**Summary of qualitative feedback on round 1 of Delphi exercise for CONSORT extension for adaptive trial designs**

**Section 1 - Title and abstract**

A total of twenty-one participants provided additional comments on checklist items in section 1. One key general methodological point was that not all adaptive designs are randomised, e.g. model-based phase 1 designs or rare disease studies. Several participants made suggestions for additions to 1b – potential adaptations and who was involved in adaptive decisions; range and final sample size; planned and the actual number of interim analyses; something about the estimand, as well description of the specific design. Conversely, other participants raised concerns about covered all sub-categories in the abstract because ‘the list of things to include continues to grow but journal article space doesn’t.’

**Section 2 - Introduction: background and objectives**

Eleven participants gave further comments on the adapted checklist item 2b. Some participants were not sure whether this was sufficiently specific to adaptive trials and should bear more relation to the objectives of a study with an adaptive design and should clarify the subtle difference between co-primary and multiple objectives. Other comments were that it wasn’t necessary to include exploratory objectives; this section could also be used to specify the estimand; and give a brief justification for inclusion of clinical utility indexes, as appropriate.

**Section 3 – Methods: Trial design**

Seventeen participants provided additional comments on the adapted (3a) and new (3b-3f) checklist items relating to trial design. For 3a, one participant commented that this was difficult to follow and another provided several suggestions for improving the wording of this item for AD. For 3b, one participant queried the necessity of justifying the use of an adaptive design, and that 3c-3e cover a lot of items that are mentioned in 3b, whereas another suggested this item could also discuss the cost-benefit ratio of adaptive vs standard trial designs. Checklist item 3c also drew several comments, including a description of pre-planned adaptations that were not implemented, or to comment on the confidence of used estimates, how many interims were planned and criteria for adaptive changes, whereas other participants queried the volume of items included here, which could be better described as examples or options for reporting.

Feedback on checklist item 3d included adding a discussion of how changes may influence conclusions and describe attribution of decisions, whereas another participant queried the purpose of this item, suggesting that this needed further clarification. Feedback on checklist item 3e suggested that although in principle the idea was plausible and it would be useful to draw the boundaries between planned adaptations at the design stage and those implemented, the feasibility of including all details on this in a journal article were questionable, and several participants remarked that this might be better covered in supplementary material. Indeed, this was a general comment on checklist items in this section.

**Section 4 – Methods: Participants**

Six participants commented on existing checklist items 4a and 4b. Two comments highlighted the importance of these items for all trials, irrespective of design. Regarding 4a, one participant suggested that where eligibility is an adaptation, it should be captured under item 3e, and another suggested that this should include biomarker status, which is crucial for biomarker enrichment designs. Another suggested included adding a time component to 4b. The other participant commented that additional demographic and clinical information would help with the transferability of results, but highlighted that this might be better addressed in supplementary material.

**Section 5 – Methods: Interventions**

Six participants provided additional comments on this existing checklist item. However, the feedback was of little relevance to the development of this CONSORT extension, e.g. stating the universal importance of the item; suggesting that some of the additional detail on interventions could be put in supplementary material or suggestions of further detail on dose, interventionists and more information about usual care as this can vary within and between countries.

**Section 6 – Methods: Outcomes**

Fifteen participants commented on these adapted checklist items for outcomes. The comments on 6a included concerns that asking for the co-primary and multiple outcomes could be too specific; including the clinical utility functions, if necessary and that the clinical trial registry used should be declared here. In addition, another participant suggested that the item should include how intercurrent events are handled as part of the estimand. There was general support for describing unplanned changes in 6b, however, several participants commented that this checklist item was a bit unclear and suggested that further guidance would be required in the explanatory document to justify the changes made. It was also suggested that ‘trials’ could be deleted from the final sentence.

**Section 7 – Methods: Sample size**

Fifteen participants provided additional feedback on these adapted checklist items for sample size. There were divergent views on the level of detail suggested by these adaptations and several participants commented that the detail should be available, but it was more feasible to include in the Statistical Analysis Plan (SAP) and/or other supplementary material to the journal article. One specific comment on 7a was that this could be edited to cover both original and modified sample size. Concern was expressed about the volume of concepts covered under 7b.

**Section 8 – Methods: Randomisation sequence generation**

Ten participants commented on checklist items under section 8, with general support for 8a and 8b in all trials. The additional comments on new checklist item 8c included adding information on whether agreement from the independent committee was sought; querying whether actual timing and frequency should be reported here or in the results section, or this section should report on when and how often planned randomization updates were due. Given some of the methodological uncertainties, full reporting of adaptive randomization was highlighted as important by several participants.

**Section 9 – Methods: Randomisation allocation concealment mechanism**

Only one participant provided additional commentary on this existing checklist item to highlight the universal importance of describing the allocation concealment mechanism in all trials, not just those with an adaptive design.

**Section 10 – Methods: Randomisation implementation**

Four participants provided further comments on this existing checklist item to reinforce the importance of detailing who implemented the random allocation sequence and documenting any non-adherence to planned implementations.

**Section 11 – Methods: Blinding**

Thirteen participants provided additional commentary on checklist items in section 11. There were several queries about the clarity of 11b with participants seeking further explanation. One participant suggested the 11a should justify why not everybody was blinded (where relevant). Whilst there was support for 11c, several participants expressed concern about covering all this material in one journal article and one suggested that the IDMC charter could be included as appendix instead. Similarly, other participants suggested that this new item needed to be further refined to identify the essential components, and one suggested that the second sentence was excessive. Other comments on 11c highlighted the potential issue with assessing processes for minimization of operational bias. Another participant queried the naming of the IDMC and suggested that this should instead be generalised to ‘(independent) adaptive decision-making committee’.

**Section 12 – Methods: Statistical methods**

Eighteen participants provided additional comments on the checklist items in this section on statistical analysis methods. There was only one additional comment on the adaptation to existing item 12a to suggest that exploratory analyses could be excluded. There were no additional comments on existing item 12b.

Overall, the comments on the proposed new checklist items 12c-12g were concerns about the feasibility of including this much detail in a given journal article and suggesting the need to provide this in supplementary material, such as the SAP. Additionally, numerous concerns about the inter-study variability of analysis methods and concerns that it wouldn’t be possible to recommend the use of contested approaches to analysis led several participants to question how checklist items 12c-12g could be improved.

**Section 13 – Results: Participant flow**

Three participants provided additional comments on these checklist adaptations, albeit minimal. Again, the same participant highlighted the universal importance of 13b for all trials. Feedback on 13a provided positive reinforcement of covering participant flow for each interim decision, and also that the example does not seem necessary and could be removed.

**Section 14 – Results: Recruitment**

Eighteen participants provided additional comments on checklist items in section 14. Suggested modification to 14a to capture different recruitment periods as a result of a trial adaptation. Several participants were confused by the presentation of 14c relative to 14d and 14e and sought clarity on this, whereas others understood the task clearly and of those providing additional comments, more preferred 14d and 14e to 14c alone. The difficulty of dividing up these concepts was acknowledged by several participants as was their importance in reporting of AD, particularly to demonstrate the integrity of this design. Other comments on 14e were that this could explicitly mention inclusion/exclusion criteria, and document who was responsible for giving permission for such deviations.

**Section 15 – Results – Baseline data**

Six participants provided additional comments in this section. With 15a, the relevance of assessing baseline comparability for adaptive designs was queried and the clarity of the proposed checklist item was queried. Three other participants commented on 15b, to highlight how providing further detail in the explanatory document to the checklist would be beneficial, that most of the additional material would be covered in supplementary information, whereas one participant raised concerns about multiple testing of the same data leading to false positive findings.

**Section 16 – Results: Numbers analysed**

Only three participants provided further comment on this proposed adaptation to checklist item 16 to suggest that this should refer to ‘…report for each treatment group’; where the interims are often, it was queried whether this item only relate to interim analyses that change the trial, and finally, one participant commented on how this section highlights the importance of ensuring easy to interpret statistics.

**Section 17 – Results: Outcomes and estimation**

Eleven participants gave additional comments on section 17. The feedback on 17a was divergent with suggestions that effects of primary and intermediate endpoints were crucial, yet secondary endpoints were not and concerns about the feasibility of reporting on each intermediate outcome, whereas other participants were keen that these should be included under this adapted item. One participant added that it could be useful to specify what to use with a small sample under 17a. Only one participant commented directly on 17b that they preferred that rates for individual treatment groups are always presented. With the new item (17c), participants suggested that this is important but may likely need to be covered in an appendix/supplementary material depending on journal requirements. Additionally, one participant suggested that this should be edited to take account for Bayesian analyses.

**Section 18 – Results: Ancillary analyses**

Six participants commented on this existing checklist item. In addition to the same participant highlighting its universal importance, other commentators shared their concerns about the feasibility of covering the results of all ancillary analyses for adaptive trial designs in one manuscript, despite the recognised importance of transparency on the volume of analyses performed.

**Section 19 – Results: Harms**

In addition to the same participant stating the universal importance of this existing checklist item, four other participants made suggestions for how this could be changed for adaptive designs. That is, to link to appropriate reporting guidance on harms, report the harm (or risk) to benefit ratio; ensure that reporting on interim analyses for harm should follow the same standards of reporting as that for effectiveness (17c) as they are often different or edit the wording to read ‘…in each intervention group or further detailed by each subpopulation as appropriate’.

**Section 20 – Discussion: Limitations**

Six participants provided additional comments on this checklist item. One participant sought further clarity as they were unclear on the meaning ‘pre-planned adaptations not implemented or enforced but should have been’, another suggested adding in a description of how trial demographics altered (or not) over time in reference to interim results. Other participants were at odds with one suggesting that this item should be further subdivided into sub-items, whereas another felt that including the examples was too much for reviewers. Other more general comments related to including one sentence from the discussion in the abstract and highlighting the general limitations of adaptive designs relative to simple RCT to aid clinical reader comprehension.

**Section 21 – Discussion: Generalisability**

Only three participants added further comments on the proposed adaptation of this checklist item. One participant suggested that generalizability did not require a specific modification for adaptive designs, whereas another highlighted the potential impact of this design on lost generalizability, suggesting that these should be listed. Again, the importance of the estimand was highlighted here.

**Section 22 – Discussion: Interpretation**

Ten participants provided further comments on this section, with most suggesting that although it would be beneficial to discuss the contribution to future research on adaptive designs (22b), there were concerns that for medical journals, this would not be feasible and perhaps it would be better described in a separate manuscript. For 22a, one participant restated the importance of this for all trials, not just adaptive designs and another adding that this should be clarified to emphasise clinical, as opposed to statistical significance.

**Section 23 – Other information: Registration**

Only two participants commented on this existing checklist item to say that a) the registration should include reference to this as an adaptive design and b) on a more general note, this item is desirable and not mandatory, suggesting that the revised guideline should leave scope to be consistent with different journal requirements.

**Section 24 – Other information: Trial documentation**

Several suggestions were made for existing checklist item 24a – remove ‘if available’ because all studies should have a protocol and clarify that all amendments should be included. One participant suggested that 24b and 24c overlap and explained that the SAP (24c) should be considered as key trial documentation. 24d could be clarified to request results from any simulations performed after interim analyses, or combined with 24a.

Edits to 24e included giving the committee a more general name, and another participant felt that this was less important as it will have been covered by earlier items on un/planned adaptations. The rationale for including 24f was queried, as was whether reviewers would have time to look at the statistical code in a meaningful way. One participant also suggested that 24f could be subsumed under 24d. The universal applicability of 24b, 24c, 24d and 24f was suggested for the general CONSORT, but if these aren’t to be added to the general CONSORT, they should not be required for AD.

**Section 25 – Other information: Funding**

No additional comments were made on checklist item 25.