**Inadequate harms reporting in randomized control trials of antibiotics for pediatric acute otitis media: A systematic review**

Stephanie W Hum, BSa; Su Golder, PhDb; Nader Shaikh, MD, MPHa,c

**Affiliations**: aUniversity of Pittsburgh School of Medicine, 3550 Terrace St, Pittsburgh, PA 15213

 bDepartment of Health Sciences, University of York, University of York, Heslington, York, YO10 5DD, UK

cChildren’s Hospital of Pittsburgh of UPMC, Division of General Academic Pediatrics, 4401 Penn Avenue, Pittsburgh PA 15224

**Address Corresponding to**: Nader Shaikh, MD, MPH, Children’s Hospital of Pittsburgh, General Academic Pediatrics, 4401 Penn Avenue, Pittsburgh PA 15224, 412-692-8111 (phone), 412-692-8516 (fax)

**Author Emails:** Stephanie Hum: hum.stephanie@medstudent.pitt.edu

 Su Golder: su.golder@york.ac.uk

 Nader Shaikh: nader.shaikh@chp.edu

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**Abbreviations:** CONSORT (Consolidated Standards of Reporting Trials); RCTs (Randomized Control Trials)

**Abstract**

**Objective:** To assess the quality of harms reporting in randomized control trials evaluating the efficacy of antibiotics used to treat pediatric acute otitis media and to investigate whether connections to pharmaceutical companies or the publication of the CONSORT-Harms extension influenced the quality of harms reporting.

**Study Design and Setting:** We considered randomized control trials that evaluated the efficacy and safety of antibiotic treatment for uncomplicated acute otitis media in children aged 0 to 19. We evaluated the quality of harms reporting using a 19-item checklist addressing the recommendations endorsed in the CONSORT-Harms extension.

**Results:** 160 studies met our inclusion criteria. Overall quality of reporting relating to harms was low; on average studies adhered to 55.2% of the checklist items on the quality of harms reporting. The reporting of methods relating the measurement of harms was particularly lacking; studies adhered to an average of only 33.2% of the checklist items. The overall quality of reporting did not change after the publication of the CONSORT-Harms extension. Connections to pharmaceutical companies did not significantly affect the quality of reporting.

**Conclusions:** Harms reporting in pediatric randomized trials, especially the reporting of methods used to collect harms data, remains inadequate.

**Keywords:** CONSORT; acute otitis media; pediatrics; harms; adverse events

**Running Title:** Harms reporting in randomized control trials of antibiotics for otitis media

**1. Introduction**

Despite the importance of medication adverse events in clinical decision making, the reporting of harms in randomized control trials is often inconsistent and inadequate.1-11 The amount of space allocated to the reporting of harms in randomized control trials is often disproportionally low.3,12,13 One meta-analysis found that one-fifth of pediatric randomized control trials failed to report any data on adverse events.2 In an effort to improve the quality of harms reporting in randomized control trials, the CONSORT (Consolidated Standards of Reporting Trials) group released an extension (with 10 recommendations) in 2004 specifically focused on the reporting of harms-related outcomes.14

The objective of our study was to assess the methodological quality of harms reporting in randomized control trials of antibiotics used to treat pediatric acute otitis media based on the recommendations of the CONSORT-Harms extension. In addition, we sought to investigate whether publication of the CONSORT-Harms extension or connections to a pharmaceutical company influenced the quality of harms reporting. We chose acute otitis media because it is the most common indication for which antibiotics are prescribed in children.15

**2. Materials and Methods**

We considered published randomized control trials that evaluated adverse events of oral or intramuscular antibiotics used to treat uncomplicated acute otitis media in children 0 to 19 years of age. We performed an electronic search of MEDLINE (via PubMed) for reports published between 11/26/1948 to 4/20/2015 (see Appendix for search strategy). We limited the search to human reports published in English. We identified additional reports by reviewing the reference lists of important review articles retrieved from the electronic search, and translated them to English before assessment if necessary.

Two authors independently assessed the titles, abstracts and, if necessary, the full text of each report found using the search strategy to determine which reports satisfied the inclusion criteria. We required included reports to be randomized control trials of oral antibiotics, intramuscular antibiotics, or placebo used to treat children aged 0 to 19 years old with uncomplicated acute otitis media. Included reports must have evaluated harms as an objective, established a plan to collect harms data, or presented harms data in the results. We excluded reports that evaluated topical antibiotics or alternative (non-antimicrobial) therapies (except placebo), children with complications of acute otitis media (e.g., mastoiditis), and children with severe comorbid medical conditions. Disagreements were resolved by discussion.

Two authors extracted data from each included report using a standardized data extraction form. Uncertainties in the data extraction were resolved by discussion. When possible, we contacted authors for clarification. When more than one publication of a report existed, we used the publication with the most complete patient data in the analyses.

Using the detailed descriptions in the CONSORT-Harms extension,14 we developed a 19-item checklist of items most relevant to the reporting of adverse events related to the use of antibiotics in children with acute otitis media (Supplement Table 1).

We also collected additional data on whether the reports had connections to pharmaceutical companies. We considered reports as having connections to pharmaceutical companies if the published report indicated that any of the authors or funding sources were affiliated with a pharmaceutical company. To assess the impact of the CONSORT-Harms extension, we compared the 16 reports that were published at least 1 year after the publication of the CONSORT-Harms extension (i.e., after 11/16/2005) to reports published before this date.

Previous studies have calculated a quality score by assigning a point to each checklist item followed.1-3,5-7,10 Because not all checklist items were applicable to every report, we did not find this method to be suitable for our study. Thus, we calculated a quality score to quantify a report’s overall quality of harms reporting; this variable was defined as the percent of applicable checklist items that were adequately addressed. We weighted checklist items equally, which is consistent with previous literature on the quality of harms reporting.1-3,5-7,10

We used Chi-squared tests to assess whether the number of reports following each checklist item changed before or after the publication of the CONSORT-Harms extension and with or without declared connections to pharmaceutical companies. To compare quality score, we used a two-sample t-test. STATA 14.0 software was used to perform all analyses.

**3. Results**

Of the 1833 articles found through the search strategy, we retrieved and reviewed 273 full text articles (Figure 1). Of these, 160 randomized control trials met our inclusion criteria and were included in our analysis.

The number of studies that adhered to each of the nineteen checklist items is shown in Table 1. The mean quality score was 55.2%, that is studies reported an average of 55.2% of the relevant checklist items. 35% of reports (56 out of 160 reports) followed less than half of the items; no reports followed all 19 items.

The reporting of methods used to collect harms data was particularly lacking; studies reported an average of only 33.2% of checklist items related to the methods used to collect harms (items 3-9). Reporting of how each adverse event was defined, how recurrent events were handled, and how withdrawal of subjects from the study due to adverse events was adjudicated were reported particularly poorly in most studies.

The quality of reporting in the results section was better than in the methods section; studies adhered to 70% of checklist items related to the reporting of adverse event data (items 10-17). Only two checklist items had low adherence rates: reporting data on severe harms and the number of times the adverse events occurred.

The mean quality score did not change significantly after the publication of the CONSORT-Harms extension (55.0% vs. 56.4% respectively) (Table 2). Reports published after the publication of the CONSORT-Harms extension did however report severe adverse events data significantly more than those published before (p = 0.04).

 The mean quality score did not differ significantly in reports with or without declared connections to pharmaceutical companies (56.8% vs 52.0% respectively). Reports with declared connections to pharmaceutical companies did however cite prior harms literature in discussions significantly more than those without declared connections to pharmaceutical companies (p = 0.02).

**4. DISCUSSION**

We found that the quality of harms reporting in randomized control trials of antibiotics used for the treatment of pediatric acute otitis media is inadequate; 35% of reports followed less than half of the checklist items from the CONSORT Harms-extension. One previous meta-analysis studying harms reporting after the publication of the CONSORT-Harms extension in 107 pediatric randomized control trials of systemic medications (excluding probiotics, hormone replacement, and vaccines) also concluded that the quality of harms reporting was lacking; the included reports followed a mean of 3 out of 10 of the CONSORT recommendations.2 The higher adhere rate observed in our study might be attributed to the fact that we selected randomized control trials that reported harms data or established harms as an objective, which has been shown to increase the quality of harms reporting.3 Previous studies of treatment harms reporting in studies of adults have yielded similar results; the reported mean/median adherence to the recommendations in the CONSORT Harms-extension ranges from 41-63% regardless of the subject area [epilepsy (49%),7 hypertension (41%),1 pain (53-61%),9,10 cancer (57-63%),6,8 and ophthalmology (60%)5]. The mean/median adherence to the recommendations in the CONSORT Harms-extension in two studies of reports published in high impact journals were similar (56%4 and 58-67%3).

The reporting of the methods of harms data collection was the area needing the most improvement. Specifically, reports need to (1) define each of the adverse events, (2) explanation how (and who) determined whether an adverse event was attributable to the study product, (3) explain how recurrent adverse events were handled, and (4) specify rules used to withdraw patients from the study. Although the reporting of adverse events data was better than the reporting of methods, reports should make an effort to include data on the frequency of severe adverse events and the number of times the adverse events occurred.

We found minimal improvements in the quality of harms reporting in reports published after publication of the CONSORT-Harms extension; only item 11, reporting data on frequency of severe adverse events, improved. However, the number of reports published after the CONSORT-Harms extension was small (n = 14), which limited our ability to fully evaluate this association. Studies in other fields has shown that after the publication of the CONSORT-Harms extension there was either no improvement,5,7 only improvements in the reporting of specific recommendations,10 or modest improvements in overall reporting.3,9 The modest improvements in the quality of harms reporting may signify a slow uptake in the CONSORT-Harms extension’s recommendations.

Reports with declared connections to pharmaceutical companies were more likely to cite prior harms literature in their discussion sections. Although not significant, there was a trend towards improvement in three other areas (methods list and define adverse events studied, methods state rules for withdrawals, and results report data on withdrawals). These trends are supported by previous literature which shows that reports with connections to pharmaceutical companies often have higher quality harms reporting than those not connected to pharmaceutical companies.2-4,6,7,9,10

There are limitations to our study that should be considered when interpreting the results. For the purposes of assessing the quality of harms reporting, we adapted the 10 CONSORT recommendations to form a 19-item checklist. This specific checklist is not validated; however, all checklist items were created using the original CONSORT-Harms extension for harms reporting. Similar checklists of different lengths have been previously used in the literature.1,6-8 Calculating a mean quality score may not have taken into account the relative importance of items with respect to one another; nevertheless, we found it to be a useful summary statistic. We were also limited in our comparison of reports with and without connections to pharmaceutical companies as some funding sources or affiliations may not have been disclosed in the published reports.

**5. Conclusion**

Overall, we conclude that the quality of harms reporting in randomized control trials of antibiotics used to treat pediatric acute otitis media, is inadequate. In particular, the methods used in the collection of harms data is often not adequately described in the methods sections of the reports. Inadequate reporting of harms limits the ability of clinicians and researchers to critically evaluate the adverse events data presented in randomized control trials. Future studies would benefit from following the recommendations in the CONSORT-Harms extension.

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**Figure 1.** Study flow diagram

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**Table 1.** Adherence to recommendations in CONSORT Harms-extension (n=160)

|  |  |
| --- | --- |
| Checklist Item(CONSORT Recommendation Number) | Adhered to Checklist Item |
| YesNo. (%) | NoNo. (%) |
| 1. Title/abstract mentions harms (1)
 | 117 (73.1) | 43 (26.9) |
| 1. Introduction mentions harms (2)
 | 99 (61.9) | 61 (38.1) |
| 1. Methods list and define adverse events studied (3)
 | 20 (12.5) | 140 (87.5) |
| 1. Methods state how adverse events were collected (4)
 | 83 (51.9) | 77 (48.1) |
| 1. Methods avoid biased questioninga (4)
 | 84 (98.8) | 1 (1.2) |
| 1. Methods state when adverse events data was collected (4)
 | 93 (58.1) | 67 (41.9) |
| 1. Methods explain how causality was attributeda (4)
 | 36 (45.6) | 43 (54.4) |
| 1. Methods state rules for withdrawals (4)
 | 20 (12.5) | 140 (87.5) |
| 1. Methods report handling of recurrent events (5)
 | 0 (0) | 160 (100) |
| 1. Results report data on withdrawals (6)
 | 123 (76.9) | 37 (23.1) |
| 1. Results report data on severe adverse events (6)
 | 62 (38.8) | 98 (61.3) |
| 1. Results report a denominator for adverse events (7)
 | 119 (74.4) | 41 (25.6) |
| 1. Results report adverse events results per treatment arm (8)
 | 149 (93.1) | 11 (6.9) |
| 1. Results report number of patients with adverse events (8)
 | 153 (95.6) | 7 (4.4) |
| 1. Results report number of times the adverse events occurred (8)
 | 35 (21.9) | 125 (78.1) |
| 1. Results break down data by adverse event type (8)
 | 141 (88.1) | 19 (11.9) |
| 1. Results include subgroup analysisb (9)
 | - | - |
| 1. Discussion mentioned harms (10)
 | 111 (69.4) | 49 (30.6) |
| 1. Discussion cited prior harms literature (10)
 | 68 (42.5)  | 92 (57.5) |
| No. (%) = number (percent) of reportsa Some reports were not applicable for evaluation of this item.  |
| b No reports used subgroup analyses, and thus this item was not applicable for evaluation. |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Checklist Item(CONSORT Recommendation Number) | Published afterNovember 2005No. (%) | p-value | Declared connections to pharmaceutical companiesNo. (%) | p-value |
| Yes(n=14) | No (n=146) | Yes(n=106) | No(n=54) |
| 1. Title/abstract mentions harms (1)
 | 9 (64.3) | 108 (74.0) | 0.44 | 78 (73.6) | 39 (72.2) | 0.85 |
| 1. Introduction mentions harms (2)
 | 7 (50.0) | 92 (63.0) | 0.34 |  67 (63.2) | 32 (59.3) | 0.62 |
| 1. Methods list and define adverse events studied (3)
 | 2 (14.3) | 18 (12.3) | 0.83 | 17 (16.0) | 3 (5.6) | 0.06 |
| 1. Methods state how adverse events were collected (4)
 | 9 (64.3) | 74 (50.7) | 0.33 | 57 (53.8) | 26 (48.2) | 0.50 |
| 1. Methods avoid biased questioning (4)a
 | 9 (100) | 75 (98.7) | 0.73 | 58 (98.3) | 26 (100.0) | 0.50 |
| 1. Methods state when adverse events data was collected (4)
 | 10 (71.4) | 83 (56.9) | 0.29 | 65 (61.3) | 28 (51.9) | 0.25 |
| 1. Methods explain how causality was attributed (4)a
 | 5 (71.4) | 31 (43.1) | 0.15 | 26 (44.1) | 10 (50.0) | 0.65 |
| 1. Methods state rules for withdrawals (4)
 | 3 (21.4) | 17 (11.6) | 0.29 | 17 (16.0) | 3 (5.6) | 0.06 |
| 1. Methods report handling of recurrent events (5)
 | 0 (0) | 0 (0) | 1.00 | 0 (0) | 0 (0) | 1.00 |
| 1. Results report data on withdrawals (6)
 | 10 (71.4) | 113 (77.4) | 0.61 | 86 (81.1) | 37 (68.5) | 0.07 |
| 1. Results report data on severe adverse events (6)
 | 9 (64.3) | 53 (36.3) | 0.04 | 43 (40.6) | 19 (35.2) | 0.51 |
| 1. Results report a denominator for adverse events (7)
 | 10 (71.4) | 109 (74.7) | 0.79 | 75 (70.8) | 44 (81.5) | 0.14 |
| 1. Results report adverse events results per treatment arm (8)
 | 13 (92.9) | 136 (93.2) | 0.97 | 99 (93.4) | 50 (92.6) | 0.50 |
| 1. Results report number of patients with adverse events (8)
 | 13 (92.9) | 140 (95.9) | 0.60 | 101 (95.3) | 52 (96.3) | 0.77 |
| 1. Results report number of times the adverse events occurred (8)
 | 1 (7.1) | 34 (23.3) | 0.16 | 24 (22.6) | 11 (20.4) | 0.74 |
| 1. Results break down data by adverse event type (8)
 | 11 (78.6) | 130 (89.0) | 0.25 | 96 (90.6) | 45 (83.3) | 0.18 |
| 1. Results include subgroup analysisb (9)
 | - | - | - | - | - | - |
| 1. Discussion mentioned harms (10)
 | 8 (57.1) | 103 (70.6) | 0.30 | 76 (71.7) | 35 (64.8) | 0.37 |
| 1. Discussion cited prior harms literature (10)
 | 7 (50.0) | 61 (41.8) | 0.55 | 52 (49.1) | 16 (29.6) | 0.02 |
| 1. Mean quality score
 | 14 (56.4) | 146 (55.0) | 0.78 | 106 (56.8) | 54 (52.0) | 0.10 |
| No. (%): number (percent) of reports that followed the checklist itema Some reports were not applicable for evaluation of this item. b No reports used subgroup analysis, and thus this item was not applicable for evaluation. |

**Table 2.** Proportion of studies that followed the CONSORT recommendations according to publication date and declared connections to pharmaceutical companies

**Appendix**

**Medline Search Strategy:**

**Interface: PubMed**

**Date Searched: 4/20/15**

The search strategy was used as below. All search terms were searched in “All Fields” except where “MeSH” was specified. The asterisk is the truncation symbol in PubMed (i.e, \*), and was used to find terms beginning with the root term.

(Infant[MeSH] OR Infant\* OR Child[MeSH] OR Child\* OR Pediatrics[MeSH] OR Paediatric\* OR Paediatric\*) AND (acute otitis media) AND (antibiotic\* OR antimicrobial\* OR amoxicillin or cefdinir or Azithromycin or cefaclor or cefprozil or ceftriaxone or placebo or cefuroxime or cefixime or cefpodoxime or penicillin or clarithromycin or loracarbef or gatifloxicin or trimethoprim OR amoxycillin)

**Supplement Table 1.** CONSORT-Harms extension recommendations14 and data items collected

|  |  |  |  |
| --- | --- | --- | --- |
| Article Section | CONSORT recommendations | Data Collected | Evaluation Criteria |
| Title & Abstract | 1. If the study collected data on harms and benefits, the title or abstract should so state
 | 1. If harms were mentioned in the title or abstract
 | 1. Credit was given if there was any mention of adverse events, harms, safety, or other similar terminology in the title, abstract or both. If the study had no abstract, the study must have mentioned harms or similar terminology in the title to receive credit. No credit was given if there was no mention of harms in the title or abstract. |
| Introduction | 1. If the trial addresses both harms and benefits, the introduction should so state
 | 1. If the introduction had background information on harms or identified safety as a purpose of the study
 | 2. Credit was given if the introduction mentioned previous studies on harms, historical concerns about harms, or statements establishing harms as a purpose of the study. No credit was given to studies that did not mention harms or safety in the introduction. |
| Methods | 1. List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs. unexpected events, reference to standardized and validated definitions, and description of new definitions)
 | 1. If the article defined the evaluated adverse events
 | 3. Credit was given if the study explicitly defined any common side effects (such as diarrhea, rash, and candida diaper dermatitis) and other specifically monitored side effects. Ideally, the article should have also specified if the adverse events were parent reported and what definitions or specifications the parents and investigators used; however, no points were deducted for not including this information. No credit was given to studies that did not define the evaluated adverse events. |
| 1. Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent)
 | 1. If the article described the mode of harms data collection (e.g. diaries, phone interviews, open ended questions, etc.)
 | 4. Credit was given to studies that specified how the harms data was collected (ie. Adverse events were asked about during a study visit or phone call, reported by a parent, reported in diaries, etc.). No credit was given to studies that failed to mention how the harms data was collected. |
| 1. If the collection method avoided bias
 | 5. Credit was given to studies that avoided biased methodology. No credit was given to studies with methodology that would lead to over or under estimation of adverse events. A ‘N/A’ designation was given to those studies that did not provide an adequate description of their collection methods. |
| 1. If the article specified when the adverse events data was collected
 | 6. Credit was given if the article specified when or at what study visits the adverse events data was collected. Studies that reported that adverse events data was collected at interval study visits or in diaries during the duration of the study were given credit. No credit was given if there was no mention of when the adverse events data was collected. |
| 1. If the article specified how or by whom causality was attributed if the article reported treatment-related adverse events data
 | 7. Credit was given if the article reported any data with treatment attribution and reported who made the attribution or the criteria for assigning attribution. No credit was given to studies that had data with treatment attribution but neglected to mention who made the attribution or the criteria used to assign the attribution. A ‘N/A’ designation was given to those studies that did not report data with treatment attributions. |
| 1. If the article specified rules for the determination of withdrawals due to reported adverse events
 | 8. Credit was given if the article specified who made the decision to withdraw patients and/or what the threshold was for withdrawing patients with severe adverse events. No credit was given if no such method was specified.  |
| 1. Describe plans for presenting and analyzing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses)
 | 1. If the article specified whether events that occurred more than once in the same participant were counted as separate events or as one event
 | 9. Credit was given if the article specified whether multiple recurrences of the same adverse events in one patient was considered as one event or if each recurrence was counted separately. Studies that dealt with this problem by reporting the number of patients with adverse events rather than events were not given credit unless they explicitly stated that this was done as a solution to the problem of recurrent adverse events. No credit was given if there was no mention of how this problem was resolved. |
| Results | 1. Describe for each arm the participant withdrawals that are due to harms and the experience with the allocated treatment
 | 1. If the article presented data on the number of participants who withdrew because of an adverse event for each treatment arm
 | 10. Credit was given if a study reported the number of patients that withdrew due to adverse events in each treatment arm. No credit was given if they did not report the number of withdrawals due to adverse events. |
| 1. If the article presented data on the number of participants with severe adverse events and/or deaths (apart from the number of withdrawals) for each treatment arm
 | 11. Credit was given to studies that mentioned any cases of severe adverse events, hospitalization of patients, or deaths apart from the reporting the number of withdrawals due to adverse events. Negative reports stating that there were no severe adverse events, hospitalizations, or deaths were also given credit. No credit was given to studies that neglected to report severe adverse events, hospitalizations, or deaths. |
| 1. Provide the denominators for analyses on harms
 | 1. If the article provided information to determine a denominator for the harms analysis for each treatment arm
 | 12. Credit was given to studies that explicitly specified the safety population, gave number of adverse events along with percentages so the total could be calculated, gave a total patient number in data tables, or any combination of information that could be used to confidently determine the safety population. No credit was given to studies that gave no information to determine the safety population or studies that had a large discrepancy between the denominator calculated from the reported data and the enrollment total. |
| 1. Present the absolute risk of each adverse event (specifying type, grade, and seriousness per arm), and present appropriate metrics for recurrent events, continuous variables and scale variables, whenever pertinent.
 | 1. If the article provided adverse events results separately for each treatment arm
 | 13. Credit was given if the article provided any adverse events data for both treatment arms. No credit was given if the article only reported adverse events data for one treatment arm or reported no adverse events data.  |
| 1. If the article provided the number or percentage of patients with adverse events
 | 14. Credit was given if the article reported any data on the number of patients who experienced adverse events. No credit was given if there was no data reported on the number of patients with adverse events. |
| 1. If the article provided the number of adverse events or occurrences
 | 15. Credit was given if the article provided any data on the number of adverse events. No credit was given if the study did not report data on the number of adverse events regardless of whether or not they reported adverse events data on number of patients who experienced adverse events. |
| 1. If the article provided the breakdown of patients or events for each reported type of adverse event
 | 16. Credit was given if the article provided a breakdown of adverse events data by type. Studies that only reported adverse events prevalence data observed in >1-5% of patients were still given credit. No credit was given if the study did not report any prevalence data for individual adverse events types. |
| 1. Describe any subgroup analyses and exploratory analyses for harms
 | 1. If the article provided information on subgroup analyses
 | 17. Credit was given if the article used a subgroup analysis and provided corresponding information. A ‘N/A’ designation was given to those studies that did not perform a subgroup analysis.  |
| Discussion | 1. Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability, and other sources of information on harms
 | 1. If the discussion mentioned safety based on reported harms data
 | 18. Credit was given if the discussion mentioned the results of the harms analysis or prevalence data from the study. No credit was given to studies that did not mention harms results in the discussion or merely mentioned that the evaluated drug was ‘safe.’  |
| 1. If the discussion cited prior literature on harms
 | 19. Credit was given if the discussion cited prior literature on harms including mentioning the results of another study or citing a study with similar results. No credit was given to studies that did not cite previous literature on harms. |
| Abbreviations: CONSORT, Consolidated Standards of Reporting Trials |

**Supplement reference list of included studies:**

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