**Adaptive designs CONSORT Extension**

**Summary report from expert stakeholder meeting – generation of potential checklist items**

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# Introduction

This report summarises the proceedings of an expert stakeholder workshop that was convened as part of the Adaptive Designs CONSORT Extension (ACE) project on 19th January 2017 at the University of Sheffield.

As such, this report includes five main sections. The workshop methodology is described in Section 2.0, and a summary of principles or tips guiding the development of the guidance document is presented in Section 3.0. The working definition of adaptive trial designs is presented in Section 4.0, along with a short discussion of key definitional issues. Section 5.0 outlines the initial classification of the CONSORT checklist items made by the expert stakeholder group. These are presented in list form in Section 5.1 and then the rationale for the classification as ‘no changes proposed’ (5.2), ‘adaptations proposed’ (5.3) and ‘new checklist item’ (5.4) is described, along with a summary of key issues, as appropriate to each checklist item. The next steps in the project are summarised in Section 6.0.

# Workshop methodology

***Aims***

The aim of this workshop was three-fold:

1. To agree a working definition of adaptive trial designs;
2. Review and discuss the existing CONSORT 2010 checklist (Schultz et al., 2010) and findings from a scoping review of guidance on adaptive trial design and reporting, in order to;
3. Generate a list of potentially important checklist reporting items for adaptive trial designs.

***Briefing materials***

Prior to the workshop, the delegates were provided with a number of briefing documents. That is, summary findings from the scoping review, the existing CONSORT 2010 checklist (Schultz et al., 2010), examples of the CONSORT extensions for pilot and feasibility studies (Eldridge et al., 2016) and cluster trials (Campbell et al., 2012), the research protocol for the ACE project, as well as a ‘brainstorming’ draft of the CONSORT extension for adaptive trial designs which was generated by the Lead Investigator (MD) to inform workshop discussions.

***Participants and methods***

Ten expert delegates attended the one-day workshop (out of 16 invited). Most delegates were academic statisticians, with eight participants from UK or European universities. The other two delegates were both from the USA and represented the pharmaceutical industry and the National Institutes of Health. With the exception of one delegate who attended the workshop via teleconference, the workshop was conducted face-to-face and was digitally recorded and transcribed verbatim to ensure that the discussions were captured accurately. LC facilitated the workshop with assistance from KB and MD.

To begin with, MD presented the background to the project and findings from the scoping review and this was followed by a short presentation from one of the delegates, Professor Doug Altman, who shared his experiences of working on previous CONSORT checklists and extensions with the group. After this, two whole group discussions were facilitated. The purpose of the first group discussion was to agree a working definition of adaptive trial designs, which would help focus the group in the second, more substantial exercise of generating the potential checklist items. The ‘brainstorming’ draft of the CONSORT extension was used as the reference point for discussions, and each item was reviewed and discussed by the group to determine its classification as ‘not relevant and should be excluded’, ‘relevant and no changes proposed’, ‘relevant and adaptations proposed’. A number of new items were also reviewed and proposed by the group.

# Summary of principles or tips guiding the development of the guidance

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The group noted that there are broad types of adaptive designs with different implications on their design, conduct, analysis, and what we want them reported. Some aspects are general; hence apply to all types of adaptive designs, whereas other aspects are only relevant to certain types of adaptive designs. The checklist should therefore capture general principles while accommodating some aspects relevant to specific adaptive designs – perhaps using conditional statements.

The importance of examples to illustrate good reporting for proposed items and explanation of why it matters was highlighted, and should be covered in the explanatory document. The examples should cover different types of adaptive designs with varying degree of complexity (form simple to ones that are more complex).

DA highlighted that the guidance should not tell researchers how to conduct research. It should focus on why the reporting of suggested items matters and how they should be reported. The explanatory document may discuss methodology underpinning certain adaptive designs aspects and it is reasonable to reflect how certain aspects should be done with supporting arguments but without using commanding language. DA drew the group’s attention to the paper published in PLOS Medicine which provides further guidance on developing health research reporting guidelines (Moher et al., 2010).

# Definition of adaptive trial designs

The group were first asked to discuss and agree a working definition of adaptive trial designs. The starting point for the discussion was the definition given in the ACE project protocol (v1.6, p5), as follows:

‘Adaptive designs use accumulating trial data in a pre-specified manner to modify aspects of an ongoing trial while preserving its validity and integrity.’

As a composite definition, it was unsurprising that the group focussed on some of the technical terms contained within the proposed definition, in particular, the meaning of ‘pre-specified’, which aspects of the trial were intended to be modified, and by implication, ensuring that the definition was not too narrow or overly prescriptive and therefore, could not usefully be applied to the varied field of adaptive trial designs.

The group were keen to clarify the timing of the pre-specified design adaptations, and debated whether this should be defined as pre-trial, pre-protocol or pre-analysis. The 2010 US Food and Drug Administration (FDA) draft guidance on adaptive designs was used as a reference point to highlight that they defined the timing as “before you look at any unblinded data” but the difficulties of proving the timing of this to the FDA were also acknowledged. The group also queried the level of pre-specification that was implied by the definition, as it is often not possible to know at the outset how the trial will be adapted, and as one participant pointed out: “[t]he problem with the term pre-specified, it’s easy to mix it up [with] the pre-specified option to modify something, …”. However, the group noted the importance of planning and specification of the intended adaptations in maintaining trial credibility although methodology may allow wide range of flexibilities.

As such, the group reflected on the actual FDA (2010, p2) definition, which is as follows: ‘…An adaptive design clinical study is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study’. The group generally agreed that qualifying and extending the definition to include the provision of an opportunity to modify elements of the trial was useful. However, there was concern about the term ‘prospectively’ as it was widely acknowledged that it is not possible to retrospectively plan adaptations. In the interests of flexibility (and time), the group instead reached a working consensus that ‘pre-planned opportunity’ captured the meaning without being too prescriptive.

There was also some debate within the group about whether the definition should extend beyond trial design, to include adaptations to the analysis. Several participants expressed caution at this because the implication is that most trials could therefore be defined as adaptive under this broader definition. The group agreed that defining the key terms under the broader umbrella definition of adaptive trial designs could offer a workable solution to this dilemma, and it whether this should be included in future ACE project publications would be considered as the work progresses. Furthermore, the group agreed to give examples of pre-planned opportunities implied as part of the guidance document to help readers and add clarity to the definition.

Taking into account the above discussion, the group was able to agree the following working definition:

‘Adaptive designs provide pre-planned opportunities to use accumulating trial data to modify aspects of an ongoing trial while preserving its validity and integrity.’

# Potential checklist items

## Summary

The group were asked to review the standard CONSORT (2010) checklist in order to classify the existing items as ‘not relevant and should be excluded’, ‘relevant and no changes proposed’ or ‘relevant and adaptations proposed’. In addition to this, the ‘brainstorming’ draft of the CONSORT extension was used as a further reference point for discussions to help identify adaptations and new items, and the results of these discussions are summarised in Table 1.

In summary, from the original 37 CONSORT checklist items, none were proposed for exclusion, it was agreed that 23 items should be retained in their original form, adaptations were proposed to 14 items and a total of 16 new items were identified by the group. A summary of the group discussions relating to checklist items within the latter three categories is presented in Sections 5.2 to 5.4 below.

**Table 1 – Classification of CONSORT checklist items for adaptive trial designs**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Section/topic and item no.** | **CONSORT 2010 Checklist item** | **Not relevant** | **No changes proposed** | **Adaptation** | **New item** |
| Title and abstract | | | | | |
| 1a | Identification as a randomised trial in the title |  | X |  |  |
| 1b | Structured summary of trial design, methods, results, and conclusions |  |  | X |  |
| Introduction  Background and objectives | | | | | |
| 2a | Scientific background and explanation of rationale |  | X |  |  |
| 2b | Specific objectives or hypotheses |  | X |  |  |
| Methods  Trial design | | | | | |
| 3a | Description of trial design (such as parallel, factorial) including allocation ratio |  | X |  |  |
| 3b | Adaptive trial design (planned potential adaptations) |  |  |  | X |
| 3c | Decision making criteria |  |  |  | X |
| 3d | Rationale for adaptive design |  |  |  | X |
| 3e (3b) | Important changes to methods after trial commencement (such as eligibility criteria), with reasons |  |  | X |  |
| 3f | Design properties |  |  |  | X |
| Participants | | | | | |
| 4a | Eligibility criteria for participants |  | X |  |  |
| 4b | Settings and locations where the data were collected |  | X |  |  |
| Interventions | | | | | |
| 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered |  | X |  |  |
| Outcomes | | | | | |
| 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed |  |  | X |  |
| 6b | Any changes to trial outcomes after the trial commenced, with reasons |  |  | X |  |
| Sample size | | | | | |
| 7a | How sample size was determined |  | X |  |  |
| 7b | When applicable, explanation of any interim analyses and stopping guidelines |  | X |  |  |
| Randomisation  Sequence generation | | | | | |
| 8a | Method used to generate the random allocation sequence |  | X |  |  |
| 8b | Type of randomisation; details of any restriction (such as blocking and block size) |  |  | X |  |
| Allocation concealment mechanism | | | | | |
| 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps to conceal the sequence until interventions were assigned |  | X |  |  |
| Implementation | | | | | |
| 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions |  | X |  |  |
| Blinding | | | | | |
| 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how |  | X |  |  |
| 11b | If relevant, description of the similarity of interventions |  | X |  |  |
| 11c | Minimisation of interim operational bias |  |  |  | X |
| Analytical methods | | | | | |
| 12a | Statistical methods used to compare groups for primary and secondary outcomes |  |  | X |  |
| 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses |  |  | X |  |
| 12c | Inference procedures |  |  |  | X |
| 12d | Estimation (including stages and combining data) |  |  |  | X |
| Results  Participant flow (a diagram is strongly recommended) | | | | | |
| 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome |  |  | X |  |
| 13b | For each group, losses and exclusions after randomisation, together with reasons |  |  | X |  |
| Recruitment | | | | | |
| 14a | Dates defining the periods of recruitment and follow-up |  | X |  |  |
| 14b | Why the trial ended or was stopped |  | X |  |  |
| 14c | Adaptation decisions |  |  |  | X |
| Baseline data | | | | | |
| 15a | A table showing baseline demographic and clinical characteristics for each group |  | X |  |  |
| 15b | Baseline data by stage |  |  |  | X |
| Numbers analysed | | | | | |
| 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups |  |  | X |  |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Outcomes and estimation | | | | | |
| 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) |  |  | X |  |
| 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended |  |  | X |  |
| 17c | Suitable representation of interim analyses outcome results (where appropriate) |  |  |  | X |
| Ancillary analyses | | | | | |
| 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory |  | X |  |  |
| Harms | | | | | |
| 19 | All important harms or unintended effects in each group |  | X |  |  |
| Discussion  Limitations | | | | | |
| 20 | Trial limitations, addressing sources of potential bias, imprecision, and if relevant, multiplicity of analyses |  |  | X |  |
| Generalisability | | | | | |
| 21 | Generalisability (external validity, applicability) of the trial findings |  |  | X |  |
| Interpretation | | | | | |
| 22a | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence |  | X |  |  |
| 22b | Contribution to future research |  |  |  | X |
| Other information  Registration | | | | | |
| 23 | Registration number and name of trial registry |  | X |  |  |
| Protocol | | | | | |
| 24a | Where the full trial protocol can be accessed, if available |  | X |  |  |
| 24b | Intentionally held info (if applicable). |  |  |  | X |
| 24c | Statistical Analysis Plan |  |  |  | X |
| 24d | Simulation protocol |  |  |  | X |
| 24e | Independent Data Monitoring Committee Charter |  |  |  | X |
| 24f | Statistical code |  |  |  | X |
| Funding | | | | | |
| 25 | Sources of funding and other support (such as supply of drugs), role of funders |  | X |  |  |

Key: Blue text is used to indicate new checklist items and adaptations to checklist item numbers

## No changes proposed

**1a Identification as a randomised trial in the title**

The group agreed that it was not necessary to change the first item on the checklist. Instead, they agreed that it would be more valuable to adapt 1b so that the abstract and key words include a reference to adaptive designs. The group were also sceptical about the feasibility of recommending a change to the title when it is observed that many journals do not permit the inclusion of so much detail on study design.

**2a Scientific background and explanation of rationale**

**2b Specific objectives or hypotheses**

**3a Description of trial design (such as parallel, factorial) including allocation ratio**

The description of the background (2a) and objectives (2b) of the study, and the trial design (3a) were agreed by the group as standard checklist items that the application of an adaptive design would not change. Rather, more detail on the adaptive design should be requested via the new checklist items proposed under ‘methods – trial design’.

**4a Eligibility criteria for participants**

**4b Settings and locations where the data were collected**

Whilst it was acknowledged that eligibility criteria could be part of the adaptive process, the group agreed to retain this checklist item in its current form because details of planned adaptations would be addressed by the new item 3b. Similarly, although one workshop participant suggested that it was important to provide details on trial centres before and after adaptations to see if there were differences, the group agreed that this would be better covered under the amended checklist items for results (12a and 12b).

**5 The interventions for each group with sufficient details to allow replication, including how and when they were actually administered**

As a general concept for every trial, the group agreed that no changes were required for this checklist item.

**7a How sample size was determined**

**7b When applicable, explanation of any interim analyses and stopping guidelines**

The group agreed that because the adaptive design properties would be requested via new checklist item 3f (see below), it was not necessary to alter 7a, but the explanatory document should clarify the links between these two aspects of reporting. In a similar way, the prominence of interim analyses within adaptive designs created some debate within the group about whether item 7b should be removed from the checklist extension because the new item 3c on decision-making criteria could cover this in sufficient depth. However, on reflection, the group erred on the side of caution, agreeing to include both items for consideration in the Delphi survey.

**8a Method used to generate the random allocation sequence**

**9 Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps to conceal the sequence until interventions were assigned**

**10 Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions**

The group agreed that no changes were required to reporting on how the randomisation was generated (8a) and implemented (9 and 10) but that the details of the adaptive randomisation should be explained in more depth under 8b (see below).

**11a If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how**

**11b If relevant, description of the similarity of interventions**

Again, these two checklist items for blinding were considered relevant to reporting of adaptive designs, but the group acknowledged the importance of adding a new related and more specific item on how interim operational bias was minimised during the trial (see 11c below).

**14a Dates defining the periods of recruitment and follow-up**

**14b Why the trial ended or was stopped**

Although the group debated the utility of requesting the dates of design adaptations via 14a, they generally agreed that this checklist item could be retained in its current form because an understanding of the number of participants by stage is more informative than the dates, and it is important for all trials to have an understanding of when the study was conducted. The group acknowledged that it would be valuable to understand whether the trial was stopped based on unexpected or pre-defined stopping results based on interim analyses, but were content that checklist item 14b did not need to change, so long as this issue was addressed within the explanatory document. To address the specific adaptive decisions, the group instead proposed a new item (14c).

**15a A table showing baseline demographic and clinical characteristics for each group**

There was debate within the group about whether this item should be adapted, or whether a new separate item to report baseline demographic and characteristic data by stage was required to explore potential population drift, which may influence interpretation of the results. Data may not need to be provided in the manuscript per se as long as it is accessible somewhere, where applicable. For the purposes of the Delphi survey, both checklist items will be included for completeness (see 15b below).

**18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory**

In contrast to the other checklist items related to analysis, the group agreed that this was a general concept that did not need to be changed for adaptive designs.

**19 All important harms or unintended effects in each group**

The group recognised that it would be useful to know whether adaptation decisions were made based on the analysis of harms data, but the proposed new item on presentation of interim analyses (17c) would address this.

**22a Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence**

Again, the group acknowledged that interpretation was a standard reporting item for all trials and therefore did not need to be changed for adaptive designs. Interestingly, the group also agreed that a second generic item could be added to this section, to consider the contribution to future related research (22b – see below).

**23 Registration number and name of trial registry**

**24a Where the full trial protocol can be accessed, if available**

**25 Sources of funding and other support (such as supply of drugs), role of funders**

The group agreed that it was not necessary to make any changes to the three final checklist items (23, 24 and 25). However, as described below, the group also suggested several new checklist items to improve the reporting of adaptive designs in particular (24b and 24d) and several more generic concepts that could improve the transparency of reporting for all studies (24c, 24e and 24f).

## Adaptations proposed

**1b Structured summary of trial design, methods, results, and conclusions**

The group agreed that this checklist item should be adapted to include an explicit reference to the adaptive design features of the study. It was also suggested that ‘adaptive design’ should be added to keywords to help improve indexing of these studies.

**3e (3b) Important changes to methods after trial commencement (such as eligibility criteria), with reasons**

To correspond with the suggested new reporting items under ‘trial design’ (see below), the group debated how this checklist item should be amended for adaptive designs. They acknowledged that the standard CONSORT (2010) statement does not specify whether the changes were planned or unplanned, and therefore for adaptive designs this item should be amended to specifically describe the unplanned changes to the trial design.

**6a Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed**

**6b Any changes to trial outcomes after the trial commenced, with reasons**

The group agreed that only some slight modifications to these two checklist items were required. That is, to describe the endpoints used to make adaptations, if different to the primary and secondary outcome measures (6a), and clarify that 6b should describe any unplanned changes in endpoint not within the scope of the adaptations.

**8b Type of randomisation; details of any restriction (such as blocking and block size)**

The group debated the extent to which the existing checklist item describing the type of randomisation needed to be amended for adaptive designs. Some participants considered this to be a general checklist item that was already broad enough to describe adaptive randomisation schemes, especially given the variety of adaptive designs used in practice, whereas others were keen to be more prescriptive about what should be reported. That is, to describe the frequency, timing and algorithm for updating randomisation (for example, when responsive adaptation is used) and changes to randomisation following adaptation such as dropping futile arm(s).

**12a Statistical methods used to compare groups for primary and secondary outcomes**

**12b Methods for additional analyses, such as subgroup analyses and adjusted analyses**

The reporting of statistical methods was, unsurprisingly amongst a group dominated by statisticians, an area of much debate. Again, given the heterogeneous nature of adaptive designs with broad implications, the group deliberated over the implications of amending checklist items 12a and 12b to describe stage-wise combination methods, raising concerns that this could render these unnecessarily prescriptive. However, they agreed to approach this inclusively and explore whether these should be changed or whether the material on inference procedures and estimation were better addressed via two new items (12c and 12d, respectively – see below) within the Delphi survey. The group also highlighted the importance of ensuring continuity between reporting items 12a and 17a.

**13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome**

**13b For each group, losses and exclusions after randomisation, together with reasons**

The group agreed that these checklist items should be amended to ensure that the participant flow for each stage of the trial (after each interim analysis) is adequately reported. The challenges of presenting this for each stage of a particularly convoluted adaptive design were acknowledged, as was the importance of defining key principles of the adaptive design within the explanatory document, e.g. stage or subgroup in the context of the specific study.

**16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups**

The group agreed that, to correspond with the changes proposed to 13a and 3b, this item should be adapted to ensure that for adaptive designs, the numbers analysed for each of the interim analyses are presented.

**17a For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)**

**17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended**

As with the description of statistical methods, reporting was also the focus of much discussion by the group. The group did not reach consensus on whether to amend items 17a and 17b to include unbiased or bias-adjusted results where applicable, or add new items to ensure the suitable representation of the interim analyses results (17c – see below).

**20 Trial limitations, addressing sources of potential bias, imprecision, and if relevant, multiplicity of analyses**

The group were content with the suggested adaptation to this checklist item in the ‘brainstorming’ draft extension, to read as follows ‘Trial limitations, addressing sources of potential statistical and operational bias, imprecision, planned adaptations not implemented or enforced, unplanned (ad-hoc) adaptations or protocol changes made.’

**21 Generalisability (external validity, applicability) of the trial findings**

Similarly, the group agreed that this checklist item should be made more specific to adaptive designs and consider the generalisability of the results from the adaptive trial and to whom the results are applicable within the context of the stated objectives or hypotheses, as suggested in the brainstorming draft.

## New checklist items

**3b Adaptive trial design (planned potential adaptations)**

**3c Decision making criteria**

To distinguish this from the general description of the trial design in 3a, the group agreed that a new checklist item to report on the type and scale/scopeof the pre-planned potential adaptations was required (3b). Correspondingly, the group also agreed that it would be valuable to introduce a new checklist item (3c) to describe the decision-making criteria that were used in the study to guide the adaptation process (such as rules for stopping a trial or treatment arm or patient subgroup, or changing randomisation) and criteria considered for rejecting the null hypotheses (declaring success). This will also capture the timing and frequency of the adaptation process.

**3d Rationale for adaptive design**

Although the group debated the placement of this checklist item under background and objectives, or trial design, they agreed on the importance of including a new item to describe the rationale for the adaptive design and its appropriateness to the research questions, or method to improve design efficiency compared to the traditional fixed sample size approach.

**3f Design properties**

The ‘brainstorming’ draft of the CONSORT extension included a separate checklist item on the validity of the statistical properties of the adaptive design. There were mixed opinions on the value of separating out this aspect of adaptive designs, because some members felt that this would already be covered in the sample size section (7a and 7b), or that adding more detail for adaptive designs was too prescriptive: “I think we can appreciate your viewpoint though, for sure, we don’t want to have higher hurdles”. However, because of concerns about how adaptive designs maintain the statistical properties, particularly type 1 error rates, they agreed to include this for review via the Delphi survey.

**11c Minimisation of interim operational bias**

The group agreed that it is necessary to include a new checklist item describing the systems, procedures and processes put into place to minimise operational bias during the conduct of the trial, due to knowledge or leakage of the interim results (as suggested in the ‘brainstorming’ draft). It was also suggested that this item should describe who was responsible for conducting the interim analyses and making interim decisions, and the role of the IDMC.

**12c Inference procedures**

**12d Estimation (including stages and combining data)**

As discussed above, the reporting of statistical methods was the subject of much discussion by the group, but they eventually agreed to include inference procedures and estimation methods as multiple options for the Delphi survey. The objective is to capture statistical methods used for estimation such as unadjusted conventional approach, unbiased or bias-adjusted estimates. In addition, where applicable, methods used to combine data or results from different stages with justification. These two items may be combined.

**14c Adaptation decisions**

The group agreed that a new item could be added to the checklist to describe all of the pre-planned opportunities for the adaptive design, and describe, as applicable, how this was enacted within the study. For example, whether treatment arms or subsets of trial participants were stopped. They also highlighted that this should be related to another new item where the stage-wise results would be reported (see 17c below).

**15b Baseline data by stage**

There was uncertainty within the group about whether reporting baseline data by stage was always essential for adaptive designs, and concern that asking for the results at each stage to be reported may be so extensive to be infeasible for some adaptive designs and for most journal requirements. Nonetheless, the group agreed to include this as a proposed addition to the checklist at this stage on the grounds that it is valuable to understand whether and how the characteristics were different between stages. Accessibility of data elsewhere is more than enough.

**17c Suitable representation of interim analyses outcome results (where appropriate)**

There were differences on opinion on the content of a new item to ensure the suitable representation of results of interim analyses because it was recognised that not all interim analyses generate an outcome or change at each stage, and at present not all results are usually recorded, just the decisions made. Indeed, the group debated whether the checklist should recommend that just the decisions should be reported, or both the decisions and the results, where applicable. Again, this plays into a larger issue of the variety of adaptive designs and “…to suggest that every trial with an adaptive design with an interim analyses should (…) include the results available at each interim analysis is a major change from what currently goes on”. However, the group agreed to explore this further via the Delphi survey. The idea of a figure showing trend of interim results was suggested where appropriate.

**22b Contribution to future research**

Although the group recognised that a potential new checklist item on the contributions made to future research could be too prescriptive and may be better placed in the associated explanatory document, they were keen to include the following item within the Delphi survey: ‘Discussion of key positive and negative lessons learned from the adaptive design implemented with recommendations for future related trials’. The group also discussed that, as with the recommendation to include the intracluster correlation coefficient (ICC) in the cluster RCT CONSORT extension, the inclusion of this item could also help to improve the reporting of adaptive designs by sharing knowledge and experience to inform the planning and design of future studies.

**24b Intentionally held info (if applicable)**

**24c Statistical Analysis Plan**

**24d Simulation protocol**

**24e IDMC Charter**

**24f Statistical code**

In addition to the protocol, the group identified and agreed that adaptive trials should also report on where a number of other key documents can be accessed, if applicable and available. That is, information intentionally withheld from the protocol, such as the detail of the adaptive process that might influence operational bias (24b); the statistical analysis plan, and any amendments made (24c). The group also agreed that checklist could include the simulation protocol and report (24d) on how the data were intended to be used to evaluate operating characteristics of the adaptive design, e.g. familywise type 1 error rate, sample size, power, and estimation bias.

Although there was less consensus within the group about requesting details of where the charter for the Independent Data Monitoring Committee could be accessed (24e), they agreed to include this in the Delphi survey, given the prominence of this within adaptive trials and the limited information often provided in protocols. The group were also keen to include ‘statistical code’ as an item in the Delphi survey (24f) to cover which statistical package was used or if the statistician used their own code.

# Next steps

The aim of this stage of the ACE project was to generate a comprehensive list of potential checklist reporting items for adaptive trial designs, which can be included in the first round of an online Delphi survey later in 2017. The next step involves the wording of the proposed checklist items in an iterative process led by MD and the Study Management Group. These will be shared with the Steering Committee for finalisation. Prior to the survey, feedback on the proposed checklist items will be sought from an external expert panel. The members of this panel will be purposively selected based on their expertise in adaptive designs and approached by the Study Management Group. The Steering Committee will review the feedback from the expert panel and determine whether to further amend the list of proposed reporting checklist items before the survey, or keep the existing list. Of course, as a CONSORT checklist extension development project, an audit trail of all key decisions made at the pre-survey stage will be maintained in the interests of transparent reporting.

Subsequent to this, there will be a second round of the Delphi survey, followed by a consensus meeting to review the survey results and finalise the reporting items to be included. The outcomes from the consensus meeting will be used to generate CONSORT adaptive trial designs reporting guidance and explanatory document. Prior to publication, the checklist will be piloted and feedback will be sought from investigators of current and completed adaptive trials. This five-stage approach is based on similar research on developing healthcare reporting guidelines (Eldridge et al., 2016).

# References

Campbell, M.K., Piaggio, G., Elbourne, D.R. and Altman, D.G. (2012). Consort 2010 statement: extension to cluster randomised trials. *Bmj*, *345*, p.e5661.

Eldridge, S.M., Chan, C.L., Campbell, M.J., Bond, C.M., Hopewell, S., Thabane, L. and Lancaster, G.A. (2016), “CONSORT 2010 statement: extension to randomised pilot and feasibility trials”, *Pilot and Feasibility Studies*, BioMed Central, Vol. 2 No. 1, p. 64.

Moher, D., Schulz, K. F., Simera, I., & Altman, D. G. (2010). Guidance for developers of health research reporting guidelines. *PLoS Med*, *7*(2), e1000217.

Schulz, K.F., Altman, D.G. and Moher, D. (2010), “CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials.”, *Annals of Internal Medicine*, Vol. 152 No. 11, pp. 726–32.

US Department of Health and Human Services Food and Drug Administration (2010). Draft guidance for industry - Adaptive design clinical trials for drugs and biologics. Available online [accessed 1 February 2017]: http://www.fda.gov/downloads/drugs/guidances/ucm201790.pdf