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Non-publication and Discontinuation of Randomised Controlled Trials in Newborns

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Short title: non-publication and discontinuation of neonatal trials

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Abstract

Aim: To determine the rate of non-publication and discontinuation of randomised controlled trials (RCTs) in newborns.

Methods: This was a retrospective, cross-sectional study of RCTs registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR) between 2008 and 2012.

Results: Fifty trials were identified, of which 23 (46%) were retrospectively registered. Thirty trials (60%) were published. After a median follow-up of 8.0 (range 4.6 to 17.4) years from Research Ethics Committee approval, 15 of 41 completed trials (37%) remained unpublished, representing 5422 neonatal trial participants. Nine trials (18%) were discontinued, including four that were published. The most frequent reason for discontinuation was poor recruitment (n=4). Sample size discrepancies between registration and publication were found in 17 (65%) of the 26 completed, published trials. In nine of these trials (35%), the calculated sample size in the method section of the published article differed from the planned sample size in the trial registry (relative difference -20% to +33%).

Conclusion: Non-publication and discontinuation of RCTs conducted in newborns is common. Additional efforts are needed to minimise the number of neonatal trial participants that are exposed to interventions without subsequent publication.

Keywords:

randomised controlled trials, publication, discontinuation, newborn

Key notes

- Non-publication and discontinuation of RCTs is concerning from an ethical, scientific and financial perspective and the scale of this problem in the neonatal population is unknown.
- Non-publication and discontinuation are common in neonatal research and expose newborns to interventions without any potential future benefit.
- Sample size discrepancies between registration and publication are concerning and highlight difficulties in trial execution and deficiencies in the peer review process.

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Background

The World Medical Association developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and others engaged in medical research involving human subjects (1). One of its basic principles declares that negative as well as positive results should be published or otherwise be made publicly available. Failure to publish findings from research studies represents lost knowledge and wasted resources (2).

In recent years, efforts have been made to improve access to unpublished human studies. This resulted in the establishment of web-based, publicly available registries of clinical studies worldwide. Since 2005, the International Committee of Medical Journal Editors (ICMJE) has required that clinical trials involving human participants must be registered *prior to* the beginning of study enrolment, in order to be considered for publication (3).

However, in randomized controlled trials (RCTs) conducted in adults, high rates of non-publication and discontinuation across a range of medical specialities have been reported (4-9). Pica et al. conducted the most extensive examination of non-publication and discontinuation in paediatric RCTs and concluded that both of these outcomes are common (10).

Little is known about the completion and publication rates of RCTs in newborns. We sought to determine the outcome of clinical trials conducted in newborns and registered with the Australian New Zealand Clinical Trials Registry (ANZCTR). Using the methods and definitions described by Pica et al. (10), our objective was to assess the prevalence of, and factors contributing to non-publication and discontinuation of RCTs in newborns.

Methods

Data Source

The ANZCTR is a web-based database of clinical trials being undertaken in Australia, New Zealand and elsewhere (11). The registry currently holds over 13,000 trials from 137 countries. The ANZCTR records a trial's objectives, main design features, recruitment status and funding source. The registrant is responsible for ensuring that this information remains accurate and up-to-date.

We conducted a cross-sectional study of randomised controlled trials (RCTs) registered in the ANZCTR that recruited newborn infants. We used the advanced search function on the ANZCTR's website to identify interventional RCTs that were registered between January 1, 2008, and December 31, 2012. The commencement date was chosen as it was after the dissemination and acceptance of the publication requirement to prospectively register trials

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(June 2005). The end date allowed a five-year period for publication. We restricted the results to paediatric trials (under 18 years of age) that were completed or had been discontinued. From these results, we manually selected trials that limited participation to preterm and term newborns (0 – 4 weeks of life). The ANZCTR query was performed on March 16th 2017.

Definitions

We used dataset definitions provided by the ANZCTR. A discontinued trial was classified as 'withdrawn', 'suspended' or 'stopped early'. Reasons for trial discontinuation were determined based on data provided in the ANZCTR entries, and by email correspondence with study investigators. We used previously published categories for trial discontinuation (10, 12): The categories included 1. patient accrual, 2. conduct problems: equipment or medication unavailable/withdrawn, 3. informative terminations: safety or efficacy findings or changes in standard of care, 4. regulatory issues: difficulties with obtaining approval by institutional review boards or other regulatory bodies, 5. principle investigator left, 6. funding issue.

We considered a trial to be published when a journal had published a peer-reviewed manuscript describing trial findings. We defined the time to publication as the interval between the actual date of last data collection and the date the publication appeared as an electronic publication. We classified a trial as unpublished if we were unable to identify a publication, and the trial investigator either did not respond to our inquiries, or informed us that the trial was unpublished.

Publication Search

We reviewed all ANZCTR trial entries to identify links to relevant publications. If no publication was available, we searched Medline via PubMed using the ANZCTR Trial ID number, trial title, author names and study keywords. A final search was completed on March 24th, 2017.

For discontinued trials without a stated reason, and for completed studies with no publication identified, we attempted to contact study investigators by email. We sent a standardised email to the investigators to inquire about recruitment and publication status, with one follow-up email two weeks later.

Statistical Analysis

Trial characteristics and the prevalence of non-publication and discontinuation are presented as frequencies and percentages. Continuous data are presented as medians and ranges.

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Variables chosen as predictors of non-publication and discontinuation were those that the authors agreed *a priori* might impact publication and completion status based on previous research and included four variables; funding, intervention type, masking and trial size (6, 8, 10). After dichotomization, these variables were included in a univariable logistic regression model where the dependent variable was either non-publication or discontinuation. Multivariable logistic regression was not performed due to the small number of included trials. A significant difference between groups was defined as a P value of < 0.05. All analyses were performed using STATA software (Intercooled V.14, StataCorp, College Station, Texas, USA).

Results

Trial Characteristics

Our initial search identified 749 trials. Of those, 699 did not meet our inclusion criteria: in 673 trials participation was not limited to newborns, in 18 trials patient recruitment had not started (n=5) or was ongoing (n=13), and eight trials used a non-randomised study design. Accordingly, 50 trials were included in the final analysis (Figure 1).

Twenty-three trials (46%) were retrospectively registered after a median interval of 1.1 (range 0.01 to 9.1) years between start of patient enrolment and trial registration. Five trials (10%) were registered after completion of patient recruitment. The median planned sample size was 92 (range 10 to 32,000). Nearly one third of all trials studied conditions related to childbirth and postnatal care, followed by interventions for respiratory (24%), dietary (10%), infectious (6%) and cardiovascular (6%) diseases (Table 1). Email queries were sent to 16 (32%) trial investigators to ascertain reasons for non-publication or discontinuation, when none was disclosed. Thirteen (81%) investigators responded to our inquiry.

Publication status

Thirty (60%) of the 50 registered trials were published. Sixteen (53%) of these trials had been retrospectively registered, ten (63%) of which were published in journals that subscribed to the ICMJE prospective trial registration guidelines. Median time to publication was 2.1 (range 1.0 to 6.7) years.

After a median follow-up of 8.0 (range 4.6 to 17.4) years from Research Ethics Committee approval, 20 (40%) of the 50 neonatal trials remained unpublished. Of the 20 unpublished trials, 15 were trials that had recruited their stated sample size. These 15 trials account for 5,422 neonatal trial participants. Reasons given by the authors for non-publication were; manuscript rejection by journal (n=3), publication of trial outcomes as abstract only (n=2), manuscript preparation in progress (n=2) and manuscript currently under peer review (n=2).

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For the remaining six trials, no response was obtained from the authors. In our logistic regression model, none of the four tested variables were associated with non-publication (Table 2).

Of the 30 published trials, four (13%) were trials that had stopped early. One trial was discontinued for each of the following reasons: slow recruitment, conduct problem (lack of availability of study drug), informative termination (futility on interim analysis) and loss of equipoise.

Completion status

A total of nine trials (18%) were discontinued prior to full recruitment. In total, 1,056 study participants were enrolled in trials that were not completed. The most common reason for trial discontinuation was difficulty with patient accrual (n=4), followed by informative terminations (n=2), conduct problem (lack of availability of study drug, n=1), principle investigator left (n=1) and lack of funds (n=1). In univariable analysis, sample size was found to be a determinant of trial discontinuation (Table 2). Trials that anticipated enrolling less than 100 participants were less likely to be discontinued (odds ratio 0.18, 95% confidence interval 0.03 – 0.99, $P = 0.05$) than larger trials.

Sample size discrepancies

We found sample size discrepancies between registration and publication in 17 (65%) of the 26 completed, published trials. In nine trials (35%), the calculated sample size in the method section of the published article differed from the planned sample size in the trial registry. Published sample sizes were smaller in five trials (relative difference -1% to -20%) and bigger in four trials (relative difference +2% to +33%). Two of these trials, and a further eight also had discrepancies between the calculated target sample size in the method, and the actual number recruited (relative difference -1% to -28%), although they were all recorded in the registry as completed. Six of these trials recruited less than 95% of their calculated target sample size.

Discussion

In our sample of neonatal RCTs, retrospective trial registration was common. We identified considerable rates of trial discontinuation and high rates of non-publication among completed trials; 40% (20/50) of clinical trials in newborns remained unpublished (mix of completed and discontinued trials), 37% (15/41) were unpublished yet complete and 10% (5/50) were

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unpublished and discontinued. In addition, discrepancies in trial design between the registry and the published article were frequent.

More than one third of completed RCTs conducted in newborns remain unpublished. This non-publication rate is similar to previous study cohorts in children (range 30 to 47%) (10, 13) and slightly lower than reported for previous cohorts in adults (range 40 to 48%) (4, 5, 14). Non-publication of clinical trial outcomes is concerning and, despite heightened ethical and legislative requirements, still common. Irrespective of all ethical concerns, failure to disseminate study outcomes represents a waste of human and material resources. In addition, unreported or selectively reported study findings bias the literature, and result in under-informed decisions when choosing medical interventions. This is even more important in research areas where the number of potential participants is limited, and where funding opportunities are scarce (15).

Previous research has shown that 19 to 40% of RCTs conducted in children are discontinued prior to completion (10, 13, 16). Our overall trial discontinuation rate was slightly lower than reported rates. This may be related to the newborn population studied, our relatively small sample size, or the small sample sizes of the included trials. In our cohort, larger trials were at higher risk of discontinuation. This is contrary to the literature where smaller trials were more likely to be discontinued (10, 13) and might in part reflect the high requirements involved in the planning and conduct of large neonatal trials.

Previous reports identified industry funding to be associated with lower odds of publication for completed paediatric trials (8, 10). In our neonatal cohort, only three trials were industry funded, which probably mirrors the lack of commercial interest in this field of research. In contrast, one third of included trials were funded by government bodies. Of note, seven (64%) of 11 completed, government funded trials were unpublished. In four of the seven trials, investigators informed us that either data analysis and manuscript preparation is ongoing (n=2) or a manuscript is currently under peer review (n=2). Thus, these trials are likely to be published considering that in our and other cohorts an average time of two years had passed between completion and publication of clinical trials (17).

We looked at deviations in sample sizes between the registry and the method section of the published article. We found differences in more than a third of completed trials ranging from -20% to + 33% of proposed sample size. The reason for deviating from the initially planned sample size was given in three of the nine trials. In the remaining six trials, this inconsistency was not resolved before publication. It may be assumed that information included with trial registration is not checked to identify unacknowledged changes during the manuscript review process. A recent survey of 1,733 reviewers of clinical trials supports this, revealing that only

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one-third of peer reviewers examined registered trial information and reported any discrepancies to journal editors (18). Prospective trial registration should help to increase transparency; however, half of our included neonatal trials were registered retrospectively, after patient enrolment. Again, this is a potential impediment to publication which could be expected to be identified at peer review.

There are several limitations to the findings presented in this report. Our sample size is relatively small. Accordingly, we could not include some well-established factors associated with non-publication or discontinuation (e.g. industry vs. non-industry funding) in our regression analysis. In addition, small sample sizes always imply an inherent risk of selection bias. Furthermore, our sample is based on studies registered in the ANZCTR; it may well be the case that there were additional Australian and New Zealand trials, registered elsewhere, that were not captured in our analysis. In addition, if investigators could not be contacted, and no publication could be identified, we were not able to verify the accuracy of the registry data.

Conclusions

Amongst this cohort of trials conducted in newborns, discontinuation was common, with poor recruitment being the most frequently reported reason. When trials were completed, non-publication of trial outcomes remained prevalent. Non-publication and discontinuation are of ethical concern and represent a considerable waste of resources, exposing a large number of neonatal trial participants to potential risks, without bringing any benefit to the community. Greater efforts are needed to enhance transparency in the planning, execution and reporting of clinical trials.

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Competing Interests

None declared.

Abbreviations:

ANZCTR: Australian New Zealand Clinical Trials Registry

ICMJE: International Committee of Medical Journal Editors

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RCT: Randomised controlled trial

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Tables

Table 1. Characteristics of included trials

Trial characteristics		**All (n=50)** n (%)	**Published (n=30)** n (%)	**Unpublished (n=20)** n (%)
Intervention	Drug	9 (18)	6 (20)	3 (15)
	Device	12 (24)	7 (23)	5 (25)
	Other	29 (58)	17 (57)	12 (60)
Assignment	Parallel	42 (84)	26 (87)	16 (80)
	Crossover	6 (12)	2 (7)	4 (20)
	Single group	1 (2)	1 (3)	0 (0)
	Factorial	1 (2)	1 (3)	0 (0)

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Control	Active	33 (66)	17 (57)	16 (80)
	Placebo	13 (26)	9 (30)	4 (20)
	Dose comparison	3 (6)	3 (10)	0 ()
	Uncontrolled	1 (2)	1 (3)	0 ()
Masking	Double blind	22 (44)	16 (53)	6 (30)
	Single blind	2 (4)	0 (0)	2 (10)
	Open label	26 (52)	14 (47)	12 (60)
Funding	Government	14 (28)	5 (17)	9 (45)
	Charities/foundations	12 (24)	9 (30)	3 (15)
	Self-funded/unfunded	8 (16)	4 (13)	4 (20)
	Hospitals	7 (14)	6 (20)	1 (5)
	Industry	3 (6)	2 (7)	1 (5)
	University	3 (6)	2 (7)	1 (5)
	Other	3 (6)	2 (7)	1 (5)
Sponsor	Hospital	19 (38)	12 (40)	7 (35)
	Individual	11 (22)	5 (17)	6 (30)
	University	9 (18)	6 (20)	3 (15)
	Government body	3 (6)	2 (7)	1 (5)
	Charities/foundations	4 (8)	2 (7)	2 (10)
	Other	4 (8)	3 (10)	1 (5)
Trial registration	Retrospectively	23 (46)	16 (53)	7 (35)
	Prospectively	27 (54)	14 (47)	13 (65)
Recruitment	Single country	45 (90)	29 (97)	16 (80)
	International	5 (10)	1 (3)	4 (20)
Sample size	Small (<100)	27 (54)	15 (50)	12 (60)
	Midsize (100-499)	13 (26)	10 (33)	3 (15)
	Large (>500)	10 (20)	5 (17)	5 (25)

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Table 2. Non-publication and discontinuation, univariable analysis

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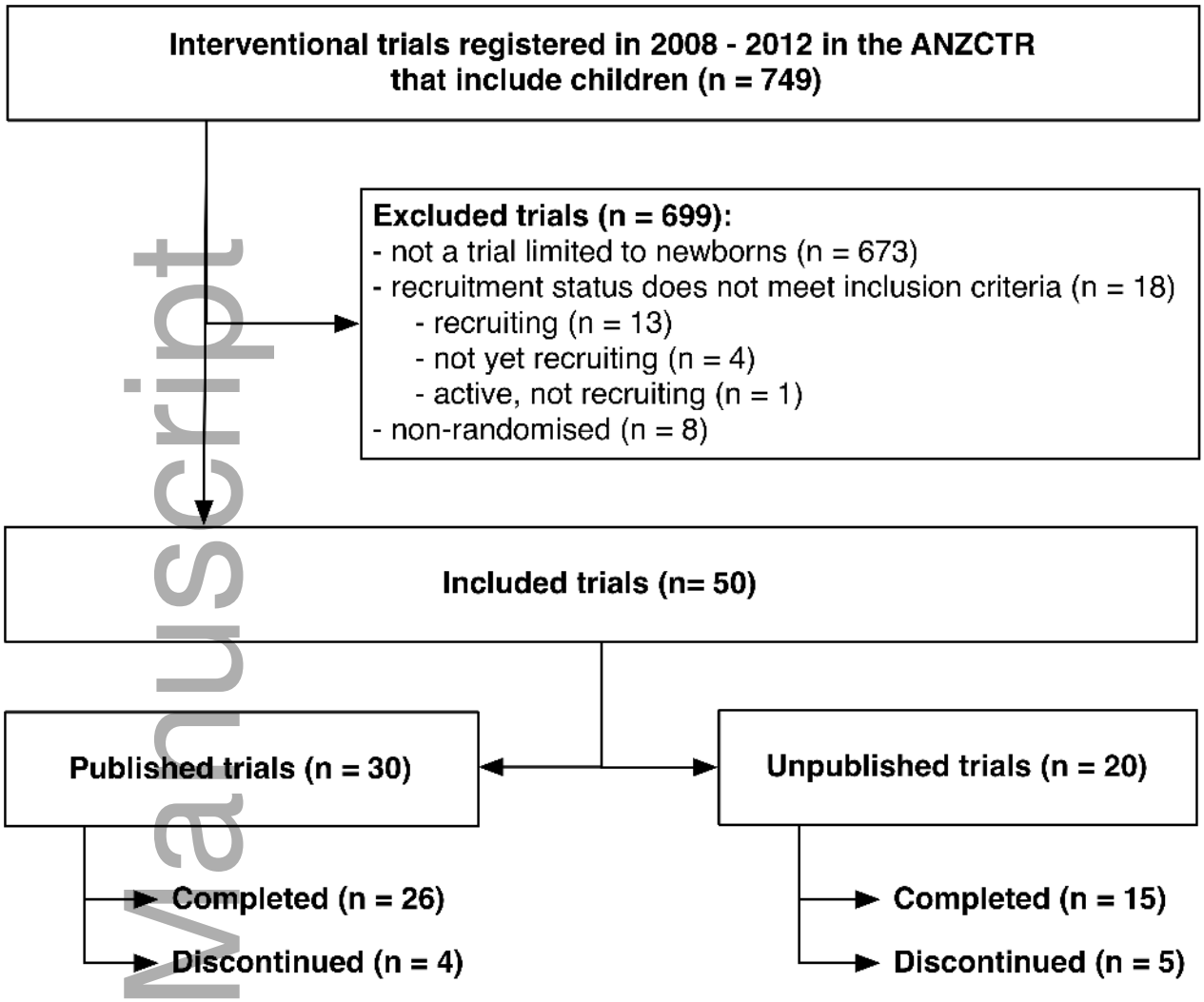
Associated factors		Non-Publication		Discontinuation	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Funding	Funded	Reference		Reference	
	Self-funded/unfunded	1.63 (0.36-7.43)	0.53	3.60 (0.68-19.16)	0.13
Intervention	Drug/device	Reference		Reference	
	Other	1.15 (0.36-3.62)	0.82	1.57 (0.34-7.13)	0.56
Masking	Double blinded	Reference		Reference	
	Single or open blinded	2.67 (0.81-8.81)	0.11	1.73 (0.38-7.86)	0.48
Trial size	Large (≥100 participants)	Reference		Reference	
	Small (<100 participants)	1.50 (0.48-4.72)	0.49	0.18 (0.03-0.99)	0.05

Figures

Figure 1. Study flow diagram

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