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More than one-third of systematic reviews did not fully report the adverse events outcome

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Abstract

Objectives: The aim of the study was to assess the risk for adverse events reporting bias in systematic reviews of health care interventions registered to PROSPERO.

Study Design and Setting: This study was a retrospective cohort study. Systematic review protocols in PROSPERO were screened and included if they focused on a health care intervention and listed an adverse event as either a primary or secondary outcome. The included systematic reviews were assessed to determine the completeness of reporting for the adverse event outcomes. Any discrepancies in reporting between protocol and review were recorded.

Results: Of 1,376 protocols for systematic reviews sifted, only 524 (38%) listed adverse events outcomes. One hundred eighty-six protocols were published in 2017 and 2018, of which 146 were included in our analysis. Among the included systematic reviews, 65% (95/146) fully reported the adverse event outcomes as intended by the protocol, 8% (12/146) entirely excluded the adverse event outcome, and the remaining 27% (39/146) either partially reported or changed the adverse event outcomes.

Conclusion: Sixty-two percent of reviews did not mention adverse events in their protocol, and 35% of PROSPERO-registered systematic reviews had discrepant outcome reporting between the protocol and publication. The findings suggest a need for the encouraged use of harms reporting guidelines and further research into adverse events reporting bias.

Keywords: Bias; Adverse events; Systematic reviews; Outcome reporting bias; Reporting; Harms

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1. Introduction

Adverse events are undesired negative outcomes, which can occur during or after an intervention, such as a drug or procedure, which may or may not be caused by the intervention, but for which there is at least a possibility of causation [1]. Adverse events, sometimes referred to as harms, are often rare and long-term, making them difficult to analyze and report as outcomes of an intervention [2]. It is also common for outcomes that are measures of an intervention's efficacy to be the focus of outcome reporting in studies rather than the adverse events [3]. Nonetheless, full reporting of adverse events is of the utmost importance, as they provide a fuller understanding of health care interventions, which is crucial to informing medical practice, public health interventions, and health policy. Patients and providers need to know about the relative benefits and harms of an intervention. It is not just those adverse events deemed to be serious that are important but also those categorized as minor. This is particularly the case when different treatment options are available, there is a narrow margin between the benefit and harm, the adverse events are persistent, the treatment is prophylactic, and the minor harms affect adherence. In many cases, adverse events may be the deciding factor when more than one treatment option is available.

Outcome reporting bias can be defined as ‘‘the selective reporting of some outcomes but not others, depending on the nature and direction of the results’’ [4].

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What is new?

Key finding

- Thirty-five percent of systematic reviews of health care interventions changed, partially reported, or excluded the adverse events outcome as specified in their respective PROSPERO-registered protocols.

What this adds to what was known?

- This study examines the risk for adverse events reporting bias in systematic reviews using PROSPERO as a source of protocols and reviews.
- Only 38% of authors of systematic reviews include an adverse events outcome at the stage of protocol development. Sixty-five percent of the protocols that do list adverse events outcomes report the outcomes in the published review as they state they intended to in the protocol.

What is the implication and what should change now?

- Systematic reviews of health care interventions are currently at high risk for adverse events reporting bias.
- Researchers should be encouraged to include adverse events outcomes in their protocol before beginning a systematic review and follow harms reporting guidelines.

Outcome reporting bias that specifically concerns harms is referred to as adverse events reporting bias and is defined as selective reporting of harms in reported or published findings [1]. Outcome reporting bias in primary studies can lead to an overestimation of treatment effects in systematic reviews [5], and poor adverse events reporting in primary studies can compound in systematic reviews [6], leading to an inaccurate picture of an intervention overall.

Despite the known risk of outcome reporting bias, little research has examined the potential for adverse events reporting bias in systematic reviews. Previous research has focused on the reporting within published reviews (with a focus on Cochrane reviews) and has found the risk of reporting bias for adverse outcomes in these reviews to be high [7], indicating a need to examine the potential for this reporting bias from protocol to published review and among other types of systematic reviews. The International Prospective Register of Systematic Reviews (PROSPERO) is an online database to publish protocols before the start of a review to reduce the risk of reporting bias [8]. This study is the first to examine adverse events reporting bias using the PROSPERO database as a source of protocols and their respective published reviews.

2. Methods

2.1. Protocol

A protocol detailing the research objectives and methods was created before the start of this study. The protocol can be found in the Supplementary Material. The initial protocol was adapted from the study by Tricco et al. [9], who examined intended primary outcomes from protocols written in advance compared with the reported primary outcomes in published systematic reviews. They did not, however, look at adverse events. We developed new methods to assess adverse events reporting in systematic reviews.

2.2. Eligibility and inclusion process

All PROSPERO protocols with completed and published reviews were screened and included if they (1) listed adverse events as a primary or secondary outcome and (2) included studies of health care interventions. When browsing all these reviews, adverse events could have been listed as adverse events, adverse effects, adverse reactions, harms, side effects, toxicity, complications, unwanted/undesirable effects/outcomes, or safety. They could also have been listed as specific outcomes known to be adverse events of the intervention, such as bleeding events for anticoagulation drug treatments. This approach is more rigorous than searching with adverse events terms because of inconsistent terminology and poor indexing used in the adverse event literature. To examine the most up-to-date reporting practices of systematic reviews, only protocols with completed reviews published in 2017 or 2018 were included.

All published systematic reviews of corresponding included protocols were located using the publication information listed on the PROSPERO database.

2.3. Data extraction

From the completed and published reviews, data were collected on authors, author affiliations, year of publication, title of review, number of studies, study designs, intervention(s) of interest, primary outcomes reported, secondary outcomes reported, main effect or result of the intervention, and funding. The health care interventions under study in each review were categorized by type. These categories were drug, surgical, behavioral, screening/diagnostic, quality of care, multiple/any intervention (i.e., protocol indicated an interest in multiple types of interventions or may not have put any restrictions on included interventions), and other (i.e., protocol indicated an interest in a single, specific health care intervention that did not fall under the other categories). The multiple/any category referred to instances where more than one type of intervention was included from more than one category. For example, a review may evaluate all interventions to treat a specific disease, which may include drug, behavioral, and surgical interventions.

2.4. Reporting codes

Each protocol-review pair was assigned a code regarding their adverse events outcome reporting. Reviews that reported all adverse events specified in their respective protocols were coded as fully reported. Reviews with adverse events reporting discrepancies between the PROSPERO protocol and published review were coded as either exclusion of adverse events outcome or change in adverse events reported. Any reviews coded as "change" were categorized further as a negative change, positive change, or a change in presentation.

Negative change indicated that authors restricted their reporting of the adverse events outcome or lowered the outcome level to one of lesser importance. The two reporting codes used to indicate a negative change from protocol to review were exclusion of specified adverse events in the published review and moving adverse effect from a primary outcome level in the protocol to a secondary outcome level in the published review.

Positive change indicated that the authors chose to broaden their reporting of the adverse events outcome or raised the outcome level to one of a higher importance. The two reporting codes used to indicate a positive change from protocol to review were inclusion of additional specified adverse events in the published review and moving adverse events from a secondary outcome level in the protocol to a primary outcome level in the published review.

Change in presentation indicated that the authors reported their adverse events outcome but did so in a manner that was different from the intentions described in their protocols (e.g., reporting as tolerability instead of safety and reporting proportions instead of counts).

2.5. Efforts to reduce error

Protocol screening, data extraction, and assignment of reporting codes were completed by the first author (R.P.) and the second author (S.G.) independently. The third author, I.W., settled any disagreements.

2.6. Contacting authors

In cases where the adverse events outcome from the protocol was excluded from the published systematic review, the contact author of the review was emailed and asked to clarify the reasons for the change in reporting.

2.7. Analysis

The codes given to the protocol and published review pairs describing the adverse events reporting allowed for the identification of discrepancies between the intended adverse events outcomes from the protocols and the reported adverse events outcomes from the reviews. From this, permutations of the changes (e.g., exclusion of adverse events, inclusion of new outcomes, a shift between primary and secondary outcome, etc.) were synthesized quantitatively.

3. Results

3.1. Systematic review cohort

From PROSPERO's inception (February 2011) until the search date March 29, 2018, there were 2,032 protocols with a completed and published systematic review. Of these protocols, 1,376 focused on a health care intervention, such as a drug or medical device. For protocols with an intervention, 524 (38%) listed adverse events as an outcome of interest.

Of those 524 protocols, 186 were for systematic reviews published in 2017 or 2018. The 186 included protocols led to 187 systematic reviews. We did not include 41 of 187 systematic reviews for the following reasons. Twenty-three of the systematic reviews could not be accessed in a full-text format, six were duplicate publications, one did not focus on health care intervention studies, three used the adverse events outcome as a measure of the intervention's effectiveness, seven were not systematic reviews, and one was not published. After excluding these studies, there were 146 systematic reviews in the final cohort (see Fig. 1 and Supplementary Material: references for included reviews and data extraction).

3.2. Reporting of adverse events outcomes

Of the 146 included systematic reviews, 95 (65%) fully reported the adverse events outcome exactly as intended from the protocol. Twelve (8%) of the reviews excluded the adverse effect outcome entirely. The remaining 39 (27%) at least partially reported adverse events or in some way changed the reporting of the outcomes (see Table 1).

There were 13 (9%) systematic reviews that changed the reporting of adverse events from the protocol in a positive way, either by adding new specific named adverse events (5/146, 3%) or by moving the adverse events outcome from a secondary to a primary outcome (8/146, 6%). Seventeen (12%) of the systematic reviews changed the adverse events reporting from the protocol in a negative way, by excluding certain specific named adverse events (10/146, 7%) or by moving the outcome from a primary to a secondary outcome level (7/146, 5%).

Nine of the systematic reviews (7%) changed the reporting from the protocol in ways regarding the presentation of the adverse events, meaning that although the outcome's data were reported fully, the manner in which the outcome was reported differed in the published review. These included changes such as presenting the outcome as "tolerability" instead of "safety," reporting on proportions instead of counts, excluding prespecified analyses, reporting only adverse events of specific grades (e.g., adverse events of grade 3 or 4) instead of all adverse events, not discussing the number of adverse events leading to drop-out as

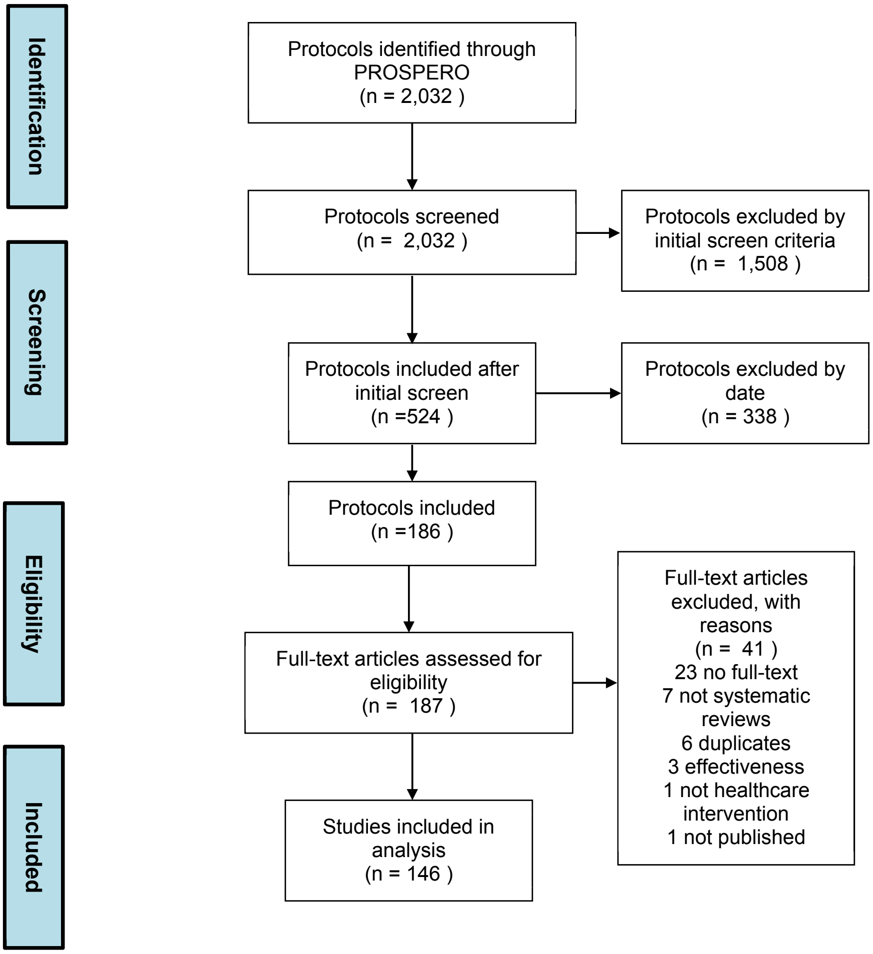

Fig. 1. Flow of systematic review screening, eligibility, and inclusion.

intended and instead reporting only the number of adverse events, not specifically identifying the adverse events outcome as a primary or secondary outcome but still fully reporting the outcome data or failing to name specific named adverse events and instead reporting under an umbrella term such as “complications.”

Table 1. Overall reporting for adverse effect outcomes

Reporting code	Number of reviews (%)[a]
Full reporting	95 (65)
Positive change	13 (8.9)
Included new specific adverse events	5 (3.4)
Raised adverse events outcome level	8 (5.5)
Negative change	17 (12)
Excluded specific adverse events	10 (6.8)
Lowered adverse events outcome level	7 (4.8)
Change in presentation	9 (6.2)
Exclusion of adverse events	12 (8.2)

Includes totals and percentages for each reporting code.

The numbers for positive change and negative change represent the sum of their respective subcategories, as explained in the following section.

[a] All percentages are out of the 146 included systematic reviews.

3.3. Adverse events reporting by intervention type

The percentage of the 1,376 protocols listing an adverse events outcome was recorded by intervention type (Fig. 2). The intervention types most likely to have an adverse events outcome listed in the protocol were drugs (275/452), surgical (93/181), and any/multiple (40/88). Those intervention types less likely to list adverse events outcomes in the protocol were screening/diagnostic (26/78), other (41/142), quality of care (14/110), and (35/327) behavioral (Fig. 2).

The level of adverse events reporting was examined across health care intervention types (see Table 2). Systematic reviews with a focus on screening/diagnostic intervention studies were the most likely to fully report the adverse events outcome although there were only four reviews in this category. Systematic reviews of drug intervention studies were the second most likely to fully report the outcome, followed by surgical, other, behavioral, and any/

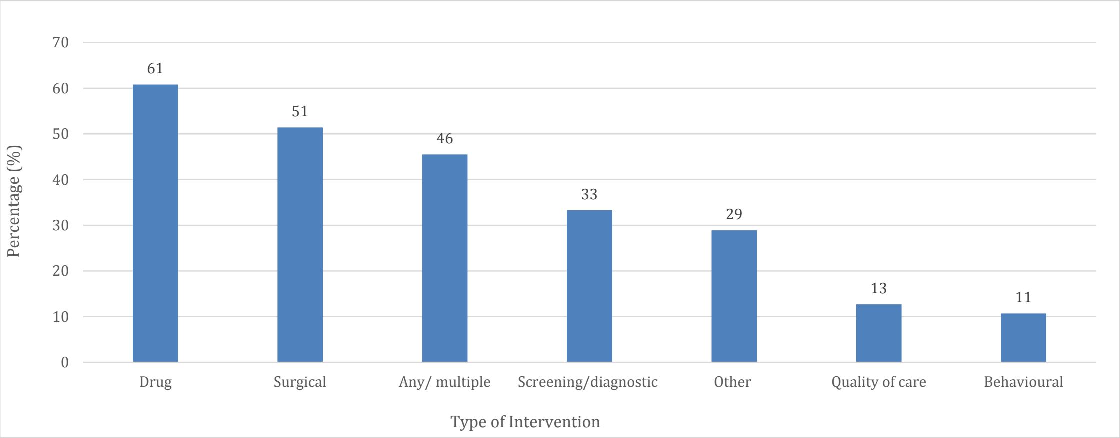

Fig. 2. Percentage of protocols including adverse effect outcomes.

multiple. None of the systematic reviews of quality of care studies fully reported the adverse events outcome. The single review interested in placebo as an intervention changed the presentation of its adverse events outcome.

The categories of drug, behavioral, quality of care, and any/multiple health care interventions included systematic reviews that excluded the adverse events outcome.

3.4. Adverse events reporting by funding source

The reporting of adverse events was recorded in relation to the funding source (public sector, industry, or not reported; Table 3). Those reviews, which had public sector funding, such as university or government health department (such as the Department of Health in the United Kingdom), reported the adverse events mentioned in the protocol in 80% of the corresponding published reviews as opposed to 63% or 64% of industry-funded reviews and reviews with funding not reported respectively. And none of the public sector–funded reviews excluded adverse events in the published review as opposed to 6% and 11% of the other reviews. Interestingly 20% of industry-funded reviews had positive changes as opposed to 13% and 3% of public sector–funded reviews and reviews with funding not reported. However, caution should be exercised as the number of reviews reporting their funding source was less than half (46%, 44/95) making any generalizations difficult.

3.5. Location of reporting

In the 134 reviews that fully reported or partially reported the adverse effect outcomes as indicated in the

Table 2. Reporting by intervention type

Intervention type	Full, *n* (%)	Positive change, *n* (%)	Inclusion of new AEs, *n* (%)	Raised level, *n* (%)	Negative change, *n* (%)	Exclusion of specific AEs, *n* (%)	Lowered level, *n* (%)	Changed presentation, *n* (%)	Excluded, *n* (%)	Total[a]
Drug	58 (70)	9 (11)	4 (5)	5 (6)	9 (11)	5 (6)	4 (5)	5 (6)	2 (2)	83
Surgical	15 (68)	1 (5)	—	1 (5)	5 (23)	4 (18)	1 (5)	1 (5)	—	22
Any/multiple	5 (42)	1 (8)	1 (8)	—	1 (8)	—	1 (8)	1 (8)	4 (33)	12
Screening/ diagnostic	3 (75)	1 (25)	—	1 (25)	—	—	—	—	—	4
Other	6 (67)	—	—	—	1 (11)	1 (11)	—	—	2 (22)	9
Quality of care	—	1 (50)	—	1 (50)	1 (50)	—	1 (50)	—	—	2
Behavioral	8 (62)	—	—	—	—	—	—	1 (8)	4 (31)	13
Placebo	—	—	—	—	—	—	—	1 (100)	—	1
All reviews	95 (65)	13 (9)	5 (3)	8 (5)	17 (12)	10 (7)	7 (5)	9 (6)	12 (8)	146

Abbreviation: AE, adverse event.

The number and percentage of systematic reviews for each health care intervention type that fell into the different codes for AEs reporting.

As with Table 1, for the subcategories for positive change and negative change (inclusion or exclusion or specific AEs and changing the outcome level), the number of reviews in the two subcategories total to equal the number included for the main positive/negative change category.

The percentages all reflect the number of reviews per reporting code out of the total number of reviews per intervention type.

[a] The total number of systematic reviews for each intervention type serves as the denominator for the percentages in each row.

Table 3. Reporting of adverse events by funding category

Funding	Full reporting, *n* (%)	Negative changes, *n* (%)	Positive changes, *n* (%)	Exclusion of adverse events, *n* (%)	Total
Public sector	12 (80)	1 (7)	2 (13)	0 (0)	15
Industry	32 (63)	6 (12)	10 (20)	3 (6)	51
Not reported	51 (64)	18 (23)	2 (3)	9 (11)	80
All	95 (65)	25 (17)	14 (10)	12 (8)	146

protocol, 109 (81%) reported the adverse events within the main text of the published systematic review. The remaining 25 reviews (19%) did not report the adverse events in the main text, choosing to report them in Supplementary Tables or Appendices.

3.6. *Contact authors' responses*

Of the 12 authors who were contacted, four responded. The first replied that the adverse events outcome referred to "any unfavorable treatment outcomes," in this case unfavorable tuberculosis treatment outcomes, which were related to the efficacy of treatment and not to adverse events as defined in this research study. Two authors stated that no adverse events had occurred in the primary studies, and one of the two also stated that there was no discussion of nonoccurrence in the systematic review because of the word limit enforced by the publishing journal. The final contact author replied that there were no eligible primary studies that included an adverse events outcome.

4. Discussion

The results of this study are consistent with past findings that systematic reviews are at risk of outcome reporting bias and discrepant outcome reporting [2−4,7,9,10]. Just more than one-third of protocols for systematic reviews of health care interventions listed adverse events as an outcome of interest on PROSPERO (either as a primary or secondary outcome). All interventions that can have an effect have the potential to have an adverse effect. It is, however, more widely accepted that drug interventions and possibly surgical interventions have the potential to have adverse events or complications. This is reflected in the percentage of protocols with adverse events outcomes—61% of drug intervention protocols and 51% of surgical procedure protocols. These percentages are still low considering the importance of adverse events. Adverse events are potentially the most dangerous outcomes following a health intervention, and the lack of protocols indicating adverse events as an outcome of interest should be of great concern to anyone looking at systematic reviews as evidence of harms for any intervention. By actively excluding adverse events, systematic reviews may be biased and not helpful when it comes to informing balanced health care decision-making.

The majority of systematic reviews in this cohort fully reported (65%) or partially reported (27%) the harm outcome in the published review, whereas only a handful excluded the outcome (8%). It appears that although few protocols specify an adverse events outcome, those that do are quite likely to at least partially, if not fully, report the adverse outcomes in their published review.

Overall, there were discrepancies between protocol and publication in the adverse outcomes reported in 35% of our included reviews. This result is consistent with those observed in previous studies. A methodological review, which focused on effectiveness outcomes rather than harm outcomes, found discrepancies in outcome reporting in 38% of Cochrane reviews [10]. The study by Tricco et al. of effectiveness outcomes in non-Cochrane reviews found that 32% of reviews had a discrepancy between protocol and publication [9].

The reasons authors provided for excluding the adverse events outcome highlight two implications. The first point that researchers may believe that the absence of adverse events in primary studies does not warrant discussion within a systematic review although the absence of adverse events is just as clinically significant as their presence when it comes to assessing the safety of an intervention. The second is that the term adverse events may not be universally understood, a fact that has been demonstrated previously [11]. A researcher's understanding of the term "adverse" will influence the way he or she identifies and discusses harm outcomes.

Future research into adverse events reporting bias should focus on systematic reviews that are non-Cochrane and do not have a protocol published on PROSPERO, as these kinds of reviews have yet to be studied in this context, and there is some evidence that non-Cochrane reviews are at greater risk of adverse events reporting bias [12]. Looking to other kinds of systematic reviews will provide a greater understanding of the potential for adverse events reporting bias across all types of reviews and may help to inform better guidelines for harms reporting in systematic reviews. Further research could also evaluate the reasons why review authors often fail to include adverse events outcomes in their protocols and why discrepancies exist between protocols and full systematic reviews. This could help inform guidance and training for reviewers.

In the meantime, researchers seeking to complete a systematic review of a health care intervention should be educated on the importance of the inclusion of adverse events outcomes. Just as certain journals have endorsed the use of various reporting guidelines in the past, journals that publish systematic reviews should consider encouraging authors to include harms outcomes and endorse harms reporting guidelines, such as the PRISMA harms checklist [6,13]. This will lead to a reduction in the risk for adverse events reporting bias and improve the quality of harms reporting. Techniques such as reporting guidelines endorsement have improved reporting quality of health research articles in the past [14,15] and could be a viable solution for improving reporting of harms.

5. Conclusions

Sixty-two percent of review authors did not mention adverse effect outcomes in their protocol. This is of concern, given the importance of adverse events in decision-making for patients and policymakers.

Also, of concern, 35% of the cohort of PROSPERO-registered systematic reviews were at risk of adverse events reporting bias from the protocol to publication stage of the review process. This figure may also be higher for reviews, which do not publish their protocols in PROSPERO.

The findings suggest a need for the encouraged inclusion of harms outcomes in systematic reviews and the use of harms reporting guidelines.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2018.12.007.

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