and model choice, where applicable.
- Update of outcome definitions following the adoption of ICH E9 (R1).
- Inclusion of simulation reports to justify trial design or sample size.
- Inclusion of code required for novel methodology.
- Inclusion of dose transition pathways.
- Amendments to wording to be more neutral to both frequentist and Bayesian methodology.

Proposed Guidelines – A Few Examples

	Original Gamble *et al.* Paper		Extension for Early Phase Trials	
Section	**Item**	**Description**	**Item**	**Description**
Section 3: Study Methods				
Trial Design	9	Brief description of trial design including type of trial (e.g., parallel group, multiarm, crossover, factorial) and allocation ratio and may include brief description of interventions	9a	Brief description of trial design, including the trial phase and the design method (dose escalation e.g., CRM or single-arm phase II e.g. Simon's Two Stage). If the trial has a randomised element to it, summary information regarding the randomisation, including the allocation ratio, should be specified.
			9b	Treatment information, including the dose levels of intervention(s). Where appropriate, and if multiple doses are used, the following should also be reported: the ordering and combination (in the instance of multiple agents under investigation) of dose levels, and the dose level to start at.
			9c	Details regarding the statistical methodology underpinning the trial, including the choice of the number of parameters in the model if applicable, its empirical form and all formulae. It is also important to ensure all model parameters are given, including where appropriate, the weights of the model.
			9d	Rules of the trial design and model. Here information on the target objective (toxicity, response, PK, or PD, either singularly or in combination), classification of overdosing, and any stopping boundaries should be given. This may include the desired certainty in these estimates. Moreover, where dose escalation is to occur, details regarding dose escalation and dose skipping should be given.
			9e	Experimental details and design specifics. For dose escalation trials, information regarding cohort size, including whether this is fixed or flexible should be given. Indication of the end of trial definition and stopping rules. For model-based and model-assisted designs, details on the prior including full skeleton (if applicable) and its elicitation should be given. For single arm phase II trials, the target sample size and, where appropriate, the timing of any interim analyses

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9a	Brief description of trial design, including the trial phase and the design method. Randomisation information, including the allocation ratio.

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			9b	Treatment information, including: • the dose levels of intervention(s), • the ordering and combination of dose levels, and • the dose level to start at.
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9c	Details regarding the statistical methodology underpinning the trial. All model parameters are given, including where appropriate, the weights of the model.

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9d	Rules of the trial design and model. Target objective, Classification of overdosing, and Any stopping boundaries. Details regarding dose escalation and dose skipping.

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Proposed Guidelines – A Few Examples

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9e	Experimental details and design specifics. Information regarding cohort size. Indication of the end of trial definition and stopping rules. Details on the prior including full skeleton. For single arm phase II trials, the target sample size and the timing of any interim analyses

Proposed Guidelines – A Few Examples

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Section/Item	**Item No**	**Description**	**Item No**	**Description**
Section 3: Study Methods				
Statistical Interim Analyses and Stopping Guidance	13a	Information on interim analyses specifying what interim analyses will be carried out and listing of time points	13a	Information pertaining to interim dose decisions (e.g. escalation, de-escalation, remain at current dose or stop early).
	13b	Any planned adjustment of the significance level due to interim analysis	13b	Information on other interim analyses specifying what and when interim analyses will be conducted.
	13c	Details of guidelines for stopping the trial early	13c	Any planned adjustment of the significance level due to interim analysis
			13d	Details of guidelines for stopping the trial early

Proposed Guidelines – A Few Examples

	Original Gamble *et al.* Paper		Extension for Early Phase Trials	
Section/Item	**Item No**	**Description**	**Item No**	**Description**
Section 4: Statistical Principles				
Analysis Populations	20	Definition of analysis populations, e.g., intention to treat, per protocol, complete case, safety.	20	Clear definition of the trial/dose cohort(s) including how cohorts will be referred to, how patients enter cohorts, the minimum number of patients needed to be in a cohort (and how long they have been in) before dose escalation decisions can be made. Trial level definitions of patient populations (e.g., per-protocol, intention to treat, safety) should also be given. Details regarding evaluable patients and specify what happens to unevaluable patients should also be made. These definitions should also be provided for any interim analysis populations.

Proposed Guidelines – A Few Examples

	Original Gamble *et al.* Paper		Extension for Early Phase Trials	
Section/Item	**Item No**	**Description**	**Item No**	**Description**
Section 6: Analysis				
Estimand Definition[b]		List and describe each primary and secondary outcome including details of		List and describe each primary and secondary estimands including details of:
	26a	specification of outcomes and timings. If applicable include the order of importance of primary or key secondary end points (e.g., order in which they will be tested)	26a	Treatment (including treatment combinations)
	26b	specific measurement and units (e.g., glucose control, hbA1c [mmol/mol or %])	26b	Population
	26c	any calculation or transformation used to derive the outcome (e.g., change from baseline, QoL score, time to event, logarithm, etc.)	26c	Variable of interest
			26d	Intercurrent event handling strategy
			26e	Summary measures

Proposed Guidelines – A Few Examples

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Section/Item	**Item No**	**Description**	**Item No**	**Description**
Section 7: Suggested SAP Appendices				
Simulation Report			33	Operating characteristics of the trial design to assess the probability of trial success under different plausible scenarios.

Proposed Guidelines – A Few Examples

	Original Gamble *et al.* Paper		Extension for Early Phase Trials	
Section/Item	**Item No**	**Description**	**Item No**	**Description**
Section 7: Suggested SAP Appendices				
Dose transition pathways			34	For dose-escalation trials, indication of the dose transition pathways (either using tables or trees/graphs) under different DLT scenarios.

Proposed Guidelines – A Few Examples

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Section/Item	**Item No**	**Description**	**Item No**	**Description**
Section 7: Suggested SAP Appendices				
Code			35	Full model specification and programming code used for evaluation of dose-escalation decisions

Proposed Guidelines – A Few Examples

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Section/Item	**Item No**	**Description**	**Item No**	**Description**
Section 7: Suggested SAP Appendices				
Reports Template			36	Optional section detailing exemplar tables, graphs and report templates.

Discussion

- One of the major updates of the extension is the development of wording regarding outcome measures and estimands.
- Another update is the inclusion of a simulation report, reports template and relevant code, no examples for which are given.
- SAP sign off: ideally prior to the trial opening, however this may not always be feasible and so the final opportunity is prior to the first analysis of clinical trial.
- Advocate a standalone SAP is written for all early phase clinical trials.
- This guidance was developed to be as generic and applicable as possible across all early phase clinical trial designs.
- There remain certain types of trials not covered by this extension or the original guidance, which will require additional considerations incorporating available regulatory and published guidance.

Publication

RESEARCH METHODS AND REPORTING

Early phase clinical trials extension to guidelines for the content of statistical analysis plans

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Data supplement

Data Supplement - Web appendix 1: Supplementary materials

Data Supplement - Web appendix 2: Survey

Data Supplement - Web appendix 3: Checklist 1: SAP Content Guidance Extension for Early Phase Clinical Trials

https://doi.org/10.1136/bmj-2021-068177

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Summary

This work supports clinical trial statisticians, triallists and peer reviewers to facilitate an improvement in the quality of analysis, the reproducibility of methods and results, and the robustness of conclusions of early phase clinical trials.

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