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Reporting issues in group sequential randomised controlled trials: a systematic review protocol of published journal articles

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Abstract

Background

Adaptive designs are somewhat underused, despite prominence given to methodology in the statistical literature. Some concerns relates to robustness of adaptive designs in decision making, acceptability of trial findings to change practice, anxiety about early stopping of trials and worry about wrong decision making. These issues could be linked to inadequate reporting of the conduct of such clinical trials. We assess the reporting of group sequential randomised controlled trials (RCTs), which are one of the most well-understood adaptive designs in the confirmatory setting.

Methods

We undertake a systematic review searching Ovid MEDLINE from 1st January 2001 to 23rd September 2014 and including parallel group confirmatory group sequential RCTs that were prospectively designed using the Frequentist approach. Eligible trials are screened for completeness in reporting against the CONSORT 2010 checklist with some proposed modifications to capture issues such as statistical bias correction following early stopping. Descriptive statistics aided with forest plots on CONSORT compliance are presented.

Discussion

Reporting of the conduct of adaptive designs is an area which has not been fully explored. Hence, the findings from this study can enlighten us on the adequacy in reporting of well-understood group sequential RCTs as a class of adaptive designs and on ways to address some of the cited concerns. Most importantly, the study can inform policy makers on the adequacy of the current CONSORT statements in enhancing reporting of such adaptive designs.

Keywords

Randomised Controlled Trials; Clinical Trials; Group Sequential; Interim Analyses; Adaptive Designs; Early Stopping; Phase 3; Transparency in Reporting; CONSORT

Introduction

The CONSORT Statement is a guidance to facilitate reporting of randomized controlled trials (RCTs), first introduced in 1996 [1] and later revised in 2001 and 2010 [2, 3]. There has been a marked improvement in the reporting of RCTs following the publication of the initial CONSORT statement and a checklist exists, which is tailored for superiority parallel group, fixed sample size design randomised controlled trials (RCTs) [4, 5]. Since then, extensions have been made to accommodate other trials designs and hypotheses such as Cluster RCTs, non-inferiority and equivalence trials, and pragmatic RCTs [6–9]. However, there are still general deficiencies in reporting of RCTs [10]. As of the 23rd September 2014, at least 30 reporting guidance documents are being developed to enhance transparency in reporting [7].

Recently, adaptive designs where planned modifications to some aspects of the trial are permissible, based on accumulating information from that ongoing trial, have been receiving some attention. There are indications that the uptake of adaptive designs is now gaining some traction [11, 12] and there have been various cross industry initiatives including regulators to facilitate and foster discussions, obtain some form of consensus and address issues associated with their use [13–19]. As a result of these initiatives, cautiously expect the uptake of adaptive designs to improve in the future due to these initiatives. However, one of the most common concerns raised by regulators and the research community associated with the use of adaptive designs , especially in confirmatory trials, is the potential to introduce bias and compromise the credibility, integrity and validity of the trial findings during trial conduct, due to the dissemination of interim results [18, 20, 22].

An important way to obviate such worry about potential bias is through transparency and adequate reporting by trialists, for consumers of research findings to make informed judgements regarding the quality of the research in front of them. Results from recent

qualitative interviews of key stakeholders in clinical trials research found that some researchers were concerned about methodological rigour and robustness, and also questioned whether the current reporting guidance framework is adequate enough for clinicians and policy makers to make informed judgements [23]. In addition, these interviews suggested that transparency in conduct and reporting is key to the acceptability of the findings from an adaptive RCT, especially in the confirmatory phase. Some recommendations for CONSORT modifications have been suggested elsewhere although they did not look at the current state of affairs in reporting of adaptive designs [19, 24]. Bearing this in mind, we undertake a review of peer reviewed and published journal reports to investigate the completeness of reporting of GS (group sequential) RCTs. A GS RCT, which is a class of adaptive designs, has been in use for a number of years in the confirmatory setting. It is described by regulators as well-understood and has promising future prospects [20–22]. We believe the findings will enlighten and inform policy on whether the reporting of GS RCTs is adequate enough within the scope of the current CONSORT guidance, as well as informing the need for a modified CONSORT guidance to accommodate adaptive designs.

Objectives

The purpose of this study is to investigate the adequacy in reporting of GS RCTs in order for consumers of research to make informed judgements about the quality of the research. The specific objectives are to;

- Investigate completeness in reporting within the scope of the current CONSORT guidance checklist
- Investigate the shortcomings of the current CONSORT guidance in enhancing the reporting of GS RCTs, that is, what sort of missing relevant information should be reported

- Provide recommendations for policy makers regarding adequate reporting of adaptive designs
- Provide a collection of case studies of GS RCTs published in "high impact" peer reviewed medical journals

Methods

Review approach and search strategy

We undertake a systematic review of published peer reviewed GS RCT reports indexed in Ovid MEDLINE. We chose to conduct the searches through Ovid due to the efficiency of the searches compared to those done through PubMed or Web of Science. We aim to maximise the number of relevant trials in our search results, whilst minimising the number of irrelevant trial reports. One of the main challenges of methodological systematic review of this nature is the lack of consistent and efficient MeSH terms to base the searches on. For instance, our scoping exercise found only one relevant MeSH term, ("Early Termination in Clinical Trials") associated with GS methodology through PubMed. This proved to be inefficient through Ovid, since no records were retrieved. In addition, it only retrieved 292 reports through PubMed which we believe is insensitive. We therefore employ keywords associated with GS methodology (Table 1) which are often used by statisticians/trialists during communication and dissemination together with filters, as discussed in Section on screening for eligibility.

Table 1: Search strategy using keywords

Search	Exact search terms	Filters
1	Group sequential	▪Check tags o Humans o Full text available o English language
2	Interim analysis Interim analyses	
3	Stopping rule	

	Stopping rules Stopping boundaries Stopping boundary	▪Publication types o Clinical trials; phase III ▪Period (01/01/2001 to 23/09/2014)
4	Interim monitoring	
5	Early stopping	
6	Early termination	
7	Accumulating data	
8	Accumulating information	

The final search can be combined using a Boolean operator "OR" as follows; (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8).

In addition, we supplement the search by using reports of known GS RCTs retrieved from another ongoing study.

Screening for eligibility

We employ the following inclusion and exclusion criteria to filter relevant or eligible reports;

- Include RCTs with two or more arms
- Include only English Language reports
    - Exclude other languages for practicalities
- Include trials with full text available otherwise it would be impossible to evaluate completeness in reporting
    - Exclude trials with abstract only
- Include trials only conducted in humans
    - No restriction on the population (paediatric and adults)
- Include all trials regardless of the nature of the primary endpoint(s)

- No restriction on the nature of the primary outcome(s): continuous, binary, time to event, ordinal, categorical and count

- Study design characteristics
  - Randomised controlled trials
    - Exclude observational studies
  - Prospectively planned group sequential RCTs regardless of the reason to stop early
  - Parallel group
    - Exclude crossover and cluster randomised trials due to the fact that these designs have certain additional specific reporting requirements
- Include only phase III or confirmatory trials
  - Exclude phase I or II or II/III or IV
- Time period takes into account the publication history of the CONSORT statement but excludes the first period to allow for publicity to the wider research community. The checklist items of the latest 2010 version are used to measure quality in reporting
  - First version to be excluded was published in 1995 and become effective in 1996) [1]
  - Second version published in 2001 [2]
  - Third latest version published in March 2010 [3]
  - Therefore, we include reports between 01/01/2001 to 29/09/2014

Data extraction and management

Citation information of retrieved reports, such as title, authors, journal details and publication year, together with the abstract, are exported to Excel or Reference Manager or Endnote software, depending on the preferences of the reviewers. Duplicate records are checked with respect to first author, title and publication year. Retrieved duplicate records are

manually cross checked before deletion. Data extraction sheet can then be used for further filtering of relevant papers. A further data extraction is then used to extract study characteristics of interests in order to answer the research question. Two reviewers independently extract study characteristics of interests and assess the quality in reporting, in line with the modified CONSORT checklist. Cross validation of the extracted material is done between two independent reviewers.

Study primary outcome

Our primary outcome is compliance to the CONSORT 2010 checklist items which is subjectively measured by two independent assessors according to an initially agreed classification system; "absent", "partially complete", "totally complete", "cannot assess" and "not applicable". Further assumptions can be made to create a binary outcome to assess CONSORT compliance using logistic regression.

Analysis and Reporting

Statistical analysis is mainly descriptive in nature and reporting in accordance with the PRISMA checklist [25, 26], includes, a flowchart describing identification of records from all different sources, screening and eligibility, and a summary of study characteristics of included eligible studies depending on the nature of the variables of interest. For instance, numbers and proportions for binary or categorical variables and numbers, mean (SD) or median (IQR) for continuous variables depending on their underlying distributions. Numbers and proportions are used to summarise trials meeting completeness in reporting of certain dimensions of the CONSORT checklist and other research driven dimensions. In addition, completeness in reporting is considered by variable of interest such as funder (private or public), intervention type (drug and non-drug), whether the journal endorse the CONSORT statement (endorsers and non-endorsers [27]) and publication period (before and after 2010 CONSORT revision). Difference in completeness for each CONSORT checklist item

stratified by factor variable is presented as Odds Ratios (ORs) with associated 95% CI using logistic regression. Furthermore, we utilise clustered histograms and forest plots to aid presentation of the findings.

Discussion

Previous literature suggested that there are general deficiencies in the reporting of RCTs [10]. The use of CONSORT statements has seen a marked improvement in completeness of reporting of RCTs in general, although it remains sub-optimal [28]. Although much research has been undertaken investigating general adherence to the CONSORT checklists in RCTs [28, 29], we are not aware of similar research investigating adequacy in reporting in the class of adaptive designs such as GS RCTs. The need for our study has been informed by a prior nested qualitative study which found fear of making wrong decisions and concerns about the robustness of adaptive designs in confirmatory decision making as some of the barriers to their uptake. In addition, varying level of practical and statistical complexity associated with adaptive designs increases the risk of the potential introduction of bias in the conduct of the studies and thereby compromising the integrity, credibility and validity of the finding. We postulate that the concerns about wrong decision making could be related to transparency in conduct and reporting. For instance, lack of detail regarding a key aspect of an adaptive trial is likely to lead to reluctance to accept the findings by the research community.

What does this study add?

Although some suggestions to modify the CONSORT guidance for adaptive designs have been proposed elsewhere [19, 24]; to the best of our knowledge, we are not aware of previous studies investigating the current state of affairs in adaptive designs in line with the current CONSORT guidance. Therefore, the findings from this study enlighten us on the adequacy in reporting of GS RCTs as a class of adaptive designs. Most importantly, it

informs policy makers on the adequacy of the current CONSORT statements in enhancing reporting of adaptive designs. Thus, it highlights whether there is scope for a modified CONSORT statement for adaptive designs; and if so, what additional information should be reported and whether previous suggested modifications are adequate.

Strength and limitations

The main strength of this study is that it is filling the gap based on adaptive designs related concerns raised by the research community and regulators identified during an ongoing study investigating the use of adaptive designs in the confirmatory setting [23]. One of the main methodological shortcomings due to resources and time limitation is restriction to the Ovid MEDLINE database. We acknowledge that there could be some GS RCT reports which may not be indexed in Ovid MEDLINE but other databases such as EMBASE and PubMed. In addition, the lack of consistent MeSH terms describing GS RCTs limited the efficiency of our searches. However, we have also supplemented the search strategy by searching reports of known and completed GS RCTs from another ongoing study. Despite the fact that our search strategy may not be exhaustive, we believe it is robust enough to answer the research question and inform us on the state of affairs of reporting of GS RCTs.

Acknowledgements

MD is fully funded by NIHR as part of a Doctoral Research Fellowship (DRF-2012-05-182). SJ, JN, DH and CC are funded by the University of Sheffield. ST is funded by the University of Reading. AS is a medical student with the University of Sheffield Medical School. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, the Department of Health or organisations affiliated to or funding them. Mike Bradburn for his comments as MD's personal fellowship tutor.

Authors contributions

All authors contributed to the development of the protocol, read and approved the final version. MD led the write up.

Abbreviations

AD: Adaptive Design; CI: Confidence Interval; CONSORT: Consolidated Standards of Reporting Trials; DRF: Doctoral Research Fellowship; GS: Group Sequential; IQR: Inter-Quartile Range; MeSH: Medical Subject Headings; NIHR: National Institute for Health Research; RCT: Randomised Controlled Trials; SD: Standard Deviation; OR: Odds Ratio

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