## Checklist 1: SAP Content Guidance Extension for Early Phase Clinical Trials

(Homer V, Yap C, Bond S, et al. Early phase clinical trials extension to guidelines for the content of statistical analysis plans. *BMJ* 2022;376:e068177)

| | Recommended Early Phase Clinical Trials Extension Guidance | | Page |
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| **Section/Item** | **Item No** | **Description** | |
| **Section 1: Administrative Information** | | | |
| **Title and trial registration** | 1a | Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle, and trial acronym (if applicable) | |
| | 1b | Trial registration number | |
| **SAP version** | 2 | SAP version number with dates | |
| **Protocol version** | 3 | Reference to version of protocol being used | |
| **SAP revisions** | 4a | SAP revision history | |
| | 4b | Justification for each SAP revision | |
| | 4c | Timing of SAP revisions in relation to interim analyses, etc. | |
| **Roles and responsibility** | 5 | Names, affiliations, and roles of SAP contributors | |
| **Signatures of:** | 6a | Person writing the SAP | |
| | 6b | Senior statistician responsible | |
| | 6c | Chief investigator/clinical lead | |
| **Section 2: Introduction** | | | |
| **Background and rationale** | 7 | Synopsis of trial background and rationale including a brief description of research question and brief justification for undertaking the trial | |
| **Objectives** | 8 | Description of specific 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). | |
| **Section 3: Study Methods** | | | |
| **Trial design** | 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.<br>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.<br>Moreover, where dose decisions (e.g. escalation, de-escalation, remain at current dose or stop early) are to occur, details regarding dose transitions and dose skipping should be given. | |
| | 9e | Experimental details and design specifics.<br>For dose escalation trials, information regarding cohort size, including whether this is fixed or flexible should be given.<br><br>Indication of the stopping rules for interim and final evaluations.<br>For model-based and model-assisted designs, details on the prior including full skeleton (if applicable) and its elicitation should be given. | |

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| | | For single arm phase II trials, the target sample size and, where appropriate, the timing of any interim analyses | |
| **Randomisation** | 10 | Where appropriate, randomisation details e.g., whether any minimisation or stratification occurred (including stratifying factors used or the location of that information if it is not held within the SAP) and where applicable, details on blinding. | |
| **Sample size** | 11 | Full sample size determination or justification or reference to relevant section in protocol (instead of replication in SAP) | |
| **Framework** | 12 | If applicable, specify whether trial is to be performed under hypothesis testing or Bayesian framework. | |
| **Statistical interim analyses and stopping guidance** | 13a | Information pertaining to interim dose decisions (e.g. escalation, de-escalation, remain at current dose or stop early). | |
| | 13b | Information on other interim analyses specifying what and when interim analyses will be conducted. | |
| | 13c | Any planned adjustment of the significance level due to interim analysis | |
| | 13d | Details of guidelines for stopping the trial early | |
| **Timing of final analysis** | 14 | Timing of final analysis, e.g., all outcomes analysed collectively or timing stratified by planned length of follow-up | |
| **Timing of outcome assessments** | 15 | Time points at which the outcomes are measured including visit "windows" | |
| **Section 4: Statistical Principles** | | | |
| **Indications of uncertainty** [a] | 16 | Level of statistical significance | |
| | 17 | Description of any planned adjustment for multiplicity, and if so, including how the type 1 error is to be controlled | |
| | 18 | Either confidence or credible intervals to be reported (appropriately picked dependent on the trial methodology). | |
| **Adherence and protocol deviations** | 19a | Definition of adherence to the intervention and how this is assessed including extent of exposure | |
| | 19b | Description of how adherence to the intervention will be presented | |
| | 19c | Definition of protocol deviations for the trial | |
| | 19d | Description of which protocol deviations will be summarized | |
| **Analysis populations** | 20 | 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.<br><br>Trial level definitions of patient populations (e.g., per-protocol, intention to treat, safety) should also be given.<br><br>Details regarding evaluable patients and specify what happens to unevaluable patients should also be made.<br><br>These definitions should also be provided for any interim analysis populations. | |
| **Section 5: Trial Populations** | | | |
| **Screening data** | 21 | Reporting of screening data (if collected) to describe representativeness of trial sample | |
| **Eligibility** | 22 | Summary of eligibility criteria | |
| **Recruitment** | 23 | Information to be included in the CONSORT flow diagram | |
| **Withdrawal/follow-up** | 24a | Level of withdrawal, e.g., from intervention and/or from follow-up | |
| | 24b | Timing of withdrawal/lost to follow-up data | |
| | 24c | Reasons and details of how withdrawal/lost to follow-up data will be presented | |
| **Baseline patient characteristics** | 25a | List of baseline characteristics to be summarised | |
| | 25b | Details of how baseline characteristics will be descriptively summarized | |
| **Section 6: Analysis** | | | |
| **Estimand definition** [b] | | List and describe each primary and secondary estimands including details of: | |

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| | 26a | Details of the treatment (including treatment combinations), and any alternative treatments to which comparisons will be made (where appropriate). For dose-finding trials, information on whether analysis will be performed per cohort, per dose received, pooled across all dose levels, or in some combination of these | |
| | 26b | The trial population, defined with reference to item 20, pertinent to each estimand | |
| | 26c | The variable of interest to be obtained for each patient that is required to address the scientific question. For outcomes recorded at multiple time points, distinction as to which of these time points are required for the estimand | |
| | 26d | Intercurrent events and their handling strategy, including adjustment to analysis | |
| | 26e | Detail the population–level summary measure for each estimand | |
| **Analysis methods** | 27a | What estimator and analysis method will be used and how the results will be presented | |
| | 27b | Any adjustments for covariates | |
| | 27c | Methods used to check assumptions of the underlying statistical methods and goodness of fit for the model | |
| | 27d | Details of alternative methods to be used if distributional assumptions do not hold | |
| | 27e | Any planned sensitivity analyses for each estimand where applicable | |
| | 27f | Any planned subgroup analyses for each estimand including how subgroups are defined | |
| **Missing data** | 28 | Reporting and assumptions/statistical methods to handle missing data (e.g., multiple imputation) | |
| **Additional analyses** | 29 | Details of any additional statistical analyses required, e.g., complier-average causal effect analysis | |
| **Harms** | 30 | Sufficient detail on summarizing safety data outside of that used for dose escalation (e.g., non-DLT safety data), e.g., information on severity, expectedness, and causality; details of how adverse events are coded or categorised; how adverse event data will be analysed, i.e., by grade, incidence case analysis, intervention emergent analysis | |
| **Statistical software** | 31 | Details of statistical packages to be used to carry out design, simulation and analyses | |
| **References** | 32a | References to be provided for nonstandard statistical methods | |
| | 32b | Reference to Data Management Plan | |
| | 32c | Reference to the Trial Master File and Statistical Master File | |
| | 32d | Reference to other standard operating procedures or documents to be adhered to | |
| **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. | |
| **Dose transition Pathways** | 34 | For dose-escalation trials, indication of the dose transition pathways (either using tables or trees/graphs) under different DLT scenarios. | |
| **Code** | 35 | Full model specification and programming code used for evaluation of dose-escalation decisions | |
| **Reports Template** | 36 | Optional section detailing exemplar tables, graphs and report templates. | |

Notes:

a. This item was called 'Confidence intervals and P values' in the Gamble *et al.* paper (1)]. It has been changed to 'Indications of uncertainty' to reflect that many early phase trials designs are underpinned by Bayesian methodology.

b. This item was called 'Outcome definitions' in the Gamble *et al.* paper (1). It has been changed to 'Estimand definitions' following the wider adoption of ICH E9 (R1; Addendum on estimands).

Abbreviations:

- CONSORT: CONsolidated Standards Of Reporting Trial
- CRM: Continual Reassessment Method
- DLT: Dose Limiting Toxicity
- PD: PharmacoDynamics

- PK: PharmacoKinetics
- SAP: Statistical Analysis Plan