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Has the reporting quality of published randomised controlled trial protocols improved since the SPIRIT statement? A meta-epidemiological study

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Title
Has the reporting quality of published randomised controlled trial protocols improved since the SPIRIT statement? A meta-epidemiological study

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ABSTRACT

OBJECTIVES

To determine the reporting quality of published randomised controlled trial (RCT) protocols before and after the *Standard Protocol Items: Recommendations for Interventional Trials* (SPIRIT) statement, and whether author, trial or journal factors are associated with the reporting quality of published RCT protocols.

DESIGN

Meta-epidemiological study.

DATA SOURCES

MEDLINE, EMBASE and CENTRAL were electronically searched using optimised search strategies.

ELIGIBILITY CRITERIA

Protocols written for an RCT of living humans, published in full-text in a peer-reviewed journal, and published in the English language.

MAIN OUTCOME

Primary outcome was the overall proportion of checklist items which were adequately reported in RCT protocols published before and after the SPIRIT statement, expressed as a percentage.

RESULTS

300 RCT protocols were retrieved; 150 from the period immediately before the SPIRIT statement (9/07/2012 – 28/12/2012), and 150 from a recent period after the SPIRIT statement (25/01/2019 – 20/03/2019). 47.9% (95% CI, 46.5-49.3%) of checklist items were adequately reported in RCT protocols before the SPIRIT statement, and 56.7% (95% CI, 54.9-58.5%) after the SPIRIT statement. This represents a mean improvement in the proportion of checklist items adequately reported since the SPIRIT statement of 8.8% (95% CI, 6.6-11.1%; p<0.0001). 51% of checklist items had a significant improvement in adequate reporting after the SPIRIT statement and 11.3% had a significant deterioration. The factors associated with higher reporting quality of RCT protocols in multiple regression analysis were author qualification in epidemiology or statistics, multicentre trials, longer protocol word length and journal policy of compliance with the SPIRIT statement.

CONCLUSIONS

There has been significant improvement in the reporting quality of RCT protocols since the SPIRIT statement, although a substantial proportion of checklist items remain poorly reported. Continued and concerted efforts are required by journals, editors, reviewers and investigators to improve the completeness and transparency of under-reported aspects of RCT protocols.

Keywords: randomised controlled trial protocol; reporting quality; completeness; SPIRIT statement

Article summary

Strengths and limitations of this study

- We conducted a meta-epidemiological study assessing the reporting quality of two equal, arbitrary samples of 150 RCT protocols published before and after the SPIRIT statement.
- We found a significant improvement in the completeness of RCT protocols published since the SPIRIT statement.
- The factors associated with higher reporting quality of RCT protocols in multiple regression analysis were one or more authors with qualifications in epidemiology or statistics, multicentre trials, longer protocol word length and journal policy of compliance with the SPIRIT statement.
- The associations found in this study may not be causal, and the improvements in reporting quality may be due to underlying secular trends whereby RCT protocol quality improves over time, unrelated to the introduction of the SPIRIT statement.
- However, the association between specific journal requirement for the SPIRIT statement, and reporting to that requirement, suggests some degree of causation.

Introduction

Background

Randomised controlled trial (RCT) protocols should enable prospective assessment of trial methodology, scientific integrity, ethical standards and safety considerations, public documentation of changes during a trial, and retrospective validation of trial conduct.[1] A well-written RCT protocol is an essential component of a high-quality RCT.

However, studies have frequently reported inconsistencies between RCT protocols and corresponding final publications,[2-5] and deficiencies in the content of RCT protocols.[4-12] Incomplete, inaccurate or poor quality reporting of RCT protocols can result in research waste and selective outcome reporting and other biases. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement was published in January 2013 and describes a 33-item minimum set of scientific, methodological, ethical and administrative components that should be routinely detailed in a trial protocol.[1] It aims to address issues with the completeness and transparency of many trial protocols by providing a standardised structure to trial plans, promoting strict accountability to trial conduct, improving the reliability and validity of trial outcomes, and facilitating the assessment of risk of bias, methodological quality and reporting quality.[1]

Objectives

The impact of the SPIRIT statement on the reporting quality of RCT protocols in all areas of health research is unknown. The primary objectives of this study are to 1) determine the reporting quality of published RCT protocols before and after the SPIRIT statement, and 2) determine whether author, trial or journal factors are associated with the reporting quality of published RCT protocols.

Methods

Study design

We conducted a meta-epidemiological study in accordance with a prospectively registered protocol (PROSPERO CRD42019126522). The reporting of this study is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13]

Setting

RCT protocols were identified by electronically searching the bibliographic databases MEDLINE, EMBASE and CENTRAL using a search strategy formulated by an experienced medical librarian (Appendix A). All searches were performed independently by two investigators on 29 March 2019.

Included protocols

RCT protocols were eligible for inclusion if they were (a) written for an RCT of living humans, (b) published in full-text in a peer-reviewed journal, and (c) published in the English language. RCT protocols were excluded if they were (a) registered on a clinical trial registry but not published in a peer-reviewed journal, or (b) reported any study results.

We retrieved two equal, arbitrary samples of 150 RCT protocols published before and after the SPIRIT statement. The sample of 150 RCT protocols published immediately before the SPIRIT statement were retrieved by searching for RCT protocols published from 28 December 2012 and proceeding retrospectively until 150 eligible RCT protocols were selected. Similarly, the sample of 150 RCT protocols published recently since the SPIRIT statement were selected by searching for RCT protocols published from 20 March 2019 and proceeding retrospectively until 150 eligible RCT protocols were retrieved. The titles and abstracts of all retrieved RCT protocols were independently screened by two investigators and the full texts of relevant RCT protocols were independently assessed for eligibility by two investigators. Any disagreements were resolved by discussion between the two investigators and, if required, arbitration by a third investigator. All eligible RCT protocols were imported into Endnote X9 (Clarivate Analytics) software. Duplicates were removed by manually screening by author, year, title and journal.

Variables

The primary variables of interest were the checklist items from the SPIRIT statement, defined in the SPIRIT statement explanation and elaboration.[1] A data extraction form was developed based on the checklist items from the SPIRIT statement. Two checklist items (items 4 and 12) were subcategorised to reflect binary criterion and provide appropriate granularity. The checklist item 'funding' was split into 'funding source', defined as sources of financial, material and other support (e.g. name and location of the funder) and 'funding type', defined as type of financial, material and other support (e.g. funds, equipment, drugs, services). The checklist item 'outcomes' was split into 'primary, secondary and other outcomes' (e.g. the specific measurement variable, analysis metric, method of aggregation and time point for each outcome), and 'explanation of clinical relevance of chosen efficacy and harm outcomes'. This resulted in a total of 53 checklist items and each item was assessed as either adequate or inadequate/unclear. The data extraction form and assessment criteria were independently piloted for ten randomly selected RCT protocols by four investigators. Disagreements were resolved by discussion between the four investigators and the definitions of adequate and inadequate/unclear for each checklist item were revised accordingly.

The secondary variables of interest related to author, trial and journal factors. Author factors included the number of authors per protocol and the presence of authors with qualifications in epidemiology or statistics (defined as one or more authors with a degree in clinical epidemiology, public health or biostatistics) per protocol. Where authors' qualifications were not reported in the publication, affiliation to a clinical epidemiology, public health or biostatistics department was used as proxy. Trial factors included the total planned sample size, centre status (e.g. multicentre or single centre) and protocol word length greater or less than 3,500. Protocol report of compliance with the SPIRIT statement and journal policy of compliance with the SPIRIT statement in the instructions to authors on the journal website, as of 2019, was also collected for RCT protocols published after the SPIRIT statement.

Data measurement

Data extraction was performed on the 300 RCT protocols. Data extraction of the first 100 RCT protocols was independently duplicated by two investigators (ZWT and HL) and data extraction of the remaining 200 RCT protocols was then completed once between two investigators (ZWT and HL). Any issues with data extraction were discussed at fortnightly roundtable meetings attended by five investigators. If a checklist item was assessed as not applicable to an RCT protocol, it was removed from the total denominator of checklist items for that RCT protocol.

Statistical methods

We performed descriptive analysis of the primary outcome by calculating the proportion (percentage) of checklist items which were adequately reported in RCT protocols. This was considered a measure of the reporting quality of RCT protocols. We also calculated the proportion (percentage) of RCT protocols which adequately reported each checklist item. Inter-rater agreement and kappa scores were calculated for the 100 RCT protocols with duplicate data extraction. We performed exploratory multiple linear regression analysis to determine whether author, trial or journal factors were associated with the reporting quality of RCT protocols. Stepwise backward linear regression was performed, using $p < 0.25$ as the criterion for inclusion in a multiple regression model, and R^2 as the criterion for removal of variables in the backward elimination model. A p value < 0.05 was considered statistically significant, and the R^2 value was used as a measure of the final model goodness of fit. All statistical analyses were stratified by publication before or after the SPIRIT statement and were performed using Stata software (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LP).

Patient and public involvement

As this was a study of RCT protocols, there was no patient or public involvement in the conception, design or conduct of the study, or the writing or editing of this paper.

Results

Included protocols

A total of 300 RCT protocols were retrieved; 150 from before the SPIRIT statement (9 July 2012 – 28 December 2012) and 150 from after the SPIRIT statement (25 January 2019 – 20 March 2019). In the full-text eligibility assessment of RCT protocols published before the SPIRIT statement, 25 studies were excluded because they did not describe an RCT protocol, two studies were excluded because they had been retracted, one study was excluded because it included study results, and one study was excluded because it was not published in full-text. In the full-text eligibility assessment of RCT protocols published after the SPIRIT statement, six studies were excluded because they did not describe an RCT protocol. All excluded studies were replaced with eligible studies. The final 300 RCT protocols were published across 45 peer-reviewed journals, with 46% (138/300) published in *Trials*.

The inter-rater agreement for data extraction of the first 100 RCT protocols ranged from 64.5% to 100%, with Kappa scores provided in Appendix B. The checklist items with the lowest and highest inter-rater agreement were 'statistical methods: statistical methods to handle missing data' and 'background and rationale: explanation for choice of comparators', respectively. The checklist items with the lowest and highest Kappa scores were 'research ethics approval' and 'background and rationale: explanation for choice of comparators', respectively.

Descriptive data

Author and trial characteristics were similar before and after the SPIRIT statement (Table 1).

Table 1. **Author and trial characteristics before and after the SPIRIT statement**

	Before the SPIRIT statement	After the SPIRIT statement
Author characteristics		
Authors per protocol (median, range)	8, 1-90	8, 2-80
Protocols with one or more authors with qualifications in epidemiology or statistics (n, %)	50, 33.3%	48, 32%
Trial characteristics		
Total planned sample size (median)	214.5	200
Protocols describing a multicentre trial (n, %)	70, 46.7%	64, 42.7%
Protocols longer than 3500 words (n, %)	105, 70%	106, 70.7%

Of RCT protocols published after the SPIRIT statement, 42.7% (64/150) reported compliance with the SPIRIT statement, and 88% (132/150) were published in a peer-reviewed journal with a policy of compliance with the SPIRIT statement.

Outcome data

Of the 150 RCT protocols published before the SPIRIT statement, an average of 47.9% of checklist items per RCT protocol were adequately reported (95% CI, 46.5-49.3%). Comparably, of the 150 RCT protocols published after the SPIRIT statement, an average of 56.7% of checklist items were adequately reported (95% CI, 54.9-58.5%). This represents a mean improvement in the proportion of checklist items adequately reported since the SPIRIT statement of 8.8% (95% CI, 6.611.1%; p<0.0001).

None of the 300 RCT protocols adequately reported all checklist items from the SPIRIT statement.

Of the 53 checklist items, 21 (40%) had a significant increase (p<0.05) in adequate reporting since the SPIRIT statement (Figure 1) and 6 (11.3%) had a significant decrease (p<0.05) in adequate reporting since the SPIRIT statement (Appendix C). 23 checklist items were inadequately or not reported in more than half of all RCT protocols (Figure 2). These were 'protocol version', 'sponsor's contact information', 'role of sponsor and funders', 'composition and roles of committees', 'interventions: criteria for discontinuation or modification', 'interventions: strategies to improve adherence', 'interventions: concomitant care', 'strategies for recruitment', 'implementation', 'emergency unblinding', 'data collection methods: plans to promote participant retention', 'statistical

method: method for additional analyses', 'composition of data monitoring committee', 'description of interim analyses and stopping guidelines', 'frequency and procedures for auditing', 'protocol amendments', 'consent or assent: ancillary studies', 'access to data', 'ancillary and post-trial care', 'authorship eligibility guidelines and any intended use of professional writers', 'access to full protocol, participant-level data set, and statistical code', 'informed consent materials' and 'biological specimens'. Only one checklist item was adequately reported in all 300 RCT protocols – 'background and rationale: description and justification of research question'. No checklist items were inadequately or not reported in all 300 RCT protocols.

Table 2 shows the multiple regression analysis of the association between author, trial and journal factors and the reporting quality of randomised controlled trial (RCT) protocols. Self-reported compliance with the SPIRIT statement was not associated with actual compliance with the SPIRIT statement. However, journal policy of compliance with the SPIRIT statement was associated with significantly improved reporting quality.

Table 2. **Multiple regression analysis of author, trial and journal characteristics associated with the reporting quality of RCT protocols**

	Increase in proportion of adequately reported checklist items from the SPIRIT statement	**p-value**
Author characteristics		
Number of authors per protocol	0.2%	0.004
Protocols with one or more authors with qualifications in epidemiology or statistics	2.6%	0.016
Trial characteristics		
Protocols describing a multicentre trial	4.6%	0.000
Protocols longer than 3500 words	6.5%	0.000
Protocols reporting compliance with the SPIRIT statement	-	0.145
Journal characteristics		
Journal policy of compliance with the SPIRIT statement	6.2%	0.000

Discussion

Key results

We assessed the reporting quality of published RCT protocols before and after the SPIRIT statement. We found a significant improvement in the completeness of RCT protocols published since the SPIRIT statement. Although our study suggests significant improvements in the reporting quality of RCT protocols published after the SPRIT statement, these significant improvements were only seen in 40% (21/53) of checklist items, and there were no RCT protocols in which all checklist items were complete.

Limitations

Our study is limited by the lack of blinding of data collectors to the date of publication of RCT protocols, introducing the possibility for researcher bias. This was minimised through strict adherence to pre-defined parameters for the assessment of the checklist items from the SPIRIT statement, fortnightly roundtable meetings, and duplication of data collection for one third of RCT protocols. Our study was also limited by the inclusion of only RCT protocols published in the English language.

The associations found in this study may not be causal, and the improvements in reporting quality may be due to underlying secular trends whereby RCT protocol quality improves over time, unrelated to the introduction of the SPIRIT statement. However, the association between specific journal requirement for the SPIRIT statement, and reporting to that requirement, suggests some degree of causation.

Interpretation

Despite the significant improvement in the reporting quality of RCT protocols suggested by our study, three checklist items from the SPIRIT statement were inadequately or not reported by greater than 90% of RCT protocols: 'consent or assent: ancillary studies', 'dissemination policy: authorship eligibility guidelines and any intended use of professional writers' and 'informed consent materials'.

The low completeness of checklist item 'consent or assent: ancillary studies' may be related to a misperception by authors that it is not necessary to report the decision that participant data or biological specimens will not be used in ancillary studies. However, deciding and reporting on the provisions of additional consent for ancillary studies is important, particularly given the increasing emphasis on data sharing plans. A similar sentiment may explain the low completeness of checklist item 'informed consent materials: model consent form and other related documentation given to participants and authorized surrogates', as authors may consider it sufficient to describe a plan to obtain informed consent and not necessary to provide the model consent form. However, providing the model consent form is important in determining that the relevant information is delivered with sufficient detail at an appropriate literacy level for the target population. Additionally, the low completeness of checklist item 'dissemination policy: authorship eligibility guidelines and any intended use of professional writers' may be underpinned by an underappreciation of the importance of disclosing the use of professional writers. A study of industry-initiated RCTs reported that 91% of 44 RCT protocols had evidence of ghost authorship.[11]

The factors associated with higher reporting quality of RCT protocols in multiple regression analysis were one or more authors with qualifications in epidemiology or statistics, multicentre trials, longer protocol word length and journal policy of compliance with the SPIRIT statement. The association between author qualification in epidemiology or statistics and higher reporting quality has previously been reported [14] and may be related to education and training in the importance of transparency and to experience in writing and reporting RCT protocols. In a similar way, the association between multicentre trials and higher reporting quality may be explained by larger nature of these studies and, by extension, the greater level of support available to these studies for writing the protocol and the greater importance of transparently and completely reporting the protocol. Additionally, the association between longer protocol word lengths and higher reporting quality may be underpinned by the capacity to more completely describe a planned RCT with more allowed words. This would support a more discretionary, individualised approach to determining appropriate word lengths of RCT protocols, rather than arbitrary, blanket cut-offs.

Interestingly, protocol report of compliance with the SPIRIT statement was not a significant predictor of reporting quality after adjusting for journal policy of compliance with the SPIRIT statement. This suggests that author self-report of compliance with the SPIRIT statement cannot be relied upon as a proxy indicator of reporting quality. Rather, the association between journal policy of compliance with the SPIRIT statement and higher reporting quality supports the role of journals and editors in improving the completeness and transparency of RCT protocols.

The findings from our research expand on those of Gao et al. (2016), who assessed the reporting quality of 142 RCT protocols in acupuncture using the checklist items from the SPIRIT statement.[15] However, we found a substantially larger number of checklist items whose completeness significantly improved after the SPIRIT statement (5 in Gao et al. (2016) and 21 in our study) [15]. This difference may be explained by the time since the SPIRIT statement; while Gao et al. (2016) assessed RCT protocols published 1-2 years after the SPIRIT statement, our study assessed RCT protocols published at 6-7 years after the SPIRIT statement. This could suggest increasing awareness and adoption of the SPIRIT statement over time. More recently, Yang et al. (2018) assessed the reporting quality of 126 trial protocols in anaesthesia against the SPIRIT statement, and found no significant improvement in the completeness of trial protocols published after the SPIRIT statement and substantially more checklist items which were inadequately or not reported by greater than 90% of included trial protocols (18 by Yang et al. (2018) and 3 in our study). However, their findings were limited by the small sample size of 18 trial protocols from after the SPIRIT statement.[16]

Overall, there remains substantial opportunity for further improvement. A study of emergency medicine journals found that reporting guidelines, including the SPIRIT statement, were endorsed infrequently,[17] and a scoping review of systematic reviews of adherence to other reporting

guidelines reported insufficient adherence.[18] These findings suggest that the challenges to improving adherence to the SPIRIT statement are shared with other reporting guidelines. The focus should be on increasing the awareness of the SPIRIT statement throughout the research community, particularly amongst trial investigators, and promoting the adoption of the SPIRIT statement in the editorial community, specifically by advocating for mandated adherence to reporting guidelines. Improving the reporting quality of RCT protocols is necessary to improve the completeness and transparency of RCTs, and, by extension, the validity and reliability of RCT outcomes which ultimately contribute to informing patient care. It is likely that continued and concerted efforts by journals, editors, reviewers and investigators to advocate for adherence to the SPIRIT statement would improve the completeness and transparency of under-reported aspects of RCT protocols.

Contributorship statement: The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ZWT contributed to the full text screening of protocols, pilot study, data collection, data analysis and interpretation, and manuscript revision. ACT contributed to the data interpretation, writing of the manuscript, and manuscript revision. SA contributed to the study concept and design, and manuscript revision. HL contributed to the full text screening of protocols, pilot study, and data collection. JT and MS contributed to the protocol searches and abstract screening of protocols. All authors met the ICMJE criteria for authorship and contributed to the revision of the manuscript. ZWT is guarantor. The corresponding author testifies that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Not applicable. This is a meta-epidemiological study of publicly available, published RCT protocols.

Data sharing: No additional data available.

Transparency statement: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned and registered have been explained.

Figure captions:
Figure 1. Checklist items with a significant increase in adequate reporting after the SPIRIT statement
Figure 2. Completeness of RCT protocols by checklist items, before and after the SPIRIT statement

References

1. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj. 2013;346:e7586.
2. Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. Jama. 2004;291(20):2457-65.
3. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PLoS ONE. 2008;3(8):e3081.
4. Hernandez AV, Steyerberg EW, Taylor GS, Marmarou A, Habbema JD, Maas AI. Subgroup analysis and covariate adjustment in randomized clinical trials of traumatic brain injury: a systematic review. Neurosurgery. 2005;57(6):1244-53; discussion -53.
5. Chan AW, Hrobjartsson A, Jorgensen KJ, Gotzsche PC, Altman DG. Discrepancies in sample size calculations and data analyses reported in randomised trials: comparison of publications with protocols. Bmj. 2008;337:a2299.
6. Pildal J, Chan AW, Hrobjartsson A, Forfang E, Altman DG, Gotzsche PC. Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study. Bmj. 2005;330(7499):1049.
7. Mhaskar R, Djulbegovic B, Magazin A, Soares HP, Kumar A. Published methodological quality of randomized controlled trials does not reflect the actual quality assessed in protocols. J Clin Epidemiol. 2012;65(6):602-9.
8. Hrobjartsson A, Pildal J, Chan AW, Haahr MT, Altman DG, Gotzsche PC. Reporting on blinding in trial protocols and corresponding publications was often inadequate but rarely contradictory. J Clin Epidemiol. 2009;62(9):967-73.
9. Scharf O, Colevas AD. Adverse event reporting in publications compared with sponsor database for cancer clinical trials. J Clin Oncol. 2006;24(24):3933-8.
10. Al-Marzouki S, Roberts I, Evans S, Marshall T. Selective reporting in clinical trials: analysis of trial protocols accepted by The Lancet. Lancet. 2008;372(9634):201.
11. Gotzsche PC, Hrobjartsson A, Johansen HK, Haahr MT, Altman DG, Chan AW. Ghost authorship in industry-initiated randomised trials. 2007;1(1):e19.
12. Lundh A, Krogsboll LT, Gotzsche PC. Access to data in industry-sponsored trials. Lancet. 2011;378(9808):1995-6.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9, W64.
14. Adie S, Harris IA, Naylor JM, Mittal R. Are outcomes reported in surgical randomized trials patient-important? A systematic review and meta-analysis. Can J Surg. 2017;60(2):86-93.
15. Gao L, Sha T, Chen B, Li M, Pan X, Chen Z, et al. Study protocols on randomized clinical trials of acupuncture: An assessment of reporting quality with the SPIRIT statement. European Journal of Integrative Medicine. 2016;8(6):881-7.
16. Yang L, Chen S, Yang D, Li J, Wu T, Zuo Y. A quality analysis of clinical anaesthesia study protocols from the Chinese clinical trials registry according to the SPIRIT statement. Oncotarget. 2018;9(37):24830-6.
17. Sims MT, Henning NM, Wayant CC, Vassar M. Do emergency medicine journals promote trial registration and adherence to reporting guidelines? A survey of "Instructions for Authors". Scand J Trauma Resusc Emerg Med. 2016;24(1):137.
18. Samaan Z, Mbuagbaw L, Kosa D, Borg Debono V, Dillenburg R, Zhang S, et al. A systematic scoping review of adherence to reporting guidelines in health care literature. Journal of Multidisciplinary Healthcare. 2013;6:169-88.

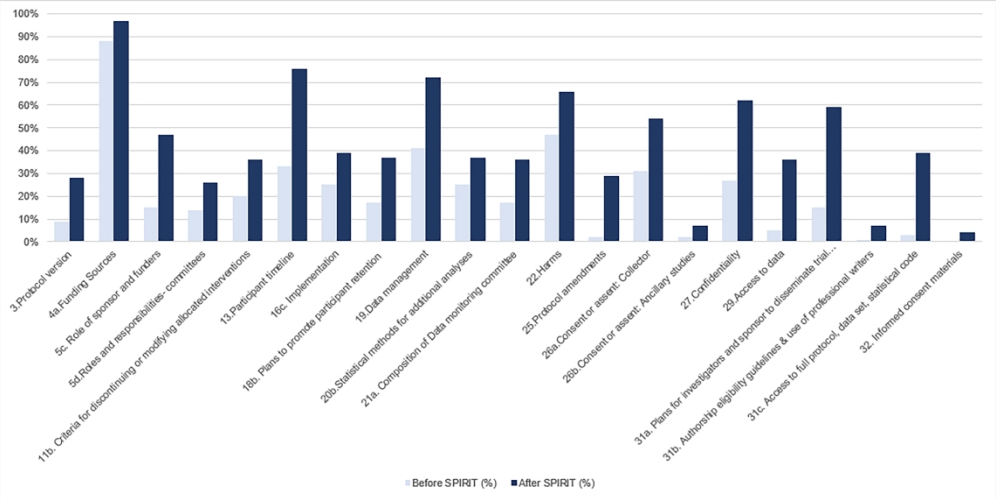

Figure 1. Checklist items with a significant increase in adequate reporting after the SPIRIT statement

276x138mm (300 x 300 DPI)

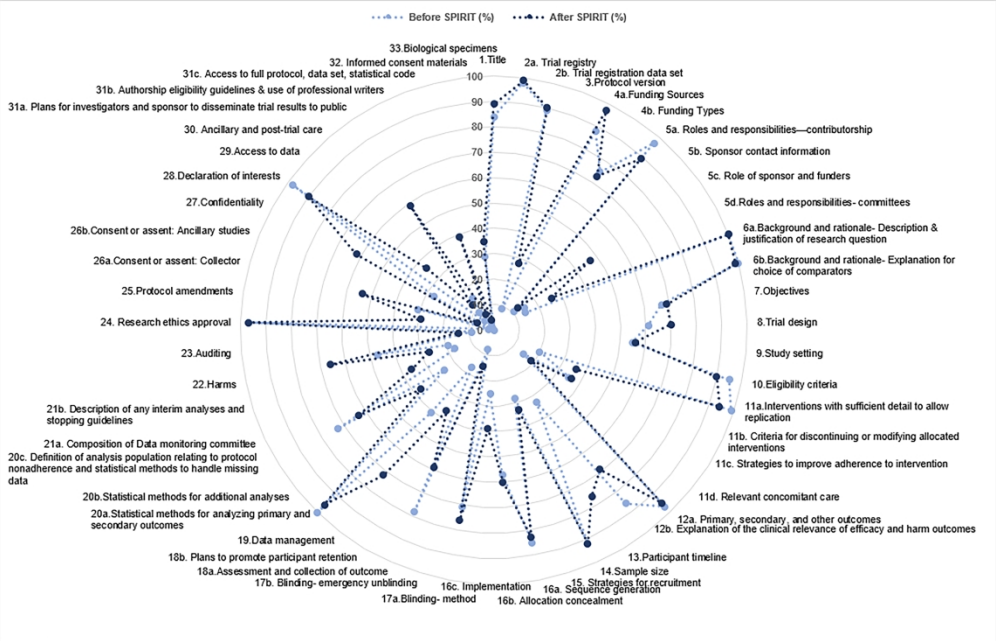

Figure 2. Completeness of RCT protocols by checklist items, before and after the SPIRIT statement

280x180mm (300 x 300 DPI)

Appendix A

Search strategy

('protocol'/exp OR (protocol):ti) AND ('randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/de OR ((random* NEAR/3 trial*)):ab,ti) AND [2008-2012]/py

('protocol'/exp OR (protocol):ti) AND ('randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/de OR ((random* NEAR/3 trial*)):ab,ti) AND [2014-2019]/py

Appendix B

Inter-rater agreement of checklist items from the SPIRIT statement

Section/Item	No.	Checklist Items	Kappa Score	Agreement (%)
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	0.49	92.3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1	100
	2b	All items from the World Health Organization (WHO) Trial Registration Data Set	0.01	75.3
Protocol version	3	Date and version identifier	0.61	83.9
Funding	4a	Funding Sources: Sources of financial, material, and other support	0.39	91.4
	4b	Funding Types: Sources of financial, material, and other support	0.15	70.7
Roles and responsibility	5a	Names, affiliations, and roles of protocol contributors	0.58	95.7
	5b	Name and contact information for the trial sponsor	0.19	78.3
	5c	Role of study sponsor and funders	0.67	83.7
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial	0.35	72
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies examining benefits and harms for each intervention	1	100
	6b	Explanation for choice of comparators	1	100
Objectives	7	Specific objectives or hypotheses	0.24	73.1
Trial design	8	Description of trial design, including type of trial, allocation ratio, and framework	0.27	67.7
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings and list of countries where data will be collected. Reference to where list of study sites can be obtained	0.29	67
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions	0.35	90.3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered.	0.07	87.1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant	0.33	69.9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	0.50	76.3
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	0.54	85
Outcomes	12a	Primary, secondary, and other outcomes, including the specific measurement variable	0.15	79.6

		pressure), analysis metric, method of aggregation, and time point for each outcome.		
	12b	Explanation of the clinical relevance of chosen efficacy and harm outcomes	0.12	66.7
Participant timeline	13	Time schedule of enrolment, interventions, assessments, and visits for participants	0.46	80.7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	0.49	97.8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	0.47	75.3
Assignment of interventions (for controlled trials)				
Allocation Sequence generation	16a	Method of generating the allocation sequence, and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.	0.50	83.9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence, describing any steps to conceal the sequence until interventions are assigned	0.44	72.8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	0.38	71
Blinding (masking)	17a	Who will be blinded after assignment to interventions, and how	0.24	71.6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	0.73	93.8
Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality and a description of study instruments along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.	0.25	68.8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	0.46	74.2
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality.	0.67	83.9
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.	-0.03	91.4
	20b	Methods for any additional analyses	0.61	80.7
	20c	Definition of analysis population relating to protocol nonadherence, and any statistical methods to handle missing data	0.25	64.5
Monitoring				
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details	0.60	81.7

		about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.		
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	0.76	90.3
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	0.67	83.9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	0.35	83.9
Ethics and dissemination				
Research ethics approval	24	Plans for seeking REC/IRB approval	-0.06	87.1
Protocol amendments	25	Plans for communicating important protocol modifications to relevant parties	0.70	89.3
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how	0.68	83.9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	0.25	92.2
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	0.70	85
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	0.13	83.9
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	0.65	83.9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	0.31	83.9
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups, including any publication restrictions	0.65	82.8
	31b	Authorship eligibility guidelines and any intended use of professional writers	0.29	88.2
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	0.55	81.7
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	0.66	98.9
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	0.62	80

Appendix C

Checklist items from the SPIRIT statement by mean completeness in RCT protocols

Section/Item	Item Number	Checklist Items	Before SPIRIT N=150	After SPIRIT N=150
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	126 (84%)	134 (89%)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	147 (98%)	149 (99%)
	2b	All items from the World Health Organization (WHO) Trial Registration Data Set	133 (89%)	135 (90%)
Protocol version	3	Date and version identifier	14 (9%)	42 (28%)
Funding	4a	Funding Sources: Sources of financial, material, and other support	131 (88%)	145 (97%)
	4b	Funding Types: Sources of financial, material, and other support	111 (75%)	108 (73%)
Roles and responsibility	5a	Names, affiliations, and roles of protocol contributors	145 (97%)	134 (89%)
	5b	Name and contact information for the trial sponsor	17 (11%)	19 (13%)
	5c	Role of study sponsor and funders	23 (15%)	69 (47%)
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial	21 (14%)	39 (26%)
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies examining benefits and harms for each intervention	150 (100%)	150 (100%)
	6b	Explanation for choice of comparators	150 (100%)	149 (99%)
Objectives	7	Specific objectives or hypotheses	100 (67%)	104 (69%)
Trial design	8	Description of trial design, including type of trial, allocation ratio, and framework	92 (61%)	105 (70%)
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings and list of countries where data will be collected. Reference to where list of study sites can be obtained	80 (55%)	84 (56%)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions	143 (95%)	135 (90%)

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered.	148 (99%)	141 (94%)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant	30 (20%)	54 (36%)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	52 (35%)	54 (36%)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	23 (15%)	28 (19%)
Outcomes	12a	Primary, secondary, and other outcomes, including the specific measurement variable pressure), analysis metric, method of aggregation, and time point for each outcome.	146 (97%)	143 (95%)
	12b	Explanation of the clinical relevance of chosen efficacy and harm outcomes	129 (86%)	103 (69%)
Participant timeline	13	Time schedule of enrolment, interventions, assessments, and visits for participants	50 (33%)	114 (76%)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	138 (92%)	137 (92%)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	42 (28%)	50 (33%)
Assignment of interventions (for controlled trials)				
Allocation Sequence generation	16a	Method of generating the allocation sequence, and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.	127 (85%)	124 (83%)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence, describing any steps to conceal the sequence until interventions are assigned	85 (57%)	90 (60%)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	37 (25%)	58 (39%)
Blinding (masking)	17a	Who will be blinded after assignment to interventions, and how	94 (71%)	102 (76%)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a	10 (8%)	20 (15%)

		participant's allocated intervention during the trial		
Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality and a description of study instruments along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.	117 (78%)	88 (59%)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	25 (17%)	56 (37%)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality.	61 (41%)	108 (72%)
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.	150 (100%)	144 (96%)
	20b	Methods for any additional analyses	38 (25%)	55 (37%)
	20c	Definition of analysis population relating to protocol nonadherence, and any statistical methods to handle missing data	110 (73%)	95 (63%)
Monitoring				
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.	25 (17%)	53 (36%)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	28 (19%)	41 (27%)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	70 (47%)	99 (66%)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be	14 (9%)	21 (14%)

		independent from investigators and the sponsor		
Ethics and dissemination				
Research ethics approval	24	Plans for seeking REC/IRB approval	145 (97%)	145 (97%)
Protocol amendments	25	Plans for communicating important protocol modifications to relevant parties	3 (2%)	44 (29%)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how	46 (31%)	81 (54%)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	3 (2%)	10 (7%)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	41 (27%)	93 (62%)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	147 (98%)	135 (90%)
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	7 (5%)	54 (36%)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14 (9%)	20 (13%)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups, including any publication restrictions	23 (15%)	88 (59%)
	31b	Authorship eligibility guidelines and any intended use of professional writers	2 (1%)	10 (7%)
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	5 (3%)	59 (39%)
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	0 (0%)	6 (4%)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	6 (29%)	8 (35%)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Not applicable to study type
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	12
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not applicable to study type
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable to study type
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable to study type
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable to study type
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable to study type
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable to study type
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8-9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

For more information, visit: www.prisma-statement.org.
Page 2 of 2

BMJ Open

Has the reporting quality of published randomised controlled trial protocols improved since the SPIRIT statement? A methodological study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038283.R1
Article Type:	Original research
Date Submitted by the Author:	25-Jun-2020
Complete List of Authors:	Tan, Zet; University of New South Wales, Faculty of Medicine Tan, Aidan; University of New South Wales, South Western Sydney Clinical School Li, Tom; University of New South Wales, Faculty of Medicine Harris, Ian; University of New South Wales, South Western Sydney Clinical School Naylor, Justine; University of New South Wales, South Western Sydney Clinical School Siebelt, Michiel; Erasmus Medical Center, Orthopaedics van Tiel, Jasper; Erasmus Medical Center, Orthopaedics Pinheiro , Marina; The University of Sydney, Institute for Musculoskeletal Health Harris, Laura; Sydney Orthopaedic Trauma and Reconstructive Surgery Chamberlain, Kira; Sydney Orthopaedic Trauma and Reconstructive Surgery Adie, Sam; University of New South Wales South Western Sydney Clinical School, South Western Sydney Clinical School
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Epidemiology
Keywords:	STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY, Clinical trials < THERAPEUTICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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ABSTRACT

OBJECTIVES

To determine the reporting quality of published randomised controlled trial (RCT) protocols before and after the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (2013), and any association with author, trial or journal factors.

DESIGN

Methodological study.

DATA SOURCES

MEDLINE, EMBASE and CENTRAL were electronically searched using optimised search strategies.

ELIGIBILITY CRITERIA

Protocols written for an RCT of living humans, published in full-text in a peer-reviewed journal, and published in the English language.

MAIN OUTCOME

Primary outcome was the overall proportion of checklist items which were adequately reported in RCT protocols published before and after the SPIRIT statement.

RESULTS

300 RCT protocols were retrieved; 150 from the period immediately before the SPIRIT statement (9/07/2012-28/12/2012), and 150 from a recent period after the SPIRIT statement (25/01/2019-20/03/2019). 47.9% (95% CI, 46.5-49.3%) of checklist items were adequately reported in RCT protocols before the SPIRIT statement, and 56.7% (95% CI, 54.9-58.5%) after the SPIRIT statement. This represents an 8.8% (95% CI, 6.6-11.1%; p<0.0001) mean improvement in the overall proportion of checklist items adequately reported since the SPIRIT statement. Whilst 40% of individual checklist items had a significant improvement in adequate reporting after the SPIRIT statement,11.3% had a significant deterioration and there were no RCT protocols in which all individual checklist items were complete. The factors associated with higher reporting quality of RCT protocols in multiple regression analysis were author expertise or experience in epidemiology or statistics, multicentre trials, longer protocol word length and publicly reported journal policy of compliance with the SPIRIT statement.

CONCLUSIONS

The overall reporting quality of RCT protocols has significantly improved since the SPIRIT statement, although a substantial proportion of individual checklist items remain poorly reported. Continued and concerted efforts are required by journals, editors, reviewers and investigators to improve the completeness and transparency of RCT protocols.

Keywords: randomised controlled trial protocol; reporting quality; completeness; SPIRIT statement

Article summary

Strengths and limitations of this study

- We conducted a methodological study in accordance with a prospectively registered protocol (PROSPERO CRD42019126522).
- We assessed the reporting quality of two equal, arbitrary samples of 150 RCT protocols published before and after the SPIRIT statement.
- Data extraction of the first 100 RCT protocols was independently duplicated by two investigators and any issues with data extraction were discussed at fortnightly roundtable meetings attended by five investigators.
- The design of this study is limited by the lack of blinding of data collectors to the date of publication of RCT protocols and by the inclusion of only RCT protocols published in the English language.
- The associations found in this study may not be causal, and the improvements in overall reporting quality may be due to underlying secular trends whereby RCT protocol quality improves over time, unrelated to the introduction of the SPIRIT statement.

Introduction

Background

Randomised controlled trial (RCT) protocols should permit prospective assessment of trial methodology, scientific integrity, ethical standards and safety considerations, public documentation of protocol changes and approved amendments, and retrospective validation of trial conduct and subsequent reporting.[1] A well-written RCT protocol is an critical component of a high-quality RCT as it allows comparison between the initial inception, possible amendments and final publication. This supports RCT investigators and sponsors by improving research quality, ethics committees and journals by improving research completeness, and participants and the public by improving research transparency.[2]

However, studies have frequently reported concerning inconsistencies between RCT protocols and their corresponding publications,[3-6] and serious deficiencies in the content of RCT protocols.[5-13] Incomplete, inaccurate or undisclosed reporting of RCT protocols can result in research misrepresentation, selective outcome reporting and other biases which undercut the credibility and validity of health research and scientific knowledge [2]. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement was published in January 2013 and describes a 33-item minimum set of scientific, methodological, ethical and administrative components that should be routinely included in a trial protocol.[1] It aims to address long-standing issues with the completeness and transparency of many trial protocols by providing a standardised structure to trial plans, promoting strict accountability to trial conduct, improving the reliability and validity of trial outcomes, and facilitating the assessment of risk of bias, methodological quality and reporting quality.[1]

Objectives

The impact of the SPIRIT statement on the reporting quality of RCT protocols in health research is unknown. The primary objectives of this study are to 1) determine the reporting quality of published RCT protocols before and after the SPIRIT statement, and 2) determine whether author, trial or journal factors are associated with the reporting quality of published RCT protocols.

Methods

Study design

We conducted a methodological study in accordance with a prospectively registered protocol (PROSPERO CRD42019126522).

Setting

RCT protocols were identified by electronically searching the bibliographic databases MEDLINE, EMBASE and CENTRAL using a search strategy formulated by an experienced medical librarian (Appendix A). All searches were performed independently by two investigators on 29 March 2019.

Included protocols

RCT protocols were eligible for inclusion if they were (a) written for an RCT of living humans, (b) published in full-text in a peer-reviewed journal, and (c) published in the English language. RCT protocols were excluded if they (a) were published only in protocol databases or online registries, or (b) reported any study results.

We screened RCT protocols until we retrieved two equal, arbitrary samples of 150 RCT protocols published before and after the SPIRIT statement. The sample of 150 RCT protocols published immediately before the SPIRIT statement were retrieved by searching for RCT protocols published from 28 December 2012 and proceeding retrospectively until 150 eligible RCT protocols were selected. Similarly, the sample of 150 RCT protocols published recently since the SPIRIT statement were selected by searching for RCT protocols published from 20 March 2019 and proceeding retrospectively until 150 eligible RCT protocols were retrieved. The titles and abstracts of all retrieved RCT protocols were independently screened by two investigators and the full texts of relevant RCT protocols were independently assessed for eligibility by two investigators. Any disagreements were resolved by discussion between the two investigators and, if required, arbitration by a third

investigator. All eligible RCT protocols were imported into Endnote X9 (Clarivate Analytics) software. Duplicates were removed by manually screening by author, year, title and journal.

Variables

The primary variables of interest were the checklist items from the SPIRIT statement, defined in the SPIRIT statement explanation and elaboration.[1] A data extraction form was developed based on the checklist items from the SPIRIT statement. Two checklist items (items 4 and 12) were subcategorised to reflect binary criterion and provide appropriate granularity. The checklist item 'funding' was split into 'funding source', defined as sources of financial, material and other support (e.g. name and location of the funder), and 'funding type', defined as type of financial, material and other support (e.g. funds, equipment, drugs, services). The checklist item 'outcomes' was split into 'primary, secondary and other outcomes' (e.g. the specific measurement variable, analysis metric, method of aggregation and time point for each outcome), and 'explanation of clinical relevance of chosen efficacy and harm outcomes'. This resulted in a total of 53 individual checklist items. Each checklist item was assessed as either adequate or inadequate/unclear. The data extraction form and assessment criteria were independently piloted for ten randomly selected RCT protocols by five investigators. Disagreements were resolved by fortnightly roundtable meetings attended by five investigators and the definitions of adequate and inadequate/unclear for each checklist item were revised accordingly.

The secondary variables of interest related to author, trial and journal factors. Author factors included the number of authors per protocol and the presence of authors with expertise or experience in epidemiology or statistics (defined as one or more authors with either a degree in clinical epidemiology, public health or biostatistics, or an affiliation to a clinical epidemiology, public health or biostatistics department [14, 15]). Trial factors included the total planned sample size, centre status (i.e. multicentre or single centre), protocol word length (i.e. greater or less than 3,500 words), and funding source (i.e. industry or non-industry funding). Protocol report of compliance with the SPIRIT statement and publicly reported journal policy of compliance with the SPIRIT statement in the instructions to authors on the journal website, as of 2019, was also collected for RCT protocols published after the SPIRIT statement.

Data measurement

Data extraction was performed on the 300 RCT protocols. Data extraction of the first 100 RCT protocols was independently duplicated by two investigators and data extraction of the remaining 200 RCT protocols was completed once between two investigators. Any issues with data extraction were discussed at fortnightly roundtable meetings attended by five investigators.

Statistical methods

The final datapoints used for analysis were the results of the duplicate data collection and discussion of disagreements. We performed descriptive analysis of the primary outcome by calculating the proportion (percentage) of checklist items which were adequately reported in RCT protocols. This was considered a measure of the overall reporting quality of RCT protocols. We also calculated the proportion (percentage) of RCT protocols which adequately reported each checklist item. Inter-rater agreement and kappa scores were calculated on the initial datapoints extracted by independent duplicate data collection (i.e. before discussion of disagreements) of the first 100 RCT protocols. We performed exploratory multiple linear regression analysis to determine whether author, trial or journal factors were associated with the reporting quality of RCT protocols. Stepwise backward linear regression was performed, using $p < 0.25$ as the criterion for inclusion in a multiple regression model, and R^2 as the criterion for removal of variables in the backward elimination model. A p value <0.05 was considered statistically significant, and the R^2 value was used as a measure of the final model goodness of fit. All statistical analyses were stratified by publication before or after the SPIRIT statement and were performed using Stata software (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LP).

Patient and public involvement

As this was a study of RCT protocols, there was no patient or public involvement in the conception, design or conduct of the study, or the writing or editing of this paper.

Results

Included protocols

A total of 300 RCT protocols were retrieved; 150 from before the SPIRIT statement (9 July 2012 to 28 December 2012) and 150 from after the SPIRIT statement (25 January 2019 to 20 March 2019). In the full-text eligibility assessment of RCT protocols published before the SPIRIT statement, 25 articles were excluded because they did not describe an RCT protocol, two because they had been retracted, one because it included study results, and one because it was not published in full-text. In the full-text eligibility assessment of RCT protocols published after the SPIRIT statement, six articles were excluded because they did not describe an RCT protocol. All excluded articles were replaced with eligible studies. The final 300 RCT protocols were published across 45 peer-reviewed journals, with 46% (138/300) published in *Trials*.

The inter-rater agreement for data extraction of the first 100 RCT protocols ranged from 64.5% to 100%, with Kappa scores provided in Appendix B. The individual checklist items with the lowest and highest inter-rater agreement were 'statistical methods: statistical methods to handle missing data' and 'background and rationale: explanation for choice of comparators', respectively. The checklist items with the lowest and highest Kappa scores were 'research ethics approval' and 'background and rationale: explanation for choice of comparators', respectively.

Descriptive data

Author and trial characteristics were similar before and after the SPIRIT statement (Table 1).

Table 1. **Author and trial characteristics before and after the SPIRIT statement**

	Before the SPIRIT statement	**After the SPIRIT statement**
Author characteristics		
Authors per protocol (median, range)	8, 1-90	8, 2-80
One or more authors with expertise or experience in epidemiology or statistics (n, %)	50, 33.3%	48, 32%
Trial characteristics		
Total planned sample size (median)	214.5	200
Multicentre status (n, %)	70, 46.7%	64, 42.7%
Protocol word length >3500 (n, %)	105, 70%	106, 70.7%
Industry funding (n, %)	8, 6%	10, 7%

Of RCT protocols published after the SPIRIT statement, 42.7% (64/150) self-reported compliance with the SPIRIT statement, and 88% (132/150) were published in a peer-reviewed journal with a publicly reported policy of compliance with the SPIRIT statement. Additionally, only 17/300 (6%) of RCT protocols were published in journals which published in print, while the remainder (94%) were published in journals which published exclusively online. The mean word count of RCT protocols published in online journals and print journals was 4387 words and 3581 words, respectively, with an 806 word difference in mean word count (95% CI 26 -1586 words, p=0.04).

Outcome data

Of the 150 RCT protocols published before the SPIRIT statement, an average of 47.9% of checklist items per RCT protocol were adequately reported (95% CI, 46.5-49.3%). Comparably, of the 150 RCT protocols published after the SPIRIT statement, an average of 56.7% of checklist items were adequately reported (95% CI, 54.9-58.5%). This represents an 8.8% (95% CI, 6.6-11.1%; p<0.0001) mean improvement in the overall proportion of checklist items adequately reported since the SPIRIT statement.

Of the 53 individual checklist items, 21 (40%) had a significant increase ($p<0.05$) in adequate reporting since the SPIRIT statement (Figure 1) and 6 (11.3%) had a significant decrease ($p<0.05$) in adequate reporting since the SPIRIT statement (Appendix C). 23 individual checklist items were inadequately or not reported in more than half of all RCT protocols (Figure 2). Only one checklist item was adequately reported in all 300 RCT protocols – 'background and rationale: description and justification of research question'. None of the 300 RCT protocols adequately reported all individual checklist items from the SPIRIT statement and no individual checklist items were inadequately or not reported in all 300 RCT protocols.

Table 2 shows the multiple regression analysis of the association between author, trial and journal factors and the reporting quality of RCT protocols. The final model had an adjusted R2 value of 0.37, indicating that 37% of the variability in SPIRIT score was explained in our model. Author self-reported compliance with the SPIRIT statement was not associated with actual compliance with the SPIRIT statement. However, publicly reported journal policy of compliance with the SPIRIT statement was associated with significantly improved reporting quality. Industry funding was not associated with compliance with the SPIRIT statement, with only a 0.3% (95% CI -4.9% - 5.6%, p=0.9) difference in mean SPIRIT scores between industry and non-industry funded trials. Similarly, publication type (either print or exclusively online) was not associated with compliance with the SPIRIT statement (p=0.29). As such, industry funding and publication type were not included in the regression analysis as our pre-planned regression modelling limited the inclusion of variables to only those with potential statistical influence.

Table 2. **Multiple regression analysis of author, trial and journal characteristics associated with the reporting quality of RCT protocols**

	Increase in proportion of adequately reported checklist items from the SPIRIT statement	**p-value**
Author characteristics		
Number of authors per protocol	0.2%	0.004
One or more authors with expertise or experience in epidemiology or statistics	2.6%	0.016
Trial characteristics		
Multicentre status	4.6%	0.000
Protocol word length >3500	6.5%	0.000
Protocols self-reporting compliance with the SPIRIT statement	-	0.145
Journal characteristics		
Journal policy of compliance with the SPIRIT statement	6.2%	0.000

Discussion

Key results

We assessed the reporting quality of published RCT protocols before and after the SPIRIT statement. We found a significant improvement in the completeness of RCT protocols published since the SPIRIT statement. Although our study suggests significant improvements in the overall reporting quality of RCT protocols published after the SPRIT statement, these significant improvements were only seen in 40% (21/53) of individual checklist items, and there were no RCT protocols in which all individual checklist items were complete.

Limitations

Our study is limited by the lack of blinding of data collectors to the date of publication of RCT protocols, introducing the possibility for researcher bias. This was minimised through strict adherence to pre-defined parameters for the assessment of the checklist items from the SPIRIT statement,

fortnightly roundtable meetings, and duplication of data collection for one third of RCT protocols. Our study was also limited by the inclusion of only RCT protocols published in the English language.

The associations found in this study may not be causal, and the improvements in overall reporting quality may be due to underlying secular trends whereby RCT protocol quality improves over time, unrelated to the introduction of the SPIRIT statement. However, the association between specific journal requirement for the SPIRIT statement, and reporting to that requirement, suggests some degree of causation.

Interpretation

Despite the significant improvement in the overall reporting quality of RCT protocols suggested by our study, three individual checklist items from the SPIRIT statement were inadequately or not reported by more than 90% of RCT protocols: 'consent or assent: ancillary studies', 'dissemination policy: authorship eligibility guidelines and any intended use of professional writers' and 'informed consent materials'.

The low completeness of checklist item 'consent or assent: ancillary studies' may be related to a misperception by authors that it is not necessary to report the decision that participant data or biological specimens will not be used in ancillary studies. However, deciding and reporting on the provisions of additional consent for ancillary studies is important, particularly given the increasing emphasis on data sharing plans. A similar sentiment may explain the low completeness of checklist item 'informed consent materials: model consent form and other related documentation given to participants and authorized surrogates', as authors may consider it sufficient to describe a plan to obtain informed consent and not necessary to provide the model consent form. However, providing the model consent form is important in determining that the relevant information is delivered with sufficient detail at an appropriate literacy level for the target population. Additionally, the low completeness of checklist item 'dissemination policy: authorship eligibility guidelines and any intended use of professional writers' may be underpinned by an underappreciation of the importance of disclosing the use of professional writers. A study of industry-initiated RCTs reported that 91% of 44 RCT protocols had evidence of ghost authorship.[12]

The factors associated with higher reporting quality of RCT protocols in multiple regression analysis were one or more authors with expertise or experience in epidemiology or statistics, multicentre trials, longer protocol word length and publicly reported journal policy of compliance with the SPIRIT statement. The association between author expertise or experience in epidemiology or statistics and higher reporting quality has previously been reported [16] and may be related to education in the importance of transparency and experience in writing RCT protocols. In a similar way, the association between multicentre trials and higher reporting quality may be explained by the larger nature of these studies and, by extension, the greater level of support available to these studies for writing the protocol and greater importance of transparently and completely reporting the protocol. Additionally, the association between longer protocol word lengths and higher reporting quality may be underpinned by the capacity to more completely describe a planned RCT with more permitted words. This would support a more discretionary, individualised approach to determining appropriate word lengths of RCT protocols, rather than arbitrary, blanket cut-offs.

Interestingly, protocol report of compliance with the SPIRIT statement was not a significant predictor of reporting quality after adjusting for publicly reported journal policy of compliance with the SPIRIT statement. A possible explanation for this finding is that some authors who are aware of either the SPIRIT statement or the journal's policy of compliance with the SPIRIT statement may decide to self-report compliance with the SPIRIT statement without actually applying the checklist. This suggests that author self-report of compliance with the SPIRIT statement cannot be relied upon as a proxy indicator of reporting quality as awareness of the SPIRIT statement does not translate into application of the checklist. Rather, the association between publicly reported journal policy of compliance with the SPIRIT statement and higher reporting quality supports the role of journals and editors in checking adherence to the SPIRIT statement to improve the completeness and transparency of RCT protocols. Some possible aids for journals and editors checking adherence to the SPIRIT statement include mandated author completed pre-submission checklists, structured online manuscript submission systems and automated manuscript reporting quality checks. Other

avenues include incorporating the SPIRIT statement into the mandatory fields required by clinical trial registries (e.g. ClinicalTrials.gov, ANZCTR and ISRCTN).

The findings from our research expand on those of Gao et al. (2016), who assessed the reporting quality of 142 RCT protocols in acupuncture using the checklist items from the SPIRIT statement.[17] However, we found a substantially larger number of checklist items whose completeness significantly improved after the SPIRIT statement (5 in Gao et al. (2016) and 21 in our study) [17]. This difference may be explained by the time since the SPIRIT statement; while Gao et al. (2016) assessed RCT protocols published 1-2 years after the SPIRIT statement, our study assessed RCT protocols published 6-7 years after the SPIRIT statement. This could suggest increasing awareness and adoption of the SPIRIT statement over time. More recently, Yang et al. (2018) assessed the reporting quality of 126 trial protocols in anaesthesia against the SPIRIT statement, and found no significant improvement in the completeness of trial protocols published after the SPIRIT statement and substantially more checklist items which were inadequately or not reported by more than 90% of included trial protocols (18 by Yang et al. (2018) and 3 in our study). However, their findings were limited by the small sample size of 18 trial protocols from after the SPIRIT statement.[18]

Overall, there remains substantial opportunity for further improvement. A study of emergency medicine journals found that reporting guidelines, including the SPIRIT statement, were infrequently endorsed,[19] and a scoping review of systematic reviews of adherence to other reporting guidelines reported insufficient adherence.[20] These findings suggest that the challenges to improving adherence to the SPIRIT statement are shared with other reporting guidelines. The focus should be on increasing the awareness of the SPIRIT statement throughout the research community, particularly amongst trial investigators, and promoting the adoption of the SPIRIT statement in the editorial community, specifically by advocating for mandated adherence to reporting guidelines. Improving the reporting quality of RCT protocols is necessary to improve the completeness and transparency of RCTs, and, by extension, the validity and reliability of RCT outcomes which ultimately contribute to informing patient care. It is likely that continued and concerted efforts by journals, editors, reviewers and investigators to advocate for adherence to the SPIRIT statement would improve the completeness and transparency of RCT protocols.

Contributorship statement: The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ZWT contributed to curating the data, analysed the data, administrated the project and contributed to reviewing the manuscript. ACT drafted the original manuscript, and edited the reviewed manuscript. MS and JT contributed to curating the data and reviewing the manuscript. TL, IH, JN, MP, LH and KC contributed to review the manuscript. SA conceptualised the study, designed the methodology, and contributed to reviewing the manuscript. All authors met the ICMJE criteria for authorship and contributed to the revision of the manuscript. ZWT is guarantor.

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Competing interests declaration: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not applicable. This is a methodological study of publicly available, published RCT protocols.

Data sharing: No additional data available.

Transparency statement: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned and registered have been explained.

Figure captions:
Figure 1. Checklist items with a significant increase in adequate reporting after the SPIRIT statement
Figure 2. Completeness of RCT protocols by checklist items, before and after the SPIRIT statement

References

1. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj. 2013;346:e7586.
2. Chan AW, Upshur R, Singh JA, Ghersi D, Chapuis F, Altman DG. Research protocols: waiving confidentiality for the greater good. Bmj. 2006;332(7549):1086-9.
3. Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. Jama. 2004;291(20):2457-65.
4. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PLoS ONE. 2008;3(8):e3081.
5. Hernandez AV, Steyerberg EW, Taylor GS, Marmarou A, Habbema JD, Maas AI. Subgroup analysis and covariate adjustment in randomized clinical trials of traumatic brain injury: a systematic review. Neurosurgery. 2005;57(6):1244-53; discussion -53.
6. Chan AW, Hrobjartsson A, Jorgensen KJ, Gotzsche PC, Altman DG. Discrepancies in sample size calculations and data analyses reported in randomised trials: comparison of publications with protocols. Bmj. 2008;337:a2299.
7. Pildal J, Chan AW, Hrobjartsson A, Forfang E, Altman DG, Gotzsche PC. Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study. Bmj. 2005;330(7499):1049.
8. Mhaskar R, Djulbegovic B, Magazin A, Soares HP, Kumar A. Published methodological quality of randomized controlled trials does not reflect the actual quality assessed in protocols. J Clin Epidemiol. 2012;65(6):602-9.
9. Hrobjartsson A, Pildal J, Chan AW, Haahr MT, Altman DG, Gotzsche PC. Reporting on blinding in trial protocols and corresponding publications was often inadequate but rarely contradictory. J Clin Epidemiol. 2009;62(9):967-73.
10. Scharf O, Colevas AD. Adverse event reporting in publications compared with sponsor database for cancer clinical trials. J Clin Oncol. 2006;24(24):3933-8.
11. Al-Marzouki S, Roberts I, Evans S, Marshall T. Selective reporting in clinical trials: analysis of trial protocols accepted by The Lancet. Lancet. 2008;372(9634):201.
12. Gotzsche PC, Hrobjartsson A, Johansen HK, Haahr MT, Altman DG, Chan AW. Ghost authorship in industry-initiated randomised trials. PLoS Med. 2007;1(1):e19.
13. Lundh A, Krogsboll LT, Gotzsche PC. Access to data in industry-sponsored trials. Lancet. 2011;378(9808):1995-6.
14. Adie S, Harris IA, Naylor JM, Mittal R. CONSORT compliance in surgical randomized trials: are we there yet? A systematic review. Ann Surg. 2013;258(6):872-8.
15. Adie S, Ma D, Harris IA, Naylor JM, Craig JC. Quality of conduct and reporting of meta-analyses of surgical interventions. Ann Surg. 2015;261(4):685-94.
16. Adie S, Harris IA, Naylor JM, Mittal R. Are outcomes reported in surgical randomized trials patient-important? A systematic review and meta-analysis. Can J Surg. 2017;60(2):86-93.
17. Gao L, Sha T, Chen B, Li M, Pan X, Chen Z, et al. Study protocols on randomized clinical trials of acupuncture: An assessment of reporting quality with the SPIRIT statement. European Journal of Integrative Medicine. 2016;8(6):881-7.
18. Yang L, Chen S, Yang D, Li J, Wu T, Zuo Y. A quality analysis of clinical anaesthesia study protocols from the Chinese clinical trials registry according to the SPIRIT statement. Oncotarget. 2018;9(37):24830-6.
19. Sims MT, Henning NM, Wayant CC, Vassar M. Do emergency medicine journals promote trial registration and adherence to reporting guidelines? A survey of "Instructions for Authors". Scand J Trauma Resusc Emerg Med. 2016;24(1):137.
20. Samaan Z, Mbuagbaw L, Kosa D, Borg Debono V, Dillenburg R, Zhang S, et al. A systematic scoping review of adherence to reporting guidelines in health care literature. Journal of Multidisciplinary Healthcare. 2013;6:169-88.

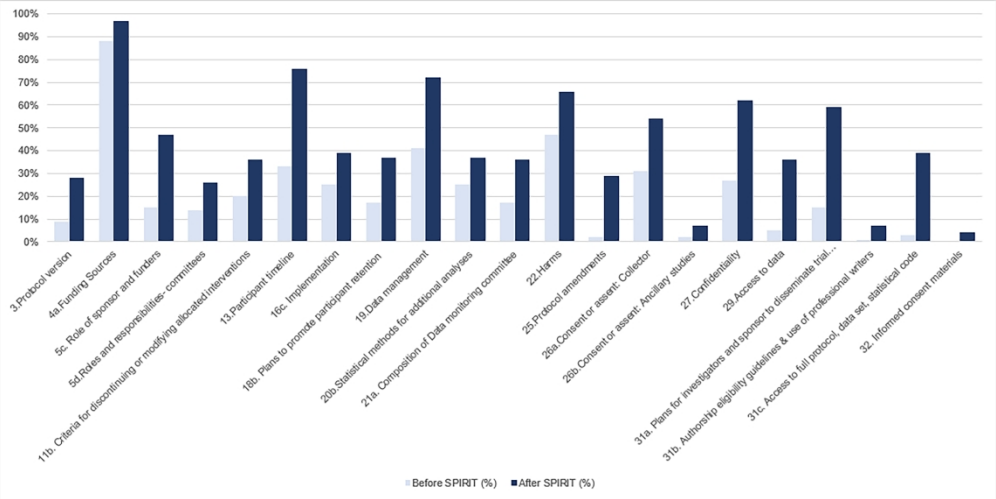

Figure 1. Checklist items with a significant increase in adequate reporting after the SPIRIT statement

276x138mm (300 x 300 DPI)

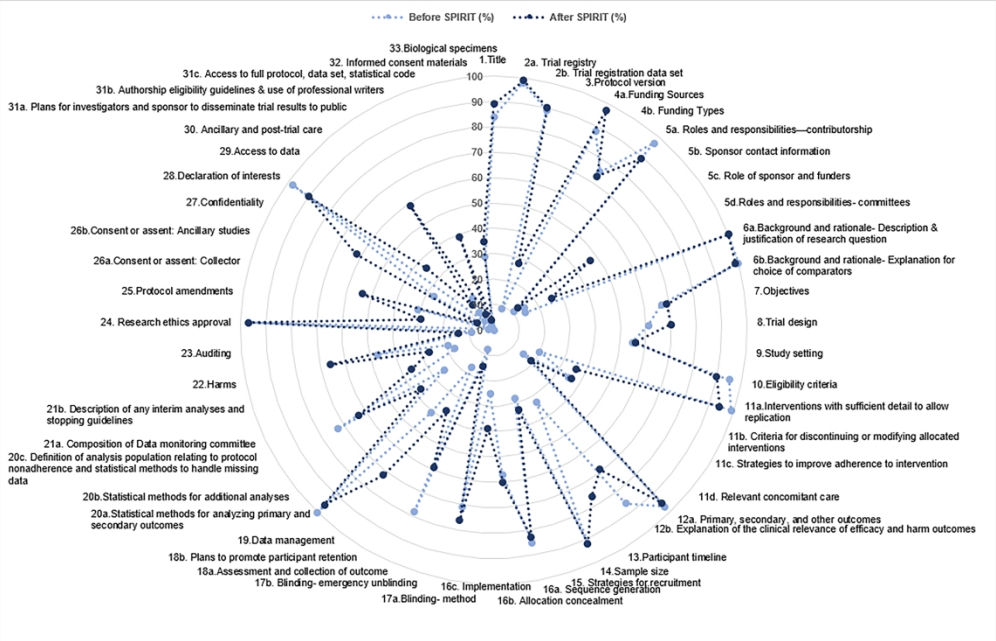

Figure 2. Completeness of RCT protocols by checklist items, before and after the SPIRIT statement

280x180mm (300 x 300 DPI)

Appendix A

Search strategy

('protocol'/exp OR (protocol):ti) AND ('randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/de OR ((random* NEAR/3 trial*)):ab,ti) AND [2008-2012]/py

('protocol'/exp OR (protocol):ti) AND ('randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/de OR ((random* NEAR/3 trial*)):ab,ti) AND [2014-2019]/py

Appendix B

Inter-rater agreement of checklist items from the SPIRIT statement

Section/Item	No.	Checklist Items	Kappa Score	Agreement (%)
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	0.49	92.3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1	100
	2b	All items from the World Health Organization (WHO) Trial Registration Data Set	0.01	75.3
Protocol version	3	Date and version identifier	0.61	83.9
Funding	4a	Funding Sources: Sources of financial, material, and other support	0.39	91.4
	4b	Funding Types: Sources of financial, material, and other support	0.15	70.7
Roles and responsibility	5a	Names, affiliations, and roles of protocol contributors	0.58	95.7
	5b	Name and contact information for the trial sponsor	0.19	78.3
	5c	Role of study sponsor and funders	0.67	83.7
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial	0.35	72
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies examining benefits and harms for each intervention	1	100
	6b	Explanation for choice of comparators	1	100
Objectives	7	Specific objectives or hypotheses	0.24	73.1
Trial design	8	Description of trial design, including type of trial, allocation ratio, and framework	0.27	67.7
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings and list of countries where data will be collected. Reference to where list of study sites can be obtained	0.29	67
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions	0.35	90.3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered.	0.07	87.1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant	0.33	69.9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	0.50	76.3
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	0.54	85
Outcomes	12a	Primary, secondary, and other outcomes, including the specific measurement variable	0.15	79.6

		pressure), analysis metric, method of aggregation, and time point for each outcome.		
	12b	Explanation of the clinical relevance of chosen efficacy and harm outcomes	0.12	66.7
Participant timeline	13	Time schedule of enrolment, interventions, assessments, and visits for participants	0.46	80.7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	0.49	97.8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	0.47	75.3
Assignment of interventions (for controlled trials)				
Allocation Sequence generation	16a	Method of generating the allocation sequence, and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.	0.50	83.9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence, describing any steps to conceal the sequence until interventions are assigned	0.44	72.8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	0.38	71
Blinding (masking)	17a	Who will be blinded after assignment to interventions, and how	0.24	71.6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	0.73	93.8
Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality and a description of study instruments along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.	0.25	68.8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	0.46	74.2
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality.	0.67	83.9
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.	-0.03	91.4
	20b	Methods for any additional analyses	0.61	80.7
	20c	Definition of analysis population relating to protocol nonadherence, and any statistical methods to handle missing data	0.25	64.5
Monitoring				
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details	0.60	81.7

		about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.		
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	0.76	90.3
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	0.67	83.9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	0.35	83.9
Ethics and dissemination				
Research ethics approval	24	Plans for seeking REC/IRB approval	-0.06	87.1
Protocol amendments	25	Plans for communicating important protocol modifications to relevant parties	0.70	89.3
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how	0.68	83.9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	0.25	92.2
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	0.70	85
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	0.13	83.9
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	0.65	83.9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	0.31	83.9
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups, including any publication restrictions	0.65	82.8
	31b	Authorship eligibility guidelines and any intended use of professional writers	0.29	88.2
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	0.55	81.7
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	0.66	98.9
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	0.62	80

Appendix C

Checklist items from the SPIRIT statement by mean completeness in RCT protocols

Section/Item	Item Number	Checklist Items	Before SPIRIT N=150	After SPIRIT N=150
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	126 (84%)	134 (89%)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	147 (98%)	149 (99%)
	2b	All items from the World Health Organization (WHO) Trial Registration Data Set	133 (89%)	135 (90%)
Protocol version	3	Date and version identifier	14 (9%)	42 (28%)
Funding	4a	Funding Sources: Sources of financial, material, and other support	131 (88%)	145 (97%)
	4b	Funding Types: Sources of financial, material, and other support	111 (75%)	108 (73%)
Roles and responsibility	5a	Names, affiliations, and roles of protocol contributors	145 (97%)	134 (89%)
	5b	Name and contact information for the trial sponsor	17 (11%)	19 (13%)
	5c	Role of study sponsor and funders	23 (15%)	69 (47%)
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial	21 (14%)	39 (26%)
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies examining benefits and harms for each intervention	150 (100%)	150 (100%)
	6b	Explanation for choice of comparators	150 (100%)	149 (99%)
Objectives	7	Specific objectives or hypotheses	100 (67%)	104 (69%)
Trial design	8	Description of trial design, including type of trial, allocation ratio, and framework	92 (61%)	105 (70%)
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings and list of countries where data will be collected. Reference to where list of study sites can be obtained	80 (55%)	84 (56%)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions	143 (95%)	135 (90%)

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered.	148 (99%)	141 (94%)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant	30 (20%)	54 (36%)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	52 (35%)	54 (36%)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	23 (15%)	28 (19%)
Outcomes	12a	Primary, secondary, and other outcomes, including the specific measurement variable pressure), analysis metric, method of aggregation, and time point for each outcome.	146 (97%)	143 (95%)
	12b	Explanation of the clinical relevance of chosen efficacy and harm outcomes	129 (86%)	103 (69%)
Participant timeline	13	Time schedule of enrolment, interventions, assessments, and visits for participants	50 (33%)	114 (76%)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	138 (92%)	137 (92%)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	42 (28%)	50 (33%)
Assignment of interventions (for controlled trials)				
Allocation Sequence generation	16a	Method of generating the allocation sequence, and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.	127 (85%)	124 (83%)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence, describing any steps to conceal the sequence until interventions are assigned	85 (57%)	90 (60%)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	37 (25%)	58 (39%)
Blinding (masking)	17a	Who will be blinded after assignment to interventions, and how	94 (71%)	102 (76%)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a	10 (8%)	20 (15%)

		participant's allocated intervention during the trial		
Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality and a description of study instruments along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.	117 (78%)	88 (59%)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	25 (17%)	56 (37%)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality.	61 (41%)	108 (72%)
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.	150 (100%)	144 (96%)
	20b	Methods for any additional analyses	38 (25%)	55 (37%)
	20c	Definition of analysis population relating to protocol nonadherence, and any statistical methods to handle missing data	110 (73%)	95 (63%)
Monitoring				
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.	25 (17%)	53 (36%)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	28 (19%)	41 (27%)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	70 (47%)	99 (66%)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be	14 (9%)	21 (14%)

		independent from investigators and the sponsor		
Ethics and dissemination				
Research ethics approval	24	Plans for seeking REC/IRB approval	145 (97%)	145 (97%)
Protocol amendments	25	Plans for communicating important protocol modifications to relevant parties	3 (2%)	44 (29%)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how	46 (31%)	81 (54%)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	3 (2%)	10 (7%)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	41 (27%)	93 (62%)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	147 (98%)	135 (90%)
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	7 (5%)	54 (36%)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14 (9%)	20 (13%)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups, including any publication restrictions	23 (15%)	88 (59%)
	31b	Authorship eligibility guidelines and any intended use of professional writers	2 (1%)	10 (7%)
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	5 (3%)	59 (39%)
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	0 (0%)	6 (4%)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	6 (29%)	8 (35%)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Not applicable to study type
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	12
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not applicable to study type
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable to study type
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable to study type
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable to study type
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable to study type
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable to study type
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8-9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

For more information, visit: www.prisma-statement.org.
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BMJ Open

Has the reporting quality of published randomised controlled trial protocols improved since the SPIRIT statement? A methodological study

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ABSTRACT

OBJECTIVES

To determine the reporting quality of published randomised controlled trial (RCT) protocols before and after the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (2013), and any association with author, trial or journal factors.

DESIGN

Methodological study.

DATA SOURCES

MEDLINE, EMBASE and CENTRAL were electronically searched using optimised search strategies.

ELIGIBILITY CRITERIA

Protocols written for an RCT of living humans, published in full-text in a peer-reviewed journal, and published in the English language.

MAIN OUTCOME

Primary outcome was the overall proportion of checklist items which were adequately reported in RCT protocols published before and after the SPIRIT statement.

RESULTS

300 RCT protocols were retrieved; 150 from the period immediately before the SPIRIT statement (9/07/2012-28/12/2012), and 150 from a recent period after the SPIRIT statement (25/01/2019-20/03/2019). 47.9% (95% CI, 46.5-49.3%) of checklist items were adequately reported in RCT protocols before the SPIRIT statement, and 56.7% (95% CI, 54.9-58.5%) after the SPIRIT statement. This represents an 8.8% (95% CI, 6.6-11.1%; p<0.0001) mean improvement in the overall proportion of checklist items adequately reported since the SPIRIT statement. Whilst 40% of individual checklist items had a significant improvement in adequate reporting after the SPIRIT statement,11.3% had a significant deterioration and there were no RCT protocols in which all individual checklist items were complete. The factors associated with higher reporting quality of RCT protocols in multiple regression analysis were author expertise or experience in epidemiology or statistics, multicentre trials, longer protocol word length and publicly reported journal policy of compliance with the SPIRIT statement.

CONCLUSIONS

The overall reporting quality of RCT protocols has significantly improved since the SPIRIT statement, although a substantial proportion of individual checklist items remain poorly reported. Continued and concerted efforts are required by journals, editors, reviewers and investigators to improve the completeness and transparency of RCT protocols.

Keywords: randomised controlled trial protocol; reporting quality; completeness; SPIRIT statement

Article summary

Strengths and limitations of this study

- We conducted a methodological study in accordance with a prospectively registered protocol (PROSPERO CRD42019126522).
- We assessed the reporting quality of two equal, arbitrary samples of 150 RCT protocols published before and after the SPIRIT statement.
- Data extraction of the first 100 RCT protocols was independently duplicated by two investigators and any issues with data extraction were discussed at fortnightly roundtable meetings attended by five investigators.
- The design of this study is limited by the lack of blinding of data collectors to the date of publication of RCT protocols and by the inclusion of only RCT protocols published in the English language.
- The associations found in this study may not be causal, and the improvements in overall reporting quality may be due to underlying secular trends whereby RCT protocol quality improves over time, unrelated to the introduction of the SPIRIT statement.

Introduction

Background

Randomised controlled trial (RCT) protocols should permit prospective assessment of trial methodology, scientific integrity, ethical standards and safety considerations, public documentation of protocol changes and approved amendments, and retrospective validation of trial conduct and subsequent reporting.[1] A well-written RCT protocol is an critical component of a high-quality RCT as it allows comparison between the initial inception, possible amendments and final publication. This supports RCT investigators and sponsors by improving research quality, ethics committees and journals by improving research completeness, and participants and the public by improving research transparency.[2]

However, studies have frequently reported concerning inconsistencies between RCT protocols and their corresponding publications,[3-6] and serious deficiencies in the content of RCT protocols.[5-13] Incomplete, inaccurate or undisclosed reporting of RCT protocols can result in research misrepresentation, selective outcome reporting and other biases which undercut the credibility and validity of health research and scientific knowledge [2]. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement was published in January 2013 and describes a 33-item minimum set of scientific, methodological, ethical and administrative components that should be routinely included in a trial protocol.[1] It aims to address long-standing issues with the completeness and transparency of many trial protocols by providing a standardised structure to trial plans, promoting strict accountability to trial conduct, improving the reliability and validity of trial outcomes, and facilitating the assessment of risk of bias, methodological quality and reporting quality.[1]

Objectives

The impact of the SPIRIT statement on the reporting quality of RCT protocols in health research is unknown. The primary objectives of this study are to 1) determine the reporting quality of published RCT protocols before and after the SPIRIT statement, and 2) determine whether author, trial or journal factors are associated with the reporting quality of published RCT protocols.

Methods

Study design

We conducted a methodological study in accordance with a prospectively registered protocol (PROSPERO CRD42019126522).

Setting

RCT protocols were identified by electronically searching the bibliographic databases MEDLINE, EMBASE and CENTRAL using a search strategy formulated by an experienced medical librarian (Appendix A). All searches were performed independently by two investigators on 29 March 2019.

Included protocols

RCT protocols were eligible for inclusion if they were (a) written for an RCT of living humans, (b) published in full-text in a peer-reviewed journal, and (c) published in the English language. RCT protocols were excluded if they (a) were published only in protocol databases or online registries, or (b) reported any study results.

We screened RCT protocols until we retrieved two equal, arbitrary samples of 150 RCT protocols published before and after the SPIRIT statement. The sample of 150 RCT protocols published immediately before the SPIRIT statement were retrieved by searching for RCT protocols published from 28 December 2012 and proceeding retrospectively until 150 eligible RCT protocols were selected. Similarly, the sample of 150 RCT protocols published recently since the SPIRIT statement were selected by searching for RCT protocols published from 20 March 2019 and proceeding retrospectively until 150 eligible RCT protocols were retrieved. The titles and abstracts of all retrieved RCT protocols were independently screened by two investigators and the full texts of relevant RCT protocols were independently assessed for eligibility by two investigators. Any disagreements were resolved by discussion between the two investigators and, if required, arbitration by a third

investigator. All eligible RCT protocols were imported into Endnote X9 (Clarivate Analytics) software. Duplicates were removed by manually screening by author, year, title and journal.

Variables

The primary variables of interest were the checklist items from the SPIRIT statement, defined in the SPIRIT statement explanation and elaboration.[1] A data extraction form was developed based on the checklist items from the SPIRIT statement. Two checklist items (items 4 and 12) were subcategorised to reflect binary criterion and provide appropriate granularity. The checklist item 'funding' was split into 'funding source', defined as sources of financial, material and other support (e.g. name and location of the funder), and 'funding type', defined as type of financial, material and other support (e.g. funds, equipment, drugs, services). The checklist item 'outcomes' was split into 'primary, secondary and other outcomes' (e.g. the specific measurement variable, analysis metric, method of aggregation and time point for each outcome), and 'explanation of clinical relevance of chosen efficacy and harm outcomes'. This resulted in a total of 53 individual checklist items. Each checklist item was assessed as either adequate or inadequate/unclear. The data extraction form and assessment criteria were independently piloted for ten randomly selected RCT protocols by five investigators. Disagreements were resolved by fortnightly roundtable meetings attended by five investigators and the definitions of adequate and inadequate/unclear for each checklist item were revised accordingly.

The secondary variables of interest related to author, trial and journal factors. Author factors included the number of authors per protocol and the presence of authors with expertise or experience in epidemiology or statistics (defined as one or more authors with either a degree in clinical epidemiology, public health or biostatistics, or an affiliation to a clinical epidemiology, public health or biostatistics department [14, 15]). Trial factors included the total planned sample size, centre status (i.e. multicentre or single centre), protocol word length (i.e. greater or less than 3,500 words), and funding source (i.e. industry or non-industry funding). Protocol report of compliance with the SPIRIT statement and publicly reported journal policy of compliance with the SPIRIT statement in the instructions to authors on the journal website, as of 2019, was also collected for RCT protocols published after the SPIRIT statement.

Data measurement

Data extraction was performed on the 300 RCT protocols. Data extraction of the first 100 RCT protocols was independently duplicated by two investigators and data extraction of the remaining 200 RCT protocols was completed once between two investigators. Any issues with data extraction were discussed at fortnightly roundtable meetings attended by five investigators.

Statistical methods

The final datapoints used for analysis were the results of the duplicate data collection and discussion of disagreements. We performed descriptive analysis of the primary outcome by calculating the proportion (percentage) of checklist items which were adequately reported in RCT protocols. This was considered a measure of the overall reporting quality of RCT protocols. We also calculated the proportion (percentage) of RCT protocols which adequately reported each checklist item. Inter-rater agreement and kappa scores were calculated on the initial datapoints extracted by independent duplicate data collection (i.e. before discussion of disagreements) of the first 100 RCT protocols. We performed exploratory multiple linear regression analysis to determine whether author, trial or journal factors were associated with the reporting quality of RCT protocols. Stepwise backward linear regression was performed, using $p < 0.25$ as the criterion for inclusion in a multiple regression model, and R^2 as the criterion for removal of variables in the backward elimination model. A p value <0.05 was considered statistically significant, and the R^2 value was used as a measure of the final model goodness of fit. All statistical analyses were stratified by publication before or after the SPIRIT statement and were performed using Stata software (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LP).

Patient and public involvement

As this was a study of RCT protocols, there was no patient or public involvement in the conception, design or conduct of the study, or the writing or editing of this paper.

Results

Included protocols

A total of 300 RCT protocols were retrieved; 150 from before the SPIRIT statement (9 July 2012 to 28 December 2012) and 150 from after the SPIRIT statement (25 January 2019 to 20 March 2019). In the full-text eligibility assessment of RCT protocols published before the SPIRIT statement, 25 articles were excluded because they did not describe an RCT protocol, two because they had been retracted, one because it included study results, and one because it was not published in full-text. In the full-text eligibility assessment of RCT protocols published after the SPIRIT statement, six articles were excluded because they did not describe an RCT protocol. All excluded articles were replaced with eligible studies. The final 300 RCT protocols were published across 45 peer-reviewed journals, with 46% (138/300) published in *Trials*.

The inter-rater agreement for data extraction of the first 100 RCT protocols ranged from 64.5% to 100%, with Kappa scores provided in Appendix B. The individual checklist items with the lowest and highest inter-rater agreement were 'statistical methods: statistical methods to handle missing data' and 'background and rationale: explanation for choice of comparators', respectively. The checklist items with the lowest and highest Kappa scores were 'research ethics approval' and 'background and rationale: explanation for choice of comparators', respectively.

Descriptive data

Author and trial characteristics were similar before and after the SPIRIT statement (Table 1).

Table 1. **Author and trial characteristics before and after the SPIRIT statement**

	Before the SPIRIT statement	**After the SPIRIT statement**
Author characteristics		
Authors per protocol (median, range)	8, 1-90	8, 2-80
One or more authors with expertise or experience in epidemiology or statistics (n, %)	50, 33.3%	48, 32%
Trial characteristics		
Total planned sample size (median)	214.5	200
Multicentre status (n, %)	70, 46.7%	64, 42.7%
Protocol word length >3500 (n, %)	105, 70%	106, 70.7%
Industry funding (n, %)	8, 6%	10, 7%

Of RCT protocols published after the SPIRIT statement, 42.7% (64/150) self-reported compliance with the SPIRIT statement, and 88% (132/150) were published in a peer-reviewed journal with a publicly reported policy of compliance with the SPIRIT statement. Additionally, only 17/300 (6%) of RCT protocols were published in journals which published in print, while the remainder (94%) were published in journals which published exclusively online. The mean word count of RCT protocols published in online journals and print journals was 4387 words and 3581 words, respectively, with an 806 word difference in mean word count (95% CI 26 -1586 words, p=0.04).

Outcome data

Of the 150 RCT protocols published before the SPIRIT statement, an average of 47.9% of checklist items per RCT protocol were adequately reported (95% CI, 46.5-49.3%). Comparably, of the 150 RCT protocols published after the SPIRIT statement, an average of 56.7% of checklist items were adequately reported (95% CI, 54.9-58.5%). This represents an 8.8% (95% CI, 6.6-11.1%; p<0.0001) mean improvement in the overall proportion of checklist items adequately reported since the SPIRIT statement.

Of the 53 individual checklist items, 21 (40%) had a significant increase ($p<0.05$) in adequate reporting since the SPIRIT statement (Figure 1) and 6 (11.3%) had a significant decrease ($p<0.05$) in adequate reporting since the SPIRIT statement (Appendix C). 23 individual checklist items were inadequately or not reported in more than half of all RCT protocols (Figure 2). Only one checklist item was adequately reported in all 300 RCT protocols – 'background and rationale: description and justification of research question'. None of the 300 RCT protocols adequately reported all individual checklist items from the SPIRIT statement and no individual checklist items were inadequately or not reported in all 300 RCT protocols.

Table 2 shows the multiple regression analysis of the association between author, trial and journal factors and the reporting quality of RCT protocols. The final model had an adjusted R2 value of 0.37, indicating that 37% of the variability in SPIRIT score was explained in our model. Author self-reported compliance with the SPIRIT statement was not associated with actual compliance with the SPIRIT statement. However, publicly reported journal policy of compliance with the SPIRIT statement was associated with significantly improved reporting quality. Industry funding was not associated with compliance with the SPIRIT statement, with only a 0.3% (95% CI -4.9% - 5.6%, p=0.9) difference in mean SPIRIT scores between industry and non-industry funded trials. Similarly, publication type (either print or exclusively online) was not associated with compliance with the SPIRIT statement (p=0.29). As such, industry funding and publication type were not included in the regression analysis as our pre-planned regression modelling limited the inclusion of variables to only those with potential statistical influence.

Table 2. **Multiple regression analysis of author, trial and journal characteristics associated with the reporting quality of RCT protocols**

	Increase in proportion of adequately reported checklist items from the SPIRIT statement	**p-value**
Author characteristics		
Number of authors per protocol	0.2%	0.004
One or more authors with expertise or experience in epidemiology or statistics	2.6%	0.016
Trial characteristics		
Multicentre status	4.6%	0.000
Protocol word length >3500	6.5%	0.000
Protocols self-reporting compliance with the SPIRIT statement	-	0.145
Journal characteristics		
Journal policy of compliance with the SPIRIT statement	6.2%	0.000

Discussion

Key results

We assessed the reporting quality of published RCT protocols before and after the SPIRIT statement. We found a significant improvement in the completeness of RCT protocols published since the SPIRIT statement. Although our study suggests significant improvements in the overall reporting quality of RCT protocols published after the SPRIT statement, these significant improvements were only seen in 40% (21/53) of individual checklist items, and there were no RCT protocols in which all individual checklist items were complete.

Limitations

Our study is limited by the lack of blinding of data collectors to the date of publication of RCT protocols, introducing the possibility for researcher bias. This was minimised through strict adherence to pre-defined parameters for the assessment of the checklist items from the SPIRIT statement,

fortnightly roundtable meetings, and duplication of data collection for one third of RCT protocols. Our study was also limited by the inclusion of only RCT protocols published in the English language.

The associations found in this study may not be causal, and the improvements in overall reporting quality may be due to underlying secular trends whereby RCT protocol quality improves over time, unrelated to the introduction of the SPIRIT statement. However, the association between specific journal requirement for the SPIRIT statement, and reporting to that requirement, suggests some degree of causation. Additionally, whilst none of the 300 RCT protocols adequately reported all individual checklist items from the SPIRIT statement, some checklist items may not be relevant to all RCT protocols and thus the level of under-reporting observed here may be a slight overestimate.

Interpretation

Despite the significant improvement in the overall reporting quality of RCT protocols suggested by our study, three individual checklist items from the SPIRIT statement were inadequately or not reported by more than 90% of RCT protocols: 'consent or assent: ancillary studies', 'dissemination policy: authorship eligibility guidelines and any intended use of professional writers' and 'informed consent materials'.

The low completeness of checklist item 'consent or assent: ancillary studies' may be related to a misperception by authors that it is not necessary to report the decision that participant data or biological specimens will not be used in ancillary studies. However, deciding and reporting on the provisions of additional consent for ancillary studies is important, particularly given the increasing emphasis on data sharing plans. A similar sentiment may explain the low completeness of checklist item 'informed consent materials: model consent form and other related documentation given to participants and authorized surrogates', as authors may consider it sufficient to describe a plan to obtain informed consent and not necessary to provide the model consent form. However, providing the model consent form is important in determining that the relevant information is delivered with sufficient detail at an appropriate literacy level for the target population. Additionally, the low completeness of checklist item 'dissemination policy: authorship eligibility guidelines and any intended use of professional writers' may be underpinned by an underappreciation of the importance of disclosing the use of professional writers. A study of industry-initiated RCTs reported that 91% of 44 RCT protocols had evidence of ghost authorship.[12]

The factors associated with higher reporting quality of RCT protocols in multiple regression analysis were one or more authors with expertise or experience in epidemiology or statistics, multicentre trials, longer protocol word length and publicly reported journal policy of compliance with the SPIRIT statement. The association between author expertise or experience in epidemiology or statistics and higher reporting quality has previously been reported [16] and may be related to education in the importance of transparency and experience in writing RCT protocols. In a similar way, the association between multicentre trials and higher reporting quality may be explained by the larger nature of these studies and, by extension, the greater level of support available to these studies for writing the protocol and greater importance of transparently and completely reporting the protocol. Additionally, the association between longer protocol word lengths and higher reporting quality may be underpinned by the capacity to more completely describe a planned RCT with more permitted words. This would support a more discretionary, individualised approach to determining appropriate word lengths of RCT protocols, rather than arbitrary, blanket cut-offs.

Interestingly, protocol report of compliance with the SPIRIT statement was not a significant predictor of reporting quality after adjusting for publicly reported journal policy of compliance with the SPIRIT statement. A possible explanation for this finding is that some authors who are aware of either the SPIRIT statement or the journal's policy of compliance with the SPIRIT statement may decide to self-report compliance with the SPIRIT statement without actually applying the checklist. This suggests that author self-report of compliance with the SPIRIT statement cannot be relied upon as a proxy indicator of reporting quality as awareness of the SPIRIT statement does not translate into application of the checklist. Rather, the association between publicly reported journal policy of compliance with the SPIRIT statement and higher reporting quality supports the role of journals and editors in checking adherence to the SPIRIT statement to improve the completeness and transparency of RCT protocols. Some possible aids for journals and editors checking adherence to

the SPIRIT statement include mandated author completed pre-submission checklists, structured online manuscript submission systems and automated manuscript reporting quality checks. Other avenues include incorporating the SPIRIT statement into the mandatory fields required by clinical trial registries (e.g. ClinicalTrials.gov, ANZCTR and ISRCTN). This is particularly relevant given many trials may be registered but do not have published protocols.

The findings from our research expand on those of Gao et al. (2016), who assessed the reporting quality of 142 RCT protocols in acupuncture using the checklist items from the SPIRIT statement.[17] However, we found a substantially larger number of checklist items whose completeness significantly improved after the SPIRIT statement (5 in Gao et al. (2016) and 21 in our study) [17]. This difference may be explained by the time since the SPIRIT statement; while Gao et al. (2016) assessed RCT protocols published 1-2 years after the SPIRIT statement, our study assessed RCT protocols published 6-7 years after the SPIRIT statement. This could suggest increasing awareness and adoption of the SPIRIT statement over time. More recently, Yang et al. (2018) assessed the reporting quality of 126 trial protocols in anaesthesia against the SPIRIT statement, and found no significant improvement in the completeness of trial protocols published after the SPIRIT statement and substantially more checklist items which were inadequately or not reported by more than 90% of included trial protocols (18 by Yang et al. (2018) and 3 in our study). However, their findings were limited by the small sample size of 18 trial protocols from after the SPIRIT statement.[18]

Overall, there remains substantial opportunity for further improvement. A study of emergency medicine journals found that reporting guidelines, including the SPIRIT statement, were infrequently endorsed,[19] and a scoping review of systematic reviews of adherence to other reporting guidelines reported insufficient adherence.[20] These findings suggest that the challenges to improving adherence to the SPIRIT statement are shared with other reporting guidelines. The focus should be on increasing the awareness of the SPIRIT statement throughout the research community, particularly amongst trial investigators, and promoting the adoption of the SPIRIT statement in the editorial community, specifically by advocating for mandated adherence to reporting guidelines. Improving the reporting quality of RCT protocols is necessary to improve the completeness and transparency of RCTs, and, by extension, the validity and reliability of RCT outcomes which ultimately contribute to informing patient care. It is likely that continued and concerted efforts by journals, editors, reviewers and investigators to advocate for adherence to the SPIRIT statement would improve the completeness and transparency of RCT protocols.

Contributorship statement: The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ZWT contributed to curating the data, analysed the data, administrated the project and contributed to reviewing the manuscript. ACT drafted the original manuscript, and edited the reviewed manuscript. MS and JT contributed to curating the data and reviewing the manuscript. TL, IH, JN, MP, LH and KC contributed to review the manuscript. SA conceptualised the study, designed the methodology, and contributed to reviewing the manuscript. All authors met the ICMJE criteria for authorship and contributed to the revision of the manuscript. ZWT is guarantor.

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Competing interests declaration: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not applicable. This is a methodological study of publicly available, published RCT protocols.

Data sharing: No additional data available.

Transparency statement: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned and registered have been explained.

Figure captions:
Figure 1. Checklist items with a significant increase in adequate reporting after the SPIRIT statement
Figure 2. Completeness of RCT protocols by checklist items, before and after the SPIRIT statement

References

1. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj. 2013;346:e7586.
2. Chan AW, Upshur R, Singh JA, Ghersi D, Chapuis F, Altman DG. Research protocols: waiving confidentiality for the greater good. Bmj. 2006;332(7549):1086-9.
3. Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. Jama. 2004;291(20):2457-65.
4. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PLoS ONE. 2008;3(8):e3081.
5. Hernandez AV, Steyerberg EW, Taylor GS, Marmarou A, Habbema JD, Maas AI. Subgroup analysis and covariate adjustment in randomized clinical trials of traumatic brain injury: a systematic review. Neurosurgery. 2005;57(6):1244-53; discussion -53.
6. Chan AW, Hrobjartsson A, Jorgensen KJ, Gotzsche PC, Altman DG. Discrepancies in sample size calculations and data analyses reported in randomised trials: comparison of publications with protocols. Bmj. 2008;337:a2299.
7. Pildal J, Chan AW, Hrobjartsson A, Forfang E, Altman DG, Gotzsche PC. Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study. Bmj. 2005;330(7499):1049.
8. Mhaskar R, Djulbegovic B, Magazin A, Soares HP, Kumar A. Published methodological quality of randomized controlled trials does not reflect the actual quality assessed in protocols. J Clin Epidemiol. 2012;65(6):602-9.
9. Hrobjartsson A, Pildal J, Chan AW, Haahr MT, Altman DG, Gotzsche PC. Reporting on blinding in trial protocols and corresponding publications was often inadequate but rarely contradictory. J Clin Epidemiol. 2009;62(9):967-73.
10. Scharf O, Colevas AD. Adverse event reporting in publications compared with sponsor database for cancer clinical trials. J Clin Oncol. 2006;24(24):3933-8.
11. Al-Marzouki S, Roberts I, Evans S, Marshall T. Selective reporting in clinical trials: analysis of trial protocols accepted by The Lancet. Lancet. 2008;372(9634):201.
12. Gotzsche PC, Hrobjartsson A, Johansen HK, Haahr MT, Altman DG, Chan AW. Ghost authorship in industry-initiated randomised trials. PLoS Med. 2007;1(1):e19.
13. Lundh A, Krogsboll LT, Gotzsche PC. Access to data in industry-sponsored trials. Lancet. 2011;378(9808):1995-6.
14. Adie S, Harris IA, Naylor JM, Mittal R. CONSORT compliance in surgical randomized trials: are we there yet? A systematic review. Ann Surg. 2013;258(6):872-8.
15. Adie S, Ma D, Harris IA, Naylor JM, Craig JC. Quality of conduct and reporting of meta-analyses of surgical interventions. Ann Surg. 2015;261(4):685-94.
16. Adie S, Harris IA, Naylor JM, Mittal R. Are outcomes reported in surgical randomized trials patient-important? A systematic review and meta-analysis. Can J Surg. 2017;60(2):86-93.
17. Gao L, Sha T, Chen B, Li M, Pan X, Chen Z, et al. Study protocols on randomized clinical trials of acupuncture: An assessment of reporting quality with the SPIRIT statement. European Journal of Integrative Medicine. 2016;8(6):881-7.
18. Yang L, Chen S, Yang D, Li J, Wu T, Zuo Y. A quality analysis of clinical anaesthesia study protocols from the Chinese clinical trials registry according to the SPIRIT statement. Oncotarget. 2018;9(37):24830-6.
19. Sims MT, Henning NM, Wayant CC, Vassar M. Do emergency medicine journals promote trial registration and adherence to reporting guidelines? A survey of "Instructions for Authors". Scand J Trauma Resusc Emerg Med. 2016;24(1):137.
20. Samaan Z, Mbuagbaw L, Kosa D, Borg Debono V, Dillenburg R, Zhang S, et al. A systematic scoping review of adherence to reporting guidelines in health care literature. Journal of Multidisciplinary Healthcare. 2013;6:169-88.

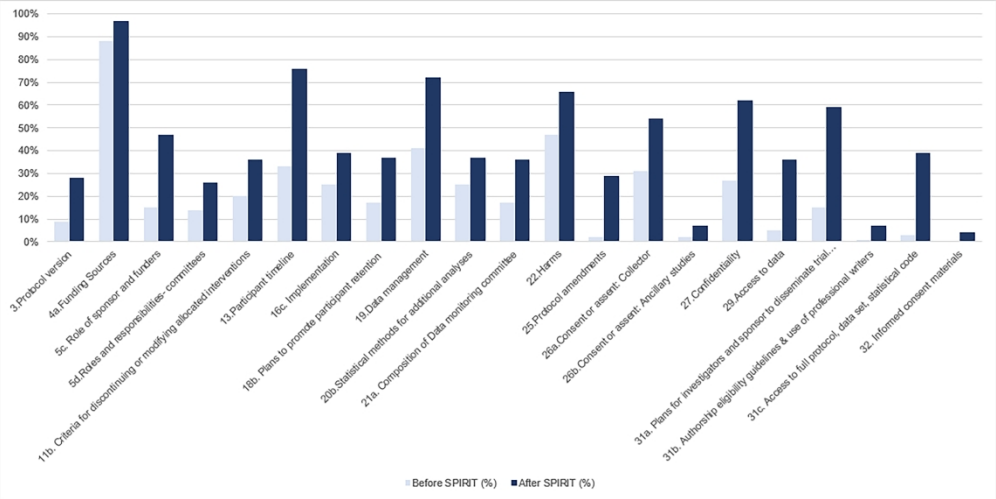

Figure 1. Checklist items with a significant increase in adequate reporting after the SPIRIT statement

276x138mm (600 x 600 DPI)

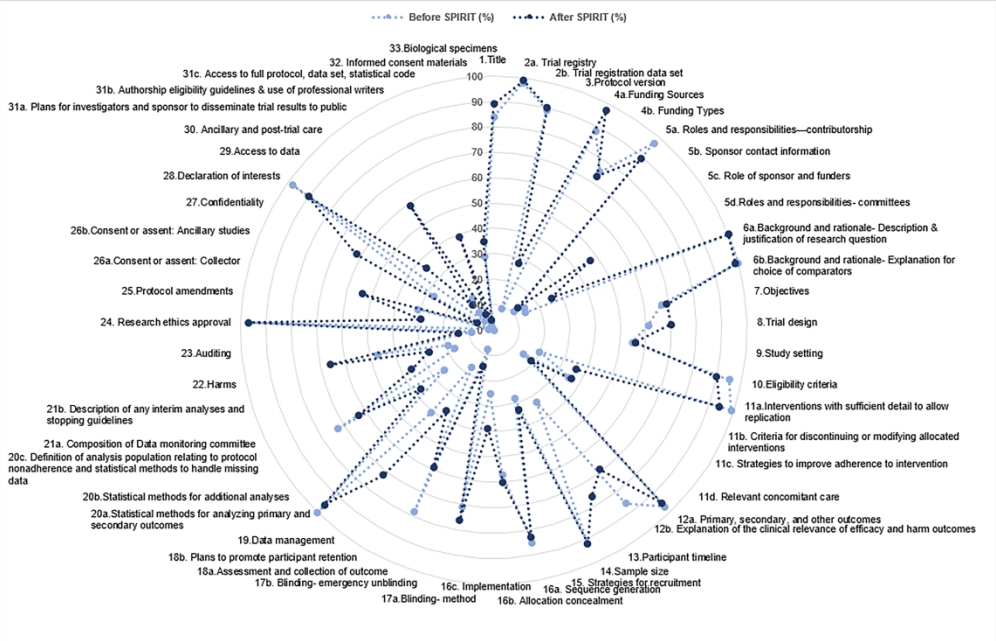

Figure 2. Completeness of RCT protocols by checklist items, before and after the SPIRIT statement

280x180mm (600 x 600 DPI)

Appendix A

Search strategy

('protocol'/exp OR (protocol):ti) AND ('randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/de OR ((random* NEAR/3 trial*)):ab,ti) AND [2008-2012]/py

('protocol'/exp OR (protocol):ti) AND ('randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/de OR ((random* NEAR/3 trial*)):ab,ti) AND [2014-2019]/py

Appendix B

Inter-rater agreement of checklist items from the SPIRIT statement

Section/Item	No.	Checklist Items	Kappa Score	Agreement (%)
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	0.49	92.3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1	100
	2b	All items from the World Health Organization (WHO) Trial Registration Data Set	0.01	75.3
Protocol version	3	Date and version identifier	0.61	83.9
Funding	4a	Funding Sources: Sources of financial, material, and other support	0.39	91.4
	4b	Funding Types: Sources of financial, material, and other support	0.15	70.7
Roles and responsibility	5a	Names, affiliations, and roles of protocol contributors	0.58	95.7
	5b	Name and contact information for the trial sponsor	0.19	78.3
	5c	Role of study sponsor and funders	0.67	83.7
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial	0.35	72
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies examining benefits and harms for each intervention	1	100
	6b	Explanation for choice of comparators	1	100
Objectives	7	Specific objectives or hypotheses	0.24	73.1
Trial design	8	Description of trial design, including type of trial, allocation ratio, and framework	0.27	67.7
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings and list of countries where data will be collected. Reference to where list of study sites can be obtained	0.29	67
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions	0.35	90.3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered.	0.07	87.1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant	0.33	69.9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	0.50	76.3
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	0.54	85
Outcomes	12a	Primary, secondary, and other outcomes, including the specific measurement variable	0.15	79.6

		pressure), analysis metric, method of aggregation, and time point for each outcome.		
	12b	Explanation of the clinical relevance of chosen efficacy and harm outcomes	0.12	66.7
Participant timeline	13	Time schedule of enrolment, interventions, assessments, and visits for participants	0.46	80.7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	0.49	97.8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	0.47	75.3
Assignment of interventions (for controlled trials)				
Allocation Sequence generation	16a	Method of generating the allocation sequence, and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.	0.50	83.9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence, describing any steps to conceal the sequence until interventions are assigned	0.44	72.8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	0.38	71
Blinding (masking)	17a	Who will be blinded after assignment to interventions, and how	0.24	71.6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	0.73	93.8
Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality and a description of study instruments along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.	0.25	68.8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	0.46	74.2
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality.	0.67	83.9
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.	-0.03	91.4
	20b	Methods for any additional analyses	0.61	80.7
	20c	Definition of analysis population relating to protocol nonadherence, and any statistical methods to handle missing data	0.25	64.5
Monitoring				
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details	0.60	81.7

		about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.		
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	0.76	90.3
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	0.67	83.9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	0.35	83.9
Ethics and dissemination				
Research ethics approval	24	Plans for seeking REC/IRB approval	-0.06	87.1
Protocol amendments	25	Plans for communicating important protocol modifications to relevant parties	0.70	89.3
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how	0.68	83.9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	0.25	92.2
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	0.70	85
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	0.13	83.9
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	0.65	83.9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	0.31	83.9
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups, including any publication restrictions	0.65	82.8
	31b	Authorship eligibility guidelines and any intended use of professional writers	0.29	88.2
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	0.55	81.7
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	0.66	98.9
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	0.62	80

Appendix C

Checklist items from the SPIRIT statement by mean completeness in RCT protocols

Section/Item	Item Number	Checklist Items	Before SPIRIT N=150	After SPIRIT N=150
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	126 (84%)	134 (89%)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	147 (98%)	149 (99%)
	2b	All items from the World Health Organization (WHO) Trial Registration Data Set	133 (89%)	135 (90%)
Protocol version	3	Date and version identifier	14 (9%)	42 (28%)
Funding	4a	Funding Sources: Sources of financial, material, and other support	131 (88%)	145 (97%)
	4b	Funding Types: Sources of financial, material, and other support	111 (75%)	108 (73%)
Roles and responsibility	5a	Names, affiliations, and roles of protocol contributors	145 (97%)	134 (89%)
	5b	Name and contact information for the trial sponsor	17 (11%)	19 (13%)
	5c	Role of study sponsor and funders	23 (15%)	69 (47%)
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial	21 (14%)	39 (26%)
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies examining benefits and harms for each intervention	150 (100%)	150 (100%)
	6b	Explanation for choice of comparators	150 (100%)	149 (99%)
Objectives	7	Specific objectives or hypotheses	100 (67%)	104 (69%)
Trial design	8	Description of trial design, including type of trial, allocation ratio, and framework	92 (61%)	105 (70%)
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings and list of countries where data will be collected. Reference to where list of study sites can be obtained	80 (55%)	84 (56%)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions	143 (95%)	135 (90%)

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered.	148 (99%)	141 (94%)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant	30 (20%)	54 (36%)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	52 (35%)	54 (36%)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	23 (15%)	28 (19%)
Outcomes	12a	Primary, secondary, and other outcomes, including the specific measurement variable pressure), analysis metric, method of aggregation, and time point for each outcome.	146 (97%)	143 (95%)
	12b	Explanation of the clinical relevance of chosen efficacy and harm outcomes	129 (86%)	103 (69%)
Participant timeline	13	Time schedule of enrolment, interventions, assessments, and visits for participants	50 (33%)	114 (76%)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	138 (92%)	137 (92%)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	42 (28%)	50 (33%)
Assignment of interventions (for controlled trials)				
Allocation Sequence generation	16a	Method of generating the allocation sequence, and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.	127 (85%)	124 (83%)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence, describing any steps to conceal the sequence until interventions are assigned	85 (57%)	90 (60%)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	37 (25%)	58 (39%)
Blinding (masking)	17a	Who will be blinded after assignment to interventions, and how	94 (71%)	102 (76%)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a	10 (8%)	20 (15%)

		participant's allocated intervention during the trial		
Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality and a description of study instruments along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.	117 (78%)	88 (59%)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	25 (17%)	56 (37%)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality.	61 (41%)	108 (72%)
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.	150 (100%)	144 (96%)
	20b	Methods for any additional analyses	38 (25%)	55 (37%)
	20c	Definition of analysis population relating to protocol nonadherence, and any statistical methods to handle missing data	110 (73%)	95 (63%)
Monitoring				
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.	25 (17%)	53 (36%)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	28 (19%)	41 (27%)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	70 (47%)	99 (66%)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be	14 (9%)	21 (14%)

		independent from investigators and the sponsor		
Ethics and dissemination				
Research ethics approval	24	Plans for seeking REC/IRB approval	145 (97%)	145 (97%)
Protocol amendments	25	Plans for communicating important protocol modifications to relevant parties	3 (2%)	44 (29%)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how	46 (31%)	81 (54%)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	3 (2%)	10 (7%)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	41 (27%)	93 (62%)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	147 (98%)	135 (90%)
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	7 (5%)	54 (36%)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14 (9%)	20 (13%)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups, including any publication restrictions	23 (15%)	88 (59%)
	31b	Authorship eligibility guidelines and any intended use of professional writers	2 (1%)	10 (7%)
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	5 (3%)	59 (39%)
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	0 (0%)	6 (4%)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	6 (29%)	8 (35%)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Not applicable to study type
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	12
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not applicable to study type
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable to study type
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable to study type
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable to study type
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable to study type
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable to study type
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8-9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

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