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Reporting on Data Monitoring Committees in Neonatal Randomised Controlled Trials is inconsistent

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Short title: Reporting on Data Monitoring Committees in Neonatal Randomised Controlled Trials

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Abstract

Aim: To evaluate the reported use of Data Monitoring Committees (DMCs), the frequency of interim analysis, pre-specified stopping rules and early trial termination in neonatal randomised controlled trials (RCTs).

Methods: We reviewed neonatal RCTs published in four high impact general medical journals, specifically looking at safety issues including documented involvement of a DMC, stated interim analysis, stopping rules and early trial termination. We searched all journal issues over an 11-year period (2003-2013) and recorded predefined parameters on each item for RCTs meeting inclusion criteria.

Results: Seventy neonatal trials were identified in four general medical journals: Lancet, New England Journal of Medicine (NEJM), British Medical Journal and Journal of American Medical Association (JAMA). 43 (61.4%) studies reported the presence of a DMC, 36 (51.4%) explicitly mentioned interim analysis; stopping rules were reported in 15 (21.4%) RCTs and 7 (10%) trials were terminated early. The NEJM most frequently reported these parameters compared to the

other three journals reviewed.

Conclusion: While the majority of neonatal RCTs report on DMC involvement and interim analysis there is still scope for improvement. Clear documentation of safety related issues should be a central component of reporting in neonatal trials involving newborn infants.

Key Notes:

- Data Monitoring Committees are an important safety aspect of RCTs, particularly in trials involving vulnerable populations.
- While the majority of RCTs included in this review reported on DMC involvement, our results highlight deficiencies in the reporting of neonatal RCTs.
- Clear documentation of safety related issues should be a central component of reporting in neonatal trials involving newborn infants.

Key words

Clinical trials, randomised controlled trials, RCTs, data monitoring committees, DMCs, stopping rules, interim analysis, neonatal

Introduction

Neonatal randomised controlled trials (RCTs) recruit a vulnerable group of patients, the protection of whom is of critical importance. The balance between risks and benefits is a central ethical issue in research involving children and the complexity of risk determination is highlighted by the recent SUPPORT (Surfactant, Positive Pressure, and Oxygenation

Randomized Trial) controversy. (1-4) Infants cannot consent to research so it is left to others, parents, researchers and regulators, to decide if the risk-benefit ratio is acceptable and that sufficient clinical equipoise exists to justify conduct of an RCT. (5) The complexities of conducting comparative research trials such as SUPPORT are highlighted in a recent editorial from the Hastings Centre.(6)

Patient safety is critical to the conduct of RCTs. One method of ensuring patient safety is the establishment of a Data Monitoring Committee (DMC). This consists of a group of external experts whose main function is to safeguard the interests of the study participants. This is achieved through vigilance over the conduct of the trial, performing analysis of safety data and predetermined interim analysis of the efficacy endpoint(s).(7-9) A DMC must consider both individual and collective factors when making recommendations regarding the appropriateness of trial continuation and, if necessary, obtain unpublished and interim data from sources outside of the trial.(4, 8) The recommendations of a DMC will affect the credibility of the trial, the validity of its results, and indirectly, their implementation in clinical practice.(9) For example, evidence suggests that treatment effects of interventions in trials that are stopped early for benefit are systematically overestimated.(10, 11)

In order to properly assess the recommendations of a DMC, their activities and considerations must be adequately reported.(9) Deficiencies in the reporting of pediatric RCTs were highlighted in a recent systematic review which found that only 17% of trials published in high-impact journals reported on DMCs, interim analysis or early termination.(9) Published guidelines are available for the appointment and operational procedures of DMCs.(12, 13) Guidance is also available regarding which types of trials require DMCs. In general, RCTs that address major health outcomes and are designed to address efficacy and safety issues should have a DMC (14) and it is appropriate establish the additional protection of a DMC in cases involving vulnerable populations. (14-16)

Neonates are one of the most vulnerable subgroups of the pediatric population and, to our knowledge, documented DMC involvement in neonatal RCTs has not been previously published. We were interested in a number of issues pertaining to DMCs in neonatal RCTs. We wanted to determine the documented use of DMCs, the frequency of interim analysis performed, the presence of pre-specified stopping rules and early trial termination of neonatal clinical trials published in high-impact general medical journals.

Methods:

Eligibility criteria

Neonatal trials published in four general medical journals (British Medical Journal (BMJ), Journal of the American Medical Association (JAMA), Lancet and The New England Journal of Medicine (NEJM)) during the years Jan 1 2003 to Dec 31 2013 were included. These journals have high impact factors and are known to publish clinical trials with the potential to significantly influence clinical practice. We included randomised controlled trials involving newborn infants investigating any therapeutic or preventive health care interventions in preterm infants or term infants younger than 28 days of life.

Literature search

All issues of each of the included journals listed above for the years 2003 to 2013 inclusive were searched by a single researcher (SG: NEJM; LP: JAMA, Lancet; IR; BMJ) to identify any neonatal RCT. Two independent reviewers (JM, ED) independently screened the full-text articles of included citations to confirm suitability for inclusion and where disagreements arose, these were resolved by consensus. The literature review was conducted over a 6-month period

between January and July 2014. We did not assess the overall quality of each manuscript, but specifically sought information pertaining to the mention of a DMC or Data Safety Monitoring Board (DSMB), whether interim analysis were performed, the presence of pre-specified stopping rules and early trial termination.

Data Extraction and Analysis

For each included article, two authors independently searched all sections of the manuscript for relevant information, including abstract and acknowledgements, and extracted data using a computerized data collection form (Microsoft Excel). Evidence-based parameters for data collection regarding DMC characteristics, interim analyses and clinical trial stopping rules were clearly defined.(12-14, 16) The following information was extracted: trial monitoring by a DMC, performance of interim analysis, pre-specified valid rules or guidelines for early trial termination (i.e. stopping rules), whether the study was terminated early, and if so why. The reported use of DMCs was estimated from the proportion of identified RCTs that explicitly mentioned the use of a DMC in the manuscript. Statistical analysis for this study was performed using IBM SPSS Statistics 22.0 (http://www.spss.com). The number of articles per journal was represented as a proportion of the overall number of RCTs published. Comparison between journals was performed using chi square analysis. All tests were two-sided and a p-value <0.05 was considered to be statistically significant.

Results

Our initial search identified a total of 3054 RCTs. The NEJM published 1107 RCTs, while the Lancet, JAMA and BMJ published 807, 588 and 552 RCTs respectively. Seventy (2.3%) of all the RCTs identified involved neonatal participants. The Lancet published the highest proportion of neonatal RCTs relative to their total number of RCTs (3.5%) and contributed the most neonatal trials to this review (n= 28, 40%). The BMJ, JAMA and NEJM published similar proportions of neonatal RCTs, at 2.0% (n=11), 1.9% (n=11) and 1.8% (n=20) respectively.

Data safety monitoring reporting by journal is displayed in table 1. Overall, 43 (61.4%) of the published clinical trials commented on the presence of a DMC, 36 articles (51.4%) explicitly mentioned interim analysis, and a total of seven (10%) neonatal trials were terminated early. There was a difference in the proportion of studies that documented the presence of a DMC. Ninety percent of the neonatal trials published in the NEJM reported on DMCs, compared to 63.2% in JAMA, 46.4% in the Lancet and 45% in the BMJ (p-value of 0.013). Interim analyses were reported in just over half (51.4%) of all studies, again there was a significant difference between journals (p=0.018).

Of the absolute number of planned interim analysis reported (n=31), on 8 occasions one interim analysis was performed, on 13 occasions there were two planned interim analysis and there were greater than 2 on 6 occasions. Stopping rules were reported in 21.4% of all studies, there was a significant difference between clinical trials published in the different journals with regard to reporting stopping rules (p=0.18). Again, the NEJM was the journal most likely to report stopping rules (45%).

We identified a total of seven (10%) RCTs terminated early. Four were terminated for benefit, two for harm and one RCT readjusted its sample size because the primary outcome was occurring at an increased frequency than estimated in the protocol. A DMC was documented in

all RCTs terminated early. A stopping rule was not reported in the published manuscript in three of these seven trials terminated early

Discussion

The safe conduct of RCTs is paramount, especially when dealing with vulnerable population groups such as newborn infants. One critical component consists of local or national ethics committees review to ensure patients are not exposed to unnecessary risks. Studies that involve medications or medical devices are also reviewed by national agencies such as the MHRA (Medicines and Healthcare Products Regulatory Agency). Another important component of the safe conduct of a clinical trial is the presence of a Data Monitoring Committee (DMC). The decision to use a DMC is based on numerous factors, including amongst others the risk to subjects, the complexity of the trial design, and the number of clinical sites involved. (15, 17) Clinical and methodological criteria are available to decide if a DMC is required for a particular trial.(16) We believe reporting the presence or absence of a DMC and its functions is an important aspect of the conduct of the clinical trial.

The development of original CONSORT statement was fueled by a lack of adequate reporting of RCTs(18). The CONSORT 2010 document explicitly states and recommends that authors report whether they or a DMC performed interim analyses, and if so, how many there were, what triggered them, the statistical methods used (including any formal stopping rule), and whether they were planned before the start of the trial.(18) Disappointingly, we found that only 61.4% of all RCTS published in these four journals reported on the involvement of a DMC, 51.4% explicitly mentioned interim analysis and only 21.4% reported a statistically valid stopping rule.

While the neonatal trials included in this review attained higher reporting standards compared to a similar review of pediatric trials(9), our results show heterogeneous practices and suboptimal reporting of these important safety concerns across the four journals. Since DMCs have the power to both safeguard trial participants and influence the outcome by way of recommending termination or continuation of studies, we believe clear and transparent reporting of their involvement is essential. We chose 2003 onwards as our initial time point because the first publications relating to consolidated reporting of clinical trials occurred in 1996 and the revised statement was published in 2001. It is important to note that we were not applying standards from CONSORT 2010 to trials published before that point. It is also important to highlight that we are not assessing the quality of the individual trials we have we included in this review; we are assessing important aspects pertaining to patient safety reported in published manuscripts.

The trials published in the NEJM demonstrated more comprehensive reporting of these parameters compared to the other included journals (table 1). It is unclear why this is the case. It is the role of investigators to include these important factors in the submitted manuscript, the role of reviewers to ensure that these critical safety issues are addressed and the role of the editorial staff to ensure these are included in the final published article. In this way physicians, allied healthcare professionals, patients, families and the general public can be reassured that trials conducted in these patient group recognize patient safety as the key aspect of these important studies.

However, despite meticulous trial conduct and reporting, controversy can still engulf a newborn trial. The SUPPORT study(3), a large US trial investigating the optimal range of target oxygen saturations for extremely premature infants, raised ethical issues regarding how the risks of research compares to the risks of standard clinical practice. In 2011 the SUPPORT trials' informed consent process was investigated by the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services. While the misgivings of the

OHRP were not shared by many in the neonatal community, it nonetheless generated apprehension regarding the conduct of clinical trials in this at risk group of patients.(2) Clinical research is crucial to the advancement of the medical science and maximizing safety features. One way of trying to alleviate concerns is ensuring complete and accurate reporting of RCTs in medical journals. Enhancing the information in the public domain with more consistent reporting of primary trials, ensuring safety aspects are consistently reported in the primary publication could help restore any perceived lack of confidence in clinicians. Whilst we acknowledge that much of this information should be provided in various databases such as clinical trials.gov we believe this information should be prioritized and included either in the body of the manuscript or as an appendix to the manuscript, which is readily accessible to the journal reader.

One of the main limitations of this study is that we identified trials from a restricted set of journals that have high-impact factors and are known to publish trials in a broad range of conditions and age categories. These studies may not be representative of the majority of neonatal trials. However, we chose high caliber medical journals with good quality studies so it is possible that the shortcomings we identified might in fact be more prevalent in neonatal trials published in other journals. We concentrated our efforts on the actual reported manuscript, and did not review various clinical trial websites as mentioned above. We did not contact journal editors to clarify their policy of this information in the published manuscript. Whilst the individual journals will have their own publication policies, the CONSORT Statement is endorsed by all 4 journals reviewed.

Where there is inconsistency in reporting clinical trials concerns can arise. Therefore, we call for clear reporting of DMC involvement or lack thereof in neonatal RCTs; submitted manuscripts should state the involvement of a DMC and interim analyses and stopping rules should be reported in accordance with evidenced based guidelines.(12, 14, 18) This should avoid confusion and provide additional clarity regarding central safety components of clinical trials

involving newborn infants and may alleviate some of the concerns that may arise amongst healthcare workers, the general public, funding agencies and government agencies of clinical trials conducted in this group of patients.

Conclusion

DMCs represent an important safety aspect of RCTs. While the majority of neonatal RCTs included in this study report on DMC involvement and interim analysis there is still scope for improvement. Clear documentation of safety related issues should be a central component of reporting in neonatal trials involving newborn infants

Abbreviations: DMC; data monitoring committee, RCT; randomized controlled trial, NEJM: New England Journal of Medicine, BMJ; British Medical Journal, JAMA; Journal of American Medical Association,

Table 1: Data safety monitoring reporting by journal

Journal	Neonatal RCTs n (%)	DMC reported n (%)	Interim Analysis n (%)	stopping rule reported n (%)	Trial terminated early n (%)
Lancet	28 (40.0)	13 (46.4)	12 (42.9)	3 (10.7)	3 (10.7)
NEJM	20 (28.6)	18 (90.0)	16 (80.0)	9 (45)	4 (20.0)
JAMA	11 (15.7)	7 (63.6)	5 (45.5)	1 (9.1)	0
BMJ	11 (15.7)	5 (45.5)	3 (27.3)	2 (18.2)	0
Total	70 (100)	43 (61.4)	36 (51.4)	15 (21.4)	7 (10.0)

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