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ORIGINAL ARTICLE

The reporting of safety among drug systematic reviews was poor before the implementation of the PRISMA harms checklist

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Abstract

Objectives: To examine, through a cross-sectional survey, how well safety information was reported among drug systematic reviews predating PRISMA harms checklist and explore factors associated with better reporting.

Study Design and Setting: We searched PubMed to identify all systematic reviews published in the Cochrane Database of Systematic Review or the core clinical journals in 2015, one year before the PRISMA harms checklist was published. We randomly selected, in a 1:1 ratio, Cochrane and non-Cochrane systematic reviews assessing drug effects (including both efficacy and safety). We used the PRISMA harms checklist published in 2016 to assess the quality of reporting of drug safety information. Multivariable linear regression analyses were used to explore the association of six prespecified variables with more complete reporting of PRISMA harms items.

Results: We included 120 systematic reviews, including 60 Cochrane and 60 non-Cochrane reviews. Scores on the PRISMA harms checklist (23 items) were low (median 4, [first, third quartile: 2, 6]), with no difference between Cochrane and non-Cochrane reviews (4.5 [2, 7] vs. 4 [2.5, 5]; $P = 0.29$). Among all eligible reviews, only one item (i.e., state conclusions in coherence with the review findings) was reported adequately (proportion of adherence 81.6%); proportion of reporting for other items ranged from 1.7% to 68.3%. The four essential reporting items from PRISMA harms checklist were also poorly complied (proportion of adherence ranged from 1.7% to 9.2%). Multivariable linear regression analyses found no significant associations between any study characteristic and reporting on the PRISMA harms, likely because of limited variability in scores across studies.

Conclusions: The reporting of safety information was poor both for Cochrane and non-Cochrane drug systematic reviews predating PRISMA harms checklist. The findings suggested a strong need to use the PRISMA harms checklist for reporting safety among drug systematic reviews. © 2018 Elsevier Inc. All rights reserved.

Keywords: Drug systematic review; Safety information; PRISMA harms checklist; Reporting quality; Poor; Cross-sectional survey

1. Introduction

Drug safety information is critical to health care and policy decisions. Well planned and rigorously conducted systematic reviews and meta-analysis of randomized and/or nonrandomized studies provide the best evidence to inform this issue [1−3]. This is particularly the case when adverse drug effects are rare [4−6], exploring length of exposure on adverse drug effects [7,8], or when assessing drug safety concerns among heterogeneous patient populations [9].

Nevertheless, adequate reporting of safety data is required to facilitate appropriate inferences. A number of previously published surveys [10−19] have investigated the reporting of systematic reviews and shown that reporting quality, as measured by the PRISMA checklist, is often inconsistent. These findings, however, are not applicable to the reporting of drug safety among systematic reviews.

Conflict of interest statement: None.

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What is new?

Key findings

- The reporting of safety information was poor both for Cochrane and non-Cochrane drug systematic reviews predating PRISMA harms checklist.
- Both the four essential and 19 desirable reporting items from PRISMA harms checklist were poorly complied.

What this adds to what was known?

- Our study clearly showed the extent to which safety is reported among drug systematic reviews predating PRISMA harms checklist.
- The findings will also be a helpful baseline from which to measure improvement in the reporting of safety.

What is the implication and what should change now?

- Our findings highlight the need to implement the PRISMA harms checklist when reporting safety among drug systematic reviews.
- Journal editors should consider requiring systematic review authors to adhere to the PRISMA harms statement regarding report of safety information.

Three surveys [20−22], specifically examined issues about adverse effects among systematic reviews. These studies either included systematic reviews published before 2011 or examined methodological details about the conduct of systematic review (not reporting). Two surveys [20,21] did not limit their assessments to drugs. The most recent survey [23], published in 2014, assessed systematic reviews that addressed harms of various health care interventions as the primary study aim and showed that systematic reviews had poor reporting of harms data. However, systematic reviews addressing effects of health care interventions are usually designed to investigate efficacy or effectiveness. Each year, only 3-5% of published systematic reviews are conducted to primarily assess harms [20,24]. The findings from this study thus have limited generalizability to most systematic reviews, which primarily address efficacy or effectiveness.

Therefore, we conducted a systematic survey to investigate the quality of reporting of safety among drug systematic reviews with a broader aim of assessment (i.e., addressing both effectiveness/efficacy and safety). This study was part of our major study that investigated the design, conduct, analysis, and reporting of safety among drugs systematic reviews. At the time we designed the major study (January 2016), the PRISMA harms checklist [25] was not yet available. We subsequently decided to use the PRISMA harms checklist for measuring the reporting. Although the included sample predated the checklist, this article aimed to investigate the extent to which safety was reported among drug systematic reviews before the PRISMA harms checklist was available. The resulting findings would help understand specifically about the safety reporting about drug systematic reviews just before the PRISMA harms checklist, which may reinforce the need to use the PRISMA harms checklist in the current drug systematic reviews.

2. Methods

2.1. Eligibility criteria

We included a report if it was a systematic review, assessed the effects of a pharmaceutical agent or combination of agents, included randomized controlled trials (RCTs) with or without nonrandomized studies, examined both drug efficacy/effectiveness and safety, and was a main study report. We excluded individual participant data meta-analyses, network meta-analyses, or systematic reviews reported as a research letter.

We defined a study as a systematic review according to the Cochrane handbook (version 5.1.0) [26]. Nonrandomized studies included nonrandomized clinical trials (non-RCTs), cohort studies, and case-control studies. We considered a systematic review to have included information about drug safety if the investigators clearly defined outcomes regarding drug efficacy/effectiveness and safety in the report (e.g., adverse drug reactions, adverse drug events).

2.2. Literature search

We searched PubMed to identify reports of Cochrane reviews and non-Cochrane systematic reviews among core clinical journals, published in any form in the year of 2015. At the time we searched the literature, the PRISMA harms checklist was not available; just one month later (February 2016), however, the checklist was published [25]. Because the current work was part of our major study that investigated the design, conduct, analysis, and reporting of safety among drug systematic reviews, we decided to continue using this sample of searched literature for the study.

The core clinical journals, previously known as the Abridged Index Medicus, were defined by the US National Library of Medicine and the National Institutes of Health, including a subset of 119 widely read journals published in English and covering all specialties of clinical medicine and public health sciences [27]. We included search terms related to systematic review, meta-analysis, and journals, and one experienced investigator (LL) developed the search strategy with reference to a previous related study [28] (Appendix 1).

2.3. Sample size and random sampling

Our sample size estimation was based on the number of study characteristics that we explored for an association

with reporting quality. In our multivariable regression analysis of study characteristics with reporting quality, we planned to include six dichotomous study characteristics. According to the empirical estimation, we estimated that 120 eligible reports would be sufficient to avoid overfitting of our model, using a criterion of 20 studies for each variable [29].

We randomly sampled the citations to acquire a 1:1 sample of Cochrane and non-Cochrane systematic reviews. We screened these two samples for eligibility and repeated the random sampling process as needed until reaching a final sample size of 120 systematic reviews.

2.4. Study process

Teams of paired reviewers, trained in trial and systematic review methods, screened abstracts and full texts for eligibility and abstracted data from eligible studies independently and in duplicate, using pilot-tested, standardized forms, together with detailed instructions. They resolved disagreements through discussion or, if needed, adjudication by a third reviewer (XS).

2.5. Data collection

We collected the following information from each eligible systematic review: (1) author, (2) year of publication, (3) review type (Cochrane or non-Cochrane review), (4) type of studies planned for inclusion in the review (RCTs, non-RCTs, cohort studies, or case-control studies), (5) number of studies included in the review, (6) total number of participants involved, (7) clinical focus (medical vs. surgical), (8) single agent or combination of therapeutic agents, (9) type of control (placebo, standard care, active medication, other [e.g., behavioral intervention, health education]), (10) involvement of a methodologist (i.e., statistician, epidemiologist, information expert), (11) high vs. lower impact journal, (12) type of funding (private for profit, private not for profit, governmental, not funded, not reported), and (13) significance of primary safety outcome (yes, no, not reported).

We judged that a systematic review involved a methodologist if any of the authors were affiliated with a department of epidemiology, statistics, or evidence-based medicine, or if a methodologist was listed in the acknowledgment section. We stratified journals into high impact groups and lower impact groups according to the total citations defined by the Web of Science [30]. High-impact journals were defined as the five journals with the highest total citations in 2016: New England Journal of Medicine, Lancet, Journal of the American Medical Association, BMJ, and Annals of Internal Medicine. Lower-impact journals were the remaining core clinical journals and Cochrane database of systematic reviews. One primary safety outcome was selected for each review, according to a previously published strategy [31]: if a systematic review specified a primary safety outcome, we selected it as the primary safety outcome for our analyses; if a systematic review specified more than one primary safety outcome, we selected the first one reported in the methods; if a systematic review did not specify a primary safety outcome in the methods, we selected the first reported safety outcome in the results.

We used the PRISMA [32] and PRISMA harms [25] to assess the quality of general reporting and reporting on safety information, respectively (Appendix 2). We used both tools to help inform the relative quality of reporting of general information and drug safety information among drug reviews. The PRISMA statement is a reporting checklist concerning the general reporting of a systematic review, and the PRISMA harms checklist specifically measures the reporting of harms among systematic reviews. The PRISMA harms checklist contains four essential reporting items, including title (“specifically mention ‘harms’ or other related terms, or the harm of interest in the review”), synthesis of results (“specify how zero events were handled, if relevant”), study characteristics (“define each harm addressed, how it was ascertained [e.g., patient report, active search], and over what time period”), and synthesis of results (“describe any assessment of possible causality”), and 19 additional desirable reporting items [25]. For each of the included systematic reviews, we assessed the reporting against the 27 items from PRISMA and the additional 23 items from PRISMA harms. Each item was assessed with the option of “Yes,” “No,” or “Can’t answer”. We judged that an item was adequately reported if it was reported by 80% or more of systematic reviews included in our study.

For a specific item, we assigned one point if the systematic review met the reporting requirement; otherwise (i.e., “no” or “can’t answer”), we assigned zero points. This scoring approach resulted in a score ranging from 0 to 27 for PRISMA and from 0 to 23 for PRISMA harms.

2.6. Statistical analysis

We conducted descriptive analyses of study characteristics of included systematic reviews. For all descriptive analyses, we used frequencies (and percentages) for dichotomous variables, and mean (and standard deviation) or median (and range) or median (and first quartile, third quartile) for continuous variables. We compared study characteristics between Cochrane and non-Cochrane systematic reviews using the chi-square test or Fisher’s exact test for dichotomous variables, t-test for continuous variables when the distribution was normal, and Mann−Whitney U test when the distribution was not normal.

We carried out univariable and multivariable linear regression analyses to explore the association of the total score for PRISMA harms and for PRISMA, with six prespecified study characteristics, respectively. These included: (1) type of systematic review (Cochrane vs. non-Cochrane), (2) journal type (high vs. lower-impact journals), (3) systematic reviews that included both RCTs

and nonrandomized studies (yes vs. no), (4) clinical focus (medical vs. surgical), (5) source of funding (government vs. nongovernment), and (6) significance of primary harm outcome (yes vs. no/not reported). We used the variance inflation factor (VIF) to explore for multicollinearity among study characteristics. A VIF of ≥5 was considered unacceptably high correlation [33].

3. Results

We randomly selected 3,001 reports from unique 3,881 articles identified through our literature search. After title and abstract screening, 227 reports proved potentially eligible. On full text screening, 120 systematic reviews, including 60 Cochrane systematic reviews and 60 non-Cochrane systematic reviews, were eligible and included in our survey (Fig. 1).

The median number of studies included among eligible reviews was 10 (range 1 to 133); the median number of participants included was 2097 (range 32 to 621,845); 93 (77.5%) assessed the effects of drugs in medical specialties and 27 (22.5%) in surgical specialties; and 61 (50.8%) were funded by government and 4 (3.3%) by a private for profit company (Table 1). There was no statistical difference between Cochrane and non-Cochrane systematic reviews in number of studies included (median 9 vs. 12, $P = 0.66$). Compared with non-Cochrane systematic reviews,

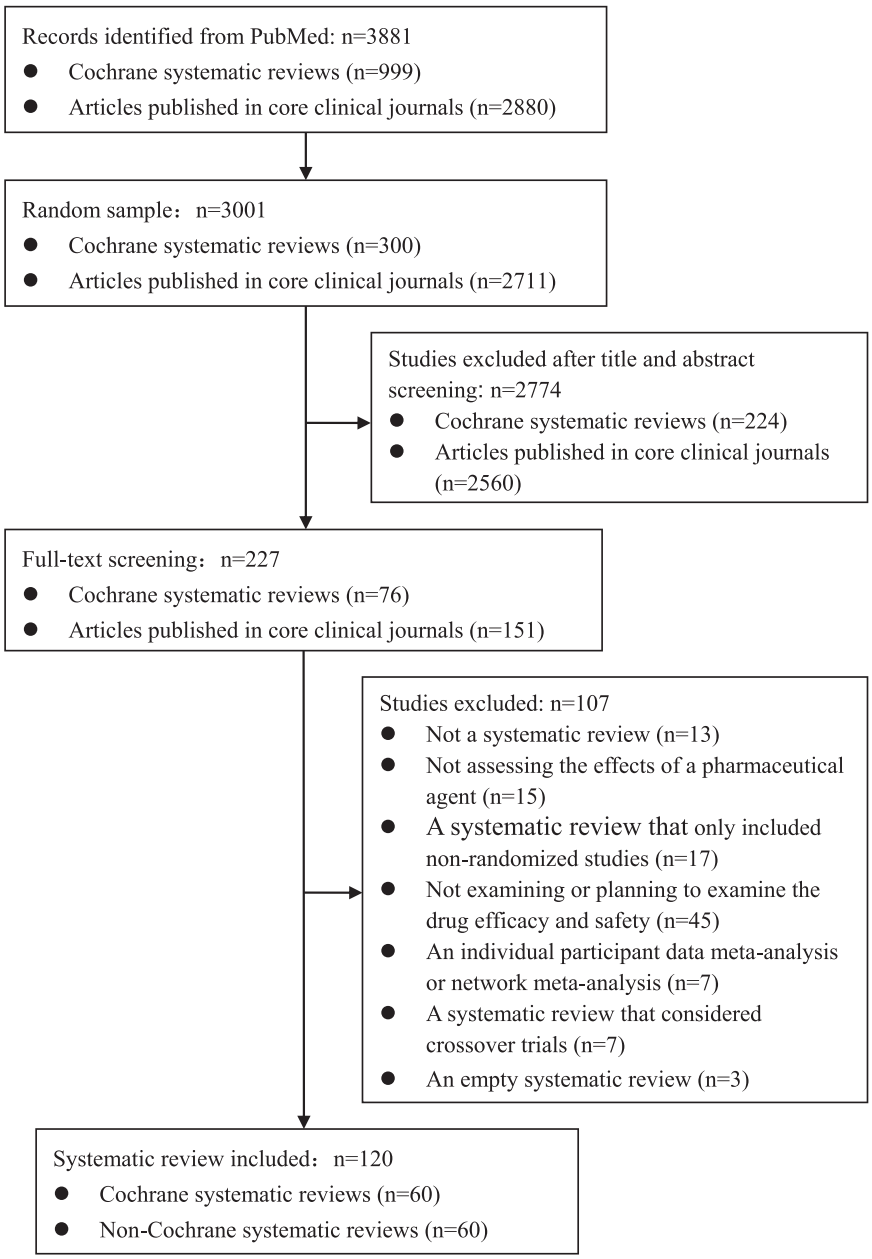

Fig. 1. Flow chart of study selection.

Table 1. Characteristics of included systematic review

Characteristics	Total (%)	Cochrane SR (%)	Non-Cochrane SR (%)	*P* Value
Journal type				0.006[a]
High-impact journals[b]	7 (5.8)	0	7 (11.7)	
Lower-impact journals	113 (94.2)	60 (100)	53 (88.3)	
Type of studies planned for inclusion				
RCTs	120 (100)	60 (100)	60 (100)	0.93
Quasi-RCTs	34 (28.3)	18 (30)	16 (26.7)	
Non-RCTs	29 (24.2)	15 (25)	14 (23.3)	
Cohort studies	35 (29.2)	15 (25)	20 (33.3)	
Case-control studies	30 (25)	15 (25)	15 (25)	
Total number of studies included[c]				
Total	10 (1-133)	9 (1-52)	12 (2-133)	0.66[d]
RCTs	9 (1-133)	9 (1-52)	9 (1-133)	0.89[d]
Quasi-RCTs	0 (0-7)	0 (0-7)	0 (0-1)	
Non-RCTs	0	0	0	
Cohort studies	0 (0-26)	0	0 (0-26)	
Case-control studies	0 (0-9)	0	0 (0-9)	
Total number of participants included[c]				
Total	2097 (32-621845)	1,069 (32-138538)	2806 (268-621845)	0.03[d]
RCTs	1,736 (32-138538)	1,049 (32-138538)	2505 (248-102479)	0.02[d]
Quasi-RCTs	0 (0-194)	0 (0-194)	0 (0-120)	
Non-RCTs	0	0	0	
Cohort studies	0 (0-548003)	0	0 (0-548003)	
Case-control studies	0 (0-57,036)	0	0 (0-57036)	
Clinical specialty				0.016
Medical	93 (77.5)	52 (86.7)	41 (68.3)	
Surgical	27 (22.5)	8 (13.3)	19 (31.7)	
Background interventions (interventions used across groups)				0.09[a]
None	57 (47.5)	30 (50)	27 (45)	
Active drug(s)	47 (39.2)	29 (48.3)	18 (30)	
Surgery	4 (3.3)	0	4 (6.7)	
Other (e.g., behavioral intervention, health education)	2 (1.7)	1 (1.7)	1 (1.7)	
Not reported	20 (16.7)	8 (13.3)	12 (20)	
Type of comparisons				0.14[a]
Drug(s) vs. drug(s)	72 (60)	35 (58.3)	37 (61.7)	
Drug(s) vs. placebo	75 (62.5)	47 (78.3)	28 (46.7)	
Drug(s) vs. no intervention/standard of care	20 (16.7)	10 (16.7)	10 (16.7)	
Drug(s) vs. other intervention	2 (1.7)	2 (3.3)	0	
Methodologists involved				<0.001
Yes	44 (36.7)	32 (53.3)	12 (20)	
No	40 (33.3)	7 (11.7)	33 (55)	
Unclear	36 (30)	21 (35)	15 (25)	
Source of funding				<0.001[a]
Private for profit	4 (3.3)	2 (3.3)	2 (3.3)	
Private not for profit	3 (2.5)	0	3 (5)	
Government	61 (50.8)	43 (71.7)	18 (30)	
Not funded	28 (23.3)	8 (13.3)	20 (33.3)	
Funding not reported	26 (21.7)	8 (13.3)	18 (30)	

Values in parentheses are percentages unless indicated otherwise.
[a] Fisher's exact test.
[b] Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine.
[c] Values are median (range).
[d] Mann–Whitney U test, others are Pearson's chi-squared test.

Cochrane reviews included fewer participants (median 1,069 vs. 2,806, $P = 0.03$) and were less likely to assess drug effects in surgical specialties (13.3% vs. 31.7%, $P = 0.02$). Cochrane reviews were more likely to involve methodologists (53.3% vs. 20.0%; $P < 0.001$).

3.1. Adherence to PRISMA harms checklist

Most systematic reviews met few requirements of the PRISMA harms checklist (Fig. 2 and Table 2). Among the 23 items from PRISMA harms checklist, only one (conclusions—statement of conclusions in coherence with the review findings) was reported adequately (proportion of adherence = 81.6%). The proportion of reporting other criteria ranged from 1.7% to 68.3%. For the four essential reporting items, 11 (9.2%) reviews specifically mentioned "harms" or other related terms, or the harm of interest in the review title; 2 (1.7%) specified how zero events were handled; 3 (2.5%) defined each harm addressed, how it was ascertained, and over what time period; and 9 (7.5%) described the assessment of possible causality.

In comparison, Cochrane reviews had better reporting with regard to the search (6.7% vs. 0%, $P = 0.04$), risk of bias across studies in methods section (16.7% vs. 0%, $P = 0.001$), study characteristics (30% vs. 10%, $P = 0.006$), results of individual studies (65% vs. 38.3%, $P = 0.003$), and risk of bias across studies in the results section (13.3% vs. 0%, $P = 0.004$). However, Cochrane reviews had poorer reporting with respect to the title (0% vs. 18.3%, $P = 0.001$), synthesis of results in the results section (1.7% vs. 13.3%, $P = 0.02$), and limitations (0% vs. 23.3%, $P < 0.001$).

3.2. Adherence to PRISMA checklist

Most systematic reviews met the requirements of the PRISMA checklist (Fig. 3 and Table 2). Among the 27 PRISMA items, 22 were adequately reported (proportion of adherence ≥80%). Four of the remaining five items were reported by most reviews, including description of protocol and registration (62.5%), presentation of full electronic search strategy for at least one database (68.3%), presentation of results regarding any assessment of risk of bias across studies (78.3%), presentation of results regarding additional analyses (69.2%), and discussion of limitations at study and outcome level and at review level (45.8%).

In comparison, Cochrane reviews were more likely to report a structured summary (Cochrane vs. non-Cochrane: 100% vs. 71.7%, $P < 0.001$), objectives (100% vs. 75%, $P < 0.001$), protocol and registration (100% vs. 25%, $P < 0.001$), search (88.3% vs. 48.3%, $P < 0.001$), data collection process (100% vs. 93.3%, $P = 0.04$), risk of bias within studies (100% vs. 86.7%, $P = 0.004$), and source of funding (86.7% vs. 66.7%, $P = 0.01$). Cochrane reviews were less likely to report data synthesis in their results section (probably because the individual studies were not possible to pool) (88.3% vs. 98.3%, $P = 0.03$) and limitations (1.7% vs. 90%, $P < 0.001$) in the Discussion section.

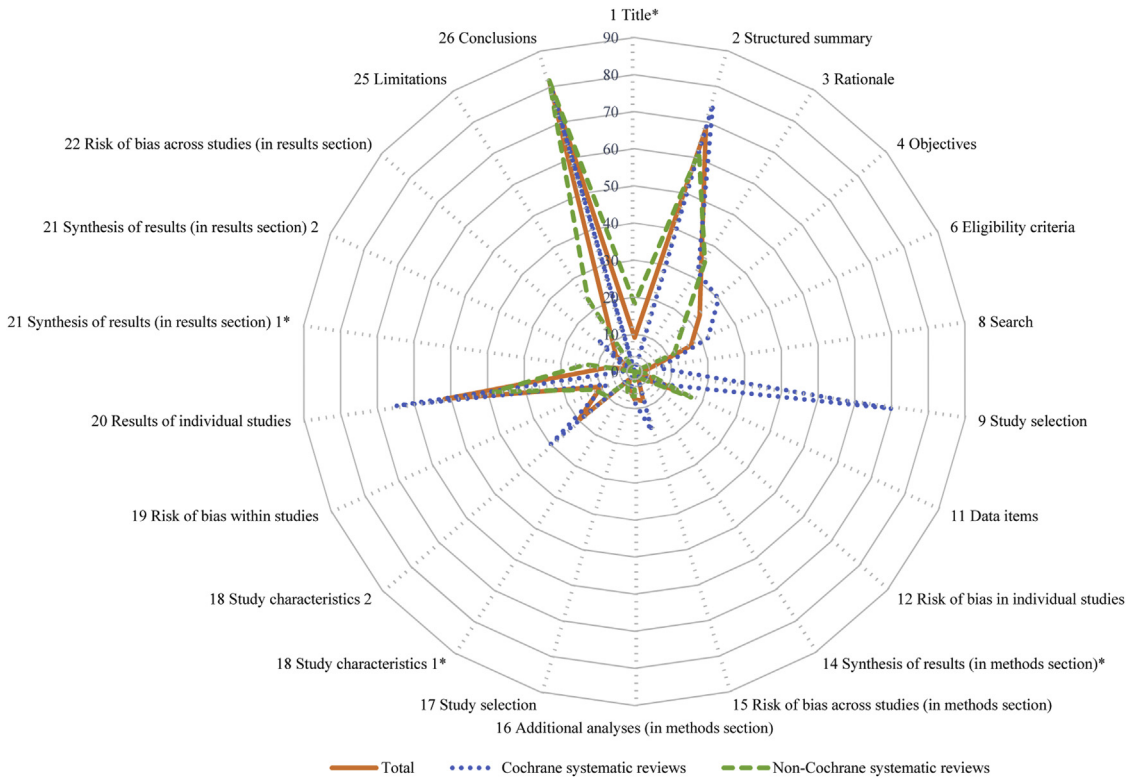

Fig. 2. Proportion of adherence to PRISMA harms checklist (%). *Essential reporting items, other items are desirable reporting items.

Table 2. Adherence of systematic review reporting

		PRISMA				PRISMA harms			
Section	Items	Total (%)	Cochrane SR (%)	Non-Cochrane SR (%)	*P* Value	Total (%)	Cochrane SR (%)	Non-Cochrane SR (%)	*P* Value
Title	1 Title[a]	116 (96.7)	60 (100)	56 (93.3)	0.12[b]	11 (9.2)	0	11 (18.3)	0.001
Abstract	2 Structured summary	103 (85.8)	60 (100)	43 (71.7)	<0.001	82 (68.3)	45 (75)	37 (61.7)	0.12
Introduction	3 Rationale	116 (96.7)	59 (98.3)	57 (95)	0.31[b]	40 (33.3)	19 (31.7)	21 (35)	0.7
	4 Objectives	105 (87.5)	60 (100)	45 (75)	<0.001	28 (23.3)	18 (30)	10 (16.7)	0.08
Methods	5 Protocol and registration	75 (62.5)	60 (100)	15 (25)	<0.001				
	6 Eligibility criteria	120 (100)	60 (100)	60 (100)	-	20 (16.7)	13 (21.7)	7 (11.7)	0.14
	7 Information sources	118 (98.3)	60 (100)	58 (96.7)	0.16[b]				0.55
	8 Search	82 (68.3)	53 (88.3)	29 (48.3)	<0.001	4 (3.3)	4 (6.7)	0 (0)	0.043
	9 Study selection	117 (97.5)	60 (100)	57 (95)	0.08[b]	2 (1.7)	0 (70)	2 (3.3)	0.16[b]
	10 Data collection process	116 (96.7)	60 (100)	56 (93.3)	0.04[b]				
	11 Data items	100 (83.3)	50 (83.3)	50 (83.3)	1	15 (12.5)	5 (8.3)	10 (16.7)	0.17
	12 Risk of bias in individual studies	113 (94.2)	59 (98.3)	54 (90)	0.052[b]	3 (2.5)	1 (1.7)	2 (3.3)	0.56
	13 Summary measures	111 (92.5)	53 (88.3)	58 (96.7)	0.08[b]				
	14 Synthesis of results[a]	113 (94.2)	54 (90)	59 (98.3)	0.052[b]	2 (1.7)	1 (1.7)	1 (1.7)	1.0[b]
	15 Risk of bias across studies	96 (80)	49 (81.7)	47 (78.3)	0.65	10 (8.3)	10 (16.7)	0 (0)	0.001
	16 Additional analyses	101 (84.2)	53 (88.3)	48 (80)	0.21	9 (7.5)	5 (8.3)	4 (6.7)	0.73[b]
Results	17 Study selection	116 (96.7)	56 (93.3)	60 (100)	0.12[b]	6 (5)	2 (3.3)	4 (6.7)	0.40[b]
	18 Study characteristics 1[a]	120 (100)	60 (100)	60 (100)	-	3 (2.5)	1 (1.7)	2 (3.3)	0.56[b]
	Study characteristics 2					24 (20)	18 (30)	6 (10)	0.006
	19 Risk of bias within studies	112 (93.3)	60 (100)	52 (86.7)	0.004	12 (10)	5 (8.3)	7 (11.7)	0.54
	20 Results of individual studies	116 (96.7)	57 (95)	59 (98.3)	0.31[b]	62 (51.7)	39 (65)	23 (38.3)	0.003
	21 Synthesis of results 1[a]	112 (93.3)	53 (88.3)	59 (98.3)	0.03[b]	9 (7.5)	1 (1.7)	8 (13.3)	0.02[b]
	Synthesis of results 2					2 (1.7)	2 (3.3)	0 (0)	0.16[b]
	22 Risk of bias across studies	94 (78.3)	46 (76.7)	48 (80)	0.66	8 (6.7)	8 (13.3)	0 (0)	0.004
	23 Additional analysis	83 (69.2)	41 (68.3)	42 (70)	0.84				
Discussion	24 Summary of evidence	120 (100)	60 (100)	60 (100)	-				
	25 Limitations	55 (45.8)	1 (1.7)	54 (90)	<0.001	14 (11.7)	0 (0)	14 (23.3)	<0.001
	26 Conclusions	120 (100)	60 (100)	60 (100)	-	98 (81.6)	49 (81.7)	49 (81.7)	1.0

(*Continued*)

Table 2. Continued

Section	Items	PRISMA				PRISMA harms			
		Total (%)	Cochrane SR (%)	Non-Cochrane SR (%)	*P* Value	Total (%)	Cochrane SR (%)	Non-Cochrane SR (%)	*P* Value
Funding	27 Funding	92 (76.7)	52 (86.7)	40 (66.7)	0.01				
Summarized scores	PRISMA or PRISMA harms scores[c]	24.5 (26, 30)	25 (23.5, 26)	24 (22, 25)	0.005	4 (2, 6)	4.5 (2, 7)	4 (2.5, 5)	0.29

Values in parentheses are percentages unless indicated otherwise.
[a] Essential reporting items from PRISMA harms checklist, other items are desirable reporting items.
[b] Fisher's exact test; others are Pearson's chi-squared test.
[c] Values are median (first quartile, third quartile) and *P* value are from Mann-Whitney U test.

3.3. Scores for the PRISMA and PRISMA harms checklist

The scores for the PRISMA harms checklist (23 items) were low (median 4, [first, third quartile: 2, 6]), for both Cochrane and non-Cochrane reviews (4.5 [2, 7] vs. 4 [2.5, 5]; $P = 0.29$). The score for the PRISMA checklist (27 items) was higher among Cochrane vs. non-Cochrane reviews (25 [23.5, 26] vs. 24 [22, 25]; $P = 0.005$).

For the PRISMA harms score, univariable analyses showed that publication in high-impact journals was associated with better reporting (Table 3). Multivariable linear regression analyses, however, showed no significant association for any study characteristic with reporting quality, likely because of low variability in PRISMA harms scores (Table 3).

For the total score of PRISMA, univariable analyses showed that Cochrane reviews, those published in high-impact journals, and government funding were associated with better reporting (Table 4). Multivariable linear regression analyses showed that Cochrane reviews (adjusted $\beta = 1.26$, 95% CI 0.22 to 2.31; $P = 0.018$) was associated with better reporting quality (Table 4).

4. Discussion

4.1. Findings and interpretations

In this cross-sectional survey, we found reporting about safety-specific information among drug systematic reviews was generally poor among Cochrane and non-Cochrane

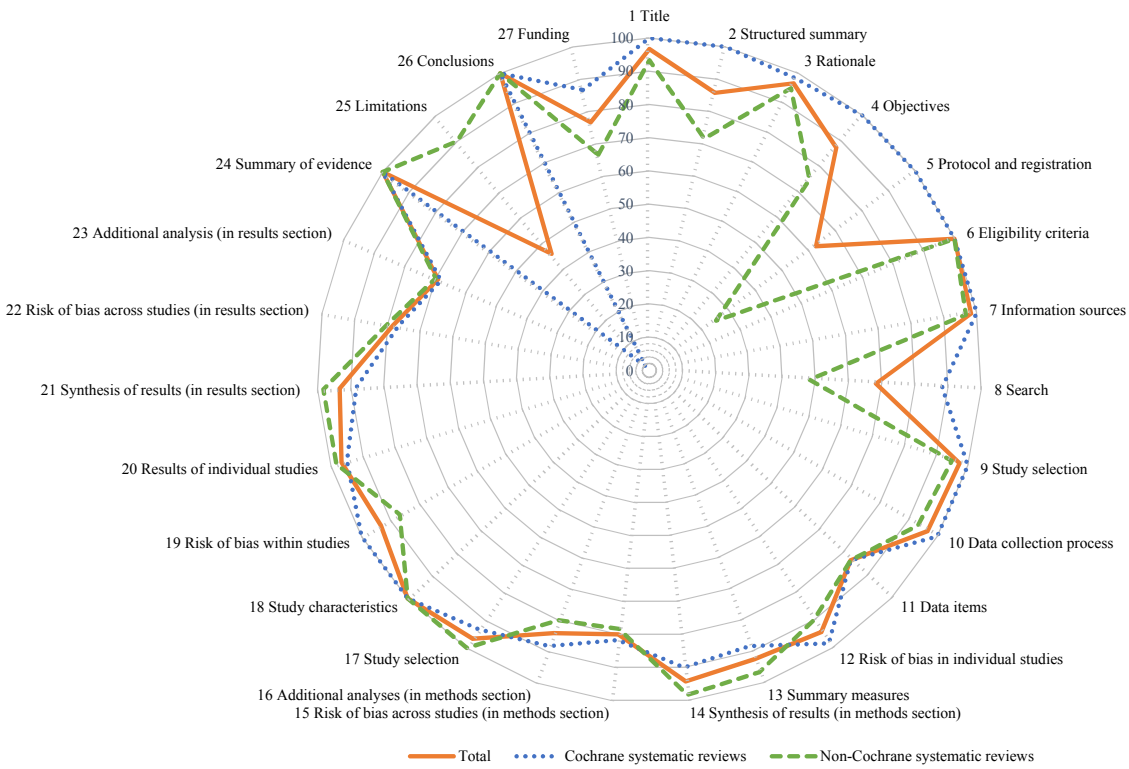

Fig. 3. Proportion of adherence to PRISMA checklist (%).

Table 3. Univariable and multivariable regression analysis of potential factors associated with reporting score measured by PRISMA harms checklist

	Univariable analysis		Multivariable analysis	
Study characteristics	**Coefficient**	***P* Value**	**Coefficient**	***P* Value**
Systematic review type (Cochrane vs. non-Cochrane SR)	0.52 (−0.4, 1.44)	0.27	0.77 (−0.36, 1.89)	0.18
Journal type (high-impact journals vs. lower-impact journals)	1.94 (−0.002, 3.88)	0.05	1.99 (−0.15, 4.13)	0.07
Systematic reviews included both RCTs and nonrandomized studies (yes vs. no)	0.82 (−0.71, 2.36)	0.29	0.87 (−0.68, 2.43)	0.27
Clinical specialty (medical vs. surgical)	0.08 (−1.02, 1.19)	0.88	−0.12 (−1.25, 1.00)	0.83
Source of funding (government vs. nongovernment)	0.38 (−0.54, 1.3)	0.42	−0.04 (−1.07, 1.00)	0.94
Significance of primary safety outcome (yes vs. no/not reported)	−0.85 (−1.86, 0.15)	0.10	−0.58 (−1.64, 0.47)	0.28

reviews. This also applied to the four essential PRISMA harm items (proportion of adherence ranging from 1.7% to 9.2%) and 19 nonessential items (proportion of adherence ranging from 1.7% to 81.6%). Our findings are consistent with a survey of systematic reviews assessing harms reporting for various health care interventions (adherence ranging from 13% to 62% [23]). The deficiency of reporting safety information may be explained, in part, because safety is not the primary aim of most reviews. We found that, in general, both Cochrane and non-Cochrane systematic reviews generally met PRISMA reporting recommendations—consistent with previous surveys [11,18,19]. We also found that Cochrane reviews were associated with better general reporting. The potential explanation is that Cochrane reviews often have mandatory reporting sections [34,35].

4.2. Strengths and limitations

Our study has several strengths. First, this was the first systematic survey to specifically investigate the quality of reporting of safety information among systematic reviews of drug therapy. Second, we randomly sampled systematic reviews from the core clinical journals. This collection represents a group of leading journals across different medical and surgical specialties. Thus, our findings are likely to be generalizable. Third, we included Cochrane reviews and non-Cochrane reviews. Fourth, we used rigorous systematic survey methods including explicit eligibility criteria, and standardized, pilot-tested forms accompanied by written instructions for study screening and data extraction.

Our study also has limitations. First, the reviews we included were published in 2015, a year before the PRISMA harms checklist was published, which means that no review authors would have been aware of this checklist. However, a high-profile 2014 review of limitations of harms reporting among systematic reviews that were the basis for the PRISMA harms checklist [23] highlighted the essential reporting issues before publication of the PRISMA harms statement. Second, as it may take up several years to see a reporting guideline being fully implemented into practice, our study did not assess the implementation of PRISMA harms checklist, and we investigated the quality of reporting of safety information among drug systematic reviews predating this checklist, which will be a helpful baseline from which to measure improvement in the reporting of safety. Third, the use of an aggregate scoring scheme for PRISMA and

Table 4. Univariable and multivariable regression analysis of potential factors associated with reporting scores measured by PRISMA checklist

	Univariable analysis		Multivariable analysis	
Study characteristics	**Coefficient**	***P* Value**	**Coefficient**	***P* Value**
Systematic review type (Cochrane vs. non-Cochrane SR)	1.17 (0.31, 2.02)	0.01	1.26 (0.22, 2.30)	0.018
Journal type (high-impact journals vs. lower-impact journals)	1.09 (−0.77, 2.96)	0.25	1.61 (−0.38, 3.59)	0.11
Systematic reviews included both RCTs and nonrandomized studies (yes vs. no)	0.63 (−0.83, 2.09)	0.40	0.79 (−0.65, 2.23)	0.28
Clinical specialty (medical vs. surgical)	0.26 (−0.79, 1.31)	0.62	−0.01 (−1.05, 1.04)	0.99
Source of funding (government vs. nongovernment)	1.14 (0.29, 2)	0.01	0.59 (−0.37, 1.56)	0.22
Significance of primary safety outcome (yes vs. no/not reported)	0.003 (−0.96, 0.97)	0.99	0.41 (−0.57, 1.39)	0.41

PRISMA harms may not be optimal, given the potential difference in item importance. Finally, as our survey excluded individual participant data meta-analyses, network meta-analyses, and systematic reviews reported as a research letter, the findings from our study may not be generalizable to these reviews.

4.3. Suggestions for reporting safety information among drug systematic reviews

Adverse effects are important issues in drug trials and subsequent meta-analyses. In drug trials, the assessment of drug safety and benefit-risk profiles is often limited, partially because of the inadequacy of the methodology in the planning, collection, analysis, reporting, and interpretation of adverse event data [36−38]. Likewise, in drug systematic reviews, authors usually focus on efficacy data and less on safety data. This survey highlights the need for systematic review authors to better report safety information among drug systematic reviews.

In the future, the authors of drug systematic reviews should adhere to the PRISMA harms checklist for reporting of drug safety information, and journals should consider formally endorsing the PRISMA harms statement. According to PRISMA harms checklist, the review authors are encouraged to include more details, both in the methods and results sections, about drug safety. They may also consider expanding discussion about the findings on drug safety or reporting these details in an Appendix.

5. Conclusions

Although both Cochrane and non-Cochrane systematic reviews generally meet reporting criteria proposed by the PRISMA statement, the reporting of safety-specific information among drug systematic reviews was poor predating PRISMA harms checklist. Our findings suggested a strong need to use the PRISMA harms checklist for reporting safety among drug systematic reviews. Both systematic reviewers and journal editors should pay more attention on the reporting of such information.

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Authors' contributions: X.S. and L.L. conceived the study. X.S. acquired the funding. L.L. and X.S. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. L.L., C.X., K.D., X.Z., and Z.L. conducted the literature searches and extracted the data. L.L., X.S., and Y.R. conducted the analysis and interpreted the data. L.L. and X.S. drafted the article. X.S., L.L., J.W.B., C.X., K.D., X.Z., Z.L., Y.R., and K.Z. critically revised the article. X.S. is the guarantor.

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Supplementary data

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References

[1] McIntosh HM, Woolacott NF, Bagnall AM. Assessing harmful effects in systematic reviews. BMC Med Res Methodol 2004;4:19.
[2] Berlin JA, Crowe BJ, Whalen E, Xia HA, Koro CE, Kuebler J. Meta-analysis of clinical trial safety data in a drug development program: answers to frequently asked questions. Clin Trials 2013;10:20−31.
[3] Loke YK, Price D, Herxheimer A. Systematic reviews of adverse effects: framework for a structured approach. BMC Med Res Methodol 2007;7(1):32.
[4] Sutton AJ, Cooper NJ, Lambert PC, Jones DR, Abrams KR, Sweeting MJ. Meta-analysis of rare and adverse event data. Expert Rev Pharmacoecon Outcomes Res 2002;2(4):367−79.
[5] Bhaumik DK, Amatya A, Normand SL, Greenhouse J, Kaizar E, Neelon B, et al. Meta-analysis of rare binary adverse event data. J Am Stat Assoc 2012;107:555−67.
[6] Singh S, Loke YK. Drug safety assessment in clinical trials: methodological challenges and opportunities. Trials 2012;13:138.
[7] Ioannidis JP. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. Arch Intern Med 2009;169:1737−9.
[8] Li H, Liu DH, Chen LL, Zhao Q, Yu YZ, Ding JJ, et al. Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. Antimicrob Agents Chemother 2014;58:511−7.
[9] Shahbazi F, Dashti-Khavidaki S. Colistin: efficacy and safety in different populations. Expert Rev Clin Pharmacol 2015;8(4):423−48.
[10] Zhang H, Han J, Zhu YB, Lau WY, Schwartz ME, Xie GQ, et al. Reporting and methodological qualities of published surgical meta-analyses. J Clin Epidemiol 2016;70:4−16.
[11] Xia L, Xu J, Guzzo TJ. Reporting and methodological quality of meta-analyses in urological literature. PeerJ 2017;5:e3129.
[12] Wasiak J, Tyack Z, Ware R, Goodwin N, Faggion CM Jr. Poor methodological quality and reporting standards of systematic reviews in burn care management. Int Wound J 2017;14(5):754−63.
[13] Tian J, Zhang J, Ge L, Yang K, Song F. The methodological and reporting quality of systematic reviews from China and the USA are similar. J Clin Epidemiol 2017;85:50−8.
[14] Oh JH, Shin WJ, Park S, Chung JS. Reporting and methodologic evaluation of meta-analyses published in the anesthesia literature according to AMSTAR and PRISMA checklists: a preliminary study. Korean J Anesthesiol 2017;70(4):446−55.
[15] Nagendrababu V, Pulikkotil SJ, Sultan OS, Jayaraman J, Peters OA. Methodological and reporting quality of systematic reviews and meta-analyses in endodontics. J Endod 2018;44(6):903−13.
[16] Ma B, Qi GQ, Lin XT, Wang T, Chen ZM, Yang KH. Epidemiology, quality, and reporting characteristics of systematic reviews of acupuncture interventions published in Chinese journals. J Altern Complement Med 2012;18(9):813−7.
[17] Ge L, Tian JH, Li YN, Pan JX, Li G, Wei D, et al. Association between prospective registration and overall reporting and

methodological quality of systematic reviews: a meta-epidemiological study. J Clin Epidemiol 2018;93:45−55.
[18] Liu P, Qiu Y, Qian Y, Chen X, Wang Y, Cui J, et al. Quality of meta-analyses in major leading gastroenterology and hepatology journals: a systematic review. J Gastroenterol Hepatol 2017;32:39−44.
[19] Zhi X, Zhang Z, Cui J, Zhai X, Chen X, Su J. Quality of meta-analyses in major leading orthopedics journals: a systematic review. Orthop Traumatol Surg Res 2017;103(8):1141−6.
[20] Golder S, Loke YK, Zorzela L. Some improvements are apparent in identifying adverse effects in systematic reviews from 1994 to 2011. J Clin Epidemiol 2013;66:253−60.
[21] Golder S, Loke Y, McIntosh HM. Poor reporting and inadequate searches were apparent in systematic reviews of adverse effects. J Clin Epidemiol 2008;61:440−8.
[22] Cornelius VR, Perrio MJ, Shakir SA, Smith LA. Systematic reviews of adverse effects of drug interventions: a survey of their conduct and reporting quality. Pharmacoepidemiol Drug Saf 2009;18(12):1223−31.
[23] Zorzela L, Golder S, Liu Y, Pilkington K, Hartling L, Joffe A, et al. Quality of reporting in systematic reviews of adverse events: systematic review. BMJ 2014;348:f7668.
[24] Ernst E, Pittler MH. Assessment of therapeutic safety in systematic reviews: literature review. BMJ 2001;323(7312):546.
[25] Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ 2016;352:i157.
[26] Green S, Higgins JPT, Alderson P, Clarke M, Mulrow CD, Oxman AD. Introduction. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. Cochrane Collaboration; 2011. Available at: http://handbook-5-1.cochrane.org/. Accessed 20 June 2017.
[27] U.S. National Library of Medicine. Abridged index medicus (AIM or ‘‘Core Clinical’’) journal titles. Available at: http://www.nlm.nih.gov/bsd/aim.html. Accessed January 16, 2016.
[28] Akl EA, Kahale LA, Agarwal A, Al-Matari N, Ebrahim S, Alexander PE, et al. Impact of missing participant data for dichotomous outcomes on pooled effect estimates in systematic reviews: a protocol for a methodological study. Syst Rev 2014;3:137.
[29] Yu J, Li X, Li Y, Sun X. Quality of reporting in surgical randomized clinical trials. Br J Surg 2017;104:296−303.
[30] Thomson Reuters. ISI Web of knowledge website. Available at: www.isiwebofknowledge.com. Accessed July 27, 2016.
[31] Bala MM, Akl EA, Sun X, Bassler D, Mertz D, Mejza F, et al. Randomized trials published in higher vs. lower impact journals differ in design, conduct, and analysis. J Clin Epidemiol 2013;66:286−95.
[32] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[33] Akinwande MO, Dikko H, Samson A. Variance inflation factor: as a condition for the inclusion of suppressor variable(s) in regression analysis. Open J Stat 2015;5:754−67.
[34] Green S, Higgins JPT. Preparing a cochrane review. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. Cochrane Collaboration; 2011. Available at: http://handbook-5-1.cochrane.org/. Accessed 20 June 2017.
[35] Moseley AM, Elkins MR, Herbert RD, Maher CG, Sherrington C. Cochrane reviews used more rigorous methods than non-Cochrane reviews: survey of systematic reviews in physiotherapy. J Clin Epidemiol 2009;62:1021−30.
[36] Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. Arch Intern Med 2009;169:1756−61.
[37] Loke YK, Derry S. Reporting of adverse drug reactions in randomised controlled trials - a systematic survey. BMC Clin Pharmacol 2001;1:3.
[38] Yazici Y. Some concerns about adverse event reporting in randomized clinical trials. Bull NYU Hosp Jt Dis 2008;66(2):143−5.