

Development of an Addaptive designs CONSORT Extension (ACE)

ACE Steering Committee:

Munyaradzi Dimairo¹, Philip Pallmann², Susan Todd³, Steven A. Julious¹, Thomas Jaki⁴, James Wason^{5,14}, Adrian P. Mander⁵, Christopher J. Weir⁶, Franz Koenig⁷, Marc K. Walton⁸, Katie Biggs¹, Elizabeth Coates¹, Jon Nicholl¹, Toshimitsu Hamasaki⁹, Michael A. Proschan¹⁰, John A. Scott¹¹, Yuki Ando¹², Daniel Hind¹, and Douglas G. Altman¹³

¹ School of Health and Related Research, University of Sheffield, United Kingdom;

² Centre for Trials Research, Cardiff University, United Kingdom;

³ University of Reading, United Kingdom;

⁴ Lancaster University, United Kingdom;

⁵ MRC Biostatistics Unit, University of Cambridge, United Kingdom;

⁶ University of Edinburgh, United Kingdom;

⁷ Centre for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Austria;

⁸ Janssen Pharmaceuticals, United States of America;

⁹ National Cerebral and Cardiovascular Center, Japan;

¹⁰ National Institute of Allergy and Infectious Diseases, National Institutes of Health, United States of America;

¹¹ Division of Biostatistics in the Center for Biologics Evaluation and Research, Food and Drug Administration, United States of America;

¹² Pharmaceuticals and Medical Devices Agency, Japan;

¹³ University of Oxford, United Kingdom;

¹⁴ Institute of Health and Society, Newcastle University, United Kingdom

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1 Background

The need to improve efficiency in the conduct of clinical trials is a priority. An adaptive design provides pre-planned opportunities to change aspects of an ongoing trial using accruing trial data during the course of that trial without undermining the validity and integrity of the trial results. Adaptive designs can improve efficiency to address research questions robustly, as quickly as possible to benefit patients, and use no more research resources than necessary.

Adaptive designs are gradually being used in practice or at least considered at the design stage and regulators are gaining more related experience ¹⁻⁹. Despite this, obstacles persist which hamper their appropriate use. These obstacles include differential lack of practical knowledge and concerns about the credibility of results from some adaptive designs ^{10,11}. Some of these obstacles can be addressed through adequate reporting ^{10,12} and literature exists which highlights the implications of inadequate reporting of health research ^{13,14}. Currently, there are deficiencies in the reporting of adaptive design clinical trials ^{15,16}. The available case studies of adaptive designs are mostly inadequately reported and hence not very useful as a practical learning resource and to address concerns relating to their use ^{1,17}.

The need for additional reporting considerations for adaptive designs has been highlighted ^{15,18-20}. However, there is no existing CONSORT Statement extension specific to the reporting of adaptive designs ¹². This project developed an Adaptive design CONSORT Extension (ACE) reporting guideline for randomised trials that use adaptive designs implementing a recommended Delphi consensus-driven process ²¹. We used this grounded methodological approach to develop a comprehensive reporting guideline that is likely to be accepted to influence practice.

2 Methods

The protocol that guided the conduct of this study is registered on the EQUATOR Network database ¹². Study ethical approval was granted by the Research Ethics Committee of the School of Health and Related Research at the University of Sheffield (ref: 012041). The CONSORT Executive Group oversaw the entire development process through its

representative on the ACE Steering Committee. We developed the ACE reporting guideline in seven overlapping stages.

2.1 Stage 1: Rationale

We built on the findings from an NIHR Doctoral Research Fellowship (DRF-2012-05-182) that investigated why adaptive designs are not often used in publicly funded trials¹⁵. This research and others investigated obstacles and potential facilitators to the use of adaptive design trials^{5,10,11,22–26} as well as deficiencies in their reporting^{1,6,15,19}. The need for a reporting guideline specific to adaptive designs with some suggested reporting considerations has been highlighted^{10,11,15,19,20,27}.

2.2 Stage 2: Scoping review

We undertook a scoping narrative review to collate any concerns about adaptive design trials or considerations that may influence their reporting, to identify any suggestions on how adaptive design trials should be reported and to establish definitions of an adaptive design and related technical terms. The goal was to inform the preliminary drafting of reporting items, working definitions for the extension checklist and to create a list of authors who had published adaptive design trials or methodology research as potential participants for the Delphi surveys. We searched the MEDLINE database via PubMed on 17 November 2016 for any articles about adaptive design randomised trials. We retrieved 237 articles, of which 186 eligible publications were reviewed. We also reviewed additional key documents that we were aware of but that were not retrieved by the search strategy, such as regulatory reflection guidance^{28–30}.

2.3 Stage 3: Drafting of the checklist

The Steering Committee met to discuss the preliminary extension checklist drafted in stage 1, focusing on what changes needed to be made and their structure with justification. A report summarising the discussions is accessible online (see <https://doi.org/10.15131/shef.data.6139631>). Following this meeting, the checklist was redrafted and refined during an iterative process through subsequent face-to-face and teleconference meetings and email correspondence involving the Steering Committee. The External Expert Panel reviewed the draft checklist and working definitions of technical terms for quality control. Emphasis was given to what were the pre-defined potential adaptations,

actually conducted adaptations, interim information utilized to perform adaptations and statistical methods implemented to address potential biases due to adaptations.

2.4 Stage 4: Delphi surveys

We undertook an online two-round Delphi process involving international, multidisciplinary, and cross-sector key stakeholders. We targeted those with adaptive designs related experience including clinical trialists, clinical investigators, statisticians, trial methodologists, and health economists; those interested in using adaptive designs; consumers of research findings, decision makers, and policy-makers in clinical trials research including journal editors, systematic reviewers, research funders, regulators, research ethicists and patient representative groups.

We asked participants to rate the importance of the proposed items and to provide related feedback. We used an importance rating scale of 0 to 9 consistent with related Delphi surveys³¹⁻³³: ‘not important’ (score 1 to 3), ‘important but not critical’ (score 4 to 6), ‘critically important’ (score 7 to 9), and ‘don’t know’ (unsure). We indicated whether items were new (N), modified (M), or remained unchanged (U) from the CONSORT 2010 checklist³⁴.

We summarised the distribution of characteristics and demographics of registered participants and responders for each Delphi round. Item rating scores were descriptively analysed. We explored whether the ratings of participants differed by specific characteristics of interest using clustered boxplots stratified by:

- Self-selected key stakeholder group (clinical trial user, clinical trialist, or methodologist);
- Current employment sector (public sector or industry);
- Self-reported regulatory assessment experience (yes or no); and
- Primary role in clinical trials research as a statistician (yes or no).

We summarised the number and proportion of participants who rated an item as ‘not important’, ‘important but not critical’, and ‘critically important’, including the ‘don’t know’ category. We analysed qualitative feedback gathered during the Delphi surveys using a simple thematic analysis³⁵ to identify common comments and elucidate feedback on

suggested items (new or modified) as well as gather additional content suggestions for the checklist.

We prespecified consensus as receiving the support of at least 70% of responders rating an item as ‘critically important’ for inclusion in the Round 2 Delphi survey ^{12,36}.

2.5 Stage 5: Consensus meeting

We held a full day consensus meeting attended by 27 delegates from the UK, USA, Europe, and Asia to advise which reporting items to retain through voting, and to discuss the structure of what to include in the supporting explanation and elaboration (E&E) document. Delegates from the public sector and industry included clinical investigators, trial statisticians, journal editors, systematic reviewers, funding panel members, methodologists, and the CONSORT Executive Group representative. The meeting was independently chaired by Professor Deborah Ashby. We took notes during the meeting and audio-recorded and transcribed the discussions to ensure that the content was accurately captured. Following the discussion of each checklist item or group of checklist items, we asked delegates to anonymously vote about the inclusion of a specific item; ‘keep’, ‘drop’, or ‘unsure or no opinion’.

Prior to the consensus meeting, we specified that the decision to retain an item should be based on achieving at least 50% support of delegates voting to ‘keep’ an item ¹². The Steering Committee used these criteria, in conjunction with the qualitative feedback gathered, to make the final decisions about reporting items to be included in the ACE guideline.

2.6 Stage 6: Refining and finalising the checklist

The Study Management Group met to discuss advisory decisions and suggestions made at the consensus meeting. The group discussed each item reflecting on the consensus report and agreed on the items to retain and the guideline structural changes required. The advisory decisions and suggestions from the consensus meeting were taken on board in consultation with the Steering Committee. The Steering Committee refined the checklist to address rewording and structural changes. The ACE Consensus Group and the Steering Committee signed off the finalised checklist on 30th April 2018.

2.7 Stage 7: Writing-up and dissemination of the E&E document.

This work was orally presented at three international conferences; Society for Clinical Trials (SCT) 39th Annual Meeting, Portland, Oregon on May 20 – 23, 2018; Central European Network – International Society for Biopharmaceutical Statistics (CEN-ISBS), Vienna, Austria on August 28 – September 1, 2017; and Evidence Live, Oxford, United Kingdom on June 18 – 20, 2017. A poster was also presented at the Global Forum on Bioethics in Research (GFBR) meeting on “the ethics of alternative clinical trial designs and methods in low- and middle-income country research”, Bangkok, Thailand on November 28 – 29, 2017.

The forthcoming research outputs to be published in open access leading journals will describe:

- The development process to reach the reporting guidance for transparency and to help other groups developing similar CONSORT extensions,
- The scope of the guideline, the definition of an adaptive design, some types of adaptive designs and trial adaptations, and an explanation of each checklist reporting item in detail including case studies in the E&E document.

We will organise a dissemination workshop following the publication of these research outputs. The research outputs will also be publicly accessible via the project webpage <https://www.sheffield.ac.uk/scharr/sections/dts/ctru/aceproject> .

3 Results

The report for our first full-day Steering Committee meeting held in Sheffield is accessible online (see <https://doi.org/10.15131/shef.data.6139631>). The draft checklists used in Round 1 and 2 Delphi surveys are accessible online, see <https://doi.org/10.15131/shef.data.6198290> and <https://doi.org/10.15131/shef.data.6198347.v1>, respectively.

Delphi surveys response rates were 94/143 (66%), 114/156 (73%), and 79/143 (55%) in Rounds 1, 2 and across both rounds, respectively. Responders were based in 19 and 21 countries in Rounds 1 and 2, respectively. The characteristics and demographics of registered participants and responders were very similar, see <https://doi.org/10.15131/shef.data.6302876>. Summaries of ratings of the proposed reporting items in Rounds 1 and 2 are accessible online, see

<https://doi.org/10.15131/shef.data.6302876>. The item ratings of responders were broadly consistent regardless of their primary role, self-identified stakeholder group, regulatory experience, and employment sector; see <https://doi.org/10.15131/shef.data.6120572>. We used the qualitative feedback gathered in Delphi rounds to inform the development process. Summary of this feedback is accessible online, see <https://doi.org/10.15131/shef.data.6139631>.

Twenty-seven delegates from Europe, the USA and Asia attended the consensus meeting in London. The report of the ACE Consensus Group discussions and advisory decisions made via voting with suggestions on related issues to address is available online, see <https://doi.org/10.15131/shef.data.6306197>.

The forthcoming main ACE checklist has seven new and nine modified items, and seven unchanged items with expanded E&E text to clarify further considerations for adaptive designs. In addition, the abstract checklist has one new and one modified item as well as an unchanged item with expanded E&E text. Our work on the ACE checklist revealed some more general reporting aspects of the overarching CONSORT 2010 Statement that should also be revised in the future due to transparency initiatives and the up-coming ICH E9 addendum on estimands. These general recommendations (not specific to the ACE) were reported back to the CONSORT Executive Group.

4 Conclusions

We have developed a CONSORT extension for all randomised trials that use an adaptive design regardless of the statistical paradigm (frequentist, Bayesian, or both) used in the design and analysis. The guideline aims to promote transparency and adequate reporting of adaptive design randomised trials and not to stifle design innovation or application. Thus the ACE checklist provides only the minimum requirements that we encourage researchers to report. It is good scientific practice to present additional information beyond this guideline if it helps with the interpretation of the trial results.

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