Major discrepancies between what clinical trial registries record and paediatric randomised controlled trials publish

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Abstract

Background: Whether information from clinical trial registries (CTRs) and published randomised controlled trial (RCTs) differs remains unknown. Knowing more about discrepancies should alert those who rely on RCTs for medical decision-making to possible dissemination or reporting bias. To provide help in critically appraising research relevant for clinical practice we sought possible discrepancies between what CTRs record and paediatric RCTs actually publish. For this purpose, after identifying six reporting domains including funding, design, and outcomes, we collected data from 20 consecutive RCTs published in a widely read peer-reviewed paediatric journal and cross-checked reported features with those in the corresponding CTRs.

Methods: We collected data for 20 unselected, consecutive paediatric RCTs published in a widely read peer-reviewed journal from July to November 2013. To assess discrepancies, two reviewers identified and scored six reporting domains: funding and conflict of interests; sample size, inclusion and exclusion criteria or crossover; primary and secondary outcomes, early study completion, and main outcome reporting. After applying the Critical Appraisal Skills Programme (CASP) checklist, five reviewer pairs cross-checked CTRs and matching RCTs, then mapped and coded the reporting domains and scored combined discrepancy as low, medium and high.

Results: The 20 RCTs were registered in five different CTRs. Even though the 20 RCTs fulfilled the CASP general criteria for assessing internal validity, 19 clinical trials had medium or high combined discrepancy scores for what the 20 RCTs reported and the matched five CTRs stated. All 20 RCTs selectively reported or failed to report main outcomes, 9 had discrepancies in declaring sponsorship, 8 discrepancies in the sample size, 9 failed to respect inclusion or exclusion criteria, 11 downgraded or modified primary outcome or upgraded secondary outcomes, and 13 completed early without justification. The CTRs for seven trials failed to index automatically the URL address or the RCT reference, and for 12 recorded RCT details, but the authors failed to report the results.

Conclusions: Major discrepancies between what CTRs record and paediatric RCTs publish raise concern about what clinical trials conclude. Our findings should make clinicians, who rely on RCT results for medical decision-making, aware of dissemination or reporting bias. Trialists need to bring CTR data and reported protocols into line with published data.

Keywords: Randomised controlled trials, Clinical trial registries, Reporting discrepancies, Selective outcome reporting, Quality reporting, Critical appraisal, Risk of bias, Dissemination bias, Reporting bias

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Background
An emerging problem that has rarely been investigated concerns the human factors that undermine clinical randomised controlled trials (RCTs) at various stages [1]. In the 1920s and 1930s two scientists in different research fields [2, 3] helped enormously to reappraise statistical theory and methodology in designing trials, thus clarifying how bias influences research. Previous papers have already compared protocols and registered data for clinical outcomes in published RCTs in various clinical settings [4–7], and three studies have investigated discrepancies in selectively reported outcomes [8, 9]. Even though concealment and blinding tools can control human factors in RCT designs [10] and the International Committee of Medical Journal Editors (ICMJE) [11] and Consolidated Standards of Reporting Trials (CONSORT) [12] receive wide consensus, a recent survey among journal editors endorsing the ICMJE and CONSORT established policies disclosed that only 27% of the 33 respondents cross-checked the data reported in the submitted manuscript against the data registered prospectively in clinical trial registries (CTRs) [13]. In recent years the Food and Drug Administration (FDA) expanded the regulatory requirements for conducting clinical trials and the truthfulness of the data submitted, and now requires authors to annually update CTRs, thus providing clear informative results [14]. Whether trial design, conduction and outcome data from the various CTRs and published RCTs differ or are incompletely reported remains unknown [4, 15, 16]. One systematic review assessed primary outcome discrepancies [17]. No studies have analysed trial reporting domains more widely, and none have addressed paediatric trials. Apart from the Critical Appraisal Skills Programme (CASp) checklist [18], nor do paediatricians and clinical researchers have tools for assessing discrepancies and risk of bias that compare what clinical researchers record in the registered study hypothesis and protocol, and what they then publish in RCTs [19–23]. Knowing more about trial discrepancies should alert paediatricians, clinical researchers, peer-reviewers, editors, and policymakers to possible dissemination or reporting bias undermining paediatric trials whose results provide the best information for medical care [24].

To help in critically appraising research relevant for clinical practice we sought possible discrepancies between what CTRs record and paediatric RCTs actually publish. For this purpose, after identifying six reporting domains, including funding, design, and outcomes, we collected data from a sample of 20 unselected consecutive RCTs published in a widely read peer-reviewed paediatric journal and cross-checked reported features with those in the corresponding CTRs.

Methods
In a study conducted from November 2012 to January 2016, to seek possible discrepancies between what CTRs record and paediatric RCTs actually publish, two reviewers, an experienced clinical paediatrician and an experienced researcher (PR and RD), identified six major reporting domains: five based on their long experience in critically appraising well-conducted clinical trials (reported funding and conflict of interest incompletely declared; discrepant or unclear sample size; inclusion and exclusion criteria not being respected or selective crossover; primary outcome downgraded and secondary outcomes upgraded and reported as primary outcomes in the publication; early study completion unjustified), and one domain (main outcome selectively reported or unreported) based on the Cochrane risk of bias tool [23, 24]. Over the first year they developed, assessed, and graded CTR-RCT discrepancy scores. Over the ensuing years five investigator pairs, supervised by two tutors (PR and RD), and attending the annual course held at Bambino Gesù Children’s Hospital, and subsequent weekly meetings on critically appraising scientific publications (G.A.L.I.L.E.O.), carefully read the 20 consecutive RCTs published monthly from July to November 2013 in the journal Pediatrics [25–44]. They then searched the CTR web link for each corresponding CTR, assessed details, and ‘history of changes’ after the initial registration, and critically appraised each published RCT with the CASp checklist. The five investigator pairs then independently mapped and coded inconsistencies for each reporting domain in the 20 trials, and repeatedly searched online (last access 20 January 2016) from the corresponding CTR websites: the United States National Institute of Health (NCT) (https://clinicaltrials.gov), the International Standard Randomised Controlled Trial Number (ISRCTN) (currently BioMed Central Open Access publishers) (http://www.isrctn.com/), the Nederlands Trials Register (NTR)
modified primary outcome measures or upgraded secondary outcomes that had been upgraded and yielded insignificant results [30]. For another clinical trial, the authors reported their previous published papers in the NCT record, but neglected to report the second published RCT giving a partially modified primary outcome in the updated NCT data, recorded after RCT publication [37]. Of the 20 clinical trials, seven CTRs (three registered in the NCT, two in the NTR, and two in the ACTRN) failed to index automatically the RCT reference or Uniform Resource Locator (URL) address, and all these trials had discrepancies in outcome data or yielded insignificant results [28, 33, 34, 37, 38, 40, 42]. Twelve CTRs reported the RCT references or URL addresses, but the authors failed to summarise the main results [25–27, 29–32, 35, 36, 39, 43, 44]. For only one clinical trial did the authors report the main results in the CTRI but neglect to report increased side effects in the intervention group [41] (Table 1, Additional file 1).

Discussion
By comparing the six reporting domains, mapping, coding and cross-checking 20 published RCTs with the matched five CTRs, our study, applied to clinical paediatric trials published in a widely read peer-reviewed journal, suggests that many trials have discrepancies in reporting domains. The medium or high combined discrepancy scores we found, when we repeatedly searched each database online until January 2016, underline major widely ranging discrepancies between what CTRs record.
### Table 1: Clinical trial registry (CTR)-randomised controlled trial (RCT) discrepancies in 20 RCTs scored by assessing and cross-checking inconsistencies in the six reporting domains identified, assessed and scored according to their importance in a well-conducted trial^a^

| CTR acronyms, registration numbers, and web link for the 20 RCTs published in the journal Pediatrics from July to November 2013 (first author and publication reference) | Cited references | Combined discrepancy scores: low ≤ 4, medium 5–9, high 10–14^b^ |
|---|---|---|
| NCT 01351064, URL: https://clinicaltrials.gov (Carroll et al. 132(3):e623-e629 Sept 2013) | [25] The RCT incompletely declared funding | - | - | - | 4 |
| NCT 01822626, URL: https://clinicaltrials.gov (Davoli et al. 132(5):e1236-e1245 Oct 2013) | [26] Number of eligible participants not provided in the CTR | - | - | - | 5 |
| ISRCTN 59061709, URL: http://www.isrctn.com/ (McCarthy et al. 132(2):e389-e395 Aug 2013) | [27] The RCT failed to respect the exclusion criteria for these infants. During study conduction one infant crossed over | - | - | - | 5 |
| NTR 1613, URL: www.trialregister.nl (van der Veek et al. 132(5):e1163-e1172 Nov 2013) | [28] Discrepant children’s age in the inclusion criteria | - | - | - | 5 |
| Clinical trial registry (CTR)-randomised controlled trial (RCT) discrepancies in 20 RCTs scored by assessing and cross-checking inconsistencies in the six reporting domains identified, assessed and scored according to their importance in a well-conducted trial | [Continued] |
|---|---|---|---|---|---|---|
| ISRCTN 72635512, URL [Field et al. 132(5):e1247-e1256 Nov 2013](http://www.isrctn.com/)(Continued) | [29] | - | - | - | - | - |
| Early study completion | The CTR automatically indexed the RCT URL address but the authors failed to report the results. The published RCT analysed selected data for randomised newborns in the intervention and control group (80 % vs 87 %) and reported an insignificant statistical difference for the primary outcome (cognitive improvement) but the authors inadequately reported more harm than benefit in the intervention group for secondary patient-centred outcomes (death, cerebral palsy) |
| ISRCTN 31707342, URL [McCarthy et al. 132(1): e135-e141 July 2013](http://www.isrctn.com/) | [31] | - | Discrepant RCT inclusion criteria | Secondary outcome upgraded in the RCT | - | - |
| Discrepancy in the number of children enrolled and analysed (the CTR failed to report that an external Data Safety Monitor Committee stopped the RCT early hence the trial failed to reach the target number of participants) | The updated CTR failed to report early stopping after a planned interim analysis | The CTR automatically indexed the RCT URL address but failed to report early stopping. The RCT unclearly reported the reason for stopping the trial (more harm than good for the primary outcome in the intervention group) |
| NCT 00548379, URL [Aluisio et al. 132(4):e832-e840 Oct 2013](https://clinicaltrials.gov) | [30] | - | Discrepant RCT inclusion criteria | Secondary outcome upgraded in the RCT | - | - |
| Discrepant RCT inclusion criteria | The CTR automatically indexed the RCT reference including the CTR primary outcome but neglected to report the RCT including the secondary outcome upgraded and showing an insignificant statistical difference between intervention and control group |
### Table 1 Clinical trial registry (CTR)-randomised controlled trial (RCT) discrepancies in 20 RCTs scored by assessing and cross-checking inconsistencies in the six reporting domains identified, assessed and scored according to their importance in a well-conducted trial (Continued)

| CTR Reference | URL | Discrepancy Type | CTR Findings | RCT Findings |  |
|---------------|-----|------------------|--------------|--------------|---|
| NCT 01307293, URL | https://clinicaltrials.gov | Discrepancy in the age of premature children enrolled | - | Early study completion (Dec 2012 instead of Jan 2013) | 8 |
| ACTRN 12608000056392, URL | www.anzctr.org.au | Discrepancy in the number of participants eligible and enrolled | Primary outcome downgraded in the RCT | - | 9 |
| NCT 00409448, URL | https://clinicaltrials.gov | Discrepancy in declared funding | Discrepant RCT exclusion criteria | - | 9 |
| ACTRN 12608000056392, URL | www.anzctr.org.au | Discrepancy in the number of participants eligible and enrolled | Primary outcome completely changed in the RCT | Published ongoing study results and follow-up not respected | 10 |
| NCT 01403623, URL | https://clinicaltrials.gov | Discrepancy in declared funding | Primary outcome measure modified in the RCT | Early study completion (Dec 2011 instead of Dec 2012) | 10 |
| NCT 00334737, URL | https://clinicaltrials.gov | Discrepancy in declared funding | Primary outcome partially modified in the RCT | Follow-up not respected (presumably an ongoing study or randomisation done for another study) | 10 |
Table 1 Clinical trial registry (CTR)-randomised controlled trial (RCT) discrepancies in 20 RCTs scored by assessing and cross-checking inconsistencies in the six reporting domains identified, assessed and scored according to their importance in a well-conducted triala (Continued)

| CTR ID | Funding | Discrepancy in the inclusion criteria | Inclusion criteria modified in the Dutch registry (NTR) only. The Australian registry (ANZCTR), retrospectively indexed failed to report inclusion criteria changes | Australian registry retrospectively indexed the trial and failed to report that the trial stopped early on an external data safety committee decision (difficulties in recruiting infants and futility) | The CTR failed to automatically index RCT URL address or reference and the authors neglected to provide results. The RCT reported results for the modified primary outcome |
|--------|---------|------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| NCT 01065272, URL https://clinicaltrials.gov (Alansari et al. 132(4):e810-e816 Sept 2013) | [38] | - | - | The RCT incompletely respected inclusion criteria | Early study completion (March 2012 instead of August 2012) |
| NCT 01810978, URL https://clinicaltrials.gov (Dilli et al. 132(4):e932-e938 Oct 2013) | [39] | - | - | Discrepancy in the inclusion criteria | Primary outcome modified and secondary outcome upgraded in the RCT | Early study completion (Apr 2013 instead of May 2013) |
| NTR 2061 and ACTRN 1261000230055, URLs www.trialregister.nl and www.anzctr.org.au (Kamlin et al. 132(2):e381-e388 Aug 2013) | [40] | Funding incompletely declared in the RCT | Discrepancy in the number of participants eligible and enrolled | Inclusion criteria modified in the Dutch registry (NTR) only. The Australian registry (ANZCTR), retrospectively indexed failed to report inclusion criteria changes | Australian registry retrospectively indexed the trial and failed to report that the trial stopped early on an external data safety committee decision (difficulties in recruiting infants and futility) | The NTR, updated on 5 Apr 2012, failed to report completed results but stated that the trial was stopped for slow recruitment and futility. The ANZCTR was retrospectively registered and not updated ('still recruiting'). The RCT abstract incompletely reported that the external data safety committee stopped the trial early owing to difficulties in recruiting infants. Data for 4 children excluded from the analysis in the RCT |
| Registry | Study Details | Reporting Domain | Reported in RCT | Discrepancy | Reported in CTR | Consequences |
|----------|---------------|------------------|----------------|-------------|-----------------|--------------|
| CTRI 2010/091/001417 | Malik et al. 132(1):e46-e52 (July 2013) | The RCT failed to report that the trial was used for a medical thesis | Discrepancy in the number of participants eligible and enrolled | The RCT reported that to achieve the final sample size patients were enrolled from an area adjacent to the setting declared | Primary outcome downgraded in the RCT | The CTR, updated by the authors on 14 Jun 2012, reported a brief summary of positive results for the downgraded primary outcome but failed to report side effects. The RCT neglected to report increased side effects in the intervention group |
| ACTRN 12612000976886 | McIntosh et al. 132(2):326-331 (Aug 2013) | - | The CTR neglected to report sample size | - | Primary outcome measure modified in the RCT | The retrospectively registered CTR failed to automatically index the RCT URL address or reference and the authors neglected to provide results. The RCT only partially reported results on the primary outcome |
| ISRCTN 03981121 | Wake et al. 132(4):e895-e904 (Oct 2013) | Discrepancy in the number of participants eligible and enrolled | - | The RCT automatically indexed the URL address of the published RCT. The RCT neglected to report results for the primary outcome (no statistical difference) but reported a significant difference for a secondary outcome |
| NCT 01604460 | Belsches et al. 132(3):e656-e661 (Sept 2013) | Discrepancy in declared funding | - | The RCT reported a modified intervention procedure for the included infants | Discrepancy in primary outcome measures | The CTR automatically indexed the URL address of the published RCT, but the authors failed to report results. The RCT only partially reported results on the primary outcome |

*Reporting domains chosen from our clinical experience in critically appraising RCTs and the Cochrane Collaboration tool for assessing risk of bias (main outcome selectively reported or unreported) [23, 24]. Upgrading secondary outcomes means reporting secondary outcomes as primary outcomes in the publication. Discrepancies in the domain ‘main outcome selectively reported or unreported’ had similar scores because inconsistencies in this domain could have made the RCT results untrustworthy or less trustworthy. CTR abbreviations: the United States National Institute of Health (NCT), the International Standard Randomised Controlled Trial Number (currently BioMed Central Open Access publishers) (ISRCTN), the Nederlands Trials Register (NTR), the Australian and New Zealand Clinical Trial Registry (ACTRN), and the Clinical Trial Registry-India (CTRI). Trials are listed and grouped according to the combined discrepancy scores. When scores are identical, trials are listed alphabetically by first author surnames. Higher discrepancy scores suggest risk of bias.

CTR clinical trial registry, RCT randomised controlled trial, URL Uniform Resource Locator
and what published paediatric RCTs then report. The discrepancies we identified in declaring funding and conflict of interests in nine trials, in the number of eligible and enrolled participants in eight clinical trials and in another nine inclusion and exclusion criteria not being respected, emphasise the generally imperfect reporting. These major discrepancies, especially those involving changes in the original study hypotheses, trial designs, study conduction and reporting outcomes raise concern on trustworthiness in scientific trials, as previous papers have underlined [5–9, 13, 15, 16].

Surprisingly, of the 20 published RCTs 11 modified or downgraded primary outcomes or upgraded secondary outcomes (reported secondary outcomes as primary outcomes in the publication), misreporting or tending to overstate positive results. This discrepancy underlines concerns about trial creditability that the CASP checklist overlooks. By assessing and scoring CTR-RCT discrepancies in six clinical trial reporting domains, our study therefore expands current knowledge, thus emphasising the need for international clinical trial regulators to make publicly available CTR-RCT discrepancies in published RCT findings, as recently underlined by the WHO Statement on public disclosure of clinical trial results (http://www.who.int/ictrp/results/reporting/en/; last accessed 20 January 2016). For example, trial (number 5 in Table 1) [29] addresses as primary outcome cognitive improvement and provides significant statistical difference between the intervention and control groups, but leaves unaddressed clinically important patient-centred outcomes, such as deaths and cerebral palsy. Even though deaths increased and cerebral palsy doubled in the intervention group, in their conclusions the investigators paradoxically report that ‘nonsignificant trends in the data suggested a small adverse effect’. In another trial (number 7 in Table 1) [31] an external DSMC decided to stop RCT completion early owing to hyperthermia in the infants enrolled in the intervention group. Neither the highlights section in the RCT nor the conclusions report this result. Although the published RCT reports when the trial stopped, our findings disclose an important clinically relevant feature, namely more harm than good for the primary outcome in the intervention group.

Another unexpected discrepancy in a multicentre trial (number 16 in the Table 1) [40] was that the authors inappropriately and unclearly reported that an external DSMC stopped the trial for futility. The numerous CTRs updated only by dataset supervisors (URL or RCTs reference cited in 12/20 trials), and failing to report results (7/20 trials) underline discrepancies involving incompletely and selectively reported clinical outcome results [5, 45–47]. This finding, along with underappreciated core patient-centred outcomes, raises ethical concerns and suggests dissemination or reporting bias [45–49]. Even though the journal Pediatrics complies with ICMJE requirements [11], and authors are required to submit a completed flowchart and checklist for the CONSORT statement [12] before publication (http://www.aappublications.org/content/pediatrics-author-guidelines#acceptance_criteria; last accessed 20 January 2016), and all the 20 published RCTs give the trial registration number on the first page, our findings underline that still today few authors endorse these rules [13, 14, 17].

An unexpected finding concerned prospective trial registration [11]. Although our study design did not require us to check clinical trial registration timing, we detected two trials (numbers 16 and 18 in Table 1) [40, 42] that had been registered retrospectively and failed to comply with ICMJE registration requirements. One of these two, a multicentre RCT (number 16 in Table 1) [40], was registered prospectively in the NTR and retrospectively in the ACTRN, and although the NTR reported that the trial had stopped for futility, the ACTRN stated ‘still recruiting’. Because a retrospectively registered trial could be hard to identify, regulators need to find new ways to encourage researchers to update information in a timely manner [50–52].

Most important, the major discrepancies our study highlighted in paediatric clinical trials give new clinically important information that researchers synthesising evidence from published RCTs in scientific literature reviews could fail to identify without cross-checking CTRs. Hence, they could provide less reliable scientific evidence, and misdirect future research priorities [49–53]. Our findings could also alert medical journals on the need to introduce rules that require investigators to submit the original Institutional Review Board-approved protocol (and its subsequent amended versions), and to explain later changes, thus helping reviewers and editors in deciding whether to publish the trial and what the final manuscript should state.

Limitations

We acknowledge that our study has several limitations. Because we applied our study method only in few unselected consecutive paediatric RCTs published in a major paediatric journal, rather than including other authoritative journals with higher impact factors, our findings require further validation. Even though our scoring for reporting domains needs further refinement, our findings should make it easier for physicians to use research results from clinical trials. Because most authors neglected to update CTRs, we were unable to seek discrepancies in what authors recorded in CTRs and reported in published RCTs by cross-checking clinical outcome results. Similarly, because none of the five CTRs recorded or the cross-checked matched 20 RCTs appraised gave the necessary information, nor were we...
able to assess data for patient nonresponse and refusal. Although we analysed a small RCT sample, we found no differences in combined CTR-RCT discrepancy scores among the various CTRs. A final limitation is that we failed to assess interobserver reliability for the different assessor times for individual items and combined CTR-RCT discrepancy scores.

Conclusions
Our study identifies major discrepancies between what CTRs record and paediatric RCTs publish. Our findings should make clinicians who rely on RCT results for medical decision-making, aware of dissemination or reporting bias. Trialists need to bring CTR data and reported protocols in line with published data. Clinical researchers and reviewers could search for CTR-RCT discrepancies to cross-check inconsistencies in core clinical trial reporting domains. Medical journals need to introduce rules that require investigators to submit the original Institutional Review Board–approved protocol (and its subsequent amended versions), and to explain any discrepancies. Assessing discrepancies would with little effort provide greater transparency, avoid wasting research resources, and encourage those who prepare medical recommendations and guidelines to think more critically. Future studies need to clarify whether the trial discrepancies we report warrant scepticism regarding study validity, or call for trialists to be more diligent about updating CTR data.

Additional file

Additional file 1: Inconsistencies in the 20 trials published in the journal Pediatrics from July to November 2013, and discrepancy scores assessed by cross-checking what CTRs and their matching RCTs reported. Description of data: an operative table describing in detail the results of the 20 unselected consecutive RCTs, published in the journal Pediatrics from July to November 2013, mapped, coded, and cross-checked in six reporting domains to assess and report inconsistencies on what the authors recorded in CTRs and what they published in RCTs, as rated by predefined CTR-RCT discrepancy scores. (DOCX 56 kb)

Authors’ contributions
FP conceived the original study and revised the manuscript. PR and RD designed the study, assessed and scored the CTR-RCT discrepancy, drafted the manuscript and revised the final version. GR, GT, RI, FG, EF, MZ, CC, VB and RF, working in pairs, searched the studies, extracted the data and revised the manuscript. CC and VB helped with the design of the tables. RF revised the manuscript, PR and RD made substantial revisions to the manuscript. All authors have read and approved the final submitted version.

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