Systematic review protocol registration and reporting guidelines: development, implementation, assessment and utility

Alison Booth

PhD

University of York

Health Sciences

October 2020

1. Abstract

It is essential that systematic reviews are methodologically robust to minimise bias and well reported so users can have confidence in the findings. Limitations in the quality of published systematic reviews prompted my research into methodological aspects with the aim of improving the robustness of systematic review evidence.

I undertook an international Delphi consultation, with 200 experts agreeing a minimum data set for systematic review protocol registration. PROSPERO was designed and implemented based on the 22 required and 18 optional items identified as key protocol registration elements. An evaluation of the utility of the register at one year showed registration was feasible, with growing international engagement and positive feedback from the survey of users. I was subsequently involved in the consensus development of reporting guidelines for systematic review protocols leading to publication of the 17-item PRISMA-P checklist.

PROSPERO became a resource for methodological research, and I undertook an examination of outcome reporting bias, previously only possible in Cochrane reviews. In comparing the details in 96 published reviews with their PROSPERO records, 32% had discrepancies in their primary outcome and 39% did not specify a primary outcome. Having a favourable result or positive conclusion did not increase the risk of a discrepancy in outcome reporting.

Registration records can be the only publicly available source of planned methods, leading to my methodological study comparing registration data with protocol reporting guideline requirements. In a random sample of 439 PROSPERO records for reviews of health interventions, 53% (14,469/227,279) of the elements compared were classified as reported. This indicates that PROSPERO records are not a substitute for public access to a full protocol.

The research landscape has changed rapidly over the last decade and there is a need to revisit and clarify or re-purpose the roles of the systematic review protocol and protocol registration.

2. Table of contents

3. List of figures

4. Acknowledgements

I am grateful to my advisors, Dr Catriona McDaid and Professor Trevor Sheldon for their wise words and advice throughout the preparation of this thesis.

I will always be grateful for the opportunity given to me by Professor Lesley Stewart to run with the development of the systematic review protocol register and thank her for all her support. My thanks extend to the members of the PROSPERO and PRISMA-P advisory groups, from whom I learned a great deal. I thank all co-authors on my publications for their collaboration and the experience of shared learning.

Many friends and colleagues have supported me to undertake this PhD and provided much appreciated encouragement. In particular I thank Dawn Craig, Alison Eastwood, David Torgerson, Catherine Hewitt and Lorna Fraser.

For being endlessly supportive, patient and for supplying copious cups of tea, I thank my husband, Michael Booth.

5. Author's declaration

The six papers forming this thesis are listed below together with details of my contribution to each publication. I confirm that the integrative chapter exploring and linking the papers is entirely my own work. I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this or any other University. All sources are acknowledged as references.

Signed:  Dated: 1st October 2020

1 Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L. **Establishing a minimum dataset for prospective registration of systematic reviews: an international consultation.** *PLoS ONE* 2011;**6.** doi.org/10.1371/journal.pone.0027319

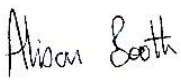
Candidate contribution: Conceived the idea, designed the study, led the consultation exercise and collected data; analysed the data; wrote the manuscript and subsequent revisions.

Signed:  Signed: 

Alison Booth Professor Lesley Stewart

2 Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, Stewart L. **The nuts and bolts of PROSPERO: an international prospective register of systematic reviews.** *Syst Rev* 2012;1:2. doi.org/10.1186/2046-4053-1-2

Candidate contribution: Conceived the idea, designed the study, undertook the Delphi consultation exercise; managed the acquisition, analysis and interpretation of the data and implemented the findings to develop the working PROSPERO register. Prepared the manuscript and subsequent revisions.

Signed:  Signed: 

Alison Booth Professor Lesley Stewart

3 Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, Stewart L. **PROSPERO at one year: an evaluation of its utility.** *Syst Rev* 2013;**2**:4. doi.org/10.1186/2046-4053-2-4

Candidate contribution: Member of advisory group who conceived the idea; designed the data collection and extraction. Designed the user survey; managed survey administration and data collection; undertook all the analyses and contributed to the interpretation of the data; produced the first draft of the article, undertook revisions and approved the final version.

Signed: Signed:

Alison Booth Professor Lesley Stewart

4. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L. [Booth A, member of PRISMA-P Group] **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: statement**. *Syst Rev* 2015;4:1-9. doi.org/10.1186/2046-4053-4-1

Candidate contribution: Member of the consensus group developing the reporting guideline; presented data from the PROSPERO Delphi to inform content of the guideline and contributed to discussions. Provided critical feedback on the draft paper, contributing intellectual content and approved the final version.

Signed: Signed:

Alison Booth Professor Lesley Stewart

5. Tricco AC, Cogo E, Page MJ, Polisena J, Booth A, Dwan K, MacDonald H, Clifford TJ, Stewart LA, Straus SE, Moher D. **A third of systematic reviews changed or did not specify the primary outcome: A PROSPERO register study**. 11 Apr 2016 Journal of Clinical Epidemiology. Doi 10.1016/jclinepi.2016.03.025

   Candidate contribution: Contributed to conceptualising and designing the study; commented on and pilot tested the data abstraction form. Obtained the PROSPERO dataset, screened the records for inclusion. Undertook data collection, appraised the quality of the included articles, edited the manuscript, and approved the final article.

   Signed: Signed:

   Alison Booth

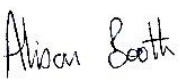
   

   Professor Lesley Stewart

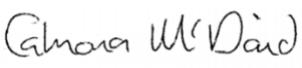
6. Booth A, Mitchell A, Mott A, James S, Cockayne S, Gascoyne S, McDaid C. **An assessment of the extent to which the contents of PROSPERO records meet the systematic review protocol reporting items in PRISMA-P [version 2; peer review: 2 approved].** F1000Research 2020; 9. DOI: 10.12688/f1000research.25181.2.

   Candidate contribution: Conceptualised the study, designed the study and developed the protocol. Developed the assessment tool and guidance, provided training and validation checks on assessments. Undertook assessments. Managed data curation, including posting documents and data on open access software. Undertook analyses, drafted the manuscript, undertook revisions and submitted for publication.

   Signed: Signed:

   Alison Booth

   Dr Catriona McDaid

6. Introduction

Health care policy and practice should be informed by the best available research evidence.[1, 2] The volume of primary research evidence being published is such that busy clinicians and policy makers struggle to keep up to date.[3] In addition, many are not prepared or equipped to accurately judge the quality and reliability of the research.[4-6] Variations in findings between studies of the same topic can lead to confusion and the potential for clinicians to believe they are following best practice while actually providing sub-optimal care or causing harm.[7] Systematic reviewing was developed as a rigorous research method for bringing together existing evidence to answer a specific question. The use of a systematic approach to the identification, selection, appraisal and synthesis of the evidence, aims to reduce the risk of biases, thereby providing reliable, robust findings. Systematic review evidence now underpins clinical policy and practice.[8, 9] Issues with the robustness of systematic review evidence led to my research to facilitate improvement in transparency of systematic review methods and quality of reporting. My six papers, published between 2011 and 2020, show progress through building and evaluating a prospective register of review protocols, publishing a protocol reporting guideline, to the use of both in methodological research.

In research, robustness may be compromised by bias, which occurs when systematic error is introduced into the research process, consciously or unconsciously. Such errors can be introduced in the design, conduct, analysis or reporting of the study. Depending on what the error is and where it occurs, the reliability of the research findings may be affected to a greater or lesser extent. Researchers need to take steps to minimise the risks of bias wherever possible. Readers of published research need to consider how biases have been addressed and what the impact might be on the findings. This can be challenging: a mapping study in 2010 identified 235 terms for biases in the literature.[10]

It was recognised from before the launch of The Cochrane Collaboration in 1992 that the same scientific principles that applied to the design, conduct, analysis and reporting of primary research should also be applied to systematic reviews.[7] Systematic reviewers need to deal with the biases of primary studies included in reviews while at the same time avoiding the introduction of bias in their own

research.[11] However, as the number of systematic reviews published increased, empirical studies demonstrated the extent of bias in the application of review methods. Compounding this problem was a lack of transparency through poor reporting and the existence of unnecessary duplication of effort where multiple reviews addressing the same question were published without clear justification, such as new trial evidence.[12-16] Increasing awareness led to international efforts to try and address these problems.

The international EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network, was set up in 2008 with the aim of,

> "*improving the reliability and value of published health research literature by promoting transparent and accurate reporting and wider use of robust reporting guidelines.*"[17]

EQUATOR activities include: supporting the development of systematic review and clinical guidelines; making reporting guidelines readily available to users; and promoting the routine use of such guidelines by researchers, editors and peer reviewers.

In 2009, the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were published, to aid the reporting of reviews.[18, 19] Fifteen of the 27 PRISMA checklist items are for elements that should be included in the review protocol. Item 5 indicates that the existence and availability of a review protocol should be reported and registration details provided if available. The authors of the PRISMA guidelines were aware that the publication and registration options for systematic review protocols were at that time limited. Nonetheless, they wanted to encourage such activities given the essential role the protocol plays in producing robust reviews. To assess whether a review has been well conducted but poorly reported or is a poorly conducted review, access to the planned methods is needed.

Developing and making publicly available a protocol setting out the methods in advance of carrying out a systematic review helps to minimise the risk of bias and aids accurate and complete reporting.[20-22] The protocol should then be followed throughout the review process. Where amendments to a protocol become necessary, the reason for the change should be justified and documented,

including the stage of the review when the change is made. By specifying criteria in advance of seeing the results of the searches for relevant studies, many potential biases may be minimised. By making the protocol publicly available researchers can provide transparency in their methods, allowing readers such as peer reviewers and clinical guideline developers to compare what was planned with what was done.

At the time I started my research the options for making review protocols publicly available were mainly limited to organisations such as the Cochrane and Campbell Collaborations, the Joanna Briggs Institute and the websites of major funders such as the USA Agency for Healthcare Research and Quality (AHRQ), the Canadian Institutes for Health Research and the UK National Institute for Health Research (NIHR). Support for prospective registration of systematic review protocols gathered momentum.[18, 19, 23] In 2010, as a member of an international advisory group I announced our intention to develop a prospective register of systematic review protocols and my first two papers report on, "Establishing a minimum dataset for registration" and "The nuts and bolts" of developing the register.[24-26] PROSPERO, international prospective register of systematic reviews was launched in February 2011 and my third paper reports, "PROSPERO at one year: an evaluation of its utility".[27]

The fourth paper in this thesis is the, "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement".[28] In addition to improving the standard of reporting, the guideline aimed to confirm the essential role a protocol plays in rigorous review methods and included calls to stakeholders for actions to ensure widespread implementation.

Protocol registration and the reporting guideline initiatives shared the goal of improving the quality of systematic reviews through their stated function. In addition, it was anticipated that the protocol register would become a resource for research on various aspects of systematic review methods and quality. PRISMA-P provided a standard against which completeness of protocol reporting could be assessed. In January 2014, the Lancet launched a series of publications by international experts on increasing value and reducing waste in research. Under-reporting, biased and incomplete reporting were identified as key contributors to waste.[29] The papers identified the provision of trial and review protocol reporting guidelines and systematic review protocol registration as

important new initiatives for improving quality.[30, 31] My fifth paper, "A third of systematic reviews changed or did not specify the primary outcome: a PROSPERO register study", demonstrates that the register quickly became a useful resource for research.[32]

Growing references to PROSPERO records as protocols in the methods literature prompted me to think about whether it had been appropriate to suggest in paper two that registrations could potentially have similar utility to producing and publishing a systematic review protocol.[26] Calls for registration carried the implicit requirement that a protocol be prepared,[18, 19, 23] and key sources for review methods [20, 33, 34] and reporting guidelines [19, 28] make a distinction between preparing a protocol and registration. My final paper is, "An assessment of the extent to which the contents of PROSPERO records meet the systematic review protocol reporting items in PRISMA-P".[35]

This integrative chapter presents my research in chronological order and in the context in which each study was undertaken. It would perhaps have been more logical to develop the protocol reporting guidelines first and then the register. However, at the time of developing the register few review protocols were published other than within the Cochrane Collaboration and reporting of the existence of a protocol although improving was still inadequate.[13] It was unclear how often *a priori* methods were documented in any form and the thought was that public availability of key methods would be better than the *status quo*. We would at least have some indication of the volume of reviews being undertaken and a record with a named contact should the review never be published. In considering the changing research landscape, attitudes and technology I reflect on the distinction between a protocol and its registration.

7. Prospective registration of review protocols

Identification of poor reporting and biases in systematic reviews led to the idea of protocol registration, and ultimately to the launch of PROSPERO the international prospective register of systematic review protocols. The first three papers in this thesis present the rationale, development and one-year evaluation of PROSPERO.[25-27]

7.1 Biases affecting systematic reviews

Systematic review evidence became increasingly influential following the establishment of the Cochrane Collaboration in 1992.[7] In recognition of the need to avoid unnecessary duplication and ensure research resources were appropriately allocated, calls for primary studies to start and end with a systematic review of the current literature were made.[36, 37] Used by clinicians to keep up to date with the latest developments in their field, reviews also became the bedrock of clinical guideline development.[9, 38] The information presented in reviews therefore had to be detailed, methodologically sound and the findings reliable. However, by 2010, there was empirical evidence of biases in the conduct of published systematic reviews and growing recognition of the need to improve the completeness and consistency of review reports.[13, 15]

A key issue highlighted was outcome reporting bias, where outcomes are selectively reported once the results are known and choice is therefore influenced by the nature and direction of the results. Omitting or misrepresenting pre-specified outcomes can distort the evidence and has been found to occur in reports of both primary studies and in systematic reviews. Review integrity can be affected in two ways. Firstly, the systematic review methods used need to account for the possibility of outcome reporting bias in included primary studies.[16] Kirkham et al (2010) found that, after adjustment for outcome reporting bias in the primary studies in 42 Cochrane meta-analyses with a statistically significant result, eight (19%) became non-significant and 11 (26%) would have overestimated the treatment effect by at least 20%.[16] Secondly, review authors need to avoid selectively reporting the outcomes of their review. The planned primary outcome should be reported as such, even if it turns out not to be the most interesting finding. A second study by Kirkham et al (2010) comparing planned outcomes in Cochrane protocols with their published review found at

least one outcome discrepancy in 22% (64/288) of reviews, most of which (75% (48/64)) related to the primary outcome of the review.[15]

Cochrane reviews are considered to be of a high standard as they adhere to a strict and transparent process. They are guided by methods set out and regularly updated in the Cochrane Handbook; facilitated by dedicated software such as RevMan, Archie and Covidence; and overseen by experienced methodologists and clinical specialty focussed editorial teams.[21, 39] Crucially including *a priori* access to the full protocol. If these issues were occurring in Cochrane reviews, there had to be concerns about the existence and prevalence of similar problems in non-Cochrane systematic reviews. The inability to easily access protocols for non-Cochrane reviews was a barrier to transparency in review methods and a risk to the validity of review evidence.[40]

Another concern at the time was publication bias, where the nature of the findings or the direction of effect influences whether a study is published or not.[41] Whether through failure to get a manuscript accepted or a lack of inclination or time to write up non-significant or negative findings, there is evidence that studies with a significant finding are more likely to be published.[11, 12, 15, 42] This results in an overall imbalance in the published literature in favour of positive results. Publication bias in primary studies has been shown to impact the pooled summary estimate in systematic reviews.[42] Measures for reviews to combat publication bias in primary studies include searching for and inclusion of unpublished studies and an assessment of risk of publication bias as part of the systematic review methods.[42] These were not measures routinely reported in reviews.[13] Because it was not known how many non-Cochrane reviews were being undertaken, it was not possible to establish how many were published. So, whether systematic reviews were also prone to publication of those with significant positive results could not be established.

Clinical trial registration had been introduced in response to growing empirical evidence of bias in methods and lack of transparency about trials being undertaken.[12, 43] Prospective trial registration aimed to make planned methods permanently available irrespective of whether the study was subsequently completed or published. In addition, having the outcomes recorded prospectively facilitated the identification of outcome reporting bias in trials, where differences in priorities were reported in trial results papers.[44, 45] Identification of similar

quality issues prompted calls for systematic review protocol registration to provide the same transparency.[18, 19, 23]

7.2 The role of protocol registration

Compounding the problems of biases, lack of access to a protocol and incomplete or ambiguous reporting of completed reviews made assessment of validity of findings difficult. Many of the methods to deal with publication bias need to be considered at the protocol development stage of a systematic review. If information is not available, it is not possible to assess whether a review has been well conducted but poorly reported or whether it is a poorly conducted review. In either case it is hard to justify relying on the findings.[13, 14] There were two ways to try and improve access to planned methods: publish protocols and register protocols. In 2009 there were limited options and few drivers for publication of non-Cochrane review protocols, and no protocol reporting guidelines. In the absence of access to a protocol, prospective registration of key methods from a protocol could enable comparison of some planned aspects with the final review. Particularly helpful if the key items include how the authors propose to minimise the risk of publication bias and specify the intended outcomes. Protocol registration could also identify the systematic review as having a planned approach. However, there were also no dedicated registration options (some trials registers accepted review protocols, but the information fields were in-appropriate for such a different research methodology). Review protocol registration had the potential to encourage the production of a protocol and even if this was not published, enable authors to make their methods prospectively and publicly available. However, in retrospect, the distinction between preparing and ideally publishing a review protocol and registering a review protocol could have been more clearly articulated.

7.3 Designing and building the protocol register

The Centre for Reviews and Dissemination (CRD) had a track record in undertaking high quality systematic reviews in healthcare and running three highly accessed databases of health research.[46, 47] With support and funding from the National Institute for Health Research (NIHR), I took the lead in developing PROSPERO, an international register of systematic review protocols.[48] The first paper presented

in this thesis reports on the development of the register and details the registration process (Figure 1).[26]

Figure 1: Abstract for "The nuts and bolts of PROSPERO: an international prospective register of systematic reviews" *Systematic Reviews*, 2012.

Abstract

Background: Following publication of the PRISMA statement, the UK Centre for Reviews and Dissemination (CRD) at the University of York in England began to develop an international prospective register of systematic reviews with health-related outcomes. The objectives were to reduce unplanned duplication of reviews and provide transparency in the review process, with the aim of minimizing reporting bias.

Methods: An international advisory group was formed and a consultation undertaken to establish the key items necessary for inclusion in the register and to gather views on various aspects of functionality. This article describes the development of the register, now called PROSPERO, and the process of registration.

Results: PROSPERO offers free registration and free public access to a unique prospective register of systematic reviews across all areas of health from all around the world. The dedicated web-based interface is electronically searchable and available to all prospective registrants. At the moment, inclusion in PROSPERO is restricted to systematic reviews of the effects of interventions and strategies to prevent, diagnose, treat, and monitor health conditions, for which there is a health-related outcome.
Ideally, registration should take place before the researchers have started formal screening against inclusion criteria but reviews are eligible as long as they have not progressed beyond the point of completing data extraction.
The required dataset captures the key attributes of review design as well as the administrative details necessary for registration.
Submitted registration forms are checked against the scope for inclusion in PROSPERO and for clarity of content before being made publicly available on the register, rejected, or returned to the applicant for clarification.
The public records include an audit trail of major changes to planned methods, details of when the review has been completed, and links to resulting publications when provided by the authors.

Conclusions: There has been international support and an enthusiastic response to the principle of prospective registration of protocols for systematic reviews and to the development of PROSPERO.
In October 2011, PROSPERO contained 200 records of systematic reviews being undertaken in 26 countries around the world on a diverse range of interventions.

Keywords: Systematic review protocol, register, PROSPERO

My starting point was to look at how trial registration was set up and the issues encountered, with a view to identifying where similar issues might arise in applying this to systematic reviews and mitigating them where possible. A driver behind the international adoption of clinical trial registration was the obligation placed on researchers to conduct their research ethically and report the finding honestly in return for the altruism of study participants.[44, 49] Although research ethics approval is not required for the secondary use of data, researchers undertaking reviews also have a moral and ethical duty to ensure their use of participant data is honest and accurate and fully reported.[50] This includes the production, registration and adherence to a review protocol. Helpfully, the International Committee of Medical Journal Editors set out a list of requirements for trials registration required for publication in member journals.[49] Similarly, the World Health Organisation set standards for registers to be included in the International Clinical Trials Registry Platform.[45, 51-55]

Development of reporting guidelines anticipates that an 'executive group' will facilitate the work emphasising the importance of stakeholder buy-in.[56] For development of the registry I was involved in setting up, and being a member of,

an international advisory group. It was important to ensure members could provide expertise in different fields and types of reviews, including clinical and public health, epidemiology, Cochrane and non-Cochrane reviews. In addition, members had experience of international trials registers. This reflected the intention for the register to be broad in its inclusion criteria. However, this was a new initiative and we had no way of knowing the likely response or volume of registrations. We therefore decided that during development and initial registration we would focus on registration of protocols for reviews of healthcare interventions. The scope for inclusion would be expanded as and when this proved desirable and possible. Advisory group members ensured that throughout development, their particular area of interest was catered for.

Based on the approach used by clinical trials registers, the key elements I identified as necessary for the register to function were:

- A searchable web-based interface
- Free open public access to search and view records
- Free to register systematic review protocol details
- A minimum dataset
- A mechanism for confirming records are in scope and complete
- Entries have a permanent unique identification number assigned

These items could all be built into the database and public interface. The most challenging step was identifying what items registrations should contain.

7.4 Identifying a minimum registration dataset

The second publication in this thesis details the research undertaken to develop the minimum dataset (Figure 2).[25] There are different methodological approaches to establishing consensus agreement such as the nominal group technique, involving a panel of 9-12 experts, or a value-weighting survey where participants allocate points to indicate their priorities.[57-59] The Consensus Development Conference method, started in the USA in the 1980's, sought consensus through a public, face to face discussion of the issues.[60] However, the most frequently used method, particularly in clinical guideline development, is the Delphi technique. The original Delphi methodology was developed in the 1960's [61, 62] and involved deriving a group decision from a set of invited experts.[57] My approach was to combine a modified Delphi technique with aspects of the Consensus Development

Conference method. This combination allowed for inclusion of a wide range of stakeholders and international participation. It provided an anonymised and therefore non-competitive opportunity for all stakeholder groups to engage with the process and for me to capture the opinions of large numbers of participants.

Figure 2: Abstract for "Establishing a minimum dataset for prospective registration of systematic reviews: an international consultation" *PLoS ONE,* 2011.

Abstract

Background: In response to growing recognition of the value of prospective registration of systematic review protocols, we planned to develop a web-based open access international register. In order for the register to fulfil its aims of reducing unplanned duplication, reducing publication bias, and providing greater transparency, it was important to ensure the appropriate data were collected. We therefore undertook a consultation process with experts in the field to identify a minimum dataset for registration.

Methods and Findings: A two-round electronic modified Delphi survey design was used. The international panel surveyed included experts from areas relevant to systematic review including commissioners, clinical and academic researchers, methodologists, statisticians, information specialists, journal editors and users of systematic reviews. Direct invitations to participate were sent out to 315 people in the first round and 322 in the second round. Responses to an open invitation to participate were collected separately. There were 194 (143 invited and 51 open) respondents with a 100% completion rate in the first round and 209 (169 invited and 40 open) respondents with a 91% completion rate in the second round. In the second round, 113 (54%) of the participants reported having previously taken part in the first round. Participants were asked to indicate whether a series of potential items should be designated as optional or required registration items, or should not be included in the register. After the second round, a 70% or greater agreement was reached on the designation of 30 of 36 items.

Conclusions: The results of the Delphi exercise have established a dataset of 22 required items for the prospective registration of systematic reviews, and 18 optional items. The dataset captures the key attributes of review design as well as the administrative details necessary for registration.

A number of organisations such as the Institute for Healthcare Improvement, the Cochrane Collaboration and CRD had documented in their respective guides to review methods, the elements they required in a systematic review protocol. The first modification for the consultation was to use these publications to compile a comprehensive list of items for use as a starting point. This by-passed the first stage of a Delphi where participants would have been asked to contribute ideas to develop this list. The focus of the exercise could then be on identifying the protocol items most relevant to a registration record. Other modifications to the methods related to who was invited to participate, and that they were not asked to confirm participation in advance. Although a face to face public discussion was not feasible, it was possible with an electronic survey to include as many participants as possible. So, in addition to directly emailing a list of experts around the world, cascading of the survey link was encouraged through relevant organisations and individuals. With these modifications I aimed not only to identify the registration dataset, but also make our intention to develop a register known, gauge the level of support for registration and promote wide engagement and ownership.

A threshold of 70% or greater agreement was set for inclusion of items as Required or Optional fields, as indicated in responses. This figure was selected being greater than two-thirds of opinions indicating a clear majority. The first round of the consultation resulted in two of the initial 40 items being dropped and five being merged. The majority of participants felt that it was not possible to anticipate publication date and that if an economic analysis was going to be undertaken it should be included in fields such as title, review question and outcomes. Primary and secondary outcomes were considered essential while recording the measures to be used was not: outcomes and measures were merged. Further 'compromise' surrounded the different elements of the planned data synthesis: leading to methods for exploring heterogeneity and the rationale for use of techniques being merged into the field for data synthesis. Two items were added in response to participant suggestions: contact phone number and other registration details. The latter was thought to be important particularly to avoid duplication of registration of Cochrane reviews; the planned mechanism for automatically uploading these was later implemented.

The Ottawa Statement set out three requirements for trial registration: acquisition of a unique registration ID; registration of the original protocol and any amendments; and thirdly registering the trial results.[44] In the advisory group we discussed at length whether in addition to adding a link to a publication of the completed review, authors should be able to add the results to their record. However, we had major concerns that simply reporting results, with no explanation or context, no discussion or supporting information would be detrimental to the register and compound the issues of poor reporting already identified in the literature.[12, 13, 16] It may also have reduced the incentives for researchers to publish a full report of their findings. Subsequent developments through calls for open access to results and the availability of data repositories has provided alternatives.[63, 64] This includes making datasets available for scrutiny, replication and/or use for further research or updates, however there are a now a number of these sites, such as FigShare, Open Science Framework (OSF), and OwnCloud, all of which need to be searched.[64]

PROSPERO was launched on 11th February 2011, offering free registration and public access for searching. Scope for inclusion was for,

> "systematic reviews of the effects of interventions and strategies to prevent, diagnose, treat and monitor health conditions for which there is a health-related outcome."

The registration form contained 22 required items and 18 optional items. The stated aims of PROSPERO were:

> *"to provide a comprehensive listing of systematic reviews registered at inception to help avoid duplication and reduce opportunity for reporting bias by enabling comparison of the completed review with what was planned in the protocol."* [48]

For the register to achieve these aims, it was necessary to raise awareness and encourage registrations. Following guidance for development of dissemination strategies,[20] and implementing reporting guidelines,[56] PROSPERO was formally launched with press releases from the Minister for Health and the Director of NIHR. Other activities included obtaining endorsements from research, funding and commissioning organisations, publishers and journals and publication of articles by supporters.[48, 65-67] To encourage implementation, publishers such as BMJ, PLoS, and BMC recommended their journal editors request protocol registration details with manuscripts of systematic reviews.[48] After initial piloting with their HTA Programme, NIHR made registration mandatory for all reviews they fund that meet the inclusion criteria.[68, 69] Promotion continued with conference presentations, blogs and letters.[23, 67, 70-73]

7.5 Assessing the utility of PROSPERO at one year

Protocol registration was a novel intervention in the systematic review process, so I planned an evaluation of progress after one year of operation and the resulting paper is the third in this thesis (Figure 3).[27] The evaluation presented statistics about users of the registration process, usage of the site, and the findings of a survey of users and those the register was aimed at.

During development of the database, I considered the routine data and outputs that would be needed to monitor progress of the register and registrations. This made collating and presenting data on aspects related to registrations such as numbers registered or rejected, and countries where reviews were being undertaken, relatively straightforward. However, available analytics to show web

traffic and usage patterns was more challenging in interpretation and consistency of presentation. For example, internet provider addresses could represent a single individual or an entire organisation such as a university or hospital. Likewise, length of visit could be measured in seconds, so it was unclear how useful a visit to a page had been for a user.

Figure 3: Abstract for "PROSPERO at one year: an evaluation of its utility" *Systematic Reviews,* 2013.

Abstract

Background: PROSPERO, an international prospective register of systematic review protocols in health and social care, was launched in February 2011. After one year of operation we describe access and use, explore user experience and identify areas for future improvement.

Methods: We collated administrative data and web statistics and conducted an online survey of users' experiences.

Results: On 21 February 2012, there were 1,076 registered users and 359 registration records published on PROSPERO. The database usage statistics demonstrate the international interest in PROSPERO with high access around the clock and around the world. Based on 232 responses from PROSPERO users (response rate 22%), almost all respondents found joining and navigation was easy or very easy (99%); turn round time was good or excellent (96%); and supporting materials provided were helpful or very helpful (80%). The registration fields were found by 80% to be relevant to their review; 99% rated their overall experience of registering with PROSPERO as good or excellent. Most respondents (81%) had a written protocol before completing the registration form and 19% did not. The majority, 136 (79%), indicated they completed the registration form in 60 minutes or less. Of those who expressed an opinion, 167 (87%) considered the time taken to be about right.

Conclusions: The first year of PROSPERO has shown that registration of systematic review protocols is feasible and not overly burdensome for those registering their reviews. The evaluation has demonstrated that, on the whole, survey respondents are satisfied and the system allows registration of protocol details in a straightforward and acceptable way. The findings have prompted some changes to improve user experience and identified some issues for future consideration.

Keywords: Systematic review protocol, Register, Prospero, Evaluation

Obtaining unbiased, honest, and representative feedback from users was also challenging. The use of online surveys was becoming routine and users of PROSPERO were assumed to have access to the internet and be computer literate. As for the Delphi exercise I decided on an open survey where the link to the questions could be shared and responses anonymous to encourage expression of all views. The survey was sent to the list of Delphi participants and to users who had signed up for an account with PROSPERO as occasional contact by email was part of the terms.

The survey was reported as far as possible in accordance with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).[74] The findings of both parts of the evaluation were positive and showed both growth in registrations and satisfaction with the process. However, no data were found or reported to show whether PROSPERO was achieving the aim of reducing duplication. There was undoubtedly a risk of bias from undertaking this evaluation 'in-house' as I and the Advisory Group authors had a vested interest in PROSPERO being seen to be achieving its aims. Those who had taken part in the Delphi and created a

PROSPERO account were also likely to be supportive of the initiative. Respondents would have variations in their priorities, for example commissioners versus researchers who had registered a review, information specialists versus statisticians. However, while largely positive, the survey feedback did result in changes being made, such as the widening of scope to include reviews of reviews and methodological reviews with at least one outcome of direct patient or clinician relevance.

8. Quality of reporting of systematic review protocols

Following the launch of PROSPERO and growing opportunities to publish review protocols, the need for a template providing succinct guidance on what should be reported in a review protocol became apparent. The fourth paper presented in this thesis is the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement (Figure 4).[28] I set out here the rationale for the guideline and my involvement in its development.

Figure 4: Abstract for "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement" *Systematic Reviews,* 2015.

Abstract

Systematic reviews should build on a protocol that describes the rationale, hypothesis, and planned methods of the review; few reviews report whether a protocol exists. Detailed, well-described protocols can facilitate the understanding and appraisal of the review methods, as well as the detection of modifications to methods and selective reporting in completed reviews. We describe the development of a reporting guideline, the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015). PRISMA-P consists of a 17-item checklist intended to facilitate the preparation and reporting of a robust protocol for the systematic review. Funders and those commissioning reviews might consider mandating the use of the checklist to facilitate the submission of relevant protocol information in funding applications. Similarly, peer reviewers and editors can use the guidance to gauge the completeness and transparency of a systematic review protocol submitted for publication in a journal or other medium.

8.1 Reporting research

The World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects states, "Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports."[75] Researchers have a duty to publish the results of studies, whatever the findings. It is unethical to undertake research, particularly with voluntary participants, and not share the results publicly and with participants.[50] I believe this also holds true for systematic reviews, as the data from included studies derives from those same participants. In addition, systematic reviews have the ability to inform decisions in health and social care policy and practice, so should be conducted and reported to the highest standards.

The publication of a paper in a peer reviewed journal is the primary mechanism for getting the results of research into the public domain. The paper may also be the only evidence that the research was undertaken and provide the only source of information on which to judge the quality of the methods and reliability of the

findings. The quality and completeness of reporting of both clinical studies and systematic reviews were known to need improving.[13, 76-79] Poorly reported research may or may not have been poorly conducted; without sufficient information about the planned methods, the reliability of the findings remains uncertain.

8.2 Improving the quality of reporting

One of the most important and influential attempts to improve the standard of research reporting started with the Consort statement, first published in 1996, which provided guidance for reporting RCTs.[80] This was followed by guidelines for reporting many other study designs, including in 2000, QUOROM for meta-analyses of RCTs.[81] Evidence subsequently showed that the use of the CONSORT statement was associated with improved reporting of RCTs.[82]

In identifying and bringing together all published reporting guidelines in the EQUATOR Network, it became apparent that although there were many guidelines, their methods of production varied.[83] To address this, "Guidance for developers of health research reporting guidelines" was published in 2010.[56]

A Cochrane systematic review found some evidence of the effectiveness of journal endorsement on the use of the CONSORT statement by authors of RCTs published in medical journals.[84] However a subsequent review of 101 other reporting guidelines, found insufficient evidence to determine whether or not journal endorsement had an effect on completeness of reporting.[85] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement was published in 2009.[19] In a scoping review of evaluations of the uptake and impact of PRISMA, Page et al (2017) found that for many items, reporting was suboptimal.[86] Intuitively, if followed, guidelines should improve completeness of reporting, but understanding the effectiveness of reporting guidelines is complex. To start with the validity of the guidelines needs to be understood. The methodology for their development and whether they include guidance on all aspects of a study and in sufficient detail for replication are important. For example, studies of interventions need to report both the details of the intervention and how it was actually delivered in the study.[77, 87] If the latter is not indicated as necessary in a guideline it may compound reporting problems. To facilitate research into whether reporting guidelines achieve their aim, journals

need not only to endorse reporting guidelines, but also encourage if not require their use.[86] A starting point could be to provide peer reviewers with instructions on how to use the relevant reporting guideline; identified as information not provided by 116 health research journals.[86, 88]

8.3 PRISMA-P reporting guidelines

Prior to the development of PRISMA-P, reporting guidelines for systematic review protocols, publication and/or registration of non-Cochrane review protocols was rare, and opportunities to do so were limited. The majority of systematic reviews being published were non-Cochrane reviews and few reported following a protocol.[13] What was unknown was the reason for not reporting a protocol in the review paper: it may have been incomplete reporting or a lack of understanding of the need for a protocol. A steering committee formed to lead on developing systematic review protocol reporting guidelines. They followed the guidance for developing reporting guidelines and first identify the need.[56] In preparing a list of potential items for consensus discussion, the second step, the steering committee would usually have carried out a Delphi exercise. However, as with PROSPERO, existing robust sources existed. These included the consensus exercise I conducted for PROSPERO, the SPIRIT and PRISMA checklists and the Institute of Medicine standards for systematic reviews.[18, 19, 25, 34, 89, 90] I was invited by the steering committee to join the PRISMA-P reporting guideline development group during the planning phase. The consensus meeting was held in June 2011, at the AHRQ headquarters in Washington DC. I presented the PROSPERO consensus exercise, shared the feedback on specific items provided by participants in the Delphi and the rationale for decisions made by the PROSPERO Advisory Group that led to the final registration list. The rest of the two-day meeting was devoted to an item by item discussion of the PROSPERO and, where relevant, PRISMA checklists to agree if and how they should be incorporated into the reporting guideline. By the end of the two days, we reached general agreement on all items.

I made critical comments on the drafts of the statement paper which was published in 2015.[28] I was also a group author on the subsequent elaboration and explanation paper.[91] The reporting checklist recommended 17 numbered items, 26 including sub-items, be reported in a systematic review protocol. The items were categorised as administrative, introduction and methods. To facilitate transfer of information once a review was completed, PRISMA-P items followed

the PRISMA template as far as possible. While the key methodological items for registration were included, the requirements were more in-depth than for PROSPERO, a reflection of their different purposes.

The statement paper (Paper 4) has over 5,000 citations and has been accessed over 225,000 times (October 2020). Journals have endorsed the use of PRISMA-P, as encouraged in the statement paper. However, as has been shown for journal endorsement of other reporting guidelines, this is only part of the answer to improving the reporting.[88, 92-94] We therefore included in the statement paper a section on implementation, recognising that work beyond publication is necessary if change is to be affected.[83] We identified a range of stakeholders, proposed actions they could take and indicated what the potential benefits of those actions might be.[28] In a comprehensive scoping review of interventions to improve adherence to reporting guidelines Blanco et al (2019) identified a wide range of strategies available to different stakeholders.[95] However, they conclude that most of the strategies require research to establish their effectiveness. Future evidence of what works to encourage complete reporting should help inform ways to improve the quality of reporting of review protocols and the content of PROSPERO records. Improving completeness and quality of reporting would then facilitate research to assess the quality of the planned methods.

The launch of PRISMA-P promoted the importance of producing a review protocol that addresses all the potential methodological issues that may arise when the review is carried out and then register the protocol as a separate action. There were by that time more opportunities for publishing protocols but the simplicity of a free open access registration process and a lack of understanding that doing both is best practice may be hard to overcome.

9. PROSPERO and PRISMA-P as resources for research

As the number of registrations in PROSPERO increased, so the database developed as a resource for methodological research. For the first time it was possible to examine the planned methods of non-Cochrane systematic reviews. Papers 5 and 6 in this thesis were undertaken four years apart and explore two different aspects of review methods. My studies are presented here with other methodological research facilitated by PROSPERO and PRISMA-P.

9.1 Assessing outcome reporting bias using PROSPERO data

As already detailed, there was strong empirical evidence of outcome reporting bias in Cochrane reviews, generally considered to be of the highest standard.[12, 15, 96] PROSPERO provided the means to explore concerns about the quality and robustness of non-Cochrane reviews, which form the majority of published systematic reviews. The fifth paper in this thesis investigated outcome reporting bias in non-Cochrane systematic reviews (Figure 5).[32]

Figure 5: Abstract for "A third of systematic reviews changed or did not specify the primary outcome: a PROSPERO register study" *Journal of Clinical Epidemiology,* 2016.

Abstract

Objectives: To examine outcome reporting bias of systematic reviews registered in PROSPERO.

Study Design and Setting: Retrospective cohort study. The primary outcomes from systematic review publications were compared with those reported in the corresponding PROSPERO records; discrepancies in the primary outcomes were assessed as upgrades, additions, omissions, or downgrades. Relative risks (RRs) and 95% confidence intervals (CI) were calculated to determine the likelihood of having a change in primary outcome when the meta-analysis result was favorable and statistically significant.

Results: Ninety-six systematic reviews were published. A discrepancy in the primary outcome occurred in 32% of the included reviews and 39% of the reviews did not explicitly specify a primary outcome(s); 6% of the primary outcomes were omitted. There was no significant increased risk of adding/upgrading (RR, 2.14; 95% CI: 0.53, 8.63) or decreased risk of downgrading (RR, 0.76; 95% CI: 0.27, 2.17) an outcome when the meta-analysis result was favorable and statistically significant. As well, there was no significant increased risk of adding/upgrading (RR, 0.89; 95% CI: 0.31, 2.53) or decreased risk of downgrading (RR, 0.56; 95% CI: 0.29, 1.08) an outcome when the conclusion was positive.

Conclusions: We recommend review authors carefully consider primary outcome selection, and journals are encouraged to focus acceptance on registered systematic reviews.

Choosing the most appropriate outcomes for a systematic review is part of the development of a review question. The recommended approach is to collate all potential outcomes then prioritise them to identify the outcomes that will provide the answer to the problem in a way that is meaningful to the end user.[20, 97] The Cochrane Methodological Expectations of Cochrane Intervention Reviews standards include three categories of outcomes: critical, important and not important in relation to clinical/policy decision making.[33] Essentially, primary outcomes should facilitate clinical decision making, including identifying potential harms; secondary outcomes are of lesser importance and usually provide

information that could explain the effects seen in the primary outcomes. Cochrane advocate excluding outcomes of little or no importance to avoid overwhelming and potentially misleading readers.[97]

Having stated the primary and secondary outcomes in the protocol, they should be reported as such in the review. As already described, outcome reporting bias is more likely to occur when the outcomes are reported in a way that differs from the original intent.

By late 2013, PROSPERO contained almost 2,500 registrations, making a study of outcome reporting bias viable. In collaboration with a review team including researchers in Canada, Australia and the UK, I was involved in and contributed to all aspects of producing paper 5 of this thesis, from initial concept to final publication. In this research we aimed to find out if, and to what extent, outcome reporting bias occurred in non-Cochrane reviews using PROSPERO data.[32] We also took the opportunity to assess the quality of reporting of the included reviews.

In preparing the study protocol we drew on methods used in other studies with the aim of standardising classifications.[15, 40, 98] For changes in how planned outcomes were reported these were: new inclusion; exclusion; upgrade; and downgrade. Similar classifications for meta-analysis results and for conclusion statements were also used. We focussed on reviews of interventions with meta-analyses so we could examine the association between the level of significance of meta-analysis results and the direction of any changes in outcome reporting. For the assessment of the methodological quality of the systematic reviews we used A MeaSurement Tool to Assess systematic Reviews (AMSTAR).[99, 100] The best validated measurement tool available at the time, AMSTAR has since been revised in light of limitations.[101]

Having contributed to the study design and protocol, I was involved in developing the data extraction form, in particular in relation to the information that was requested in PROSPERO records, and subsequently undertook data extraction from the registration record and the publication. One of the methodological aspects I led on was specifying the data set to use. We wanted to include records where the status had been updated to show the review had been completed and published. These records therefore had more than one version; all versions remaining available in PROSPERO for transparency. As changes to any part of the

record could be made at the time of updating, there was no guarantee that the methods had not been altered after the results were known. My advice was to use the version that was live immediately prior to the record being updated to say the review was completed. This should have ensured we were using *a priori* registration details. Lack of resources meant we did not search to identify PROSPERO records that had not been updated to say completed and published. As has been subsequently demonstrated, PROSPERO record are frequently not kept up to date by their owners.[102] However in the first few years, it appeared that Named Contacts, the owners of records, were in the main recording progress to publication. This may have been because those who knew about the option of protocol registration were more methodologically alert and there may also have been a novelty factor as with many innovations. Certainly a different approach would be needed now, given Rombey et al's (2019) findings that 49 out of 75 (65.3%) published reviews were still registered as 'ongoing'.[102]

After applying eligibility criteria to the 140 potentially relevant PROSPERO records, 96 registration/published review pairings were included in the study.[32] We explored a number of hypotheses, using methods of analysis that would facilitate comparison with similar work in Cochrane reviews.[15, 16] We found that 32% of the non-Cochrane systematic reviews examined had a discrepancy between the primary outcome in the review compared to their registration record. Having a favourable and statistically significant meta-analysis was not associated with a significant increased risk of adding or upgrading (RR, 2.14; 95% CI: 0.53, 8.63) or decreased risk of downgrading (RR, 0.76; 95% CI: 0.27, 2.17) an outcome. Likewise, having a positive conclusion was not related to a significant increased risk of adding or upgrading (RR, 0.89; 95% CI: 0.31, 2.53) or decreased risk of downgrading (RR, 0.56; 95% CI: 0.29, 1.08) an outcome. These results were consistent with a review of studies examining discrepancies in outcomes in Cochrane reviews.[103] We also observed that over a third of the review reports did not specify a primary outcome; and that both the included studies and the reviews themselves used multiple outcomes and measures. Both issues that PROSPERO and PRISMA-P try to direct researchers away from during the development and reporting of the protocol.

Seventy-two (75%) of the reviews met our cut off score of 8 or more out of a possible 11 using the AMSTAR tool to assess methodological quality.[100] We

suggested that journals consider focussing on publishing registered reviews as they appeared to be of high methodological quality: a cautious recommendation in the absence of a comparator. However, consistent key omissions in reports were: conflicts of interest; no assessment of publication bias where it would have been appropriate; and not considering quality or risk of bias in the conclusions. All are items covered in the PRISMA reporting guidelines and should have been picked up by journal editors and peer reviewers.

Our report was the first to present data and results for non-Cochrane reviews registered in PROSPERO. The characteristics of included reviews presented in the paper were interesting in their own right. A more robust sample size however, would have enabled exploration of possible sources of heterogeneity and sub-group analyses. While demonstrating new accessibility to non-Cochrane reviews and their key protocol details, our data on primary outcome reporting and methodological quality provides baseline data for future studies as the volume of registrations grows.

9.2 Assessing PROSPERO record content using PRISMA-P

A surprising finding of the Kirkham et al (2010) study of outcome reporting bias in Cochrane reviews was that 24 out of 297 reviews (8%) did not have a protocol in the relevant section of the Cochrane Library.[15] The case for non-Cochrane reviews is worse. The study of outcome reporting bias (Figure 5), found that of the 96 reviews included, 91 (95%) had not published their protocol in a journal, making their PROSPERO registration the only source for planned methods.[32] More recently, Viguera-Guerra et al (2019) report that, although the number of review protocols published in journals is increasing, most review protocols are only registered in PROSPERO.[104] Registrations may contain a protocol as an attachment, but this is rare and the file can be 'hidden' until the review is published. This means PROSPERO records are frequently the only access to *a priori* methods for comparison with the final report for publishers, peer reviewers and others interested in assessing the potential for bias. However comprehensive a registration, the contents of records are not assessed for methodological completeness, appropriateness or rigor, whereas a published protocol is subject to the editorial and peer review process, although this has been shown to be a flawed and inadequate process.[105-108] A lack of clarity in understanding the roles of a protocol and registration may contribute to this situation.

In the absence of a publicly available protocol, ideally the registration would have to be sufficiently detailed to allow comparison with the review report. In Paper 6, I undertook a comparison study to assess the extent to which the contents of PROSPERO records include the items listed in PRISMA-P and to establish whether PROSPERO records can act as the sole public record of the planned review methods (Figure 6).[35] It was important to first establish the level of detail being provided in PROSPERO records, so future research exploring the methodological rigour in registrations could focus to where data could be found.

Figure 6: Abstract for "An assessment of the extent to which the contents of PROSPERO records meet the systematic review protocol reporting items in PRISMA-P" *F1000Research,* 2020.

Abstract

Background: PROSPERO is an international prospective register for systematic review protocols. Many of the registrations are the only available source of information about planned methods. This study investigated the extent to which records in PROSPERO contained the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).

Methods: A random sample of 439 single entry PROSPERO records of reviews of health interventions registered in 2018 was identified. Using a piloted list of 19 PRISMA-P items, divided into 63 elements, two researchers independently assessed the registration records. Where the information was present or not applicable to the review, a score of 1 was assigned. Overall scores were calculated and comparisons made by stage of review at registration, whether or not a meta-analysis was planned and whether or not funding/sponsorship was reported.

Results: Some key methodological details, such as eligibility criteria, were relatively frequently reported, but much of the information recommended in PRISMA-P was not stated in PROSPERO registrations. Considering the 19 items, the mean score was 4.8 (SD 1.8; median 4; range 2-11) and across all the assessed records only 25% (2081/8227) of the items were scored as reported. Considering the 63 elements, the mean score was 33.4 (SD 5.8; median 33; range 18-47) and overall, 53% (14,469/27,279) of the elements were assessed as reported. Reporting was more frequent for items required in PROSPERO than optional items. The planned comparisons showed no meaningful differences between groups.

Conclusions: PROSPERO provides reviewers with the opportunity to be transparent in their planned methods and demonstrate efforts to reduce bias. However, where the PROSPERO record is the only available source of *a priori* reporting, there is a significant shortfall in the items reported, compared to those recommended. This presents challenges in interpretation for those wishing to assess the validity of the final review.

In this study I assessed a random sample of 2018 PROSPERO records with no related protocol against reporting items for systematic review protocols listed in PRISMA-P 2015. The choice of registration year was to allow time for the reporting guidelines to become widely known. Some of the PRISMA-P items were

either not asked for in PROSPERO or could not be extracted to match specific reporting items. Nineteen of the 26 PRISMA-P items and sub-items were relevant. Where the description included more than one specific item of the information, these were identified and listed as 63 elements. Assessment was undertaken at both the overall 19 item level and for the 63 elements, with presence of an item/element scoring 1 and absence scoring 0.

The primary outcome for the study was the compliance of PROSPERO registration records with PRISMA-P reporting items. The outcome measures were the overall scores for the assessed dataset at item and element levels. Demographics from the assessed dataset were presented with the non-assessed records from the 2018 dataset. I chose to limit inclusion to systematic reviews of healthcare interventions as both PROSPERO and PRISMA-P were originally designed specifically for reviews of interventions. I posted the detailed study protocol on the Open Science Framework (OSF) prior to sight of the dataset.[109] It is important to provide transparency in the conduct and reporting of all research, including methodological studies.

There were 2,194 eligible registration records and 439 (20%) of these were randomly selected for assessment. Six records were later excluded meaning 433 were included in the analysis. There were no substantial differences between the assessed and not-assessed datasets, suggesting we had a representative data set.

None of the PROSPERO records assessed against the eligibility criteria reported on all elements in each of the items recommended for a systematic review protocol in the PRISMA-P guidelines. The mean total score for individual PROSPERO records for the 19 items, was 4.8, the standard deviation 1.8, the median 4, and range 2 to 11. Considering all items across all the assessed records, only 25% (2081/8227) of the items were scored as reported. The mean total score for individual PROSPERO records for the 63 elements of the reporting guidelines was 33.4, the standard deviation 5.8, the median 33 and the range 18-47. Overall, 53% (14,469/27,279) of the elements were considered as reported.

There were no significant differences in any of the pre-defined subgroup comparisons of: the stage of review at registration; whether or not information was reported on source of funding, sponsorship or support and where none was indicated; and whether or not the relevant box in the registration form had been

ticked to indicate a meta-analysis was planned. Scores for the ten countries and topics with the highest number of assessed records, and for number of authors indicated that none of these factors had a marked influence on the number of PRISMA-P items or elements reported in PROSPERO records.

The iterative process of developing a protocol allows for consideration of how an increasing number of issues will be addressed in the review.[20] Once finalised or near to completion the key methodological details should be registered.[19] In 2011 when PROSPERO was launched, there were few options for publishing protocols and the ability to register protocol details on a free open access database provided what might have been seen as an alternative. It may then be considered inappropriate to expect a registration record to meet the PRISMA-P criteria. However, one of the stated aims of registration is to enable comparison of planned methods with the final report. It would therefore seem reasonable to expect the mandatory fields in PROSPERO to be fully completed, but this was not the case. My study found that some key methodological details were relatively frequently reported, but much of the information recommended in PRISMA-P was missing from registrations. While reporting was unsurprisingly more frequent for items that are mandatory in PROSPERO there were still gaps. Of particular concern is the lack of detail related to outcome measures, assessment of risk of bias and quantitative analysis methods. PROSPERO records are unlikely to meet all the PRISMA-P recommended items, given the differences in purpose between a protocol and registration. However, it is important to understand what information is available where registration is the only public source. It may be reasonable to expect researchers using the register in this way to provide sufficient information. The role of the protocol and registration may need clarifying.

Eligibility criteria and type of analysis planned are separate required fields in PROSPERO and were most frequently reported in registration records. However, study selection process (Item 26 Data extraction (selection and coding) in PROSPERO), which is optional, was also a more frequently reported item. This finding may be a reflection of a lack of experience and understanding of review methods, with familiar items such as eligibility criteria being reported, while missing items which may require more in-depth methodological knowledge such as naming the statistical method, how study results will be converted to the same

format and how missing data will be handled in the synthesis. Or it could be an indication of what the researchers themselves feel is important to register. It should be remembered that registrants of the included records were providing details required to register their review and that only some of the items are mandatory. As the included registrations did not have links to a protocol, I assumed they were the only public source of *a priori* methods, but this may not have been the case.

PRISMA-P is a reporting guideline and not a rating scale so the assessments for paper 6 involve a degree of subjectivity. Examining the elements within the PRISMA-P items has highlighted where there are consistent gaps in reporting. This has the potential to aid the PROSPERO administrators in checking these fields more closely for new applications and requesting further information where this is insufficient. However, the administrators are not methodologists and simply check for 'sense': further training and possibly clarification for applicants and administrators of what is required may not result in significant improvements. Other potential responses to the findings of this study are to: promote calls for comprehensive protocol documents to be uploaded with registrations; raise awareness in the reviewing community through training and dissemination of information of the importance of preparing and making a protocol available, as well as registering it focussing on the areas not currently well reported; encourage journal editors and peer reviewers to identify and comment on short comings in provision of *a priori* methods. The findings could also be used as a prompt to review of the roles of the review protocol and registration and consider whether the register should be redesigned to better achieve its purpose.

Systematic review protocol registration on PROSPERO provides the opportunity for researchers to be transparent in their planned methods and efforts to minimise bias. However, my findings indicate that in the absence of a publicly available protocol, there is a considerable shortfall in the items reported, even where mandatory, compared to those expected in a PRISMA-P compliant protocol. Where registration is the only source of *a priori* methods, this presents challenges in interpretation for those wishing to assess the validity of the final review.

9.3 PROSPERO and PRISMA-P use in the literature

PROSPERO has facilitated a growing number and wide range of methodological studies. Tsujimoto et al (2017) found that only 60/284 (21%) of reviews had registered their protocols, though the proportion was increasing over time.[110] They went on to find no statistically significant association between outcome reporting bias and registration. Page et al (2018) in an analysis of a random sample of PROSPERO registrations found that no information about the primary outcome other than the domain (e.g. timing, effect measures) was pre-specified in 44/150 records (29%).[111] Sideri et al (2018) found reviews registered in PROSPERO were associated with higher review quality.[112] Other studies have used PROSPERO data to look at: registration characteristics as predictors for publication;[113] the time and number of researchers needed to conduct systematic reviews;[114] the planned use of risk of bias tools;[115] the reporting of adverse outcomes;[116] and compared a range of planned methods in PROSPERO records with published reviews.[117, 118] Whether and how often editors or peer reviewers access registration records (or indeed protocols) when examining a final report, is not known. Comparison with protocol or registration details was not identified as an activity peer reviewers are encouraged to do in any of the journal instructions to peer reviews examined by Hirst and Altman (2012).[88]

Noticeable in the growing literature is how often registration records are referred to and/or treated as protocols.[115-119] Delgado and Delgado (2017) refer to registrations as protocols without clarifying if the registrations contained a full protocol.[120] Viguera-Guerra et al (2019) talk about PROSPERO as a protocol repository, and while the uploading of a protocol file is facilitated, this is rarely the case.[104] A further example is Farrah et al (2019) who consistently refer to 'PROSPERO protocols'.[115] The interchangeable use of 'registration' and 'protocol' may be a reflection of and/or promoting a wider understanding that they are indeed interchangeable. Allers et al (2018) rightly question whether PROSPERO registration alone is sufficient and can replace published systematic review protocols.[119] Paper 6 of this thesis shows that registration is currently not a substitute for a comprehensive protocol.[35]

An advantage of registration on a dedicated database, is the ability to search a single site for existing and on-going reviews. Success in avoiding unplanned duplication of reviews, an aim of PROSPERO, is difficult to assess. There are a

number of papers highlighting duplication of reviews and meta-analyses.[121-123] However, what is unknown is how frequently a search of PROSPERO has resulted in a review question no longer being pursued or being amended to avoid duplication. Sigurdsun et al (2020) found redundant meta-analyses are common in genetic epidemiology and suggest more widespread registration of protocols on genetic topics would aid identification of pre-existing efforts.[124] Sadly, the 2281 registrations for systematic reviews on Covid-19 related topics in humans (2 October 2020) would suggest that there is still a lack of understanding about the need to consider on-going and published reviews when refining a review question.[48]

Although PRISMA has been used in a number of publications to assess the quality of reporting of reviews,[86] there is currently limited use of the PRISMA-P reporting guideline to assess protocols. A study of the publicly available peer reviews of 53 published systematic review protocols based their assessment on the PRISMA-P items and found: 342 comments (76%) suggested more transparency was needed in the planned methods and 108 (24%) suggested a protocol amendment.[106] They found authors had implemented, in the published protocol, the suggestions for more transparency in 291 (85.1%) and protocol amendments in 80 (73.7%). The same paper identified that, paradoxically, PROSPERO (in the instructions for researchers) urges caution in the timing of registration, and PRISMA-P recommends including the registration details in the protocol. Although not contradictory, these instructions could be revised for more clarity.

Also of interest in the literature is the apparent use of PRISMA-P as a methodological guide: “The data were analysed according to the PRISMA-P guidelines.”[125] and “…assessed articles for study inclusion using the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) for data reporting.”[126] Perhaps a review of the respective roles of review reporting guidelines and methodological texts is also needed.

10. Discussion

The publications in this thesis were undertaken across a time span starting from where there were limited options for publication or registration of systematic review protocols, to a time where there is a heavily subscribed register and guidelines for reporting them. This has, in just a few years, provided a rich data source for methodological research providing insight into reporting issues and where further research is needed.

As a response to calls for improved transparency and reduction in waste in research, PROSPERO may be considered to be succeeding in its purpose, at least in some respects. In October 2019, over 54,800 non-Cochrane reviews were registered on PROSPERO, and even if records do not contain all the details that they ideally should,[35] this provides more information than was previously available. There are a number of reasons why reported data may be incomplete. These include lack of clarity and/or possibly understanding about the purpose and requirements of a protocol and of protocol registration; a lack of knowledge about specific aspects of review methods; concerns about developed ideas being 'stolen'; and lack of time. Completeness may also be influenced by motivation for registering, for example if in response to a mandate from funders or journals and seen as an additional burden.[85] Although the itemised registration format is thought to promote more complete reporting in trial registration,[95] it is not known whether in PROSPERO this promotes more complete reporting or engenders a 'tick-box' approach.

While the completeness of PROSPERO records falls short of what ideally should appear in a protocol,[35] for the purposes of registration, the finer methodological details may not be so necessary. For example, statistical analysis plans are not required in trial registration, so review protocol registration may not require full details of the planned synthesis. There may be an argument that the aim of providing sufficient information in a registration record to facilitate comparison with the final review report was over ambitious. By making registration requirements so detailed, the differences between a protocol and registration may have been further obscured.

Examining the chronology of the development of tools to improve the conduct and reporting of systematic reviews demonstrates the need for action. PROSPERO

was developed in 2009/10 at a time when opportunities for publishing review protocols were very limited and it was unclear how many non-Cochrane reviews were being undertaken and how many had protocols.[25, 26] There are now numerous free to use, open access platforms where protocols may be made public if time and cost stand in the way of journal publication. PRISMA-P was developed a few years later as opportunities for publishing protocols started to open up and demands for increased transparency grew. The cost of publishing protocols makes non-peer reviewed posting on an open data website attractive. However, there is an argument that, while also far from a perfect system,[107, 108, 127] high quality peer review may be more important and valuable for ensuring sound methods in research protocols than for the final manuscript. The protocol stage is when missing and/or flawed methods can be corrected. Of course, there are differences between protocols produced for projects for major funders, who have their own internal checks, and reviews that have no independent or external input. Obtaining editorial and peer review comments on a protocol paper that are mindful of reporting guidelines is another reason why the registration record is not currently a replacement for a published protocol. However, my research shows the need to revisit and then clarify or re-purpose the roles of the systematic review protocol and protocol registration. There are three key areas where research is needed to shape the future for PROSPERO.

- *Methodological issues*

Important areas for investigation include: whether protocols are registered at an early enough stage in the review process to establish whether they are truly *a priori*; repeating the study on outcome reporting bias to address some of the limitations such as precision, with a larger sample size and generalisability by inclusion of other fields/topics; examining the effects of other types of bias such as selection and publication bias; and assessing the quality of systematic review protocols.

- *Research on registration*

The volume of records on PROSPERO, and the international reach and range of topics covered, mean that the database provides a rich data source supporting research on research. For registration, the starting point is a mapping review of the existing methodological literature examining aspects of systematic review

protocols, particularly those utilising PROSPERO data, and identifying suggested improvements related to protocols and registration. Such a review could help formulate an agenda for open debate in the systematic review community around the future for protocol registration.

- *The future of publishing and registering protocols*

Technological advances over the last 10 years have significantly changed the publishing landscape, access to information and ways of collaborating. Text mining, machine learning technologies and open data repositories present new opportunities for transparency in carrying out research and facilitating more research on research. For example, technological interventions could be designed to improve the quality of protocol reporting and registration and facilitate closer alignment.

Drivers for change are the widespread recognition that limited research resources need to be used wisely to maximise value and processes designed to minimise researcher burden.[29, 128] My research has increased transparency in systematic reviews and provided evidence to stimulate future research and promote debate to further improve the reliability of review evidence.

11. References

1. Dickersin K, Straus SE and Bero LA. Evidence based medicine: increasing, not dictating, choice. *BMJ* 2007; 334: s10-s10. DOI: 10.1136/bmj.39062.639444.94.
2. Ham C, Hunter DJ and Robinson R. Evidence based policymaking. *BMJ* 1995; 310: 71-72. DOI: 10.1136/bmj.310.6972.71.
3. Bastian H, Glasziou P and Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? *PLoS Medicine* 2010; 7. DOI: 10.1371/journal.pmed.1000326.
4. Lavis JN, Robertson D, Woodside JM, McLeod CB and Abelson J. How can research organizations more effectively transfer research knowledge to decision makers? *Milbank Quarterly* 2003; 81: 221-248, 171-222. 2003/07/05. DOI: 10.1111/1468-0009.t01-1-00052.
5. Orton L, Lloyd-Williams F, Taylor-Robinson D, O'Flaherty M and Capewell S. The use of research evidence in public health decision making processes: systematic review. *PLoS One* 2011; 6: e21704. 2011/08/06. DOI: 10.1371/journal.pone.0021704.
6. Tricco AC, Cardoso R, Thomas SM, Motiwala S, Sullivan S, Kealey MR, et al. Barriers and facilitators to uptake of systematic reviews by policy makers and health care managers: a scoping review. *Implementation Science* 2016; 11: 4. 2016/01/13. DOI: 10.1186/s13012-016-0370-1.
7. Chalmers I, Dickersin K and Chalmers TC. Getting to grips with Archie Cochrane's agenda. *Bmj* 1992; 305: 786-788. 1992/10/03. DOI: 10.1136/bmj.305.6857.786.
8. Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, et al. "The 2011 Oxford CEBM Levels of Evidence (Introductory Document)". *Oxford Centre for Evidence-Based Medicine*.
9. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual *Process and methods [PMG20]* October 2018.
10. Chavalarias D and Ioannidis JP. Science mapping analysis characterizes 235 biases in biomedical research. *Journal of Clinical Epidemiology* 2010; 63: 1205-1215. 2010/04/20. DOI: 10.1016/j.jclinepi.2009.12.011.
11. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan A-W, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS ONE* 2008; 3: e3081. DOI: 10.1371/journal.pone.0003081.
12. Silagy CA, Middleton P and Hopewell S. Publishing protocols of systematic reviews: comparing what was done to what was planned. *JAMA* 2002; 287: 2831-2834. 2002/06/01.
13. Moher D, Tetzlaff J, Tricco AC, Sampson M and Altman DG. Epidemiology and reporting characteristics of systematic reviews. *PLoS Medicine* 2007; 4. DOI: 10.1371/journal.pmed.0040078.
14. The PLoS Medicine Editors. Many reviews are systematic but some are more transparent and completely reported than others. *PLoS Medicine* 2007; 4: e147. DOI: 10.1371/journal.pmed.0040147.
15. Kirkham JJ, Altman DG and Williamson PR. Bias due to changes in specified outcomes during the systematic review process. *PLoS ONE* 2010; 5. DOI: 10.1371/journal.pone.0009810.
16. Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010; 340. DOI: 10.1136/bmj.c365.

17. EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network, https://www.equator-network.org/ (accessed 12 March 2020).
18. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009; 6. DOI: 10.1371/journal.pmed.1000100.
19. Moher D, Liberati A, Tetzlaff J and Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009; 6: e1000097. 2009/07/22. DOI: 10.1371/journal.pmed.1000097.
20. Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care* University of York, 2009.
21. Higgins J, Thomas J and Eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated September 2019)*. 2nd ed.: Wiley-Blackwell, 2019.
22. Petticrew M and Roberts H. *Systematic Reviews in the Social Sciences: A Practical Guide*. Oxford: Blackwell 2006, p.352.
23. Straus S and Moher D. Registering systematic reviews. *Canadian Medical Association Journal* 2010; 182. DOI: 10.1503/cmaj.081849.
24. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M and Stewart L. An international registry of systematic-review protocols. *The Lancet* 2010; Available online 12 July 2010. DOI: 10.1016/s0140-6736(10)60903-8.
25. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M and Stewart L. Establishing a minimum dataset for prospective registration of systematic reviews: an international consultation. *PLoS ONE* 2011; 6. DOI: 10.1371/journal.pone.0027319.
26. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, et al. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. *Systematic Reviews* 2012; 1: 2. 2012/05/17. DOI: 10.1186/2046-4053-1-2.
27. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, et al. PROSPERO at one year: an evaluation of its utility. *Systematic Reviews* 2013; 2: 4. 2013/01/17. DOI: 10.1186/2046-4053-2-4.
28. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015; 4: 1-9. journal article. DOI: 10.1186/2046-4053-4-1.
29. Macleod MR, Michie S, Roberts I, Dirnagl U, Chalmers I, Ioannidis JPA, et al. Biomedical research: increasing value, reducing waste. *The Lancet* 2014; 383: 101-104. DOI: https://doi.org/10.1016/S0140-6736(13)62329-6.
30. Ioannidis JPA, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D, et al. Increasing value and reducing waste in research design, conduct, and analysis. *The Lancet* 2014; 383: 166-175. DOI: 10.1016/S0140-6736(13)62227-8.
31. Chan A-W, Song F, Vickers A, Jefferson T, Dickersin K, Gøtzsche PC, et al. Increasing value and reducing waste: addressing inaccessible research. *The Lancet* 2014; 383: 257-266. DOI: 10.1016/S0140-6736(13)62296-5.
32. Tricco AC, Cogo E, Page MJ, Polisena J, Booth A, Dwan K, et al. A third of systematic reviews changed or did not specify the primary outcome: a PROSPERO register study. *Journal of Clinical Epidemiology* 2016; 79: 46-54. 2016/04/16. DOI: 10.1016/j.jclinepi.2016.03.025.
33. Higgins J, Lasserson T, Chandler J, Tovey D, Thomas J, Flemyng E, et al. Methodological Expectations of Cochrane Intervention Reviews (MECIR). *Standards for the conduct and reporting of new Cochrane Intervention Reviews, reporting of protocols and the planning, conduct and reporting of updates*. Cochrane Community. Version March 2020

34. Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness Research. In: Eden J, Levit L, Berg A, et al. (eds) *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington (DC): National Academies Press (US), 2011.
35. Booth A, Mitchell A, Mott A, James S, Cockayne S, Gascoyne S, et al. An assessment of the extent to which the contents of PROSPERO records meet the systematic review protocol reporting items in PRISMA-P [version 2; peer review: 2 approved]. *F1000Research* 2020; 9. DOI: 10.12688/f1000research.25181.2.
36. Clarke M, Hopewell S and Chalmers I. Clinical trials should begin and end with systematic reviews of relevant evidence: 12 years and waiting. *The Lancet* 2010; 376: 20-21. 2010/07/09. DOI: 10.1016/s0140-6736(10)61045-8.
37. Young C and Horton R. Putting clinical trials into context. *The Lancet* 2005; 366: 107-108. 2005/07/12. DOI: 10.1016/s0140-6736(05)66846-8.
38. Oxman AD, Cook DJ and Guyatt GH. Users' guides to the medical literature. VI. How to use an overview. Evidence-Based Medicine Working Group. *JAMA* 1994; 272: 1367-1371. 1994/11/02. DOI: 10.1001/jama.272.17.1367.
39. Chandler J and Hopewell S. Cochrane methods - twenty years experience in developing systematic review methods. *Systematic Reviews* 2013; 2: 76. DOI: 10.1186/2046-4053-2-76.
40. Tricco AC, Tetzlaff J, Pham B, Brehaut J and Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. *Journal of Clinical Epidemiology* 2009; 62: 380-386.e381. 2009/01/09. DOI: 10.1016/j.jclinepi.2008.08.008.
41. Song F, Hooper L and Loke Y. Publication bias: what is it? How do we measure it? How do we avoid it? *Open Access Journal of Clinical Trials* 2013; 5:71-81. DOI: https://doi.org/10.2147/OAJCT.S34419.
42. Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technology Assessment* 2010; 14: iii, ix-xi, 1-193. 2010/02/26. DOI: 10.3310/hta14080.
43. Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC and Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004; 291. DOI: 10.1001/jama.291.20.2457.
44. Krleza-Jeric K, Chan AW, Dickersin K, Sim I, Grimshaw J and Gluud C. Principles for international registration of protocol information and results from human trials of health related interventions: Ottawa statement (part 1). *BMJ* 2005; 330: 956-958. 2005/04/23. DOI: 10.1136/bmj.330.7497.956.
45. Askie L, Ghersi D and Simes J. Prospective registration of clinical trials. *Australian Journal of Physiotherapy* 2006; 52: 237-239. 2006/11/30. DOI: 10.1016/s0004-9514(06)70002-2.
46. Booth AM, Wright KE and Outhwaite H. Centre for Reviews and Dissemination databases: value, content, and developments. *International Journal of Technology Assessment in Health Care* 2010; 26: 470-472.
47. Sheldon T and Chalmers I. The UK Cochrane Centre and the NHS Centre for Reviews and Dissemination: respective roles within the information systems strategy of the NHS R&D Programme, coordination and principles underlying collaboration. *Health Economics* 1994; 3: 201-203. DOI: 10.1002/hec.4730030308.
48. Centre for Reviews and Dissemination. PROSPERO International prospective register of systematic reviews, https://www.crd.york.ac.uk/PROSPERO/ (accessed 12 March 2020).
49. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of

Medical Journal Editors. *Annals of Internal Medicine* 2004; 141: 477-478. 2004/09/10. DOI: 10.7326/0003-4819-141-6-200409210-00109.
50. Moher D. Reporting research results: A moral obligation for all researchers. *Canadian Journal of Anesthesia* 2007; 54: 331. DOI: 10.1007/BF03022653.
51. Ghersi D and Pang T. En route to international clinical trial transparency. *The Lancet* 2008; 372: 1531-1532. 2008/11/06. DOI: 10.1016/s0140-6736(08)61635-9.
52. Tharyan P and Ghersi D. Registering clinical trials in India: a scientific and ethical imperative. *National Medical Journal of India* 2008; 21: 31-34. 2008/05/14.
53. Van Der Weyden MB and Ghersi D. The Australian Clinical Trial Registry. *The Medical Journal of Australia* 2005; 183: 7. 2005/07/05.
54. Viergever RF and Ghersi D. The ClinicalTrials.gov results database. *New England Journal of Medicine* 2011; 364: 2169-2170; author reply 2170. 2011/06/03. DOI: 10.1056/NEJMc1103910.
55. Viergever RF, Karam G, Reis A and Ghersi D. The quality of registration of clinical trials: still a problem. *PLoS One* 2014; 9: e84727. 2014/01/16. DOI: 10.1371/journal.pone.0084727.
56. Moher D, Schulz KF, Simera I and Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Medicine* 2010; 7. DOI: 10.1371/journal.pmed.1000217.
57. Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CF, Askham J, et al. Consensus development methods, and their use in clinical guideline development. *Health Technology Assessment* 1998; 2: i-iv, 1-88. 1998/04/30.
58. Jones J and Hunter D. Consensus methods for medical and health services research. *BMJ* 1995; 311: 376–380.
59. Paul CL, Sanson-Fisher R, Douglas HE, Clinton-Mcharg T, Williamson A and Barker D. Cutting the research pie: a value-weighting approach to explore perceptions about psychosocial research priorities for adults with haematological cancers. *European Journal of Cancer Care* 2011; 20: 345-353. DOI: 10.1111/j.1365-2354.2010.01188.x.
60. Fink A, Kosecoff J, Chassin M and Brook RH. Consensus methods: characteristics and guidelines for use. *American Journal of Public Health* 1984; 74: 979-983. DOI: 10.2105/AJPH.74.9.979.
61. Dalkey N and Helmer O. An experimental application of the DELPHI method to the use of experts. *Management Science* 1963; 9: 458-467. DOI: 10.1287/mnsc.9.3.458.
62. Pill J. The Delphi method: Substance, context, a critique and an annotated bibliography. *Socio-Economic Planning Sciences* 1971; 5: 57-71. DOI: https://doi.org/10.1016/0038-0121(71)90041-3.
63. Goldacre B and Gray J. OpenTrials: towards a collaborative open database of all available information on all clinical trials. *Trials* 2016; 17: 164. DOI: 10.1186/s13063-016-1290-8.
64. Ip S, Hadar N, Keefe S, Parkin C, Iovin R, Balk EM, et al. A Web-based archive of systematic review data. *Systematic Reviews* 2012; 1: 15. DOI: 10.1186/2046-4053-1-15.
65. Chien PF, Khan KS and Siassakos D. Registration of systematic reviews: PROSPERO. *BJOG* 2012; 119: 903-905. 2012/06/19. DOI: 10.1111/j.1471-0528.2011.03242.x.
66. Palepu A, Kendall C and Moher D. Open Medicine endorses PROSPERO. *Open Medicine* 2011; 5: e65-66. 2011/11/03.

67. Stewart L, Moher D and Shekelle P. Why prospective registration of systematic reviews makes sense. *Systematic Reviews* 2012; 1: 7. DOI: 10.1186/2046-4053-1-7.
68. Davies S. The importance of PROSPERO to the National Institute for Health Research. *Systematic Reviews* 2012; 1: 5. 2012/05/17. DOI: 10.1186/2046-4053-1-5.
69. National Institute for Health Research. Approvals, registration and governance, https://www.nihr.ac.uk/researchers/manage-your-funding/manage-your-project/approvals-registration-and-governance.htm (accessed 7 July 2020).
70. Booth A. Celebrating PROSPERO's first year. *BMJ (opinion)* 2012; 2012.
71. Booth A and Stewart L. Trusting researchers to use open trial registers such as PROSPERO responsibly. *BMJ* 2013; 347: f5870. 2013/10/04. DOI: 10.1136/bmj.f5870.
72. Krumholz H. The case for duplication of meta-analyses and systematic reviews. *BMJ* 2013; 347: f5506. DOI: 10.1136/bmj.f5506.
73. Waugh N. Misgivings about PROSPERO in solving the problem of duplicate systematic reviews. *BMJ* 2013; 347: f5496. 2013/09/12. DOI: 10.1136/bmj.f5496.
74. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). *Journal of Medical Internet Research* 2004; 6: e34-e34. DOI: 10.2196/jmir.6.3.e34.
75. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310: 2191-2194. DOI: 10.1001/jama.2013.281053.
76. Mallett S, Deeks JJ, Halligan S, Hopewell S, Cornelius V and Altman DG. Systematic reviews of diagnostic tests in cancer: review of methods and reporting. *BMJ* 2006; 333: 413. DOI: 10.1136/bmj.38895.467130.55.
77. Glasziou P, Meats E, Heneghan C and Shepperd S. What is missing from descriptions of treatment in trials and reviews? *BMJ* 2008; 336: 1472-1474. DOI: 10.1136/bmj.39590.732037.47.
78. Chalmers I and Glasziou P. Avoidable waste in the production and reporting of research evidence. *The Lancet* 2009; 374: 86-89. DOI: 10.1016/S0140-6736(09)60329-9.
79. Chan AW and Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *The Lancet* 2005; 365: 1159-1162. 2005/03/30. DOI: 10.1016/s0140-6736(05)71879-1.
80. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials: The CONSORT statement. *JAMA* 1996; 276: 637-639. DOI: 10.1001/jama.1996.03540080059030.
81. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM Statement. *The Lancet* 1999; 354: 1896-1900. DOI: https://doi.org/10.1016/S0140-6736(99)04149-5.
82. Moher D, Jones A, Lepage L and for the CONSORT Group. Use of the CONSORT statement and quality of reports of randomized trials. A comparative before-and-after evaluation. *JAMA* 2001; 285: 1992-1995. DOI: 10.1001/jama.285.15.1992.
83. Simera I, Altman DG, Moher D, Schulz KF and Hoey J. Guidelines for Reporting Health Research: The EQUATOR network's survey of guideline authors. *PLoS Medicine* 2008; 5: e139. DOI: 10.1371/journal.pmed.0050139.
84. Turner L, Shamseer L, Altman DG, Weeks L, Peters J, Kober T, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals.

Cochrane Database of Systematic Reviews 2012. DOI: 10.1002/14651858.MR000030.pub2.
85. Stevens A, Shamseer L, Weinstein E, Yazdi F, Turner L, Thielman J, et al. Relation of completeness of reporting of health research to journals' endorsement of reporting guidelines: systematic review. *BMJ* 2014; 348: g3804. DOI: 10.1136/bmj.g3804.
86. Page MJ and Moher D. Evaluations of the uptake and impact of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement and extensions: a scoping review. *Systematic Reviews* 2017; 6: 263. 2017/12/21. DOI: 10.1186/s13643-017-0663-8.
87. Arundel C, James S, Northgraves M and Booth A. Study reporting guidelines: How valid are they? *Contemporary Clinical Trials Communications* 2019: 100343. DOI: https://doi.org/10.1016/j.conctc.2019.100343.
88. Hirst A and Altman DG. Are peer reviewers encouraged to use reporting guidelines? A survey of 116 health research journals. *PLoS ONE* 2012; 7: e35621. DOI: 10.1371/journal.pone.0035621.
89. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of Internal Medicine* 2013; 158. DOI: 10.7326/0003-4819-158-3-201302050-00583.
90. Chan A, Tetzlaff JM, Gøtzsche PS, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; 346. DOI: 10.1136/bmj.e7586.
91. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration & explanation. *BMJ* 2015; 350. DOI: 10.1136/bmj.g7647.
92. Turner L, Shamseer L, Altman DG, Schulz KF and Moher D. Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane reviewa. *Systematic Reviews* 2012; 1: 60. DOI: 10.1186/2046-4053-1-60.
93. Zuñiga-Hernandez JA, Dorsey-Treviño EG, González-González JG, Brito JP, Montori VM and Rodriguez-Gutierrez R. Endorsement of reporting guidelines and study registration by endocrine and internal medicine journals: meta-epidemiological study. *BMJ Open* 2019; 9: e031259. DOI: 10.1136/bmjopen-2019-031259.
94. Hopewell S, Altman DG, Moher D and Schulz KF. Endorsement of the CONSORT Statement by high impact factor medical journals: a survey of journal editors and journal 'Instructions to Authors'. *Trials* 2008; 9: 20. DOI: 10.1186/1745-6215-9-20.
95. Blanco D, Altman D, Moher D, Boutron I, Kirkham JJ and Cobo E. Scoping review on interventions to improve adherence to reporting guidelines in health research. *BMJ Open* 2019; 9: e026589. DOI: 10.1136/bmjopen-2018-026589.
96. Dwan K, Kirkham JJ, Williamson PR and Gamble C. Selective reporting of outcomes in randomised controlled trials in systematic reviews of cystic fibrosis. *BMJ Open* 2013; 3: e002709. DOI: 10.1136/bmjopen-2013-002709.
97. McKenzie JE, Brennan SE, Ryan RE, Thomson HJ, Johnston RV and Thomas J. Chapter 3: Defining the criteria for including studies and how they will be grouped for the synthesis. In: Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (ed) *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane, 2019.
98. Parmelli E, Liberati A and D'Amico R. Reporting of outcomes in systematic reviews: comparison of protocols and published systematic reviews. *Evidence-*

based health care for all Abstracts of the 15th Cochrane Colloquium. Sao Paulo, Brazil 23-27 Oct 2007.
99. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007; 7: 10. 2007/02/17. DOI: 10.1186/1471-2288-7-10.
100. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *Journal of Clinical Epidemiology* 2009; 62: 1013-1020. 2009/02/24. DOI: 10.1016/j.jclinepi.2008.10.009.
101. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017; 358: j4008. DOI: 10.1136/bmj.j4008.
102. Rombey T, Doni K, Hoffmann F, Pieper D and Allers K. More systematic reviews were registered in PROSPERO each year, but few records' status was up-to-date. *Journal of Clinical Epidemiology* 2019; 117: 60-67. 2019/10/08. DOI: 10.1016/j.jclinepi.2019.09.026.
103. Page MJ, McKenzie JE, Kirkham J, Dwan K, Kramer S, Green S, et al. Bias due to selective inclusion and reporting of outcomes and analyses in systematic reviews of randomised trials of healthcare interventions. *Cochrane Database of Systematic Reviews* 2014: Mr000035. 2014/10/02. DOI: 10.1002/14651858.MR000035.pub2.
104. Viguera-Guerra I, Ruano J, Aguilar-Luque M, Gay-Mimbrera J, Montilla A, Fernández-Rueda JL, et al. Evolution of international collaborative research efforts to develop non-Cochrane systematic reviews. *PLoS ONE* 2019; 14: e0211919. DOI: 10.1371/journal.pone.0211919.
105. Kravitz RL, Franks P, Feldman MD, Gerrity M, Byrne C and Tierney WM. Editorial peer reviewers' recommendations at a general medical journal: are they reliable and do editors care? *PLoS One* 2010; 5: e10072. 2010/04/14. DOI: 10.1371/journal.pone.0010072.
106. Rombey T, Allers K, Mathes T, Hoffmann F and Pieper D. A descriptive analysis of the characteristics and the peer review process of systematic review protocols published in an open peer review journal from 2012 to 2017. *BMC Medical Research Methodology* 2019; 19: 57. 2019/03/15. DOI: 10.1186/s12874-019-0698-8.
107. Smith R. Peer review: a flawed process at the heart of science and journals. *Journal of the Royal Society of Medicine* 2006; 99: 178-182. DOI: 10.1258/jrsm.99.4.178.
108. Stahel PF and Moore EE. Peer review for biomedical publications: we can improve the system. *BMC Medicine* 2014; 12: 179-179. DOI: 10.1186/s12916-014-0179-1.
109. Booth A, James S, Cockayne S, Mott A, Gascoyne S and Mitchell A. PROSPERO and PRISMA-P. *Open Science Framework osfio/cpjfw* 2020.
110. Tsujimoto Y, Tsujimoto H, Kataoka Y, Kimachi M, Shimizu S, Ikenoue T, et al. Majority of systematic reviews published in high-impact journals neglected to register the protocols: a meta-epidemiological study. *Journal of Clinical Epidemiology* 2017; 84: 54-60. DOI: https://doi.org/10.1016/j.jclinepi.2017.02.008.
111. Page MJ, Shamseer L and Tricco AC. Registration of systematic reviews in PROSPERO: 30,000 records and counting. *Systematic Reviews* 2018; 7: 32. 2018/02/22. DOI: 10.1186/s13643-018-0699-4.

112. Sideri S, Papageorgiou SN and Eliades T. Registration in the international prospective register of systematic reviews (PROSPERO) of systematic review protocols was associated with increased review quality. *Journal of Clinical Epidemiology* 2018; 100: 103-110. 2018/01/18. DOI: 10.1016/j.jclinepi.2018.01.003.
113. Ruano J, Gomez-Garcia F, Gay-Mimbrera J, Aguilar-Luque M, Fernandez-Rueda JL, Fernandez-Chaichio J, et al. Evaluating characteristics of PROSPERO records as predictors of eventual publication of non-Cochrane systematic reviews: a meta-epidemiological study protocol. *Systematic Reviews* 2018; 7: 43. 2018/03/11. DOI: 10.1186/s13643-018-0709-6.
114. Borah R, Brown AW, Capers PL and Kaiser KA. Analysis of the time and workers needed to conduct systematic reviews of medical interventions using data from the PROSPERO registry. *BMJ Open* 2017; 7: e012545. 2017/03/01. DOI: 10.1136/bmjopen-2016-012545.
115. Farrah K, Young K, Tunis MC and Zhao L. Risk of bias tools in systematic reviews of health interventions: an analysis of PROSPERO-registered protocols. *Systematic Reviews* 2019; 8: 280. DOI: 10.1186/s13643-019-1172-8.
116. Parsons R, Golder S and Watt I. More than one-third of systematic reviews did not fully report the adverse events outcome. *Journal of Clinical Epidemiology* 2019; 108: 95-101. DOI: https://doi.org/10.1016/j.jclinepi.2018.12.007.
117. Khaleel S, Cleveland B, Kalapara A, Sathianathen N, Balaji P and Dahm P. The fate of urological systematic reviews registered in PROSPERO. *World Journal of Urology* 2019 2019/12/01. DOI: 10.1007/s00345-019-03032-x.
118. Khaleel S, Sathianathen N, Balaji P and Dahm P. Quality of urological systematic reviews registered in PROSPERO. *BJU International* 2019; 124: 195-196. 2019/03/14. DOI: 10.1111/bju.14742.
119. Allers K, Hoffmann F, Mathes T and Pieper D. Systematic reviews with published protocols compared to those without: more effort, older search. *Journal of Clinical Epidemiology* 2018; 95: 102-110. DOI: https://doi.org/10.1016/j.jclinepi.2017.12.005.
120. Delgado AF and Delgado AF. Inconsistent Reporting Between Meta-analysis Protocol and Publication - A Cross-Sectional Study. *Anticancer Research* 2017; 37: 5101-5107. 2017/09/06. DOI: 10.21873/anticanres.11928.
121. Siontis KC, Hernandez-Boussard T and Ioannidis JPA. Overlapping meta-analyses on the same topic: survey of published studies. *BMJ* 2013; 347: f4501. DOI: 10.1136/bmj.f4501.
122. Osnabrugge RL, Head SJ, Zijlstra F, ten Berg JM, Hunink MG, Kappetein AP, et al. A systematic review and critical assessment of 11 discordant meta-analyses on reduced-function CYP2C19 genotype and risk of adverse clinical outcomes in clopidogrel users. *Genetics in Medicine* 2015; 17: 3-11. 2014/06/20. DOI: 10.1038/gim.2014.76.
123. Ingoe HMA, Coleman E, Eardley W, Rangan A, Hewitt C and McDaid C. Systematic review of systematic reviews for effectiveness of internal fixation for flail chest and rib fractures in adults. *BMJ Open* 2019; 9: e023444. DOI: 10.1136/bmjopen-2018-023444.
124. Sigurdson MK, Khoury MJ and Ioannidis JPA. Redundant meta-analyses are common in genetic epidemiology. *Journal of Clinical Epidemiology* 2020; 127: 40-48. DOI: 10.1016/j.jclinepi.2020.05.035.
125. González-Becerra K, Ramos-Lopez O, Barrón-Cabrera E, Riezu-Boj JI, Milagro FI, Martínez-López E, et al. Fatty acids, epigenetic mechanisms and chronic diseases: a systematic review. *Lipids in health and disease* 2019; 18: 178-178. DOI: 10.1186/s12944-019-1120-6.

126. Payne LE, Gagnon DJ, Riker RR, Seder DB, Glisic EK, Morris JG, et al. Cefepime-induced neurotoxicity: a systematic review. *Critical Care* 2017; 21: 276-276. DOI: 10.1186/s13054-017-1856-1.
127. Couzin-Frankel J. Journals under the microscope. *Science* 2018; 361: 1180-1183. DOI: 10.1126/science.361.6408.1180.
128. Ioannidis JP. The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. *Milbank Quarterly* 2016; 94: 485-514. 2016/09/14. DOI: 10.1111/1468-0009.12210.

12. Abbreviations and glossary

AHRQ	Agency for Healthcare Research and Quality
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
Archie	Cochrane's central database for managing contact details and documents
BMC	BioMed Central
BMJ	British Medical Journal
Campbell Collaboration	A non-profit organization that promotes evidence-based decisions and policy through the production of systematic reviews and other types of evidence synthesis in: Business & Management, Climate Solutions, Crime & Justice, Disability, Education, International Development, Knowledge Translation & Implementation, Methods, and Social Welfare. https://campbellcollaboration.org/
Cochrane Collaboration (Now known as Cochrane)	Cochrane is a global independent network of researchers, health professionals, patients, carers and policy makers. It includes 53 review groups based at research institutions worldwide. The group conducts systematic reviews of health-care interventions and diagnostic tests and publishes them in the Cochrane Library https://www.cochranelibrary.com
Covidence	Software for the management of systematic reviews from import of citations, through initial and full text screening, data extraction and risk of bias to the export of a file compatible with most statistics packages www.covidence.org
CRD	Centre for Reviews and Dissemination (Originally called NHS CRD, then CRD as scope of work expanded; NIHR CRD when core funded by NIHR; now known as CRD)
CRD databases	Database of Abstracts of Reviews of Effects (DARE) NHS Economic Evaluation Database (NHS EED) Health Technology Assessment (HTA) https://www.crd.york.ac.uk/CRDWeb/
EQUATOR network	The EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network is an international initiative that seeks to improve the reliability and value of published health research literature by promoting transparent and accurate reporting and wider use of robust reporting guidelines https://www.equator-network.org
FigShare	Open content platform for sharing research datasets
HTA	Health Technology Assessment
Joanna Briggs Institute	An international research organisation that develops and delivers evidence-based information, software, education and training designed to improve healthcare practice and health outcomes https://joannabriggs.org
NIHR	National Institute for Health Research
OSF	Open Science Framework: platform for sharing research datasets
OwnCloud	Client–server software for creating and using file hosting services

PLoS	Public Library of Science
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis - Protocols
PROSPERO	An international prospective register of systematic reviews (PROSPERO is not an acronym)
RCTs	Randomised Controlled Trials
RevMan	Review Manager: the software developed by Cochrane to support preparing and maintaining systematic reviews.
RR	Risk Ratio
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
UK	United Kingdom
USA	United States of America

12. Appendix 1

Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, Stewart L. **The nuts and bolts of PROSPERO: an international prospective register of systematic reviews.** *Systematic Reviews* 2012; 1

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3348673/pdf/2046-4053-1-2.pdf

- Published paper

Booth et al. Systematic Reviews 2012, 1:2
http://www.systematicreviewsjournal.com/content/1/1/2

SYSTEMATIC REVIEWS

METHODOLOGY Open Access

The nuts and bolts of PROSPERO: an international prospective register of systematic reviews

Alison Booth[1*], Mike Clarke[2], Gordon Dooley[3], Davina Ghersi[4], David Moher[5,6], Mark Petticrew[7] and Lesley Stewart[1]

Abstract

Background: Following publication of the PRISMA statement, the UK Centre for Reviews and Dissemination (CRD) at the University of York in England began to develop an international prospective register of systematic reviews with health-related outcomes. The objectives were to reduce unplanned duplication of reviews and provide transparency in the review process, with the aim of minimizing reporting bias.

Methods: An international advisory group was formed and a consultation undertaken to establish the key items necessary for inclusion in the register and to gather views on various aspects of functionality. This article describes the development of the register, now called PROSPERO, and the process of registration.

Results: PROSPERO offers free registration and free public access to a unique prospective register of systematic reviews across all areas of health from all around the world. The dedicated web-based interface is electronically searchable and available to all prospective registrants. At the moment, inclusion in PROSPERO is restricted to systematic reviews of the effects of interventions and strategies to prevent, diagnose, treat, and monitor health conditions, for which there is a health-related outcome.
Ideally, registration should take place before the researchers have started formal screening against inclusion criteria but reviews are eligible as long as they have not progressed beyond the point of completing data extraction.
The required dataset captures the key attributes of review design as well as the administrative details necessary for registration.
Submitted registration forms are checked against the scope for inclusion in PROSPERO and for clarity of content before being made publicly available on the register, rejected, or returned to the applicant for clarification.
The public records include an audit trail of major changes to planned methods, details of when the review has been completed, and links to resulting publications when provided by the authors.

Conclusions: There has been international support and an enthusiastic response to the principle of prospective registration of protocols for systematic reviews and to the development of PROSPERO.
In October 2011, PROSPERO contained 200 records of systematic reviews being undertaken in 26 countries around the world on a diverse range of interventions.

Keywords: Systematic review protocol, register, PROSPERO

Background

Following the 2010 publication of the PRISMA statement advocating registration of systematic review protocols [1,2] and in response to user demand and increased recognition of the importance of accurate prospective registers of research [3], the Centre for Reviews and Dissemination (CRD) at the University of York in England began to develop PROSPERO, an international prospective register of systematic reviews. The objectives were to reduce unplanned duplication of systematic reviews and to provide transparency in the review process with the aim of minimizing reporting bias [4]. The development process recognized both the academic need for a register and the practical requirements of creating and

* Correspondence: alison.booth@york.ac.uk
[1]Centre for Reviews and Dissemination, University of York, Alcuin B Block, Heslington, York, UK, YO10 5DD
Full list of author information is available at the end of the article

maintaining one, and was able to take advantage of CRD's existing database infrastructure and information technology (IT) platform supporting the Database of Abstracts of Reviews of Effects (DARE), the NHS Economic Evaluations Database (NHS EED) and the Health Technology Assessment (HTA) database [5].

Methods

A small international advisory group was formed to help guide the development of the register. The members of the group brought systematic review expertise, including Cochrane, Campbell, and the Evidence-based Practice Centre (EPC) program review methods, experience of clinical trials registers, and authorship of the PRISMA statement [1,2].

The advisory group sought the opinions of a wide range of people for whom the register would be relevant, including clinical and academic researchers, commissioners, and journal editors, through an international consultation process. A two-round electronic modified Delphi survey was used to identify the minimum dataset (Required fields) for PROSPERO and to identify what would represent useful but not essential data (Optional fields) [6]. Participants in the survey were also asked their views on aspects of the functionality of the register. The feedback from the Delphi process and pilot testing were used to develop PROSPERO. This article describes the process of registration that is now in place.

Results and discussion

Design of the register

The web-based register offers open public access; registering a review and searching the register is free of charge. (Figure 1) The register is electronically searchable; open to all prospective registrants; requires the submission of a minimum data set; and has a validation mechanism to ensure that entries fall within scope and are complete. A unique identification number is issued for each review protocol accepted for registration which becomes part of the review identity and facilitates linkage between the registration record and subsequent publications. PROSPERO records are permanent and an audit trail of any changes to the record is maintained. This allows readers to see how the review has developed or changed over time.

Feedback from many of the 266 participants who completed one or both of the Delphi surveys confirmed the need to balance collection of sufficient information to achieve the objectives of the register, with making sure the registration process was not overly burdensome. The process of registering a review has been made as straightforward, intuitive and user friendly as possible, for example through the use of drop down menus for several items.

A nominated 'Named contact' is responsible for ensuring that the information submitted is accurate and kept up to date, including provision of a link to the report of the review when it is completed. Because detailed information about the planned methods is needed, the Named contact should be the principal investigator or lead researcher, but is not necessarily the 'author' since the protocol may not (and the full review will not) have been published at the time of registration. This requirement for a single contact person should encourage review teams to nominate one person to this role and so help avoid a review being registered more than once.

Scope for inclusion

The long term aim is to have broad inclusion criteria for PROSPERO, such that any systematic review that has a health related outcome will be eligible. However, to reach this aim without making the process too complex or time consuming, a stepped approach is being taken. The initial focus for inclusion is on systematic reviews of the effects of interventions and strategies to prevent, diagnose, treat, and monitor health conditions, for which there is a health related outcome. This includes systematic reviews undertaken before and after clinical trials to help design the trial or to place the results in context [7]. The inclusion of other reviews will be phased in over time.

Systematic reviews that are regarded as 'rapid reviews' will be accepted if they meet the inclusion criteria and researchers can complete the application within the time frame of the review and in accordance with the requirements of PROSPERO.

Scoping reviews and reviews of reviews are not being included at this time, but this decision will be re-considered in the future. The decision to exclude these types of knowledge syntheses was based on practical considerations: it is not clear if the initial registration template will be suitable for much broader types of knowledge syntheses where the methods vary and may not be as well defined as those that use well-accepted systematic review methodology.

Reviews of methodological issues will not be included in PROSPERO as the findings are likely to relate to recommendations about changes in methods rather than direct effects on health outcomes [8]. Methods reviews often cross boundaries between health and other areas, and like other types of knowledge syntheses, are also likely to require a different data entry structure. A centralized database of such reviews would be useful, but is outside the current aims and remit of PROSPERO. Likewise, systematic reviews of animal studies are excluded as they involve studies with different methodologies and objectives.

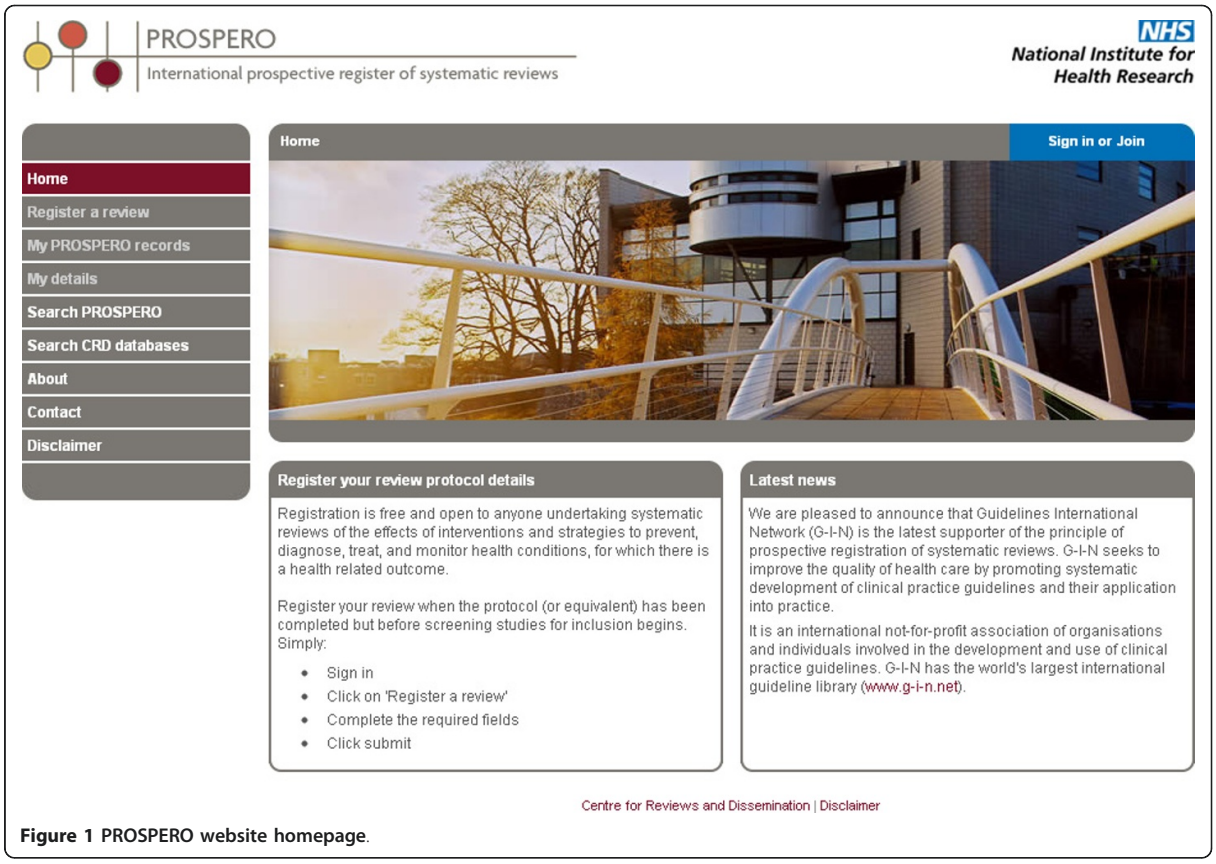


Figure 1 PROSPERO website homepage.

The inclusion of protocols for Cochrane Reviews is desirable to ensure a comprehensive overview of ongoing systematic reviews. To minimize additional work for authors of Cochrane Reviews, an electronic mechanism for their automatic upload from *The Cochrane Library* is being developed. Contact authors will simply be asked to verify that the information has been transferred accurately to the PROSPERO database. To avoid future duplication, Cochrane Reviews are therefore not registered independently on PROSPERO.

Timing of registration

As registration requires the completion of a minimum dataset, it can only take place after key issues have been considered, preferably as part of the development of the review protocol. For PROSPERO to achieve its aim of providing transparency and helping identify potential bias, registration should ideally take place before formal screening against inclusion criteria has begun, this being an early point at which bias could be introduced. However, the systematic review process is iterative by nature and some experimentation with searching is likely to be essential in developing the review. It also has to be recognized that researchers are often aware of some of the potentially eligible studies, and have an opinion on whether they are likely to include or exclude these, some time before they start formal screening.

Registering a review too soon might lead to multiple amendments to records as the protocol and the plans for the review are finalized; registration late in the process may mean that the aim of publishing methods before any results are known is not achieved. A practical approach to the timing of registration has been taken, initially. Registrants are asked to indicate the stage of progress of the review at the time of registration, and at any subsequent revisions, by selecting the relevant stage from a list, with the option of adding further information in a free text field. All records and revisions are automatically dated when published in the register.

In recognition that authors of reviews that are already underway during PROSPERO's first year might wish to register them, systematic reviews that have not progressed beyond the point of completing data extraction are being considered for inclusion. The issue of timing of registration will be reviewed as part of a planned evaluation of the register in 2012.

Registering a review

Registrants need to 'Join' PROSPERO to obtain a username and password, which are then used to sign in and activate the 'Register a review' option. Selecting this option opens a page detailing a summary of the inclusion criteria, to help users to avoid wasting time on inappropriate submissions. Once registrants are satisfied that their review fulfills the inclusion criteria, a single click opens a new electronic registration form. (Figure 2)

There are four sections to the form: title and timescale; review team details; methods; and general information. All the 'Required' fields in each section are indicated by an asterisk (*) in the on-line form and below, and these must be completed before the registration can be submitted. A registration application can be saved and returned to at any time, to add or edit information before submission. Information can be entered by typing directly into the form or by pasting from another document. Once all the required information has been provided, the 'Submit' option is activated.

The PROSPERO registration form

1. Review title and timescale

The first section in a PROSPERO entry asks for the title of the review in English* and the original language if this is not English. Registrants are asked to give the anticipated or actual start date* and the anticipated completion date for the review*. Unless 'fixed' by a funder, these dates can be difficult to estimate. However, they are operationally necessary for scheduling automatic updates and reminders, as well as for the integrity of the record. The dates can be revised at any time by submission of an amendment. The Delphi consultation revealed some differences of opinion about when a review 'starts'. For PROSPERO purposes this is considered to be when screening studies for inclusion begins, although it is recognized that a large amount of essential work takes place before this.

2. Review team details

This section includes address, phone, and email* contact details for the Named contact*. These fields are automatically completed from the 'Join' information, but can be edited. For example, information in optional fields can

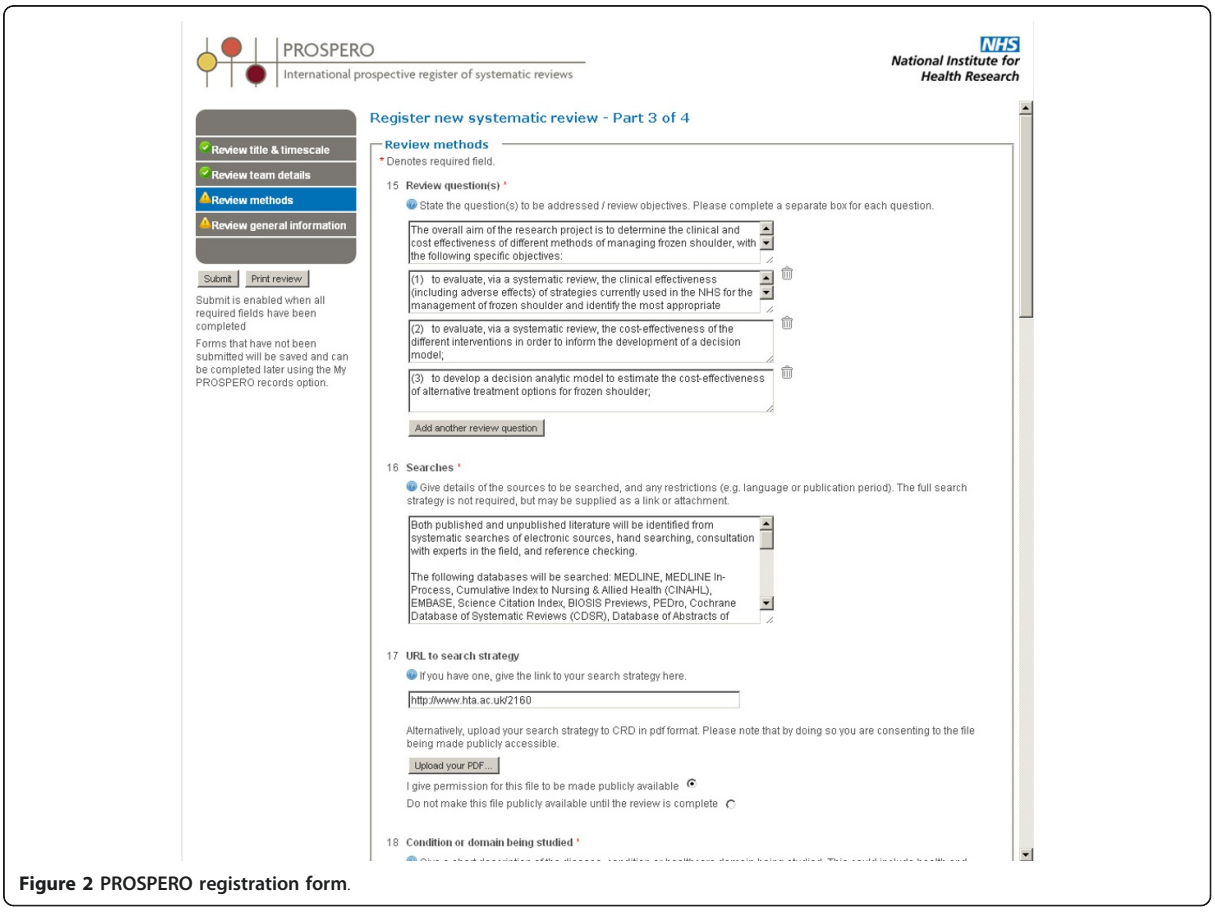


Figure 2 PROSPERO registration form.

be deleted so that it does not appear in the public record.

The organizational affiliation of the review*, funding sources/sponsors* and conflicts of interest* were categorized as essential details by respondents to the consultation. The names of review team members and their organizational affiliations and information about collaborators were considered by respondents to the Delphi survey to be useful indicators of the range of skills and experience of those undertaking the review, but not essential to the register.

3. Review methods

There are 15 fields to capture the review methods, 12 of which are 'Required'*:

Review methods fields • Review question(s)*
- Searches*
- URL to search strategy
- Condition or domain studied*
- Participants/population*
- Intervention(s), exposure(s)*
- Comparator(s)/control*
- Types of study to be included initially*
- Context
- Primary outcome(s)*
- Secondary outcomes*
- Data extraction, (selection and coding)
- Risk of bias (quality) assessment*
- Strategy for data synthesis*
- Analysis of subgroups or subsets*

The structure aims to facilitate data entry for registrants while also providing users of the database with consistent, clear access to the planned methods for a review. Registrants are asked to provide sufficient detail to allow comparison of planned methods with the subsequent published review. The information to be provided will vary according to the type of review and the topic, and not all fields will be relevant to all reviews (with 'not relevant' being an acceptable response, where appropriate). Within the registration form, brief instructions are given for what is required for each field and users can access expanded guidance with examples either within the information tabs for each field or from the 'About' pages on the PROSPERO site.

The review methods fields were agreed through the Delphi consultation and are based on the protocol requirements for a variety of reviews of the effects of interventions, ranging from a straightforward comparison (for example, a drug versus a placebo) to the assessment of complex interventions (for example, smoking cessation), hence the inclusion of a field such as Context. To achieve the long term aim of a broad scope for PROSPERO, it is anticipated that other templates may need to be developed in consultation with experts in particular fields (such as for reviews of qualitative research).

4. Review general information

Additional general information about the type of review, language, countries involved, other registration details, dissemination plans, keywords and existing reviews on the same topic by the same authors were identified as useful but not essential during the consultation.

Respondents to the consultation suggested that other registration details be recorded, but that these should not be mandatory. This would allow appropriate cross-linkage, and help avoid registration duplication. This information has been incorporated into the registration form as one of the 18 optional fields.

Respondents also agreed that where a protocol had been published for a review and was publicly accessible, the citation and URL should be included in the PROSPERO record. The challenges and opportunities for publishing protocols vary across different areas of health and social care, with limited scope up to now to publish review protocols outside *The Cochrane Library*. However, the launch of the journal *Systematic Reviews* should improve this situation.

While publication of review protocols is recommended and encouraged, submission of a review to PROSPERO is not dependent on it. 'Publication' is considered in a wider sense than inclusion in a peer reviewed journal. For example, protocols made available on organizational websites are acceptable and can be linked to from PROSPERO. Alternatively, registrants can submit a pdf of their protocol, which will be hosted on a CRD web server and linked to from within the register record. In either case, the named contact is responsible for the integrity and maintenance of the protocol. If a protocol is not available in a published record, users of PROSPERO are advised to get in touch with the named contact for any further information they wish to obtain about the review.

The Current review status* field is an administrative requirement to indicate the progress of the review through the process from design to full review.

Registrants can add any further information they think relevant to their registration in a free text field. The last field is for recording details of the final report or publication when the review has been completed.

Administration of submissions

On submission, registrants receive an automated email confirming receipt and outlining the administration process. Submitted application forms are checked for eligibility for PROSPERO, which includes consideration of the current stage of review. Forms are also examined for clarity of content, for example whether: the information provided makes literal sense; the information has been

entered in the correct field; the information given is not contradictory; or only partial information is provided in a required field. Submissions are approved and published on the register, returned to the applicant for clarification, or rejected. The checks made do not constitute peer review or imply approval of the methods proposed for the review being registered.

Applications are reviewed within five working days of submission and details of the final decision are sent to the named contact in a confirmation email. In the case of accepted records, a unique ID number is given in the email. All records published in PROSPERO remain permanently available through the register.

Recording protocol amendments

Protocol development is an iterative process and legitimate changes and amendments to the registration record may be necessary. It is particularly important for transparency to document and justify major changes to methods, particularly those which could be seen as potentially introducing biases through increased knowledge of potentially eligible studies, resulting, for example, in the narrowing of objectives or the addition of new outcome measures.

Registrants can access and update their records at any time via a 'My PROSPERO records' page, except during the PROSPERO administration phase, when access to the record is locked. The named contact is tasked with recording any major changes or substantial amendments to the planned methods in the PROSPERO record. This is done by making the necessary changes in the record, updating the stage of review and re-submitting it. A 'Revision note' facility requires a brief outline of the changes and the reason for making them to be recorded. This is made available in the public record, as part of the audit trail for the PROSPERO entry.

The most recent version of a record appears in the public interface, with previous versions marked as 'Archived' and made accessible through dated links on the record page.

On completion of a registered review

There was strong support in the Delphi consultation for PROSPERO to include publication details or details of where unpublished results could be viewed, once the review is completed. It was considered that such links would be hard to maintain, but the consensus was that this would be necessary to provide a complete thread for a systematic review. However, there was also concern that the register should not become a new database of completed reviews. The addition of details of the completed review is an option available to registrants. There are currently no plans for the PROSPERO administration team to be responsible for identifying publications or adding links within PROSPERO records.

Email reminders are sent to the named contact on the completion date entered in the PROSPERO record, asking for an anticipated publication date (or revision to the completion date). The named contact is prompted to add a statement if the review will not be published, including brief details of the reason. This can be entered in the final report/publication field.

If a registered review is not to be completed, the option of 'Abandoned' can be selected and brief details of the reason why recorded in a free text field, for display in the public record.

If a registered review is completed and a critical abstract for its publication is included in the Database of Abstracts of Reviews of Effects (DARE), a link to the DARE abstract will be added to the PROSPERO record.

As part of the consultation, participants were asked about the inclusion of summary results in the PROSPERO record, given that a sizeable proportion of initiated systematic reviews are never published [9]. Some major concerns were expressed. These included that publishing results on the register could jeopardize subsequent peer review publication; and that, as publication can take a long time, it may be seen as an alternative and delay or prevent more formal publication by some review teams (for example, where their funding has ended). It was also thought that if researchers had not published the review, it was likely they would have lost interest and would not provide this information anyway. Of more concern was the inability to check the validity of the data posted, and the potential lack of context for it, which might be misleading if users of PROSPERO read the record and not the full publication of the review. In light of these concerns, it was decided that summary results would not be included in PROSPERO records, at this time.

Updating an existing review

The intention of including protocol details for updates to existing reviews prompted a discussion on how to deal with these updates, and how to decide if the modifications to an existing protocol constitute a new review rather than an update. The advisory group agreed on the following definitions, which are included in PROSPERO's guidance notes:

What is an update of a review?

Updating a systematic review is a discrete event during which efforts are made to identify and incorporate new evidence into a previously completed systematic review [10].

An 'update' may be any modified version of a review that includes the findings of a more recent search than

the previously completed version of the review. It can still be considered an update even if the new search reveals no additional studies. Any newly identified studies should be assessed and, if appropriate, incorporated into the updated review. An update might also be an opportunity to conduct new analyses or add additional information to the review.

What constitutes a new review rather than an update?

It can be difficult to decide whether an update to a review is in fact a new review. There is little published guidance on this. PROSPERO adopts a pragmatic approach. If changes to the review questions or methods are so substantial that they require major changes to the original protocol, this should be regarded as a new review rather than an update.

Examples that would constitute a new review:

- addition of new treatment comparisons, for example, direct comparison of different drugs, when the old review included only comparisons of drug with placebo
- substantial changes to the population being studied, for example, adding adults to a review that was previously restricted to children
- exclusion criteria in the old review become inclusion criteria in the new review
- introduction of new analysis techniques, for example, a switch from aggregate data meta-analyses to individual participant meta-analyses.

Updates of registered reviews will retain the original number and the version history will be available, which will mean that links to the full audit trail and the existing review will be readily accessible to users.

Conclusions

Current and future developments

PROSPERO was launched in February 2011 by the UK Health Minister Lord Howe and at an international meeting in Vancouver, Canada organized by the Canadian Institute for Health Research (CIHR).

Initial publicity efforts have gone into raising awareness of PROSPERO among those commissioning and undertaking reviews. There has been an enthusiastic international response to the development of PROSPERO, alongside support for the principle of systematic review protocol registration from organizations, including the International Network of Agencies for Health Technology Assessment (INAHTA), The Cochrane and Campbell Collaborations and the Guidelines International Network (G-I-N). A number of commissioning organizations, such as the UK National Institute for Health Research (NIHR) and the Canadian Institute of Health Research (CIHR), are making registration a requirement for all their grant holders who are undertaking relevant systematic reviews.

Public Library of Science journals and the *Systematic Reviews* journal support the prospective registration of systematic reviews and their instructions to authors ask that the registry number be included in the abstract of the reports of all prospectively registered systematic reviews. Other journals are being encouraged to follow suit.

In October 2011, eight months after launch, PROSPERO contained 200 records of systematic reviews

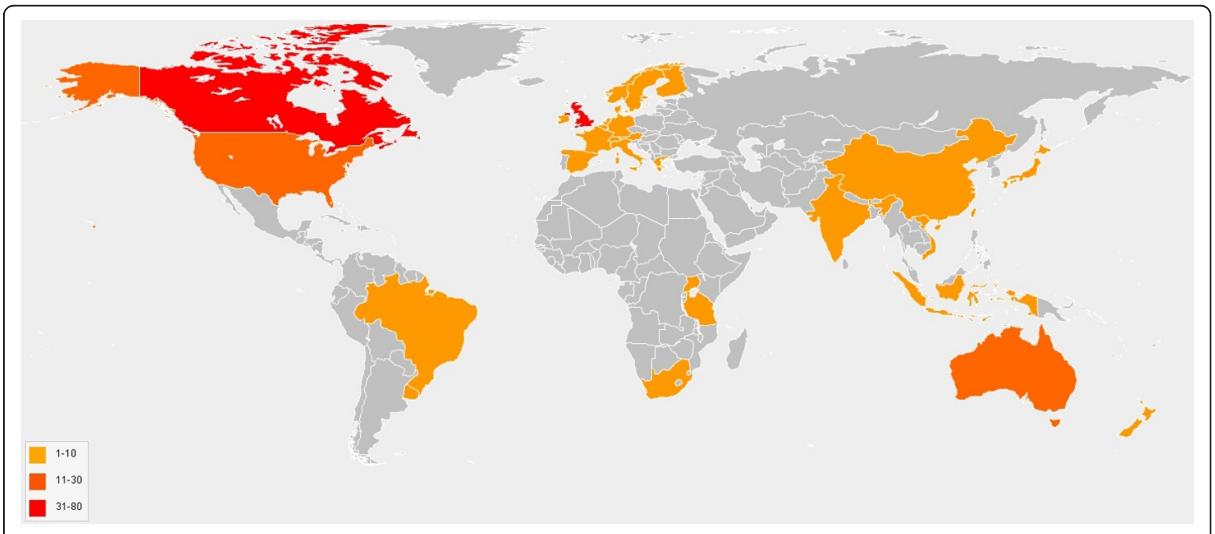


Figure 3 Countries where registered reviews are being undertaken.

being undertaken in 26 different countries (Figure 3) on a diverse range of interventions.

Feedback from users is welcome (to crd-register@york.ac.uk) as part of an ongoing process of improvement and refinement. A detailed evaluation of the registration process is planned for early 2012. The findings of this will be used to make an initial assessment of PROSPERO's fitness for purpose and guide the next stages in its ongoing development.

Acknowledgements
We would like to thank all those who took part in the Delphi exercise for their contributions which have been used to inform the development of PROSPERO.

Author details
[1]Centre for Reviews and Dissemination, University of York, Alcuin B Block, Heslington, York, UK, YO10 5DD. [2]Centre for Public Health, Institute of Clinical Sciences, Block B, Queen's University Belfast, Royal Victoria Hospital, Grosvenor Road, Belfast, UK, BT12 6BA. [3]Metaxis Ltd, Elmbank Offices, Elmbank Court, Main Road, Curbridge, Oxford, UK, OX29 7NT. [4]Research Translation Branch, National Health & Medical Research Council, 16 Marcus Clarke Street, Canberra City ACT 2600, Australia. [5]Department of Epidemiology, Clinical Epidemiology Program, Ottawa Hospital Research Institute, 725 Parkdale Avenue Ottawa, Ontario, Canada, K1Y 4E9. [6]Community Medicine, Faculty of Medicine, University of Ottawa, 451 Smyth Road, Ottawa, Ontario, Canada K1H 8M5. [7]Department of Social and Environmental Health Research, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK WC1E 7HT.

Authors' contributions
All the authors made substantial contributions to the Delphi consultation exercise and the subsequent development of PROSPERO. AB managed the acquisition of the data; all the authors contributed to the analysis and interpretation of the data and conversion into the working register, PROSPERO. AB produced the first draft of the article and MC, GD, DG, DM, MP, and LS critically commented. All the authors have read and approved the final version being submitted.

Authors' information
All the authors are members of the PROSPERO advisory group and have been since the inception of the register.

Competing interests
The authors declare that they have no competing interests.
The development of PROSPERO is being funded by the NIHR Centre for Reviews and Dissemination at the University of York, England.

Received: 6 November 2011 Accepted: 9 February 2012
Published: 9 February 2012

References

1. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.** *PLoS Med* 2009, **6**: e1000100.
2. Moher D, Tetzlaff J, Altman DG, The PRISMA Group: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.** *PLoS Med* 2009, **6**:e1000097.
3. Dwan K, Altman D, Cresswell L, Blundell M, Gamble C, Williamson P: **Comparison of protocols and registry entries to published reports for randomised controlled trials.** *Cochrane Database of Systematic Reviews* 2011, , **Issue 1:** Art. No.: MR000031.
4. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L: **An international registry of systematic review protocols.** *Lancet* 2011, **377**:108-109.
5. Booth A, Wright K, Outhwaite H: **Centre for Reviews and Dissemination databases: value, content, and developments.** *Int J Technol Assess Health Care* 2010, **26**:470-472.
6. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L: **Establishing a minimum dataset for prospective registration of systematic reviews: an international consultation.** *PLoS ONE* 2011, **6**:e27319.
7. Clarke M, Hopewell S, Chalmers I: **Clinical trials should begin and end with systematic reviews of relevant evidence: 12 years and waiting.** *Lancet* 2010, **376**:20-21.
8. Tricco A, Tetzlaff J, Sampson M, Fergusson D, Cogo E, Horsley T, Moher D: **Few systematic reviews exist documenting the extent of bias: a systematic review.** *J Clin Epidemiol* 2008, **61**:422-434.
9. Tricco A, Pham B, Brehaut J, Tetroe J, Cappelli M, Hopewell S, Lavis J, Berlin J, Moher D: **An international survey indicated that unpublished systematic reviews exist.** *J Clin Epidemiol* 2009, **62**:617-623.
10. Moher D, Tsertsvadze A: **Systematic reviews: when is an update an update?** *Lancet* 2006, **367**:881-882.

doi:10.1186/2046-4053-1-2
Cite this article as: Booth *et al.*: The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. *Systematic Reviews* 2012 **1**:2.

13. Appendix 2

Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L. **Establishing a minimum dataset for prospective registration of systematic reviews: an international consultation.** *PLoS ONE* 2011;6(11):e27319 http://www.plosone.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pone.0027319&representation=PDF

- Published paper
- Figure S1. Participant demographic information
- Table S1. Professional information about respondents: role.
- Table S2. Professional information about respondents: health areas of interest.
- Table S3. Professional information about respondents: review method of interest.
- Table S4. Professional information about respondents: number of systematic reviews authored.
- Table S5. Professional information about respondents: number of systematic reviews involved with other than as an author.
- Table S6. Professional information about respondents: proportion of work related to research methodology.
- Table S7 Professional information about respondents: membership of relevant organisations

OPEN ACCESS Freely available online

PLoS one

Establishing a Minimum Dataset for Prospective Registration of Systematic Reviews: An International Consultation

Alison Booth[1]*, Mike Clarke[2], Davina Ghersi[3], David Moher[4,5], Mark Petticrew[6], Lesley Stewart[1]

1 Centre for Reviews and Dissemination, University of York, York, United Kingdom, **2** Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom, **3** International Clinical Trials Registry Platform, World Health Organisation, Geneva, Switzerland, **4** Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Canada, **5** Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Canada, **6** Department of Social and Environmental Health Research, London School of Hygiene and Tropical Medicine, London, United Kingdom

Abstract

Background: In response to growing recognition of the value of prospective registration of systematic review protocols, we planned to develop a web-based open access international register. In order for the register to fulfil its aims of reducing unplanned duplication, reducing publication bias, and providing greater transparency, it was important to ensure the appropriate data were collected. We therefore undertook a consultation process with experts in the field to identify a minimum dataset for registration.

Methods and Findings: A two-round electronic modified Delphi survey design was used. The international panel surveyed included experts from areas relevant to systematic review including commissioners, clinical and academic researchers, methodologists, statisticians, information specialists, journal editors and users of systematic reviews. Direct invitations to participate were sent out to 315 people in the first round and 322 in the second round. Responses to an open invitation to participate were collected separately. There were 194 (143 invited and 51 open) respondents with a 100% completion rate in the first round and 209 (169 invited and 40 open) respondents with a 91% completion rate in the second round. In the second round, 113 (54%) of the participants reported having previously taken part in the first round. Participants were asked to indicate whether a series of potential items should be designated as optional or required registration items, or should not be included in the register. After the second round, a 70% or greater agreement was reached on the designation of 30 of 36 items.

Conclusions: The results of the Delphi exercise have established a dataset of 22 required items for the prospective registration of systematic reviews, and 18 optional items. The dataset captures the key attributes of review design as well as the administrative details necessary for registration.

Citation: Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, et al. (2011) Establishing a Minimum Dataset for Prospective Registration of Systematic Reviews: An International Consultation. PLoS ONE 6(11): e27319. doi:10.1371/journal.pone.0027319

Editor: Erik von Elm, IUMSP, CHUV/University of Lausanne, Switzerland

Received September 17, 2011; **Accepted** October 13, 2011; **Published** November 16, 2011

Funding: The development of PROSPERO including this consultation exercise is being funded by the UK NIHR Centre for Reviews and Dissemination at the University of York. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: alison.booth@york.ac.uk

Introduction

A protocol should be an integral part of a systematic review, and is important because it pre-specifies the objectives and methods to be used. Having a protocol can help restrict the likelihood of biased post hoc decisions in review methods, such as selective outcome reporting (because it specifies outcomes of primary interest, how information about those outcomes will be extracted, and the methods that might be used to summarize the outcome data quantitatively). An examination of 47 Cochrane reviews revealed indirect evidence for possible selective reporting bias for systematic reviews. Almost all (n = 43) contained a major change, such as the addition or deletion of outcomes, between the protocol and the full publication [1]. However, whether (or to what extent) the changes reflected bias, as opposed to unreported but legitimate changes in methods as the review methods were developed, was not clear. For example, the protocol might have aimed to include specific outcomes, which were then found to be absent from all of the included studies, leading the reviewers to remove these outcomes from their final review. Similarly, setting out inclusion and exclusion criteria prior to author knowledge of the available studies reduces the potential for selective inclusion based on study findings. Publication of a protocol additionally promotes transparency of methods and, as it facilitates identification of reviews that are in process, reduces the potential for unplanned duplication and allows public review of the planned methods.

Capturing the key elements of a systematic review at the protocol stage (or at the design stage if there is no formal protocol) and making these publicly available has similar utility to producing and publishing systematic review protocols. Additionally, a register providing a single point of access should be of great benefit in avoiding unplanned duplication of effort. The issuing of a unique

identifier linked to a permanent registration record allows comparison of final reports of reviews with what was planned at registration.

Support for prospective registration of systematic review protocols has been gathering momentum, reflected in a number of recent publications [2,3,4,5]. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions advocates registration and the PRISMA 2009 Checklist requires protocol registration details, if available, to include a registration number and details of the existence of and access to the protocol [2,3].

Until now there has been no widely adopted process to register systematic reviews formally, outside of specific collections of reviews, such as those produced by the Cochrane Collaboration. Recognising the need for registration, the Centre for Reviews and Dissemination (CRD), in collaboration with an international Register Advisory Group, took the initiative in establishing PROSPERO, an international prospective register of systematic reviews with health outcomes that is freely accessible online (www.crd.york.ac.uk/PROSPERO).

The aim of PROSPERO is to prospectively register systematic reviews at the protocol stage; capturing the key attributes of the protocol or plan; maintaining an audit trail of any subsequent protocol amendments; and adding details of final publications, including peer-reviewed articles, and other documents as they become available. This will provide a permanent public record and unbiased listing of registered reviews. PROSPERO can therefore assist in planning new reviews and updating existing ones by providing stakeholders with information about reviews already in the pipeline. This should help to reduce unplanned duplication of effort and to optimise often limited use of research funds.

It will also provide transparency of process, and facilitate comparison between planned methods and reported results enabling readers to make judgements about the importance of any discrepancies [6]. Ultimately this may serve to discourage bias in the conduct and reporting of reviews.

To achieve these aims, the register needs to capture and make available relevant information related to potential for bias in a timely, transparent, and accessible way. At the same time it should be user friendly and not overly burdensome for those completing the registration details. It also needs to be able to accommodate methodological variations between different types of systematic reviews. The development team recognised that support for and use of the register would require the involvement of a range of interested parties including, for example, clinical and academic researchers, commissioners and journal editors. An international consultation was therefore undertaken with the primary objective of establishing the minimum dataset required for registration of systematic reviews at the protocol stage. A secondary objective was to raise awareness of the development of the register.

Methods

The international Register Advisory Group consists of a small number of key individuals recruited by CRD to assist in taking forward the development of the register. The advisory group members collectively have a wide range of systematic review experience with a variety of methodological interests and significant statistical expertise. In addition members have a detailed knowledge of the Cochrane Collaboration approach to registration of review protocols; experience of clinical trials registers and authorship of the PRISMA statement. The advisory group proposed the use of a Delphi exercise to establish the minimum dataset and subsequently guided each stage of the process.

Design

A modified Delphi exercise was carried out to obtain opinions from international experts in the field of systematic review about which individual constituents of a review protocol should be included in a registration record. The Delphi technique is a method of collecting in a structured and iterative way, the anonymous, individual opinions of a panel with relevant expertise in the topic where a consensus is required. The basic principle is for the panel to receive successive questionnaires, each one containing the anonymous responses to the previous round, and for them to modify their responses until a consensus is reached [7,8,9]. We modified the basic Delphi technique for practical reasons.

The survey population of interest had a high level of Internet and email access, were likely to be familiar with the use of electronic online submission processes and to use email as the principal mode of communication. We aimed to include wide international participation, minimise cost, and ensure accurate and efficient collection and analysis of responses. The questionnaires were therefore administered electronically using on-line survey software Survey Monkey (www.surveymonkey.com).

Participants

The opinions of international experts in health and social care involved in undertaking, commissioning, or developing methods for systematic reviews, or in guideline development, were sought, as were those of healthcare journal editors.

Two lists of participants were prepared; a core panel of individuals, and an 'open list' of organisations, groups, and electronic mailing lists. The initial circulation list for the core panel contained 350 names. These individuals were nominated by members of the register Advisory Group or identified through existing networks (e.g., the PRISMA Group, the International Network of Agencies for Health Technology Assessment; and International Committee of Medical Journal Editors). Email addresses were collected from personal contact lists and publicly available sources (e.g., organisational websites). All emails were personalised to individuals.

The open list included groups such as Guidelines International Network and the Health Technology Assessment International Information Resources Group, for onward dissemination to their members and electronic mailing lists (e.g., Cochrane Methods Groups and the Coordinating Editors of Cochrane Review Groups; LIS-MEDICAL and EVIDENCE-BASED-HEALTH, and World Association of Medical Editors). The open invitation was also posted on websites (e.g., CRD, National Institute for Health Research (NIHR), Cochrane Collaboration, Committee on Publication Ethics) and placed in newsletters (e.g., CRD, Cochrane Collaboration, NIHR). Details of the exercise were published in a Lancet comment paper, which directed readers to the CRD website for further information. This appeared in the e-version of the Lancet during the survey [10] and in the print version at a later date [11].

Separate response collectors were used within Survey Monkey for the two different types of invitation. Anyone responding on a link cascaded by a core panellist would have been included in the core panel collector.

The second round was sent to everyone in the core panel again, including non-responders unless they had requested removal from the list. In addition those from the open list who completed the first round and supplied their email addresses were added to the

revised core panel list. Again, separate collectors were used for the core panel and open lists. The second (final) round of the survey required participants to indicate whether they had taken part in the first round. It was accompanied by a summary report on the responses to the first round (available from http://www.york.ac.uk/inst/crd/projects/register.htm).

All responses were anonymous; it was not possible to tell who responded or to link names to responses even when individuals informed us they had responded. It was hoped that this would encourage participation in both rounds and expression of personal opinion, rather than conforming to group opinion or dropping out after the first round [9].

In order to assess representation of different stakeholder groups and identify any differences in the responses between them, simple demographic details were requested in each questionnaire. These were designation; membership of organisations; health area of interest; review method of interest; number of systematic reviews authored; number of systematic reviews in which involved other than as author; proportion of work that relates to methodology; country; and English as a first language.

Instrumentation

The exercise was limited to two rounds, although provision had been made for subsequent rounds if these were judged necessary by the register Advisory Group. The questionnaires were piloted before distribution.

The time in which the questionnaires were 'open' for responses was limited to two weeks for each round. Reminder emails were sent to all members of the core panel approximately one week before the close of each round.

A mixture of 'pick lists', pre-specified response options, and free text responses were used to facilitate ease of response and analysis of data from a wide consultation, with large numbers from diverse groups, many of whom may not have English as their first language. In order to ensure that sufficient data were collected and that key areas addressed fully, 'pick list' questions were made mandatory. That is respondents had to make a choice before they could submit their answers. It was not mandatory to put anything into the free text boxes.

The questionnaires were prepared by CRD with advice from the register Advisory Group. None of those involved in designing, administering or advising on the questionnaires completed the survey.

The focus for the questions, the language, and explanations used were informed by lessons learned from the development of trials registers, and in particular the requirements for registers as set out by the WHO trials register platform (http://www.who.int/ictrp/en/) [12].

Question formulation

A pragmatic decision was taken not to approach panellists in advance to ask for their participation. This was to minimise the burden on named individuals who were likely to have limited time to devote to the process. For the same reason, we drew up a list of candidate items for inclusion in the minimum data set based on established guidance for writing systematic review protocols [13,14,15,16], the PRISMA statement [3] and information from the WHO trials registry (http://www.who.int/ictrp/en/).

The first round questionnaire sought preferences for 41 candidate items as to whether they should be included in the minimum data set. Respondents were asked to indicate whether they thought each item was 'Essential', 'Desirable' or 'Not necessary'. The focus for responses was on the inclusion of data that would help identify ongoing reviews and enable assessment of bias when the review was completed. Opinions on the scope of the register, allocation of unique ID; timing of registration, dealing with amendments to protocols, publications, and updating of reviews, and existence of other protocol registers were also sought. However, these items relating to the development and implementation of a register are not presented in detail here, but are included in the summary reports, available at http://www.york.ac.uk/inst/crd/projects/register.htm.

The second round questionnaire set out suggestions for which items should be mandatory and which should be optional, based on the register Advisory Group's interpretation of the first round responses. Participants were asked to 'Agree', or 'Disagree' with the suggested categorisation, to state that an item was 'Not needed' or state that they had 'No opinion'. If they disagreed with a categorisation, they were asked to indicate the direction of the disagreement, e.g., that an item suggested as compulsory should be down-weighted to optional. Again the focus for responses was to identify the minimum dataset to achieve the aims of registration. As with the first round questionnaire, free text boxes for comments and suggestions were provided but not mandatory.

The majority vote for 'Essential' or 'Desirable' in the first round was used to categorise fields as 'Required' or 'Optional', respectively for the second round questionnaire.

Analysis

All responses were collated in 'Survey Monkey' for tabulation and analysis. A summary report on each round was compiled and circulated to both distribution lists (available from http://www.york.ac.uk/inst/crd/projects/register.htm).

Where possible, decisions were based on achieving consensus at a designated level of 70% agreement. This level of consensus was agreed by the Advisory Group as being greater than two-thirds of opinion, indicating a clear majority. Other decisions were made taking into consideration the distribution of alternative responses.

Ethical approval

Formal written consent was not sought; submission of completed questionnaires was taken as implied consent. The research was approved by the University of York Humanities and Social Sciences Ethics Committee (HSSEC 12-2009/10).

Results

Responses and respondents

The first round core panel list included 327 direct invitations, 12 were excluded as their emails were returned as undelivered, making the initial list 315. Five people declined to take part and were removed from the mailing list.

The second round core panel list included 322 direct invitations, four were excluded (three emails were returned as undelivered and one was known to be unavailable while the survey was open), making the list 318. One declined to take part and was removed from the mailing list.

A separate collector was set up for the open list invitation to participate. Both the first and second round questionnaires were sent to a general contact at 15 different organisations, and to a named contact for internal circulation in five other organisations or groups.

There were 194 (143 invited and 51 open) respondents with a 100% completion rate in the first round and 209 (169 invited and 40 open) respondents with a 91% completion rate in the second round. Of those who took part in the second round, 113 (54%) said they had taken part in the first round; 72 (34%) said they had not; and 24 (12%) could not remember (Table 1). A comparison of

Table 1. Number of responses to questionnaires.

	Number on core panel list	Number who started the survey	Core panel collector	Open collector	Number who completed the survey (%)
First round	315	194	143	51	194 (100)
Second round	318	209	169	40	190 (91)

doi:10.1371/journal.pone.0027319.t001

responses to the second round questionnaire showed no significant differences between those taking part in both rounds and those only taking part in the second round.

There were no significant differences between role designations (Table S1); areas of health interest (Table S2); review methods of interest (Table S3); authorship of (Table S4), or involvement in systematic reviews (Table S5); or proportion of work related to research methodology (Table S6); between the first and second round respondents.

There was little difference between the responses of those who were members of The Cochrane Collaboration and those who were not. There were three items in round one and two items in round two where the differences were of statistical significance. After Bonferroni adjustment for multiple comparisons, these were no longer statistically significant (Table S7).

In the first round, 128 (66%) respondents said English was their first language. In the second round, English was the first language for 124 (65%) of respondents. Respondents to both the first and second rounds were based in 34 countries, with an additional six countries represented in the first round only, and a different five countries represented in the second round only (Figure S1).

In the second round we specifically asked participants whether they supported the principle of registration of ongoing systematic reviews; 199 (95.2%) of participants said they did; three (1.4%) did not and seven (3.3%) had no opinion.

Minimum dataset

Following review of the first round responses, it was decided that the Anticipated publication date field would not be included in the second round. This was because of the large number of comments requesting that the list of items be kept as small as possible, and 158 (82%) respondents felt this field should be optional or was not necessary. The field would be difficult for researchers to estimate at the protocol stage and its inclusion in the register was not integral to achieving the stated aims.

Likewise, 121 (63%) respondents felt it was ''Desirable'' or ''Not necessary'' to include the Economic Evaluations field. As this information could and should be included in the Review Question field and elsewhere, it was not included in the second round questionnaire.

Taking into account first round feedback on the need to keep the dataset to the minimum and focus on information that would contribute to reducing bias, it was proposed that although the majority of respondents felt that the Context and Data extraction fields should be required fields, they should be included as optional fields. None of the fields in the first round had a majority in favour of 'Not needed'.

In the first round of questions, primary and secondary outcomes were presented as separate items from effect measures in order to find out if participants felt both were needed. As only 9% and 12% of the respondents, (respectively for primary and secondary outcomes), felt that effect measures were not necessary, these fields were combined for the second round (Table 2). Time points were added as a requirement in response to suggestions from participants.

Informed by the responses to the Delphi exercise, the register Advisory Group confirmed that all items with 70% or greater agreement would be included as Required or Optional fields as responses indicated.

In round one, there was $\geq$70% agreement on 14 of 40 items; 60–69% agreement on 7 items; 50–59% agreement on 8 items; 40–49% agreement on 10 items and 30–39% on one item.

After the second round, a 70% or greater agreement was reached on whether 30 of 36 items should be required or optional. There was 60–69% agreement on two and 50–59% agreement on the remaining four items (Table 2).

The final PROSPERO dataset agreed by the register Advisory Group consists of 40 items, 22 of which are required, and the remainder are optional. Of the required fields, 12 are for details of review methods, 10 are related to the review title, timescale and review team (Table 3). In addition, the unique identification number was designated as part of the dataset by the Advisory Group as PROSPERO creates a unique number for each accepted registration record.

Discussion

Although the drivers for trials registration differ in some respects (e.g., legal ethical requirement [17]), systematic review protocol registration faces the same potential barriers as trials registration. In order to avoid the problems arising from the existence of multiple trials registers [18,19] by providing a free, single, comprehensive, open access register, a balance between level of detail required and utility was sought. The proposed level of information to be entered for each field was included in the survey as the quality of data recorded in trials registers has been found to vary considerably [20,21].

The aims of registering a systematic review include the provision of sufficient information to (i) determine whether reviews already in the pipeline might negate the need to initiate a new review, (ii) enhance the transparency and completeness of the plans for the systematic review, and (iii) make informed judgements about potential risk of bias. The objective of this Delphi process was to establish the minimum data set that will achieve these three aims. The Delphi process did not seek to capture the attributes of the wider information that should be included in a full protocol for a systematic review, or to determine all the variables that people might wish to record in registers of systematic reviews that would be used for other purposes.

The Delphi technique was chosen for its flexibility and adaptability in gathering and analysing the necessary data, and in particular for the utility of the process in garnering views and opinions from a broad spectrum of people [8]. The commissioning, undertaking, publishing and use of systematic reviews involves diverse disciplines, each with their own particular perspective, with both inter- and intra-disciplinary differences of opinion. For the

Table 2. Registration dataset response rates for Delphi round one and two.

	Field title	Delphi first round responses (194)			Delphi second round responses (209)			
		Essential	Desirable	Not necessary	Agree should be Required*/ Optional	Disagree should be Optional/ Required*	Disagree, not needed	No opinion
1	Review title	174 (90%)	17 (9%)	3 (2%)	189 (98%)*	4 (2%)	0 (0%)	0 (0%)
2	Named contact	186 (96%)	5 (3%)	3 (2%)	187 (97%)*	5 (3%)	0 (0%)	1 (1%)
3	Organisational affiliation of the review	136 (70%)	51 (26%)	7 (4%)	162 (84%)*	23 (12%)	1 (1%)	7 (4%)
4	Named contact address	74 (38%)	91 (47%)	29 (15%)	148 (77%)	30 (16%)*	9 (5%)	6 (3%)
5	Named contact phone number	Item not included in first round			151 (78%)	13 (7%)*	21 (11%)	8 (4%)
6	Named contact email	166 (86%)	26 (13%)	2 (1%)	180 (93%)*	11 (6%)	0 (0%)	2 (1%)
7	Review team	76 (39%)	82 (42%)	36 (19%)	129 (67%)	49 (25%)*	10 (5%)	5 (3%)
8	Review team members' rsorganisational affiliations	48 (25%)	104 (54%)	42 (22%)	146 (76%)	27(14%)*	12 (6%)	8 (4%)
9	Collaborators	35 (18%)	106 (55%)	53 (27%)	147 (76%)	18 (9%)*	19 (10%)	9 (5%)
10	Anticipated or actual start date	125 (64%)	57 (29%)	12 (6%)	170 (89%)*	18 (9%)	1 (1%)	3 (2%)
11	Anticipated completion date	91 (47%)	88 (45%)	15 (8%)	152 (79%)*	33 (17%)	3 (2%)	4 (2%)
12	Anticipated publication date	36 (19%)	109 (56%)	49 (25%)	Item not included in second round			
13	Funding sources/sponsors	155 (80%)	31 (16%)	8 (4%)	179 (93%)*	12 (6%)	1 (1%)	0 (0%)
14	Conflicts of interest	152 (78%)	31 (16%)	11 (6%)	173 (90%)*	14 (7%)	3 (2%)	2 (1%)
15	Other registration details	Item not included in first round			134 (70%)	50 (26%)*	8 (4%)	0 (0%)
16	Organisation reference number	55 (28%)	88 (45%)	51 (26%)	139 (72%)	17 (9%)*	18 (9%)	18 (9%)
17	Language	110 (57%)	65 (34%)	19 (10%)	103 (54%)	72 (38%)*	10 (5%)	7 (4%)
18	Country	67 (35%)	83 (43%)	44 (23%)	136 (71%)	33 (17%)*	17 (9%)	6 (3%)
19	Key words	133 (69%)	47 (24%)	14 (7%)	114 (59%)	69 (36%)*	6 (3%)	3 (2%)
20	Any other information	30 (16%)	101 (52%)	63 (33%)	170 (89%)	6 (3%)*	8 (4%)	8 (4%)
21	Review question(s)	186 (96%)	6 (3%)	2 (1%)	186 (97%)*	4 (2%)	1 (1%)	0 (0%)
22	Economic Evaluations	73 (38%)	85 (44%)	36 (19%)	Item not included in second round			
23	Searches	131 (68%)	42 (22%)	21 (11%)	155 (81%)*	32 (17%)	3 (2%)	1 (1%)
24	URL to search strategy	51 (26%)	93 (48%)	50 (26%)	143 (75%)	28 (15%)*	14 (7%)	6 (3%)
25	Types of study to be included	167 (86%)	23 (12%)	4 (2%)	167 (87%)	21 (11%)	3 (2%)	0 (0%)
26	Condition or domain being studied	150 (77%)	35 (18%)	9 (5%)	177 (93%)	11 (6%)	3 (2%)	0 (0%)
27	Participants/population	176 (91%)	14 (7%)	4 (2%)	178 (93%)	12 (6%)	1 (1%)	0 (0%)
28	Intervention(s), exposure(s)	176 (91%)	15 (8%)	3 (2%)	184 (96%)	6 (3%)	1 (1%)	0 (0%)
29	Comparator(s)/control	168 (87%)	24 (12%)	2 (1%)	180 (94%)	9 (5%)	1 (1%)	1 (1%)
30	Context[a]	99 (51%)	77 (40%)	18 (9%)	106 (56%)	77 (40%)	3 (2%)	5 (3%)
31	Primary outcome(s)	180 (93%)	13 (7%)	1 (1%)	177 (93%)	11 (6%)	3 (2%)	0 (0%)
32	Effect measures for primary outcome(s)	126 (65%)	51 (26%)	17 (9%)	(Merged with item 31)			
33	Secondary outcome(s)	130 (67%)	55 (28%)	9 (5%)	146 (76%)	38 (20%)	5 (3%)	2 (1%)
34	Effect measures for secondary outcome(s)	82 (42%)	88 (45%)	24 (12%)	(Merged with item 33)			
35	Data extraction, (selection and coding)[a]	100 (52%)	58 (30%)	36 (19%)	102(53%)	76 (40%)	11 (6%)	2 (1%)
36	Risk of bias (quality) assessment	118 (61%)	54 (28%)	22 (11%)	142 (74%)	35 (18%)	11 (6%)	3 (2%)
37	Strategy for data synthesis	131 (68%)	46 (24%)	17 (9%)	136 (71%)	41(22%)	10 (5%)	4 (2%)
38	Methods for exploring heterogeneity 1[b]	93 (48%)	67 (35%)	34 (18%)	(Merged with 35 and 36 into item 37)			
39	Methods for exploring heterogeneity 2[c]	78 (40%)	76 (40%)	40 (20%)	(Merged with 34 and 36 into item 37)			
40	Definition and rationale for use of specific techniques	73 (38%)	71 (37%)	50 (26%)	(Merged with 34 and 35 into item 37)			
41	Analysis of subgroups or subsets	(Presented in items 34, 35, 36 in first round)			134 (70%)	42 (22%)	10 (5%)	5 (3%)
42	Dissemination plans	35 (18%)	98 (51%)	61 (31%)	151 (79%)	10 (5%)	24 (13%)	6 (3%)
43	Details of any existing review of the same topic by the same authors	139 (72%)	39 (20%)	16 (8%)	124 (65%)	54 (28%)	8 (4%)	5 (3%)

[a]The majority of respondents in round one selected this as 'essential'.
[b]How heterogeneity will be explored. Under what circumstances will a meta-analysis be considered appropriate.
[c]Covariates to be explored with method of analysis.
doi:10.1371/journal.pone.0027319.t002

Table 3. PROSPERO dataset.

Review title and timescale		
1	**Review title***	The working title of the review.
2	**Original language title**	The working title in the language of the review where this is not English.
3	**Anticipated or actual start date***	The date when the systematic review commenced, or is expected to commence.
4	**Anticipated completion date***	The date by which the review is expected to be completed.
5	**Stage of review at time of registration***	The stage of progress of the review at the time of initial registration.
Review team details		
6	**Named contact***	The named contact acts as the guarantor for the accuracy of the information presented in the Register record.
7	**Named contact email***	The electronic mail address of the named contact.
8	**Named contact address**	The full postal address for the named contact.
9	**Named contact phone number**	The telephone number for the named contact, including international dialling code.
10	**Review team members and their organisational affiliations**	Names of all members of the review team and their organisational affiliations.
11	**Organisational affiliation of the review***	Details of the organisational affiliations for this review.
12	**Funding sources/sponsors***	Details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review.
13	**Conflicts of interest***	Any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
14	**Collaborators**	The name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.
Review methods		
15	**Review question(s)***	The question(s) to be addressed by the review.
16	**Searches***	Details of the sources to be searched, and any restrictions (e.g. language or publication period).
17	**URL to search strategy**	A link to the search strategy or an example of a search strategy for a specific database.
18	**Condition or domain being studied***	A short description of the disease, condition or healthcare domain being studied, including health and wellbeing outcomes.
19	**Participants/population***	Summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
20	**Intervention(s)/exposure(s)***	Full and clear descriptions of the nature of the interventions or the exposures to be reviewed.
21	**Comparator(s)/control***	Details of the alternatives against which the main subject/topic of the review will be compared.
22	**Types of study to be included initially***	Details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
23	**Context**	Summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
24	**Primary outcome(s)***	The most important outcomes, including information on timing and effect measures, as appropriate.
25	**Secondary outcomes***	Any additional outcomes that will be addressed, including information on timing and effect measures, as appropriate.
26	**Data extraction (selection and coding)**	The procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved.
27	**Risk of bias (quality) assessment***	Whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
28	**Strategy for data synthesis***	The planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned.
29	**Analysis of subgroups or subsets***	Any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
General information		
30	**Type of review**	The type of review.
31	**Language**	The language(s) in which the review is being written and will be made available.
32	**Country**	The country or countries in which the review is being carried out.
33	**Other registration details**	Other places where the systematic review is registered (such as with The Cochrane Collaboration, The Campbell Collaboration, or The Joanna Briggs Institute).
34	**Reference and/or URL for published protocol**	The citation and link for the published protocol, if there is one.

Table 3. Cont.

35	**Dissemination plans**	Brief details of plans for communicating essential messages from the review to the appropriate audiences.
36	**Keywords**	The words or phrases that best describe the review.
37	**Details of any existing review of the same topic by the same authors**	Details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.
38	**Review status***	Indicate the current status of the review.
39	**Any other information**	Any further information the review team consider relevant to the registration.
40	**Link to publication of final report**	The full citation for the final report or publication of the systematic review, including the URL where available.

*Indicates a required field.
doi:10.1371/journal.pone.0027319.t003

register to fulfil its aims and cater for all potential users it was important to ensure that experts from all the relevant disciplines be invited to contribute their opinions in order to reach a consensus. It would not have been possible to arrange face to face meetings with the number of participants achieved by this approach. The Delphi approach allowed us to carry out the consultation with complete anonymity and maintain a broad heterogeneity in participants without any one discipline or individual having more influence than another.

For pragmatic reasons we modified the standard Delphi technique, and discuss here the limitations of the methods we used.

The notion of an 'international expert' in the defined areas is largely subjective. We hoped to minimise any inadvertent bias in the selection of the core panel by also issuing an open invitation to participate. However, because of the option of sharing email invitations, we cannot be sure that only core panel members responded to the core panel collector. Nonetheless, a comparison of the data from the two collectors showed little variation in response between the two groups.

Ideally, the same participants should respond to each round of a Delphi process. The pragmatic decision not to approach participants in advance to confirm commitment to the whole exercise, was balanced against the number being invited to take part. Just over half the respondents participated in both rounds. A comparison of second round responses between returning respondents and new participants showed no significant differences. It is unlikely therefore that the approach taken introduced additional bias.

Normally the first round of a Delphi would present open questions such as '*What items do you think should be included in the registration of systematic reviews at the protocol stage?*' However, given that the items that should be included in a systematic review protocol are already well established and to reduce the burden on participants, we invited the first round respondents to comment on the utility of a pre-prepared list of candidate items. Respondents also had the opportunity to suggest additional items. The suggestions that were received and adopted were: the addition of an optional field to record other registration details (e.g., on The Cochrane Library); the requirement of time points to be included in the primary and secondary outcomes fields; and an optional field for telephone contact details.

Based on 315 invitations to participate in the first round, and 143 respondents, the response rate was 45%. In the second round 318 invitations were sent out and 169 responses received, making the response rate 54%. However, the true response rates may be lower as we cannot know how many individuals received a cascaded invitation.

Our decision not to use a pre-determined list of participants for the two rounds was based on the desire to ensure a range of respondents, but could have led to an unrepresentative sample of participants. In the event, responses were received from all key groups and those people who labelled themselves as researchers/reviewers were divided similarly in each round between members (119 round one; 105 round two) and non-members (75 round one; 81 round two) of The Cochrane Collaboration.

We succeeded in gathering the opinions and judgments of a large and diverse range of relevant experts. Given the heterogeneity of the respondents and their interests, we believe that the degree of consensus achieved is acceptable, but we will keep the list of data items under review and will revisit it after it has been in use for a year, as part of a wider evaluation of the utility of PROSPERO.

Conclusion

The consultation revealed widespread support for the principle of registration of systematic reviews, and the Delphi exercise established a dataset of 22 required items for the prospective registration of systematic reviews, and 18 optional items. The dataset captures the key attributes of review design, as well as the administrative details necessary for registration. The findings were also used to inform the development and implementation of the technical and process elements of PROSPERO.

Supporting Information

Figure S1 Participant demographic information: Which country are you based in?
(DOC)

Table S1 Professional information about participants: role.
(DOC)

Table S2 Professional information about respondents: health areas of interest.
(DOC)

Table S3 Professional information about respondents: review method of interest.
(DOC)

Table S4 Professional information about respondents: number of systematic reviews authored.
(DOC)

Table S5 Professional information about respondents: number of systematic reviews involved with other than as an author.
(DOC)

Table S6 Professional information about respondents: proportion of work related to research methodology.
(DOC)

Table S7 Professional information about respondents: membership of relevant organisations.
(DOC)

Acknowledgments

We would like to thank all those who took part in the Delphi exercise. All responses have been considered and the expertise provided and time taken by participants is much appreciated.

Author Contributions

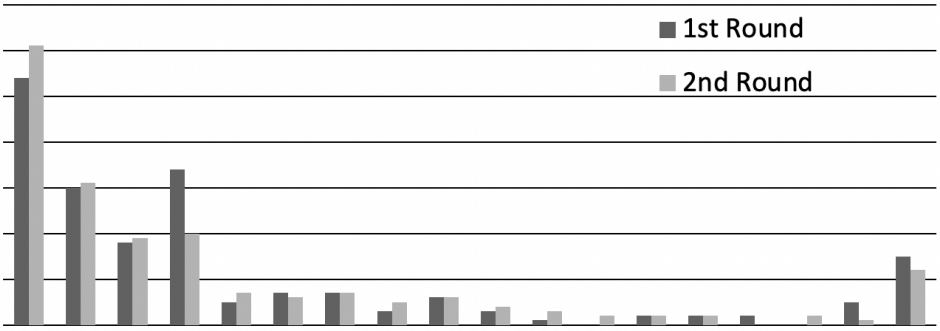
Final decisions on the dataset: AB MC DG DM MP LS. Conceived and designed the experiments: AB MC DG DM MP LS. Performed the experiments: AB. Analyzed the data: AB MC DG DM MP LS. Wrote the paper: AB MC DG DM MP LS.

References

1. Silagy CA, Middleton P, Hopewell S (2002) Publishing protocols of systematic reviews: comparing what was done to what was planned. JAMA 287: 2831–2834.
2. Liberati A, Altman DG, Tetzlaff J, Mulrow C, the PRISMA Group (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 6: e1000100.
3. Moher D, Tetzlaff J, Altman DG, for the PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 339: b2535.
4. Straus S, Moher D (2010) Registering systematic reviews. CMAJ 182(1): 13–14. doi:10.1503/cmaj.081849 Available: http://www.cmaj.ca/cgi/content/full/182/1/13.
5. Jüni P, Egger M (2009) PRISMAtic reporting of systematic reviews and meta-analyses. The Lancet 374: 1221–1223.
6. PLoS Medicine Editors (2007) Many reviews are systematic but some are more transparent and completely reported than others. PLoS Med 4(3): e147. doi:10.1371/journal.pmed.0040147.
7. Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, et al. (1998) Consensus development methods, and their use in clinical guideline development. Health Technol Assess 2(3): 1–88.
8. Hsu C-C, Sandford BA (2007) The Delphi Technique: Making Sense of Consensus. Practical Assessment Research & Evaluation 12(10, Available: http://pareonline.net/getvn.asp?v=12&n=10.
9. Sinha IP, Smyth RL, Williamson PR (2011) Using the delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. PLoS Med 8(1, doi:10.1371/journal.pmed.1000393. Available: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000393.
10. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, et al. (2010) An international registry of systematic review protocols. The Lancet doi:10.1016/S0140-6736(10)60903-8 Available: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60903-8/fulltext.
11. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, et al. (2011) An international registry of systematic review protocols. The Lancet 377(9760): 108–109. doi:10.1016/S0140-6736(10)60903-8.
12. Ghersi D, Pang T (2009) From Mexico to Mali: four years in the history of clinical trial registration. Journal of Evidence Based Medicine 2: 1–7.
13. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions The Cochrane Collaboration.
14. Centre for Reviews and Dissemination (2009) Core principles and methods for conducting a systematic review of health interventions. In: Systematic reviews: CRD's guidance for undertaking reviews in health care;York: University of York, 2–99. Available: http://www.york.ac.uk/inst/crd/index_guidance.htm.
15. Petticrew M, Roberts H (2006) Systematic reviews in the social sciences: a practical guide. Malden, MA: Blackwell Publishing.
16. Egger M, Davey Smith G, Altman D, eds. Systematic reviews in health care: Meta-analysis in context: BMJ Publishing.
17. World Medical Association (2008) WMA Declaration of Helsinki - ethical principles for medical research involving human subjects. World Medical Association. Available: http://www.wma.net/en/30publications/10policies/b3/index.html. Accessed 7 June 2011.
18. World Health Organisation International clinical trials registry platform (ICTRP). World Health Organisation. Available: http://www.who.int/ictrp/en/. Accessed 7 June 2011.
19. Viergever RF, Ghersi D (2011) The quality of registration of clinical trials. PLoS ONE 6(2), doi:10.1371/journal.pone.0014701.
20. Liu X, Li Y, Yu X, Feng J, Zhong X, et al. (2009) Assessment of registration quality of trials sponsored by China. J Evidence-Based Med 2: 8–18.
21. Moja LP, Moschetti I, Nurbhai M, Compagnoni A, Liberati A, et al. (2009) Compliance of clinical trial registries with the World Health Organization minimum data set: a survey. Trials 10(56), doi:10.1186/1745-6215-10-56.

Supporting Information for Establishing a Minimum Dataset for Prospective Registration of Systematic Reviews: An International Consultation

Figure S1.



Participant demographic information: Which country are you based in?

Other countries are: Bahrain, Finland, Ireland, Republic of Korea, Mexico, Pakistan, Taiwan, (one response in first and second rounds). Columbia, Greece, Hong Kong, India, Israel, New Zealand, (one respondent in first round; none in second round). Argentina, France, Peru, Saudi Arabia, Thailand, (no respondents in first round; one in second round).

Table S1. Professional information about respondents: role.

Role	First round response	Second round response
Academic clinician	58	53
Clinician	12	10
Commissioner/funder of reviews	14	9
Health economist	20	9
Information specialist	15	27
Journal Editor/board member/involved in publishing	35	44
Researcher (but not a systematic reviewer)	37	25
Statistician	20	12
Systematic reviewer	110	106
Other	19	21

N.B. A response to this question was mandatory in the first round: 194 responded. In the second round the question was optional: 190 responded, 19 skipped the question.

Table S2. Professional information about respondents: health areas of interest.

Health areas	First round Response	Second round Response
Blood and immune system	16	8
Cancer	35	30
Cardiovascular	22	25
Care of the elderly	11	13
Child health	27	28
Complementary therapies	10	9
Dental	7	5
Digestive system	9	11
Ear, nose and throat	9	12
Endocrine and metabolic disorders	15	16
Eye disorders	8	9
Infections and infestations	24	19
Mental health and behavioural conditions	31	25
Musculoskeletal	25	18
Neurological	19	16
Obstetrics and gynaecology	22	17
Oral health	5	8
Perioperative care	7	6
Public health (including social determinants of health)	75	69
Respiratory disorders	18	20
Service delivery	30	23
Skin disorders	12	12
Urological	11	11
Wounds, injuries and accidents	11	13
No specific health area of interest	53	61
Other	36	17

N.B. A response to this question was mandatory in the first round: 194 responded. In the second round the question was optional: 190 responded, 19 skipped the question.

Table S3. Professional information about respondents: review method of interest.

Review methods	First round response	Second round response
Effects of health and social care interventions (including rehabilitation and prevention)	145	110
Review methodology	135	132
Reporting of reviews	78	75
Reviews of reviews	64	73
Diagnosis	66	62
Adverse effects	71	58
Qualitative research	38	43
Scoping reviews	30	42
Single technology appraisals	38	39
Economic evaluation	61	39
Prospective meta-analysis	39	36
Screening	30	35
Risk factors	39	32
Prognosis	27	29
Individual participant data	24	19
Study level data	24	17
Genetics	13	14
Other	17	13

N.B. A response to this question was mandatory in the first round: 194 responded. In the second round the question was optional: 190 responded, 19 skipped the question.

Table S4. Professional information about respondents: number of systematic reviews authored.

	First round Response	Second round Response
0	24	24
1-5	85	67
6-10	30	32
>10	55	67

N.B. A response to this question was mandatory in the first round: 194 responded. In the second round the question was optional: 190 responded, 19 skipped the question.

Table S5. Professional information about respondents: number of systematic reviews involved with other than as an author.

	First round Response	Second round Response
0	16	16
1-5	41	44
6-10	30	27
>10	107	103

(e.g., Peer review; searching; advisory panel).

N.B. A response to this question was mandatory in the first round: 194 responded. In the second round the question was optional: 190 responded, 19 skipped the question.

Table S6. Professional information about respondents: proportion of work related to research methodology.

	First round Response	Second round Response
0	10	8
1-40%	98	110
41-60%	48	40
>60%	38	32

N.B. A response to this question was mandatory in the first round: 194 responded. In the second round the question was optional: 190 responded, 19 skipped the question.

Table S7. Professional information about respondents: membership of relevant organisations.

Organisation	First round response	Second round response
AHRQ Evidence-based Practice Centers (EPC) Network	5	12
The Campbell Collaboration	27	21
The Cochrane Collaboration	119	105
Committee on Publication Ethics (COPE)	3	7
Council of Science Editors	1	2
Deutsches Netzwerk evidenzbasierte Medizin	1	7
Evaluation of Genomic Applications in Practice and Prevention, U.S. Centers for Disease Control (A working group)	1	1
Guidelines International Network (G-I-N)	1	18
Health Technology Assessment International (HTAi)	43	48
International Committee of Medical Journal Editors (ICMJE)	2	3
International Network of Agencies for Health Technology Assessment (INAHTA)	2	29
International Clinical Epidemiology Network (INCLEN) TRUST	1	4
International Society of Drug Bulletins (ISDB)	1	1
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	6	9
Partners in Health Technology Assessment (PiHTA)	1	1
Society for Medical Decision Making	1	6
Society for Research Synthesis Methodology (SRSM)	11	10
World Association of Medical Editors (WAME)	4	11
None of these	41	28
Others from 1st round: National Institute for Health and Clinical Excellence (1) Others from 2nd round: The Joanna Briggs Institute (2); Agency for Healthcare Research and Quality/USPSTF program (1); CILIP (1); CRD advisory Board (1); GRADE member (1); HESG (1); HuGENet (1); Independent Meta-analysis Group (MRC) (1); International Society of Pharmacoepidemiology (1); METCARDIO (www.metcardio.org) (1); Saudi research group (1); Society for Social Medicine (1).		

N.B. A response to this question was mandatory in the first round: 194 responded. In the second round the question was optional: 190 responded, 19 skipped the question.

14. Appendix 3

Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, Stewart L.

PROSPERO at one year: an evaluation of its utility. *Systematic Reviews* 2013; 2:4

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3563608/pdf/2046-4053-2-4.pdf

- Published paper

- Addition file 1: Survey Questions
- Additional file 2: Survey Responses
- Additional file 3: Modifications made to PROSPERO in response to user survey findings

Booth et al. Systematic Reviews 2013, 2:4
http://www.systematicreviewsjournal.com/content/2/1/4

SYSTEMATIC REVIEWS

RESEARCH Open Access

PROSPERO at one year: an evaluation of its utility

Alison Booth[1*], Mike Clarke[2], Gordon Dooley[3], Davina Ghersi[4], David Moher[5,6], Mark Petticrew[7] and Lesley Stewart[1]

Abstract

Background: PROSPERO, an international prospective register of systematic review protocols in health and social care, was launched in February 2011. After one year of operation we describe access and use, explore user experience and identify areas for future improvement.

Methods: We collated administrative data and web statistics and conducted an online survey of users' experiences.

Results: On 21 February 2012, there were 1,076 registered users and 359 registration records published on PROSPERO. The database usage statistics demonstrate the international interest in PROSPERO with high access around the clock and around the world. Based on 232 responses from PROSPERO users (response rate 22%), almost all respondents found joining and navigation was easy or very easy (99%); turn round time was good or excellent (96%); and supporting materials provided were helpful or very helpful (80%). The registration fields were found by 80% to be relevant to their review; 99% rated their overall experience of registering with PROSPERO as good or excellent. Most respondents (81%) had a written protocol before completing the registration form and 19% did not. The majority, 136 (79%), indicated they completed the registration form in 60 minutes or less. Of those who expressed an opinion, 167 (87%) considered the time taken to be about right.

Conclusions: The first year of PROSPERO has shown that registration of systematic review protocols is feasible and not overly burdensome for those registering their reviews. The evaluation has demonstrated that, on the whole, survey respondents are satisfied and the system allows registration of protocol details in a straightforward and acceptable way. The findings have prompted some changes to improve user experience and identified some issues for future consideration.

Keywords: Systematic review protocol, Register, Prospero, Evaluation

Background

PROSPERO, an international database of prospectively registered systematic reviews in health and social care, was launched in February 2011. The aim of the register is to help reduce unplanned duplication of reviews, provide transparency and to help minimise reporting bias by enabling comparison of reported review findings with what was planned in the protocol [1]. PROSPERO is funded through the National Institute for Health Research in the UK and is free to register and free to search.

Researchers provide key features from their review protocol which are recorded and maintained as a permanent record in PROSPERO. The registration form contains 22 required fields and 18 optional fields, agreed through international consultation [2]. 'Required' fields contain ownership details and key protocol methods, such as participants, outcomes and analyses; they must be completed before a registration form can be submitted [3]. 'Optional' fields provide more administrative information, such as review team members and their affiliations and dissemination plans.

PROSPERO was designed to collect and process registration details accurately while keeping the process of registration as straight forward as possible in order to minimise work for researchers registering their systematic reviews.

After one year of operation, an evaluation of the registration process was undertaken to identify areas for improvement and further development. This paper outlines the evaluation and findings and discusses issues raised.

Methods

Data relating to registered users, submitted registration forms, the administration process and web statistics for

* Correspondence: alison.booth@york.ac.uk
[1]Centre for Reviews and Dissemination, University of York, Alcuin B Block, Heslington, York YO10 5DD, UK
Full list of author information is available at the end of the article

access and usage were collated for the period 22 February 2011 to 21 February 2012. Feedback and suggestions for future development were sought from those who had submitted registration requests within the same time frame of interest using electronic questionnaires, which were prepared in SurveyMonkey®, Palo Alto, CA, USA. (www.surveymonkey.com). The survey questions are listed in Additional file 1.

Emails containing the link to the survey were sent out to 1,076 registered users on 27 February 2012 with a reminder sent out 12 March 2012. The survey was closed on 21 March 2012. There were 29 emails returned with permanent failure to deliver messages. There were also 39 named individuals who had 'joined' more than once using different email addresses and who accounted for 87 registered users. As all distinct email addresses were included in the survey, some people will have received invitations to participate at more than one email address. However, SurveyMonkey was set to permit only one response per computer to minimise multiple responses from the same person. The number of individual registered users receiving the survey was 1,009.

Results

Registration data

Registration activity

On 21 February 2012, there were 359 published records on PROSPERO. Of these, 339 were on-going, 15 had been completed but not yet published and 3 had been completed and published [4-6], subsequent to registration. Two were updates of existing reviews previously registered.

In the same time period, a total of 89 submissions were ineligible for inclusion in PROSPERO and not accepted for registration (Table 1). Of these, 37 were already completed and 33 were too far advanced (progressed beyond data extraction). Nine were methodological reviews with no direct clinically related outcome; five did not have a health intervention or health related outcome; four were reviews of reviews and one was in Spanish.

For the period 1 March 2011 to 21 February 2012 the average administrative turn round time for accepted submissions was 1.0 working day.

Published records

On 21 February 2012, 359 systematic reviews were registered on PROSPERO. The reviews were being undertaken in 33 different countries (Figure 1), many of them in collaboration between two or more countries. The 10 countries with the most registrations are listed in Table 2.

All the registrations were in English as other languages are not accepted. All but one of the reviews will be written in English; one will also be available in German, two also in Norwegian and one in Spanish only.

The overall trend for submission of registrations increased exponentially, but there were a number of peaks in activity that may be explained by a variety of activities (Figure 2):

1. 22 February 2011. Launch events in UK and Canada and press releases sent to all relevant agencies and organizations (for example, INAHTA, G-I-N);
2. 1 May 2011. NIHR piloted mandatory registration for all HTA programme funded reviews, and contacted all those already funded to register if still within acceptance criteria.
3. 27 July 2011. Letters sent to all INAHTA member organisations encouraging support for PROSPERO by making registration part of the funding process.
4. 21 October 2011. Presentation on PROSPERO given at the Cochrane Colloquium in Madrid.
5. 16 November 2011: Paper about the international consultation to establish the minimum dataset published in PLoS ONE [2].
6. Mid-end November 2011. NIHR rolled out mandatory registration across all their other

Table 1 Eligibility criteria (February 2011 to March 2012)

Aspect	Criteria
Scope	PROSPERO will initially include systematic reviews of the effects of interventions and strategies to prevent, diagnose, treat, and monitor health conditions, for which there is a health related outcome.
	The long-term aim is to include details of all ongoing systematic reviews that have a health related outcome in the broadest sense (for example, reviews of risk factors and genetic associations). Reviews of animal studies will not be included.
Review types excluded	Scoping reviews, reviews of reviews, and reviews of methodological issues are not currently included in PROSPERO.
Timing	Registration should take place once the systematic review protocol has been finalised, but ideally before screening studies for inclusion begins. However, during the initial period of operation we will accept registration of reviews that are already underway up to the point of completion of data extraction. Completed reviews should not be registered.
Cochrane Review Protocols	An electronic upload of Cochrane Protocols from the Cochrane library is being developed. To avoid duplication of records, Cochrane protocols should not be registered separately with PROSPERO.
Language	Submissions must be in English.
	If you are in any doubt about the eligibility of your review or the stage of progress please contact crd-register@york.ac.uk for advice.

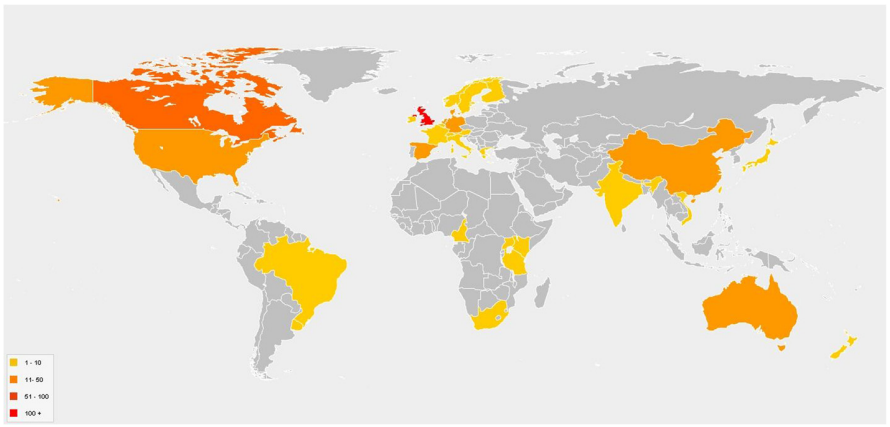


Figure 1 Countries where registered reviews are being undertaken.

programmes, and contacted all those already funded to register if within acceptance criteria [7].

7. End of November 2011: Website 'About' pages revised and expanded; training materials made available to download [8].
8. January 2012: Paper promoting PROSPERO published in prominent Chinese Medical Journal [9].
9. 9 February 2012: New BMC journal Systematic Reviews published a thematic series on 'The importance of registering systematic reviews', including commentaries from Dame Sally Davies (NIHR), Ian Graham (CIHR), the editors of the journal and an article on the nuts and bolts of PROSPERO [10].

The first record to be published on PROSPERO was for a systematic review and multiple treatment meta-analysis of drug-trials for hypertension carried out by the Norwegian Knowledge Centre for the Health Services, which was completed and published in April 2012 [11,12]. The last record published before the first year cut-off was a Joanna Briggs Institute review funded by the Australian Agency for International Development. This review is looking at demand-side financing measures to increase maternal health service utilization and improve health outcomes in low and middle income countries and is due for completion in September 2012 [13].

Table 2 Top ten countries

Country	Sole country undertaking the review	Additional reviews being undertaken in collaboration with other countries	Total
England	113	28	141
Canada	38	12	50
United States of America	22	16	38
Australia	22	10	32
Brazil	16	3	19
Netherlands	8	11	19
Scotland	8	9	17
China	12	1	13
Denmark	7	6	13
Germany	9	4	13

There were 171 Treatment, 46 Prevention, 40 Service delivery, 36 Diagnostic, 31 Prognostic and 39 'Other' reviews registered on the database (categories selected from a drop-down menu). Funding sources included government agencies (130), institutional (university/hospital) (71), pharmaceutical company (10), miscellaneous other funders (11) and no funding (137). Organisational affiliation included government agencies (4), hospital/medical centers (56), research institutes (82), University/Medical schools (169) and pharmaceutical companies (4). Forty-four gave no organisational affiliation (providing this information is currently optional).

There were 435 registered users who had 'joined' but never created a form and 266 who had created but never submitted a form. This included users who had registered more than once, using different email addresses. Those who had never created or submitted a form were asked why in the questionnaire. The reasons given included: interest in seeing the form but not in a position to register a review (for example, team member not lead; Cochrane review; took part in formulating minimum dataset); found their review did not meet the inclusion criteria (for example, it was too far advanced); were considering registering but as yet undecided; were about to submit their form.

Database usage

The total number of hits on the PROSPERO website between 22 February 2011 and 21 February 2012 was

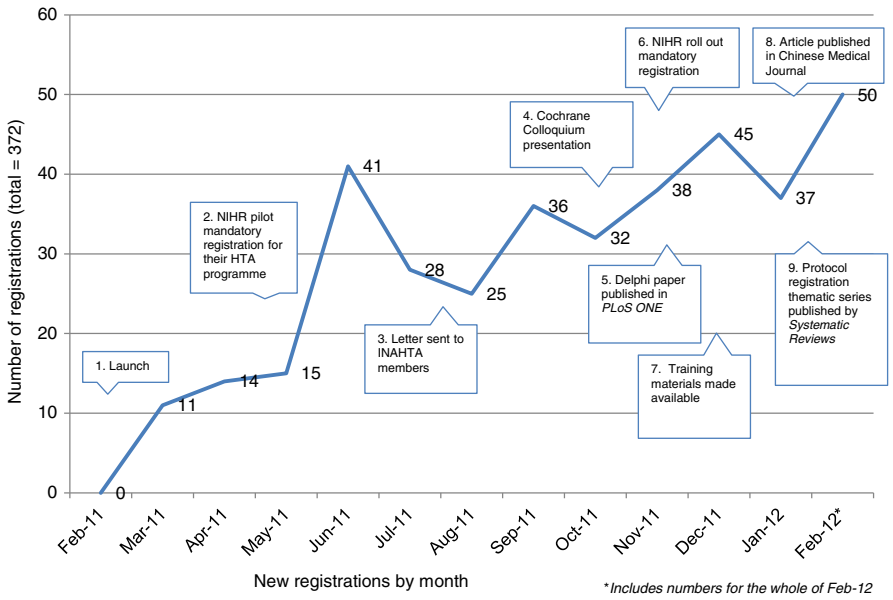


Figure 2 Rate of new registrations.

406,730; there were 829,766 page views by 13,607 visitors (Figure 3).

Users in 28 identified countries and territories around the world accessed the database (Figure 3). The highest use was from the UK, USA, Canada and China. The international nature of the register was further demonstrated by around the clock access (Figure 4).

The five identifiable websites that referred most visitors were: http://www.crd.york.ac.uk/; http://www.york.ac.uk/; http://www.google.co.uk/; http://www.prisma-statement.org/; http://www.google.com/. The search engines referring most visitors were Google, Bing and Yahoo. The top five search phrases used to find PROSPERO were: prospero; prospero crd; prospero systematic reviews; prospero systematic review; and prospero York.

User experience

The survey link was sent to the active email accounts of 1,047 registered user accounts of which 48 were duplicate accounts for the same named contact and as the questionnaire blocked more than one response per computer, we anticipated a maximum return of 999. A total of 232 responses were received, giving a response rate of 23%. None of the questions were compulsory so the number of responses per question varied.

Overall, the feedback on functionality and ease of use was positive. Brief details are given here with additional information provided in Additional file 2. The joining process and navigation around the registration form were considered to be easy or very easy by 99% of users. Supporting materials, including guidance, references and

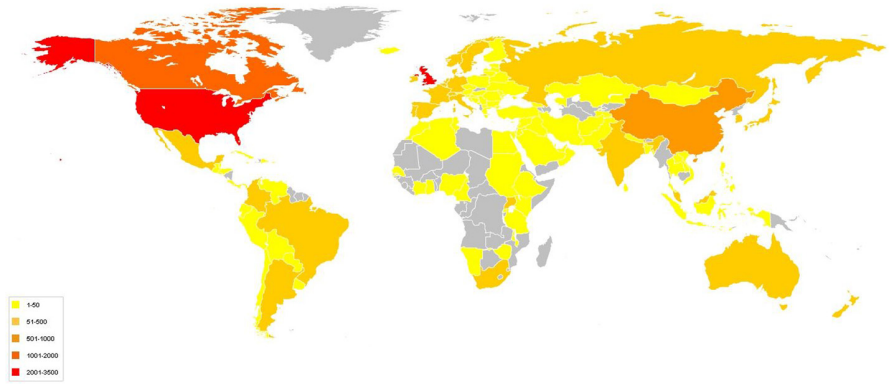


Figure 3 Countries accessing PROSPERO: map.

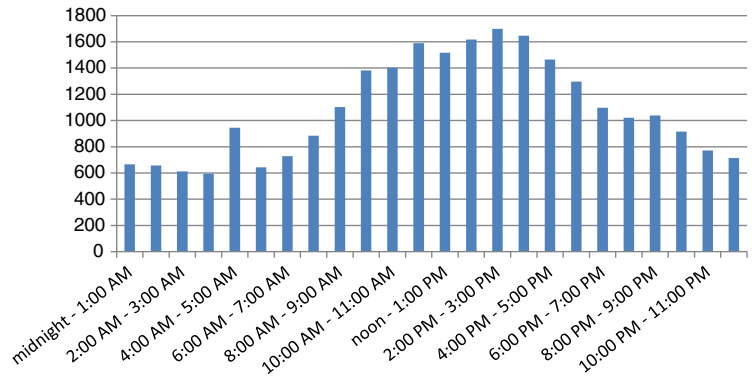


Figure 4 Visitors by time of day (GMT).

links to other resources, were found to be helpful or very helpful by 67% of respondents; most people (177 (82%)) found all or most of the registration fields of relevance to the systematic review protocols they had registered or were likely to register.

The majority of respondents, 176 (81%) had a written protocol for their systematic review before completing the PROSPERO registration form. Of those who did not have a protocol; 42 (19%) used their grant proposal or detailed project description to complete the registration form. In two cases, the protocol was designed using the headings from PROSPERO. Others found that completing the registration form helped improve their protocol by making them formalise less detailed areas. One registrant had split the protocol for a review looking at two different clinical areas, funded by a single grant.

Completing the registration form

Most submissions took between 30 minutes and 1 hour to complete; 136 (79%) indicated they completed the registration form in 60 minutes or less. The majority, 167 (87%), considered the time taken to be about right; 24 (12%) felt it took too long and 2 (1%) too short a time. Comments received indicated that for those with a prepared protocol, completion was quick. Where protocols were in a different format completion took longer, but there appeared to be a willingness to change to the PROSPERO format. Some used the registration form as a guide for 'tidying up' the protocol and some prepared responses to each of the questions in a separate document, and circulated it to colleagues to ensure it was ready before cutting and pasting into the PROSPERO form. Some felt the time taken depended on the subject of the review, and that completion of the form would become easier with familiarity.

A guideline developer with multiple reviews for each guideline indicated that they were weighing the time/resources involved against the benefits of registration.

Overall, there appeared to be recognition that for registration to be of good quality it needs an adequate amount of time to be spent on it and the protocol, and that the process helped.

Respondents reported that they were 'impressed with the turnaround time and the very friendly contact' and the majority rated the turn round time for a decision (121 (97%)) and information provided in correspondence (99 (79%)) as excellent or very good.

All seven respondents who had had a submission rejected said the reason for rejection was made clear in the email response. However, two said eligibility was not clear in the information given in the form or on the PROSPERO website; two did not look at the time; and three said that on reflection the information was available at the time. One commented that the inclusion criteria could be more obvious to site users.

PROSPERO compared favourably with previous experiences of trials registration, being 'on a par' with the ANZCTR (Australian New Zealand Clinical Trials Registry) and 'much easier' than clinicaltrials.gov. The absence of registration fees was identified as helpful. Although a number of respondents felt that PROSPERO was easier, quicker and more flexible than registering a Cochrane Review protocol, the majority acknowledged that the systems are different, particularly in the editorial process.

Overall, 189 (86%) respondents rated their experience of registering their review protocol details on PROSPERO as excellent or good; 21 (10%) as adequate and 9 (4%) as poor. None of those who rated their experience as poor had actually submitted a form, although eight said they are likely to do so in the future and gave positive responses to other questions in the survey. Thirty-two people had two records published, five had three records published, two had four records published, and one individual had seven reviews registered.

Positive comments were made about the information provided in correspondence, how useful the process was for learning how to write a complete protocol for a

systematic review, and satisfaction in knowing your work is out in the public domain. The only negative comments were about email enquiries made which had received no response. This flagged a problem in the system which we believe has subsequently been fixed.

Nearly all the respondents who had created a record or previously submitted a registration form said they were very likely or likely to register a systematic review protocol in the future, 207 (94%). However, three (1%) said they would only register if the commissioner of a review made it a requirement. Comments were received from one person who registered only because it was required, one who was required to register but would have done so any way and one who would do so if the commissioners/funders allow it.

General feedback

Survey respondents were invited to make additional further comments or suggestions. Some reiterated their support for the planned broadening of scope for inclusion of systematic reviews beyond those of effects. Others asked for more flexibility within the form while still acknowledging the good intent. Suggestions for improvements to the search facility in the public interface were also given.

The majority of comments supported the principle of protocol registration and PROSPERO. Comments ranged from '*A very useful tool for a not-very-experienced reviewer. Thank you*'. to '*the resources/references are fantastic. the idea is fantastic and I will persevere, but the form is initially daunting*'. Many said '*Thank you*' and '*Congratulations*'.

Discussion and conclusions

A main aim of this evaluation exercise was to assess the utility of the registration process, and its 'fitness for purpose'. Inevitably any survey is limited by the response rate and we cannot make assumptions about the views of non-responders. However, the response rate of 23% is typical for an electronic survey [14,15]. The feedback from users about their experiences has provided reassurance that on the whole the process is working well and has prompted some changes and planned developments to improve the user experience (Additional file 3). Requests to include alternative review types were made in the survey and by separate request; in particular, that reviews of reviews and methodology reviews be accepted. The PROSPERO Advisory Group have since agreed that reviews with a methodological focus, which also include an outcome of direct patient or clinical relevance, should be included in PROSPERO. The advisory group also agreed that systematic reviews of reviews should in future be included in PROSPERO; all other inclusion/exclusion criteria would still apply. One of the most encouraging findings is the range of reviews being registered not only in terms of countries, organisational affiliations and funding but also in countries collaborating on reviews.

Database usage statistics demonstrate the international interest in PROSPERO with high access around the clock and across the week. We are aware that PROSPERO is being routinely searched prior to new reviews being commissioned and, therefore, is already helping to avoid unintended duplication of reviews.

Additional files

Additional file 1: Survey questions.

Additional file 2: Survey responses.

Additional file 3: Modifications made to PROSPERO in response to user survey findings.

Competing interests

All the authors are members of the PROSPERO advisory group and have been since the inception of the register. The authors declare they have no other competing interests.

Authors' contributions

The decision to undertake an evaluation of utility at one year and the elements to be included was made by members of the PROSPERO Advisory Group. AB drafted the list of statistics to be collected from the website and administrative system and questions to be asked in the user survey. MC, MP and LS made substantial contributions to the lists for data collection and the questionnaire. AB managed the acquisition of the statistical data and survey administration and responses. AB presented the results to the PROSPERO Advisory Group (MC, GD, DG, DM, MP and LS) for interpretation and action. All the authors contributed to the analysis and interpretation of the data. AB and LS produced the first draft of the article and MC, GD, DG, DM and MP critically commented. All the authors have approved the final version submitted.

Acknowledgements

The authors would like to thank everyone who has submitted a registration form to PROSPERO and particularly those who provided feedback on the process. Feedback is welcome at any time via the registrant feedback form or directly to crd-register@york.ac.uk.

PROSPERO was developed and is managed by the Centre for Reviews and Dissemination (CRD) at the University of York, York, UK. CRD receives core funding through the National Institute for Health Research (NIHR), England; the Department of Health, Public Health Agency, Northern Ireland; and the National Institute for Social Care and Health Research, Welsh Assembly Government.

The development of PROSPERO is being funded by the Centre for Reviews and Dissemination at the University of York, England.

Author details

[1]Centre for Reviews and Dissemination, University of York, Alcuin B Block, Heslington, York YO10 5DD, UK. [2]Centre for Public Health, Institute of Clinical Sciences, Block B, Queen's University Belfast, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, UK. [3]Metaxis Ltd, Elmbank Offices, Elmbank Court, Main Road, Curbridge, Oxford OX29 7NT, UK. [4]Research Translation Branch, National Health & Medical Research Council, 16 Marcus Clarke Street, Canberra City ACT 2600, Australia. [5]Department of Epidemiology, Clinical Epidemiology Program, Ottawa Hospital Research Institute, 725 Parkdale Avenue Ottawa, Ottawa, ON K1Y 4E9, Canada. [6]Community Medicine, Faculty of Medicine, University of Ottawa, 451 Smyth Road, Ottawa, ON K1H 8M5, Canada. [7]Department of Social and Environmental Health Research, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK.

Received: 16 October 2012 Accepted: 4 December 2012
Published: 15 January 2013

References

1. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L: **An international registry of systematic review protocols.** *Lancet* 2011, **377:**108–109.
2. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L: **Establishing a minimum dataset for prospective registration of systematic reviews: an international consultation.** *PLoS One* 2011, **6:**e27319.
3. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, Stewart L: **The nuts and bolts of PROSPERO: an international prospective register of systematic reviews.** *Syst Rev* 2012, **1:**2.
4. Suchdev PS, De-Regil LM, Walleser S, Vist GE, Peña-Rosas JP: **Multiple micronutrient powders for home (point of use) fortification of foods in pregnant women: a systematic review**. In *WHO e-Library of Evidence for Nutrition Actions*. Geneva: World Health Organization; 2011.
5. Selk A, Kroft J: **Misoprostol in operative hysteroscopy: a systematic review and meta-analysis.** *Obstet Gynecol* 2011, **118:**941–949.
6. Chambrone L, Pannuti CM, Tu YK, Chambrone LA: **Evidence-based periodontal plastic surgery. II. An individual data meta-analysis for evaluating factors in achieving complete root coverage.** *J Periodontol* 2012, **83:**477–490.
7. PROSPERO International Prospective Register of Systematic Reviews: About PROSPERO: Encouraging registration in PROSPERO. http://www.crd.york.ac.uk/PROSPERO/about.asp.
8. PROSPERO International Prospective Register of Systematic Reviews: About PROSPERO: Training Materials. http://www.crd.york.ac.uk/PROSPERO/about.asp.
9. Yang ZR, Zhan SY: **PROSPERO: the new register of non-Cochrane reviews.** *Zhong Hua Yi Xue Za Zhi* 2012, **92:**422–425.
10. Moher D, Shekelle P, Stewart L (Eds): ***The importance of registering systematic reviews.*** *Systematic Reviews (On-line article collection) 2012*:1:2–7. http://www.systematicreviewsjournal.com/series/RegistrationSeries.
11. Fretheim A, Odgaard-Jensen J, Brørs O, Flottorp S, Kristiansen IS, Njølstad I, Norheim OF, Svilaas A, Thürmer H: ***Systematic review and multiple treatment meta-analysis of drug-trials for hypertension.*** PROSPERO 2011. CRD42011001066. Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42011001066.
12. Fretheim A, Odgaard-Jensen J, Brørs O, Madsen S, Njølstad I, Norheim OF, Svilaas A, Kristiansen IS, Thürmer H, Flottorp S: **Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis.** *BMC Med* 2012, **10:**33.
13. Hunter B, Murray SF, Bick D, Ensor T, Bisht R: **Demand-side financing measures to increase maternal health service utilisation and improve health outcomes: a systematic review of evidence from low- and middle-income countries.** 2012:CRD42012002056. Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002056.
14. Manfreda KL, Bosnjak M, Berzelak J, Haas I, Vehovar V, Berzelak N: **Web surveys versus other survey modes.** *A meta-analysis comparing response rates. Int J Mark Res* 2008, **50:**79–104.
15. Shih TH, Fan X: **Comparing response rates from web and mail surveys: a meta-analysis.** *Field Methods* 2008, **20:**249–271.

doi:10.1186/2046-4053-2-4
Cite this article as: Booth *et al.*: **PROSPERO at one year: an evaluation of its utility.** *Systematic Reviews* 2013 **2**:4.

Additional file 1

Survey Questions

1. How would you rate the ease of the 'Join' process, which allowed you to create a user account for PROSPERO?

2. We are interested in why you have completed the ‘Join’ process for PROSPERO but do not currently appear to have submitted a registration form as Named Contact. (Please tick all that apply)

- *Took part in the Delphi consultation: interested in result*
- *Curious to see registration process*
- *Found my review was not eligible so did not submit*
- *Will be registering in the near future*
- *Another team member took responsibility for registration*

(N.B. Question only sent to emails of registered users who had not submitted a registration form.)

3. How would you rate the ease of navigating around the registration form?

- *Very easy*
- *Easy*
- *Not easy*
- *Difficult*

4. How useful did you find the following supporting materials?

- *Information about field content given in the form*
- *Full information about field content accessed via the ? icon in the form*
- *The 'About PROSPERO' pages on the website*
- *The 'References and resources' provided on the website*
- *The pdf of the Guidance notes for completing the registration form*

5. Please indicate the type of review you are likely to register/have submitted for registration

- *Type of review*
- *Diagnostic*
- *Service Delivery*
- *Prevention*
- *Prognostic*
- *Treatment*
- *Other (please specify)*

6. In the registration form you were asked to indicate the stage of your systematic review as 'started' or 'completed' for each of the options listed below. How relevant do you think these options are for indicating the stage of your systematic review from initial submission to completion of the review?

- *Preliminary searches*
- *Piloting of the study selection process*
- *Formal screening of search results against eligibility criteria*
- *Data extraction*
- *Risk of bias (quality) assessment*
- *Data analysis*

7. On a few submissions, registrants indicated they had started (but not completed) Data extraction, Risk of bias (quality) assessment, and Data analysis.

We anticipated that data analysis would not begin until data extraction had been completed. To inform a review of the timing for acceptance of registrations, we would be interested to know the circumstances in which all these stages are active at the same time. Details of your experience of this and/or your comments are welcome.

8. In general, how relevant were the registration fields to the systematic review protocol you were registering? / are likely to register?

- *All relevant*
- *Mostly relevant*
- *Mostly irrelevant*
- *I cannot remember*

9. If you had any problems deciding what information to enter in which field, please describe the problems.

10. How useful did you find the following technical facilities within the registration form?

- *Highlighting of Required fields*
- *'Save' button on each page*
- *'Validate this page' facility*
- *Ability to print a copy of the form*
- *Ability to upload pdf of search strategy*
- *Ability to upload pdf of protocol*

11. How useful would you find it to be able to do the following?

- *Save a draft form as a pdf file*
- *Save a draft form as a document that could be edited in word processing software*
- *Save the submitted form as a pdf file*
- *Save the submitted form as a document that could be edited in word processing software*

12. How long did it take you to complete the registration form?

- *Up to 30 minutes*
- *30 to 60 minutes*
- *Over 60 minutes*
- *I cannot remember*

13. Did you feel the time taken to complete the registration form was:

- *Response*
- *Too long*
- *About right*
- *Too short*
- *No opinion*

14. Did you have a written protocol for your systematic review before you completed the PROSPERO registration form?

- *Yes*
- *No*

15. Following submission of your registration form, how would you rate the following?

- *The turnaround time for a decision*
- *The information provided in correspondence*

16. If your submission was rejected, was the reason for rejection made clear in the email response?
    - *Options*
    - *Yes*
    - *No*
    - *Can't remember*

17. If your submission was rejected, on reflection, was the reason for rejection clear in the information given in the form or on the PROSPERO website?
    - *No, not at the time of submission*
    - *Yes on checking, the information was available at the time*
    - *Did not look at the time*
    - *Can't remember*
    - *Information on eligibility was not clear at the time*
    - *Information currently provided is still not clear*
    - *Information is now provided and clear*

18. If you have experience of registering a systematic review protocol or any other piece of research anywhere else, we would be interested to hear your opinion of how PROSPERO compares with other registers.

19. Overall, how do you rate your experience of registering your systematic review protocol on PROSPERO?

    - *Excellent*
    - *Good*
    - *Adequate*
    - *Poor*

20. How likely are you to (return and) register a systematic review protocol in the future?
    - *Very likely*
    - *Likely*
    - *Unlikely*
    - *Only if the commissioner or funders require it*

21. If you have any further comments or suggestions please make them here or email us at crd-register@york.ac.uk

---

Additional file 2

Survey responses

Registering a review

The joining process and navigation around the registration form was considered to be easy or very easy by 99% of registrants.

Of those who had registered as users but not yet submitted a registration form, 39 (45%) said they would register their review in the near future; 26 (30%) found their review was not eligible and so did not submit; 24 (27%) were interested to see the process (three had taken part in the Delphi consultation); and 18 (21%) said another team member took responsibility for registering their review.

Supporting materials such as brief and full guidance about field content, general information about PROSPERO and references and links to other resources are provided on the website and within the registration form. These supporting materials were found to be helpful or very helpful by 67% of respondents; 28% were unaware of them or aware but did not use them. Two respondents suggested that the eligibility criteria could be placed more prominently on the website. One person registering a 'slightly less conventional systematic review' did not find the guidance given really helped. Another person suggested providing a sample of a review protocol.

Type of review

Respondents were asked to indicate the type of review they had or were likely to register. Of the current options: 110 (56%) indicated a treatment review; 33 (17%) prevention; 24 (12%) service delivery; 19 (10%) diagnostic; and 12 (6%) a prognostic review. The numbers were very similar for those who had already submitted a review and those who planned to in the future. A list of 39 'Other' types were given in the free text comments box; of these 20 were felt to fit existing categories. Three were methodology reviews and two reviews of reviews. Five referred to method to be use in conducting the review, e.g. meta analysis or IPD. The remaining nine were epidemiology related.

Stage of progress

Every submission and subsequent revision requires details of the stage of the systematic review by indicating whether key stages of the review have been 'started' or 'completed'. Respondents found these options to be very relevant: Preliminary searches 176 (81%); Piloting of the study selection process 147 (67%); Formal screening of search results against eligibility criteria 192 (88%); Data extraction 187 (86%); Risk of bias (quality) assessment 170 (78%); Data analysis 186 (85%).

A few submissions indicated that data extraction, risk of bias (quality) assessment, and data analysis had been started but not completed. When designing PROSPERO we anticipated that data analysis would not begin until data extraction had been completed. The questionnaire therefore asked for circumstances in which these stages might be active concurrently. Responses included: none; the re-running of searches; delayed receipt of information for inclusion; different parts of a review or reviewers progressing at differing rates; entry of extracted data directly into analysis software; a characteristics table being

compiled during data extraction as part of the analysis; and for qualitative systematic reviews quality assessment, data extraction, and data analysis would be concurrent and iterative.

Relevance of fields

The majority of respondents (177 (82%)) found all or most of the registration fields relevant to the systematic review protocols they had registered or were likely to register. Three commented that they were not well tailored for reviews including qualitative studies and another asked for more flexibility in the information required in fields; specifically primary and secondary objectives.

There were a few reported problems concerning decisions about what information to enter in which field. These related to non-intervention systematic reviews, qualitative systematic reviews and reviews done as part of a multiple strand project, but had not prevented completion and submission of a registration form. Some fields were felt to be a bit redundant (but not named).

Functionality of the registration form

The technical facilities within the registration form were felt to be useful or very useful by the majority of those who were aware of them. One hundred and sixty three (77%) found highlighting of required fields useful or very useful, 44 (20%) did not use or were unaware of the highlighting; one person commented that it could be clearer.

The 'save' button on each page was useful or very useful for 175 (82%); 32 (15%) did not use or were unaware of the save button; a number commented that although the system automatically saves changes when the user exits a field, being able to ‘manually save’ gave good reassurance and the confidence to be able to complete the form in stages.

The 'validate this page' facility, which highlights any required fields that have not yet had any information entered, was useful or very useful to 153 (72%) of respondents.

The ability to print a copy of the form was useful or very useful to 150 (71%) of respondents.

The option of being able to upload pdfs of the search strategy and/or protocol was considered to be very useful or useful by 135 (63%) and 138 (65%) respectively.

The majority of respondents (86%) indicated that being able to save the draft and submitted form as either a pdf file or a document that could be edited in word processing software would be very useful or useful. Reasons given were around facilitating distribution amongst co authors to assist with joint formulation of submissions and subsequent updates/revisions of existing records.

Additional file 3

Modifications made to PROSPERO in response to user survey findings

The PROSPERO year one user survey findings reflected a positive experience for those who responded, but also identified some areas for improvement and some for consideration in the next phase of development. The actions taken and future considerations are outlined here.

Scope for inclusion

Inclusion criteria have been made more prominent on the PROSPERO website, and included in the full guidance notes. Future developments to accommodate the inclusion of other types of review will similarly be accompanied by relevant guidance. Examples of information required for each field are given in the full guidance notes and PROSPERO now contains numerous examples which all registrants can access. The PROSPERO 'Help with registration: Inclusion criteria' page on the website has also been revised. [http://www.crd.york.ac.uk/PROSPERO/inclusion_criteria.asp]

Support materials

A few users commented that while supporting information was useful, it was not necessarily presented in the most accessible way. As a result separate tabs for 'About PROSPERO', 'Help with registration', and 'References and resources' have been created and the appropriate information placed under sub-headings into each of these pages. The full guidance is being prepared in alternative formats to suit a range of user preferences.

Type of review

Some respondents selected the 'other' category for type of review because the review fitted in more than one category; as from Nov 2011 it has been possible to make multiple selections. As a result of feedback, additional information about what is expected in each type of review will be added to the guidance. The option of Treatment has been amended to Intervention and the guidance notes revised.

Some supplied an alternative descriptor to those listed, but the majority of these were found to fit within existing options. This reflects a degree of confusion over the meaning of 'type' seen in both submitted registrations and in the user survey. A few misunderstood and detailed the methods to be used, for example IPD; meta-analysis; qualitative. An alternative descriptor to 'type' has been sought but all alternatives had similar potential for misinterpretation.

Responses also identified the potential need to include the addition of a term to cover epidemiological type reviews as an option. However there are a range of terms in use, for example epidemiological could be aetiological or observational; prevalence; risk. The most inclusive and widely understood and used term for this category of reviews is being considered before being added to the list. The categories will need to be reviewed regularly as scope for inclusion broadens.

Stage of review at time of submission

This field is important to users of the database as an indication of the stage the review is at when first registered, and when subsequent amendments and updates are made to the

record. As a result of feedback, an additional option of Started – Yes/No is being added to the field; and the option of Prospective Meta-Analysis removed. Consideration will be given to other changes when a review of the dataset is undertaken.

Relevance of fields

The dataset currently required was agreed for the initial inclusion of reviews of the effects of interventions, with the understanding that modifications or alternative templates would probably be required as the scope for inclusion expanded. The majority of respondents found all or most of the registration fields of relevance to the systematic review protocols they had registered or were likely to register. A few respondents felt the fields were not well tailored for some reviews, for example when including qualitative studies. Given the range and variety of reviews now registered, the system would appear to have a good degree of flexibility, supported by a pragmatic approach to inclusion by the administration team.

The terminology and separation of 'primary' and 'secondary' objectives, was questioned for being related to trials rather than systematic reviews. However, as this is the language used by The Cochrane Collaboration, in the PRISMA statement and agreed through international consultation, it was not felt necessary to change at this time. The advisory group also felt the separation of the terms is appropriate for the current inclusion criteria, as it requires the focus of the review to be clearly stated a priori, with the option of including secondary objectives if required.

A full evaluation of the required dataset will be undertaken in the future and relevance of fields considered during the stepped approach to expansion of the scope for inclusion.

Functionality of the registration form

Enabling a copy of the draft and submitted form to be saved as a pdf file and a word processing document to facilitate editing by multiple authors is a feature that will be added to the registrant interface as soon as this can be technically achieved. (In the meantime, clicking on the Print review button, then viewing the list of printer options should identify a way of saving the form as a pdf.)

General issues

Five respondents commented that they had not received a response to an email enquiry. None supplied contact details so we are unable to follow them up individually. However, all enquiries received at CRD-register@york.ac.uk (and at alison.booth@york.ac.uk) have been responded to. Response time is generally same or next day. A note has been added to the PROSPERO contact page saying: "We aim to respond to all enquiries within 5 working days. We have recently experienced some problems receiving emails, so if after 5 days you have not heard from us, please try emailing crd@york.ac.uk, call, fax or write to us."

Finally, a number or respondents commented that they could not remember specific aspects of the registration process well enough to comment on the experience. However many also said they would be willing to give feedback at the time of registration if this option was made available. All registrants are now invited to take part in a short on-line survey via a link in the email confirming acceptance or rejection of a submission.

15. Appendix 4

Moher D, Shamseer L, Clarke M, et al. **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement**. *Systematic Reviews* 2015; 4: 1-9. Journal article. DOI: 10.1186/2046-4053-4-1. http://www.systematicreviewsjournal.com/content/pdf/2046-4053-4-1.pdf

- Published paper

Moher et al. Systematic Reviews 2015, 4:1
http://www.systematicreviewsjournal.com/content/4/1/1

SYSTEMATIC REVIEWS

RESEARCH Open Access

Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement

David Moher[1*], Larissa Shamseer[1], Mike Clarke[2], Davina Ghersi[3], Alessandro Liberati[^], Mark Petticrew[4], Paul Shekelle[5], Lesley A Stewart[6] and PRISMA-P Group

Abstract

Systematic reviews should build on a protocol that describes the rationale, hypothesis, and planned methods of the review; few reviews report whether a protocol exists. Detailed, well-described protocols can facilitate the understanding and appraisal of the review methods, as well as the detection of modifications to methods and selective reporting in completed reviews. We describe the development of a reporting guideline, the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015). PRISMA-P consists of a 17-item checklist intended to facilitate the preparation and reporting of a robust protocol for the systematic review. Funders and those commissioning reviews might consider mandating the use of the checklist to facilitate the submission of relevant protocol information in funding applications. Similarly, peer reviewers and editors can use the guidance to gauge the completeness and transparency of a systematic review protocol submitted for publication in a journal or other medium.

Background

Systematic reviews are the reference standard for synthesizing evidence in health care because of their methodological rigor. They are used to support the development of clinical practice guidelines and inform clinical decision-making. They are becoming increasingly common; in 2010, 11 new reviews were estimated to be published daily [1]. Ideally, systematic reviews are based on pre-defined eligibility criteria and conducted according to a pre-defined methodological approach as outlined in an associated protocol.

The preparation of a protocol is an essential component of the systematic review process; it ensures that a systematic review is carefully planned and that what is planned is explicitly documented before the review starts, thus promoting consistent conduct by the review team, accountability, research integrity, and transparency of the eventual completed review. A protocol may also reduce arbitrariness in decision-making when extracting and using data from primary research, since planning provides an opportunity for the review team to anticipate potential problems. When clearly reported protocols are made available, they enable readers to identify deviations from planned methods in completed reviews and whether they bias the interpretation of a review results and conclusions. Bias related to the selective reporting of outcomes has been characterized as a serious problem in clinical research, including systematic reviews [2-7].

Until recently, systematic review protocols were generally available only through select organizations, such as The Cochrane [8] and Campbell Collaborations and the Joanna Briggs Institute, for which the preparation of a protocol is mandatory. Outside of these organizations, the existence of a protocol is infrequently reported in completed reviews [9,10]. Fewer than half of 300 systematic reviews indexed on MEDLINE in November 2004 (most recent generalizable sample; 2014 update underway) report working from a protocol [10], 80% of which are non-Cochrane affiliated. Of the non-Cochrane therapeutic reviews, only 11% mentioned the existence of a protocol [10]. The majority of reviews in health care are

* Correspondence: dmoher@ohri.ca
[^]Deceased
[1]Ottawa Hospital Research Institute and University of Ottawa, Ottawa, Canada
Full list of author information is available at the end of the article

conducted and published outside of Cochrane, however [10]. The paucity of protocols may be due, in part, to the authors' lack of knowledge about how to write them and what to include. Currently, little succinct guidance is available for those preparing systematic review protocols, although the recent Standards for Systematic Reviews prepared by the Institute of Medicine (IOM) provide some guidance toward addressing this gap [11].

Many groups have called for the widespread preparation and registration of systematic review protocols in order to increase the availability and accessibility of *a priori* methods for systematic reviews [12-14]. Such an effort may reduce the duplication of effort [15] and reduce the publication bias of systematic reviews. This challenge has been taken up by the Centre for Reviews and Dissemination, University of York, which has spearheaded the establishment of an international register—PROSPERO (International Prospective Register of Ongoing Systematic Reviews, http://www.crd.york.ac.uk/prospero) [16,17]. The register, which enables the permanent documentation of 22 mandatory (and 18 optional) items about the *a priori* design and conduct of a review, was launched in February 2011. At the time of writing, >5,000 systematic review protocols from over 70 countries have been registered since its inception. Starting in October 2013, new Cochrane protocols were and continue to be automatically added to PROSPERO.

Along with the improved accessibility of protocols through registration comes the need for strengthened transparency, accuracy, and completeness of the reports of protocols intended for dissemination. A template to aid in the preparation of systematic review protocols, such as a reporting guideline, may help achieve this. Furthermore, such guidance will enable authors to create a clear and complete document of their *a priori* methods, which may facilitate the registration of key information into the PROSPERO database. Building on an established guideline for systematic reviews and meta-analyses of studies evaluating health care interventions—the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA, www.prisma-statement.org) [12,13]—we have developed PRISMA for Protocols (PRISMA-P) 2014. Table 1 summarizes the difference in intentions between PRISMA-P and PROSPERO.

The aim of PRISMA-P 2015 is to improve the quality of systematic review protocols, similar to the impact achieved by other reporting guidelines [18-20]. By helping authors document an *a priori* road map of their systematic review, PRISMA-P also has the potential to improve the conduct of systematic reviews, as has been suggested of other reporting guidelines [21]. This Statement paper summarizes the development of the guideline and presents the PRISMA-P checklist.

Terminology

There is no standard definition for a systematic review and meta-analysis protocol, and we note that some terminology contained within these definitions may carry different meanings for different readers (i.e., 'systematic search'). The terms 'systematic review', 'meta-analysis,' and 'protocol' are defined in Table 2. The former two terms are in accordance with the definitions reported in the PRISMA Statement [13] and are in line with those used by the Agency for Healthcare Research and Quality's Evidence-based Practice Center (EPC) program [22], The Cochrane Collaboration [23], and the 2011 guidance from the Institute of Medicine [11]. The definition provided is a culmination of the terminology used by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 initiative [24], the PROSPERO register, and the IOM Standards (Table 2).

Scope

The PRISMA-P checklist is intended primarily for the preparation of protocols of systematic reviews and meta-analyses that summarize aggregate data from studies,

Table 1 PROSPERO and PRISMA-P

	Definition and objective
PROSPERO: International Prospective Register of Systematic Reviews	An online portal through which to register the intention to conduct a systematic review, with health-related outcomes, before it is initiated [16]. One of the main goals of PROSPERO is to make the intent of systematic reviews known before they are conducted in order to reduce the unplanned duplication of systematic reviews [15]. In addition, by requiring the documentation of *a priori* methods, the register facilitates increased transparency in the review process by allowing readers of systematic reviews to compare methods, outcomes, and analyses carried out with those planned in advance and judge whether such changes impact the results of a review.
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols	A guideline to help authors prepare protocols for planned systematic reviews and meta-analyses that provides them with a minimum set of items to be included in the protocol. A protocol is intended to provide the rationale for the review and pre-planned methodological and analytic approach, prior to embarking on a review. Investigators should prepare a review protocol in advance of registering it in PROSPERO so that details requiring further consideration may be thought through in advance, avoiding the need for multiple amendments to registration information. PRISMA-P items have been derived largely from the PRISMA checklist and items of the PROSPERO register, in order to facilitate seamless registration.

Table 2 PRISMA-P terminology

Term	Definition
Systematic review	A systematic review attempts to collate all relevant evidences that fits pre-specified eligibility criteria to answer a specific research question. It uses explicit, systematic methods to minimize bias in the identification, selection, synthesis, and summary of studies. When done well, this provides reliable findings from which conclusions can be drawn and decisions made [25,26]. The key characteristics of a systematic review are (a) a clearly stated set of objectives with an explicit, reproducible methodology; (b) a systematic search that attempts to identify all studies that would meet the eligibility criteria; (c) an assessment of the validity of the findings of the included studies (e.g., assessment of risk of bias and confidence in cumulative estimates); and (d) systematic presentation, and synthesis, of the characteristics and findings of the included studies
Meta-analysis	Meta-analysis is the use of statistical techniques to combine and summarize the results of multiple studies; they may or may be contained within a systematic review. By combining data from several studies, meta-analyses can provide more precise estimates of the effects of health care than those derived from the individual studies
Protocol	In the context of systematic reviews and meta-analyses, a protocol is a document that presents an explicit plan for a systematic review. The protocol details the rationale and *a priori* methodological and analytical approach of the review

particularly the evaluations of the effects of interventions. There are many review types that are outside of this scope. As such, given the general lack of protocol guidance for other types of reviews, we encourage reviewers preparing any type of review protocol to make use of PRISMA-P as applicable. Readers can also use the checklist to assess the completeness of the reporting of published protocols. However, it is not recommended to use the checklist as an assessment tool to gauge the appropriateness of the methods of a systematic review protocol; it has not been validated for that purpose.

Development of PRISMA-P 2015

An international steering committee (MC, DG, AL, DM, MP, PS, and LAS) comprising members with wide-ranging experience in systematic review methodology, protocol registry development, and reporting guideline development led the development of PRISMA-P, coordinated by LS. The process proposed by the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network was used to guide PRISMA-P development [27]. The process has 18 step-by-step recommendations grouped into five main stages:

1. Initial steps (determine the need for a reporting guideline);
2. Pre-meeting activities (identify contributors, conduct Delphi exercise, generate a list of potential items, and prepare for face-to-face meeting);
3. Face-to-face consensus meeting (present results of pre-meeting activities and relevant evidence);
4. Post-meeting activities (develop guidance Statement, Explanation and Elaboration document, and a publication strategy);
5. Post-publication activities (encourage uptake of guideline).

The first stage, 'Initial steps,' was described above; details of the remaining four steps are below.

Pre-meeting activities

In developing the PRISMA-P checklist, the steering committee compiled a list of items from various tools relating to the preparation of systematic review protocols for discussion at a consensus meeting of experts. Specifically, we mapped items from a Delphi exercise carried out during the development of PROSPERO [28], PROSPERO register items, PRISMA checklist items [13], SPIRIT 2013 checklist items [29], and items of IOM Standard 2.6 [11] against each other to identify unique and overlapping concepts. Lessons learned from the development of the SPIRIT checklist with respect to the concept and content of research protocols were used to guide discussion and debate at the meeting.

PRISMA-P consensus meeting

Twenty-three international experts attended the PRISMA-P consensus meeting on June 23–24, 2011, in Rockville, MD, USA to gain consensus on and reduce the number of potential PRISMA-P items. Delegates included journal editors, systematic review methodologists (including directors and representatives from international Cochrane Centres, Agency for Healthcare Research and Quality's (AHRQ's) Evidence-based Practice Centres, and the UK National Institute for Health Research), reporting guideline developers, information specialists, biostatisticians, and health research funders. Through group discussion at the meeting, 38 potential checklist items were reduced to 22.

Post-meeting activities

Following the meeting, the steering committee revised the draft 22-item checklist and refined their wording such that they accurately reflected meeting discussions. The draft checklist was also presented to the PROSPERO group, at a scientific meeting of the Cochrane Collaboration, for input and feedback and to AHRQ's Learning Network. After each of these reviews, the steering committee made minor amendments to the items.

The checklist was then circulated to all meeting invitees for critical input.

The PRISMA-P 2015 checklist

The final PRISMA-P 2015 checklist contains 17 numbered items (26 including sub-items) Items are categorized into three main sections: administrative information, introduction, and methods (Table 3).

We made a conscious effort to harmonize the PRISMA-P checklist items with the items of the PRISMA checklist to facilitate authors in transitioning their protocol into a report of a systematic review. Thirteen PRISMA-P sub-items have existing PRISMA counterparts. Where PRISMA wording or content did not sufficiently address protocol reporting, checklist items were modified.

Readers familiar with PRISMA will notice that PRISMA-P does not contain a flow diagram documenting the flow of studies throughout the systematic review process. Such documentation is possible only after a review has been carried out and remains an essential component to include in the report of a completed systematic review or meta-analysis; for further guidance, see the PRISMA Explanation and Elaboration document [12].

We strongly recommend that the present document and the accompanying PRISMA-P 2015 Explanation and Elaboration document [30], which includes examples of good reporting, rationale, and evidence (where available), be read together with the PRISMA-P 2015 checklist.

PRISMA-P 2015 explanation and elaboration

Once the steering committee prepared the PRISMA-P 2015 Statement and checklist, they drafted the content of an Explanation and Elaboration document, with assistance from the larger PRISMA-P group. The explanatory text was derived largely from discussions at the PRISMA-P meeting (recorded at the time) as well as the PRISMA Explanation and Elaboration document [12]. Examples of well-reported PRISMA-P items came from protocols registered in the PROSPERO database, AHRQ's EPC Program, and the Cochrane Database of Systematic Reviews or those published elsewhere. After the entire group had an opportunity to suggest additions, deletions, and changes, the steering committee combined all amendments to create the PRISMA-P 2014 Explanation and Elaboration document [30].

Post-publication activities

The post-publication activities recommended by EQUATOR include seeking and responding to criticism, encouraging the endorsement of and adherence to the guideline from various stakeholders, translating the guideline into other languages, evaluating its impact, ensuring website development, and updating of the guideline. The PRISMA-P 2015 checklist and related publications are freely available on the websites of the PRISMA Group (www.prisma-statement.org) and EQUATOR Network (www.equator-network.org). The PROSPERO register also contains a link to the guidance to encourage registrants to prepare a complete documentation of their protocol if they have not done so already.

We plan to develop an educational webinar about the rationale, usefulness, and potential impact of PRISMA-P, similar to what was done for PRISMA [31]. In addition, the potential for PRISMA-P 2015 to be used as an educational tool for authors, peer reviewers, and editors will be explored. Targeted implementation activities for PRISMA-P will be developed in a systematic manner together with experts in knowledge translation. The PRISMA website and social media (@PRISMAStatement, www.twitter.com/PRISMAStatement) will be used to make announcements about the launch of PRISMA-P and educational initiatives.

Endorsement

We encourage journals publishing systematic review products to modify their 'Instructions for Authors' section to endorse PRISMA-P 2015 and to consider publishing systematic review protocols, if they do not do so already. We plan to communicate with known endorsers of PRISMA (http://prisma-statement.org/endorsers.htm) as well as to other, relevant non-endorsing journals, to ask them to consider extending their support to PRISMA-P.

To help ensure optimal uptake by systematic reviewers, we propose a uniform endorsement policy across organizations and journals involved in the development and publication of systematic review protocols, demonstrated by the adoption of the following statement:

> *'[this organization/journal] requires a completed PRISMA-P 2015 checklist as a condition of submission of systematic review protocols. We recommend that, while completing the PRISMA-P 2015 checklist, you ensure your protocol addresses all items. Taking the time to ensure that your protocol adheres to these basic reporting elements will improve your manuscript and potentially enhance its chances of eventual acceptance.'*

Such a statement could be included in a journal's 'Instructions to Authors,' or for funding agencies and those commissioning systematic reviews, in their Application Guidelines, recommending that applicants developing the proposals of systematic reviews for funding use PRISMA-P 2014. Peer reviewers and scientific committees can also use the checklist to gauge the extent to which protocols include necessary information.

As has been done for previous reporting guidelines [18,32] we plan to evaluate whether and to what degree

Table 3 PRISMA-P 2015 checklist: recommended items to include in a systematic review protocol[a]

Section/topic	Item #	Checklist item
ADMINISTRATIVE INFORMATION		
Title		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number
Authors		
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor/ funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data		
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned

Table 3 PRISMA-P 2015 checklist: recommended items to include in a systematic review protocol[a] *(Continued)*

Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)

PRISMA-P Preferred Reporting Items for Systematic review and Meta-Analysis Protocols.
[a]It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration [30] for important clarification on the items. Amendments to a review protocol should be tracked and dated.

endorsement of PRISMA-P 2015 by journals (and potentially by other organizations) influences the completeness of reported protocols. Such an evaluation will be planned after allowing sufficient time for the wide dissemination of PRISMA-P 2015.

Implementation

The current system of implementing reporting guidelines is not optimal. At present, their primary mechanism of uptake is through endorsement by journals at their discretion, if at all. In journals that do endorse

Table 4 Proposed stakeholders, actions, and potential benefits for supporting adherence to PRISMA-P

Stakeholder	Proposed action	Potential benefits
Funders	Promote or mandate adherence to PRISMA-P or use PRISMA-P as a template for systematic review proposals for grant applications	Improved quality, completeness, and consistency of systematic review proposal submissions
		Standardized protocol content will improve peer review efficiency and investigator understanding of requirements
Systematic review authors/ groups/organizations	Use/adhere to PRISMA-P during protocol development	Improved quality, completeness, and consistency of protocol content
		Enables reviewers to anticipate and avoid future changes to review methods (i.e., outcomes)
		Increased awareness of minimum content for protocol reporting
		Improved completeness of reporting of completed reviews
PROSPERO (and other review registries)	Encourage the development of PRISMA-P-based protocols	Improved quality of registry entries
		Improved consistency across registry entries, protocols, and systematic reviews
Practice guideline developers	Use PRISMA-P to gauge the completeness of protocols and facilitate detection of selective reporting when considering reviews for guideline inclusion	Enables easy comparison across protocols, registry entries, and completed systematic reviews
Policymakers	Advocate use of PRISMA-P by those funding and carrying out systematic reviews	May yield better quality, more complete, and more consistent reviews to inform decision-making
Journal editors	Encourage compliance to PRISMA-P for authors submitting protocols for publication	Improved quality, completeness, and consistency of protocols over those published in journals not endorsing PRISMA-P
	Offer PRISMA-P as a template to assist in protocol writing for publication	Increased efficiency in protocol peer and author understanding of journal requirements
		Improved transparency and interpretation of reviews by readers
Educators	Use PRISMA-P as a training tool	Simplified teaching and grading of protocols
	Encourage adherence in students submitting protocols for coursework	Improved quality, completeness, and consistency of protocol content
Students	Develop protocols for coursework or research using PRISMA-P	Improved understanding of the minimum protocol content
		Well-trained systematic reviewer going into the workforce

guidelines, language describing their support is often vague, leaving authors unclear on what they are supposed to do with a given reporting guideline during the submission process [33]. Furthermore, policies around how journal editors and peer reviewers should ensure and/or enforce adherence to reporting checklists are even less clear, if they exist at all [34]. Other barriers to implementation may include a lack of awareness of the guideline and perceived burden of using a reporting guideline checklist during the editorial process [35].

Some well-known checklists, such as PRISMA, include a column to the right of the main checklists in which users report the page number on which a specific item is reported. This was initially intended to help authors ensure each checklist item is addressed and to aid peer reviewers in locating reported text for each item within a document. However, this system is not optimal. One major problem is that peer reviewers still have to search within a considerable body of text to locate the exact text describing a checklist item. When multiple items are listed separately but reported together or vice versa, this problem is compounded, because exactly which content pertains to each item may remain unclear.

The lack of implementation and adherence to reporting guidelines is systemic; additional authorities encountered early in the research process should promote a clearer message about author adherence to reporting standards if improvements in reporting are to be made. In targeting protocols of systematic reviews, PRISMA-P has a unique opportunity to not only affect the way in which protocols are reported but to also impact the way in which reviews are eventually conducted, perhaps allowing for a more seamless transition into a completely reported systematic review.

To overcome known challenges with reporting guideline uptake [36,37], we are developing a prospective implementation strategy for PRISMA-P 2015 using knowledge translation principles involving theoretically derived interventions [37] which have demonstrated effectiveness in the development of implementation interventions for clinical practice guidelines [38,39]. An initial list of proposed stakeholders who can assist in the implementation of PRISMA-P, along with proposed actions and benefits, is provided in Table 4.

Discussion

Studies comparing trial protocols to final reports have widely documented both the presence and the extent of reporting biases in publications of randomized trials [2,40]. Protocols for systematic reviews are rarely available for such comparisons, with the exception of select organizations. Of 288 reviews with available protocols in a 2006/2007 cohort, 64 (22%) were observed to have at least one discrepant outcome with their completed reviews; only 4 described reasons for the change in the completed review [3]. Discrepant outcomes added or upgraded from secondary to primary at the review stage were more likely to be statistically significant than those outcomes that had not changed. This practice (i.e., including, excluding, or changing outcomes in association with the strength or direction of findings) has the potential to bias the findings of any meta-analysis and the review's conclusions. As review protocols are expected to become increasingly available with the advent of PROSPERO, clear reporting will become essential to facilitate the identification of discrepancies between protocol and review by readers and help them determine whether they need to be cautious in interpreting findings.

Reporting and publishing protocols is an important step in increasing the transparency of the research process and reliability of published papers. For example, some journals require a copy of the protocol as part of the peer review process of randomized trials. As of 1 March 2014, BioMed Central has published 4,158 trial protocols across 66 of its 258 open-access journals, including 1,026 in *Trials*. *Systematic Reviews*, a BioMed Central journal launched in February 2012, is committed to publishing systematic review products, including protocols [41], and has published 142 protocols since inception (to 8 June 2014).

Journals, granting agencies, and systematic review organizations are encouraged to endorse PRISMA-P 2015 in their 'Instructions to Authors' and guidance for applicants and to implement its use during their peer review process of systematic review proposals. Reviewers are encouraged to use the PRISMA-P checklist and Explanation and Elaboration [30] document to guide them through the documentation of a protocol. Doing so will enhance the completeness of reporting of review protocols, facilitate the assessment of potential in systematic reviews, and hopefully strengthen the methodological quality and reliability of completed systematic reviews.

Competing interests

The PRISMA-P 2015 initiative was supported by the AHRQ, USA (Contract No. HHSA 290 2007 10059 I) and the Canadian Institutes for Health Research (Reference No. 114369). This manuscript does not reflect the opinions of either agency; one author, SC, is an employee of AHRQ. MC, DG, DM, MP, and LAS are members of the Advisory Board for PROSPERO. DGA, SC, MC, JG, MH, JM, and MP are members of the Editorial Board, and DM, PS, and LAS are co-Editors in Chief of *Systematic Reviews*. None of the authors who are editors of *Systematic Reviews* were involved in the handling of this paper or the decision to publish it.

Authors' contributions

DM, LS, MC, DG, AL, MP, PS, and LAS conceived this paper. DM and LS drafted the article, and all authors critically revised it for important intellectual content. All authors approved the final version of this article. DM is the guarantor of this work.

Acknowledgements

The PRISMA-P steering committee would like to thank the following staff from the Ottawa Hospital Research Institute (OHRI): Jodi Peters for her efforts organizing the PRISMA-P consensus meeting, Michael Zhao for his assistance

in preparing documents for the PRISMA-P meeting, Dr. Mohammed Ansari for valuable input and feedback throughout the process, and Justin Thielman for his assistance during the preparation of the PRISMA-P manuscripts.

Dedication

The PRISMA-P 2015 initiative is dedicated to our colleague Alessandro Liberati (1954–2012) who passed away during the time in which PRISMA-P 2015 was under development and whose contributions to this work were invaluable.

PRISMA-P group (listed alphabetically)

Douglas G Altman, DSc, Centre for Statistics in Medicine (CSM), University of Oxford, (Oxford, UK); Alison Booth, Centre for Reviews and Dissemination (CRD), University of York (York, UK); An-Wen Chan, Women's College Research Institute, University of Toronto (Toronto, Canada); Stephanie Chang, Agency for Healthcare Research and Quality (Rockville, USA); Mike Clarke, Queen's University of Belfast (Belfast, Ireland); Tammy Clifford, Canadian Agency for Drugs and Technologies in Health (CADTH) (Ottawa, Canada); Kay Dickersin, Johns Hopkins Bloomberg School of Public Health; Matthias Egger, Institut für Sozial-und Präventivmedizin; Davina Ghersi, National Health and Medical Research Council (Canberra, Australia); Peter C Gøtzsche, Nordic Cochrane Centre (Copenhagen, Denmark); Jeremy M Grimshaw, Canadian Cochrane Centre and OHRI (Ottawa, Canada); Trish Groves, The BMJ (London, UK); Mark Helfand, AHRQ EPC Scientific Resource Center, Portland VA Research Foundation (Portland, USA); Julian Higgins, School of Social and Community Medicine (Bristol, UK); Toby Lasserson, Cochrane Editorial Unit (London, UK); Joseph Lau, Center for Evidence-based Medicine, Brown University (Providence, USA); Alessandro Liberati, University of Modena (Modena, Italy); Kathleen Lohr, Research Triangle Institute-University of North Carolina EPC (Research Triangle Park, USA); Jessie McGowan, University of Ottawa (Ottawa, Canada); David Moher, Clinical Epidemiology Program, OHRI, and University of Ottawa (Ottawa, Canada); Cynthia Mulrow, Annals of Internal Medicine (San Antonio, USA); Melissa Norton, PLoS Medicine (London, UK); Matthew Page, Monash University (Australia); Mark Petticrew, London School of Hygiene and Tropical Medicine (London, UK); Margaret Sampson, Children's Hospital of Eastern Ontario (Ottawa; Canada); Holger Schünemann, McMaster University (Hamilton, Canada); Larissa Shamseer, Clinical Epidemiology Program, OHRI, and University of Ottawa (Ottawa; Canada); Paul Shekelle, Southern California EPC, (Los Angeles, USA); Iveta Simera, CSM, University of Oxford (Oxford, UK); Lesley A Stewart, CRD, University of York (York, UK); William Summerskill, *The Lancet* (London, UK); Jennifer Tetzlaff, Clinical Epidemiology Program, OHRI (Ottawa, Canada); Thomas A Trikalinos, Center for Evidence-based Medicine, Brown University (Providence, USA); David Tovey, The Cochrane Library (London, UK); Lucy Turner, Clinical Epidemiology Program, OHRI (Ottawa Canada); Evelyn Whitlock, Kaiser Permanente Research Affiliates EPC (Portland, USA).

Author details

[1]Ottawa Hospital Research Institute and University of Ottawa, Ottawa, Canada. [2]Queen's University Belfast, Belfast, Ireland. [3]National Health and Medical Research Council, Canberra, Australia. [4]London School of Hygiene and Tropical Medicine, London, UK. [5]Southern California Evidence-based Practice Center, Santa Monica, CA, USA. [6]Centre for Reviews and Dissemination, University of York, York, UK.

Received: 27 August 2014 Accepted: 26 November 2014
Published: 1 January 2015

References

1. Bastian H, Glasziou P, Chalmers I: **Seventy-five trials and eleven systematic reviews a day: how will we ever keep up?** *PLoS Med* 2010, **7**(9):e1000326.
2. Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG: **Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles.** *JAMA* 2004, **291**(20):2457–2465.
3. Kirkham JJ, Altman DG, Williamson PR: **Bias due to changes in specified outcomes during the systematic review process.** *PLoS ONE* 2010, **5**(3):e9810.
4. Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, Williamson PR: **The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews.** *BMJ* 2010, **340**:c365.
5. Dwan K, Gamble C, Williamson PR, Kirkham JJ, Reporting Bias Group: **Systematic review of the empirical evidence of study publication bias and outcome reporting bias—an updated review.** *PLoS ONE* 2013, **8**(7):e66844.
6. Norris SL, Holmer HK, Ogden LA, Fu R, Abou-Setta AM, Viswanathan MS, McPheeters ML: *Selective Outcome Reporting as a Source of Bias in Reviews of Comparative Effectiveness (Prepared by the Oregon Evidence-Based Practice Center Under Contract no. 290-2007-10057-I).* Rockville: Agency for Healthcare Research and Quality; 2012. Report No.: AHRQ Publication No. 12-EHC110-EF.
7. Page MJ, McKenzie JE, Kirkham J, Dwan K, Kramer S, Green S, Forbes A: **Bias due to selective inclusion and reporting of outcomes and analyses in systematic reviews of randomised trials of healthcare interventions.** *Cochrane Lib* 2014, (10):Art No.:MR000035. doi:10.1002/14651858.MR000035.pub2.
8. Higgins JPT, Green S (Eds): *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: updated March 2011.* The Cochrane Collaboration; 2011. Available from [www.cochrane-handbook.org]
9. Ma B, Guo J, Qi G, Li H, Peng J, Zhang Y, Ding Y, Yang K: **Epidemiology, quality and reporting characteristics of systematic reviews of traditional Chinese medicine interventions published in Chinese journals.** *PLoS ONE* 2011, **6**(5):e20185.
10. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG: **Epidemiology and reporting characteristics of systematic reviews.** *PLoS Med* 2007, **4**(3):e78.
11. Institute of Medicine. In *Finding What Works in Health Care: Standards for Systematic Reviews.* Edited by Eden J, Levit L, Berg A, Morton S. Washington, DC: The National Academies Press; 2011.
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.** *PLoS Med* 2009, **6**(7):e1000100.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement.** *BMJ* 2009, **339**:b2535.
14. Straus S, Moher D: **Registering systematic reviews.** *CMAJ* 2010, **182**(1):13–14.
15. Moher D, Booth A, Stewart L: **How to reduce unnecessary duplication: use PROSPERO.** *BJOG* 2014, **121**:784–786.
16. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L: **An international registry of systematic-review protocols.** *Lancet* 2011, **377**(9760):108–109.
17. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, Stewart L: **The nuts and bolts of PROSPERO: an international prospective register of systematic reviews.** *Syst Rev* 2012, **1**:2.
18. Turner L, Shamseer L, Altman DG, Schulz KF, Moher D: **Does use of the CONSORT statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review.** *Syst Rev* 2012, **1**:60.
19. Smidt N, Rutjes AWS, Van der Windt D, Ostelo R, Bossuyt PM, Reitsma JB, Bouter LM, de Vet HCW: **The quality of diagnostic accuracy studies since the STARD statement: has it improved?** *Neurology* 2006, **67**(5):792–797.
20. Prady SL, Richmond SJ, Morton VM, MacPherson H: **A systematic evaluation of the impact of STRICTA and CONSORT recommendations on quality of reporting for acupuncture trials.** *PLoS ONE* 2008, **3**(2):e1577.
21. Williams HC: **Cars, CONSORT 2010, and clinical practice.** *Trials* 2010, **11**:33.
22. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, AHRQ Publication No. 10(14)-EHC063-EF. Rockville: Agency for Healthcare Research and Quality; 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
23. Green S, Higgins JPT, Alderson P, Clarke M, Mulrow CD, Oxman AD: **1.2.2. What is a systematic review?** In *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: updated March 2011.* Edited by Higgins JPT, Green S. The Cochrane Collaboration; 2011 [www.cochrane-handbook.org]
24. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin JA, Doré C, Parulekar WR, Summerskill WSM, Groves T, Schulz KF, Sox HC, Rockhold FW, Rennie D, Moher D: **SPIRIT 2013 statement: defining standard protocol items for clinical trials.** *Ann Intern Med* 2013, **158**(3):200–207.
25. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC: **A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts: treatments for myocardial infarction.** *JAMA* 1992, **268**(2):240–248.

26. Oxman AD, Guyatt GH: **The science of reviewing research.** *Ann N Y Acad Sci* 1993, **703:**125,33. discussion 133–134.
27. Moher D, Schulz KF, Simera I, Altman DG: **Guidance for developers of health research reporting guidelines.** *PLoS Med* 2010, **7**(2):e1000217.
28. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L: **Establishing a minimum dataset for prospective registration of systematic reviews: an international consultation.** *PLoS ONE* 2011, **6**(11):e27319.
29. Chan A, Tetzlaff JM, Gøtzsche PS, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Paruleka WR, Krleža-Jerić K, Laupaucis A, Moher D: **SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials.** *BMJ* 2013, **346:**e7586.
30. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, PRISMA-P Group: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: *elaboration & explanation*.** *BMJ* 2015, **349:**g7647.
31. Cochrane Canada: **David Moher on crystal clear reporting of systematic reviews and EQUATOR Network**. In 2010 [https://www.youtube.com/watch?v=TVFYenon1Jo]
32. Stevens A, Shamseer L, Weinstein E, Yazdi F, Turner L, Thielman J, Altman DG, Hirst A, Hoey J, Palepu A, Schulz KF, Moher D: **Relation of completeness of reporting of health research to journals' endorsement of reporting guidelines: systematic review.** *BMJ* 2014, **348:**g3804.
33. Hopewell S, Altman DG, Moher D, Schulz KF: **Endorsement of the CONSORT statement by high impact factor medical journals: a survey of journal editors and journal 'Instructions to Authors'.** *Trials* 2008, **9:**20.
34. Hirst A, Altman DG: **Are peer reviewers encouraged to use reporting guidelines? A survey of 116 health research journals.** *PLoS ONE* 2012, **7**(4):e35621.
35. Shamseer L, Weeks L, Turner L, Straus S, Grimshaw J, Moher D: **Identifying barriers to uptake and implementation of the CONSORT statement**. In *The Seventh International Congress on Peer Review and Biomedical Publication: 8–10 Sept 2014: Chicago, USA.*
36. Mills E, Wu P, Gagnier J, Heels-Ansdell D, Montori VM: **An analysis of general medical and specialist journals that endorse CONSORT found that reporting was not enforced consistently.** *J Clin Epidemiol* 2005, **58**(7):662–667.
37. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M: **Developing and evaluating complex interventions: the new medical research council guidance.** *BMJ* 2008, **337**(0959–535):a1655.
38. Davies P, Walker AE, Grimshaw JM: **A systematic review of the use of theory in the design of guideline dissemination and implementation strategies and interpretation of the results of rigorous evaluations.** *Implement Sci* 2010, **5:**14.
39. Carlsen B, Glenton C, Pope C: **Thou shalt versus thou shalt not: a meta-synthesis of GPs' attitudes to clinical practice guidelines.** *Br J Gen Pract* 2007, **57**(545):971–978.
40. Dwan K, Altman DG, Cresswell L, Blundell M, Gamble CL, Williamson PR: **Comparison of protocols and registry entries to published reports for randomised controlled trials.** *Cochrane Database Syst Rev* 2011, **1:**MR000031.
41. Moher D, Stewart L, Shekelle P: **Establishing a new journal for systematic review products.** *Syst Rev* 2012, **1:**1.

doi:10.1186/2046-4053-4-1
Cite this article as: Moher *et al.*: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1.

16. Appendix 5

Tricco AC, Cogo E, Page MJ, Polisena J, Booth A, Dwan K, MacDonald H, Clifford TJ, Stewart LA, Straus SE, Moher D. **A third of systematic reviews changed or did not specify the primary outcome: A PROSPERO register study**. 11 Apr 2016 *Journal of Clinical Epidemiology.* Doi 10.1016/jclinepi.2016.03.025 https://www.sciencedirect.com/science/article/pii/S0895435616300762?via%3Dihub

- Published paper
- Appendix A. Study protocol
- Appendix Table A. Data abstraction explanation and elaboration document
- Appendix Figure A. NonCochrane vs Cochrane Reviews' Conclusions Statements
- Appendix Table B. Quality Assessment using AMSTAR*
- Appendix Table C. References to Studies
- Appendix Table D. AMSTAR results for included systematic reviews (N=96)
- Appendix Table E. Meta-analysis results
- Appendix Table F. Sensitivity analyses results, meta-analysis results by overall statistical significance: All primary outcomes (both explicit and derived)
- Appendix Table G. Sensitivity analyses results, meta-analysis results by overall statistical significance: Explicitly reported primary outcomes alone
- Appendix Table H. Meta-analysis results for systematic reviews with funding and without funding
- Appendix Table I. Sensitivity analyses, meta-analysis results by funding: All primary outcomes (both explicit and derived)
- Appendix Table J: Sensitivity analyses, meta-analysis results by funding: Explicitly reported primary outcomes alone
- Appendix Table K. Conclusion results for all included systematic reviews
  Appendix Table L. Sensitivity Analyses results, Conclusions Statements

ELSEVIER

CrossMark

Journal of Clinical Epidemiology 79 (2016) 46–54

Journal of Clinical Epidemiology

A third of systematic reviews changed or did not specify the primary outcome: a PROSPERO register study

Andrea C. Tricco[a,b,*], Elise Cogo[a], Matthew J. Page[c], Julie Polisena[d,e], Alison Booth[f], Kerry Dwan[g], Heather MacDonald[a], Tammy J. Clifford[d], Lesley A. Stewart[f], Sharon E. Straus[a,h], David Moher[i]

[a]*Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael's Hospital, 209 Victoria Street, East Building, Toronto, Ontario M5B 1T8, Canada*

[b]*Epidemiology Division, Dalla Lana School of Public Health, University of Toronto, 155 College Street, 6th Floor, Toronto, Ontario M5T 3M7, Canada*

[c]*School of Public Health & Preventive Medicine, The Alfred Centre, Monash University, Level 6, 99 Commercial Road, Melbourne, Victoria 3004, Australia*

[d]*Canadian Agency for Drugs and Technologies in Health (CADTH), 865 Carling Avenue Suite 600, Ottawa, Ontario K1S 5S8, Canada*

[e]*Department of Epidemiology and Community Medicine, University of Ottawa, 451 Smyth Road, Ottawa, Ontario K1H 8M5, Canada*

[f]*Centre for Reviews and Dissemination, University of York, Heslington, York YO10 5DD, United Kingdom*

[g]*Department of Biostatistics, Institute of Translational Medicine, University of Liverpool, Crown Street, Liverpool L69 3BX, United Kingdom*

[h]*Department of Geriatric Medicine, University of Toronto, 27 King's College Circle, Toronto, Ontario M5S 1A1, Canada*

[i]*Ottawa Methods Centre, Ottawa Hospital Research Institute, The Ottawa Hospital, 501 Smyth Road, PO Box 201B, Ottawa, Ontario K1H 8L6, Canada*

Accepted 10 March 2016; Published online 11 April 2016

Abstract

Objectives: To examine outcome reporting bias of systematic reviews registered in PROSPERO.

Study Design and Setting: Retrospective cohort study. The primary outcomes from systematic review publications were compared with those reported in the corresponding PROSPERO records; discrepancies in the primary outcomes were assessed as upgrades, additions, omissions, or downgrades. Relative risks (RRs) and 95% confidence intervals (CI) were calculated to determine the likelihood of having a change in primary outcome when the meta-analysis result was favorable and statistically significant.

Results: Ninety-six systematic reviews were published. A discrepancy in the primary outcome occurred in 32% of the included reviews and 39% of the reviews did not explicitly specify a primary outcome(s); 6% of the primary outcomes were omitted. There was no significant increased risk of adding/upgrading (RR, 2.14; 95% CI: 0.53, 8.63) or decreased risk of downgrading (RR, 0.76; 95% CI: 0.27, 2.17) an outcome when the meta-analysis result was favorable and statistically significant. As well, there was no significant increased risk of adding/upgrading (RR, 0.89; 95% CI: 0.31, 2.53) or decreased risk of downgrading (RR, 0.56; 95% CI: 0.29, 1.08) an outcome when the conclusion was positive.

Conclusions: We recommend review authors carefully consider primary outcome selection, and journals are encouraged to focus acceptance on registered systematic reviews.

Keywords: Bias; Methodology; Quality; Reporting; Systematic reviews; Outcome reporting bias

Conflict of interest: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no financial support for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; A.B., L.A.S., and D.M. are members of the PROSPERO Advisory Group; A.C.T. is an author of one of the included systematic reviews but was not involved with the AMSTAR appraisal or data abstraction for this review and was blinded to the author names during the analysis, she is also an Associate Editor for the journal but was not involved with the decision to publish; S.E.S. and D.M. are part of the journal's Policy Advisory Board but were not involved with the decision to publish; no other relationships or activities that could appear to have influenced the submitted work.

Funding: No funding was received for this study. A.C.T. is funded by a Canadian Institutes of Health Research New Investigator Award in Knowledge Synthesis, S.E.S. is funded by a Tier 1 Canada Research Chair in Knowledge Translation, A.B. and L.A.S. are funded by the National Institute for Health Research, and D.M. is funded by a University of Ottawa Research Chair.

Ethics approval: Ethics approval was not required.

Transparency declaration: A.C.T. accepts full responsibility for the finished article, had access to all the data, and controlled the decision to publish. A.C.T. 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 no discrepancies from the study as planned occurred.

* Corresponding author. Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael's Hospital, 209 Victoria Street, East Building, Room 716, Toronto, Ontario M5B 1W8 Canada. Tel.: 416-864-6060x77521; fax: 416-864-6057.

E-mail address: triccoa@smh.ca (A.C. Tricco).

http://dx.doi.org/10.1016/j.jclinepi.2016.03.025

1. Introduction

The Cochrane Handbook for Systematic Reviews of Interventions [1] states that systematic reviewers should prepare a systematic review protocol before their review conduct, to encourage transparency of reporting hypotheses and methods (including outcomes) and avoid outcome reporting bias. This is consistent with the Institute of Medicine Standards for Systematic Reviews [2]. As well, the Cochrane Handbook [1] and Preferred Reporting Items for Systematic reviews and Meta-Analyses Statement [3] state that any changes to the protocol should be fully documented and explained in the systematic review publication. Despite this guidance, research consistently has found that more than one-third of published systematic reviews have an undisclosed discrepancy between the outcomes reported in the protocol vs. final review [4–7].

In the most simplistic definition, outcome reporting bias "occurs when a study in which multiple outcomes were measured reports only those that are (statistically) significant" [8]. Previous studies have compared final Cochrane review methods to those reported in the review protocols [4–7], including a recent Cochrane methodology review on outcome reporting bias [9]. One of these studies found evidence of outcome reporting bias, in which statistically significant outcomes were more likely to be upgraded (i.e., promoted from secondary to primary) or added in the final publication compared to the protocol [5]. All these studies included a sample of systematic reviews published in the Cochrane Database of Systematic Reviews before the year 2009.

The International Prospective Register of Systematic Reviews (PROSPERO) was established in 2011 [10] and is the only open-access online facility to prospectively register non-Cochrane systematic reviews. Because most published systematic reviews are not Cochrane reviews [11], this register of review protocol details is likely a more representative sample of systematic reviews in the literature. No previous study has explored outcome reporting bias of systematic reviews registered in PROSPERO. As such, we aimed to (1) examine whether outcome reporting bias exists, and to what extent, in published systematic reviews registered in PROSPERO and (2) assess the methodological quality of published systematic reviews that were registered in PROSPERO.

2. Methods

2.1. Protocol

Before conducting this retrospective cohort study, we created a project plan, which outlined our study methods. Our protocol was revised after receiving feedback from all authors. The final protocol can be found in Appendix A at www.jclinepi.com. Because this study was not a systematic review, it was not eligible to be registered with the PROSPERO repository.

2.2. Sample of systematic reviews

We aimed to identify all completed systematic reviews of interventions that were registered in PROSPERO. On November 29, 2013, all records from the PROSPERO database identified as "completed and published" were downloaded. These records also include the citation/link to the final publication. PROSPERO includes an audit trail for protocol amendments and progress reports. In this study, the protocol record used was the version immediately before the version where the Named Contact updated the record to report that the review had been completed. Our scope was limited to systematic reviews of interventions to allow the comparison of statistically significant meta-analysis results, which would not be feasible for other review products (e.g., diagnostic reviews, prognostic reviews, prevalence reviews). Only non-Cochrane reviews were included. Completed reviews not published in English were also excluded, due to resource limitations.

2.3. Data abstraction process

A data abstraction form with an explanation guide was developed (Appendix Table A at www.jclinepi.com) and calibrated through a team exercise. Specifically, the team independently pilot tested the forms using a random sample of 10 included systematic reviews. Data abstraction did not commence until high agreement (>90%) was achieved. Subsequently, three pairs of reviewers abstracted each of the systematic review publications, independently. To ensure consistency across the team regarding the classification of outcomes, one team member verified all the data (E.C.) and resolved discrepancies.

2.4. Data items

The data items were abstracted from both the protocol details and the publication and included study characteristics (e.g., year of publication, number of studies included, type of studies included, whether meta-analysis was conducted, source of funding), number of primary outcomes, changes in primary outcomes from the PROSPERO record to review publication, reasons for changes in primary outcomes (if reported), meta-analysis results, and conclusions. The reason we focused on primary outcomes is because this is the outcome of greatest interest and importance. Similar research on outcome reporting bias has used this approach [4–7].

If the primary outcome(s) was not explicitly stated in the publication (i.e., not specifically called a "primary" outcome), the following decision-tree approach [12,13] was used to "derive" the primary outcome(s), by selecting the outcome that met the first of the following criteria: (1) the outcome(s) listed in the title; (2) the outcome(s) listed in the objectives; and (3) the most serious outcome (e.g., mortality). To facilitate comparison across studies, all changes in primary outcomes from the

What is new?

Key finding

- Many systematic reviews that are registered in PROSPERO have discrepancies in primary outcomes between their record and review publication.

What this study adds to what was known?

- This is the first study to examine outcome reporting bias using the PROSPERO register, a database for prospectively registering systematic reviews that was established in 2011.
- Previous studies have compared outcomes reported in Cochrane reviews to those reported in the corresponding review protocols. These studies found that more than one-third of published systematic reviews had a discrepancy between the outcomes reported in the protocol vs. final publication. One study found evidence of outcome reporting bias, in which statistically significant outcomes were more likely to be upgraded (i.e., promoted from secondary to primary) or added in the final publication compared to the protocol.
- We found that approximately one-third of published systematic reviews had a discrepancy between the outcomes reported in the PROSPERO record vs. the review publication. However, evidence of outcome reporting bias was not observed.

What is the implication and what should change now?

- Our study suggests that non-Cochrane review authors have similar outcome reporting behaviors to Cochrane review authors. We recommend that all non-Cochrane reviews are registered with PROSPERO, review authors carefully consider the selection of primary outcomes, peer reviewers should check PROSPERO to see if there are any discrepancies between the record and review publication, and journals are encouraged to focus acceptance on registered systematic reviews.

PROSPERO record to the systematic review publication were coded using the same classification scheme used in the Parmelli et al. [7] and Kirkham et al. [5] studies. These categories were new inclusion of outcomes (or additions), exclusion, upgrade, and downgrade of outcomes (Box 1). The meta-analysis results were categorized using a previous approach [13], including favorable and statistically significant, favorable and not statistically significant, neutral, unfavorable and not statistically significant, and unfavorable and statistically significant (Box 1, Appendix Fig. A at www.jclinepi.com). The conclusions were obtained from the abstract and discussion sections from the systematic reviews and were categorized using a previous approach [13], including positive, neutral, negative, and indeterminate (Box 1).

Box 1 Classification: primary outcomes, meta-analysis results, and conclusion statements

Classification of changes to primary outcomes:

- New (inclusion or addition): the addition of a completely new primary outcome;
- Exclusion: the omission of a primary outcome in the publication;
- Upgrade: when a secondary outcome in the protocol was changed to a primary outcome in the publication;
- Downgrade: when a primary outcome in the protocol was changed to a secondary or undefined outcome in the publication.

Classification of meta-analysis results:

- Favorable, statistically significant (i.e., effect in favor of the intervention with $P \leq 0.05$);
- Favorable, nonstatistically significant;
- Neutral (effect size between 0.95 and 1.05 and the confidence interval crosses 1);
- Unfavorable, statistically significant (i.e., effect in favor of the nonintervention comparator with $P \leq 0.05$);
- Unfavorable, nonstatistically significant.

Categorization of conclusion statements

- Positive (authors stated that there is evidence of effectiveness);
- Neutral (no evidence of effectiveness or they reported no opinion);
- Negative (authors advised against the use of the intervention or it was not recommended); or
- Indeterminate (authors stated that there is insufficient evidence or that more research is required).

We used the same hierarchy reported by Kirkham et al. [5] to select meta-analyses from systematic reviews with multiple treatment group comparisons. Specifically, we selected the first intervention comparison which met the following criteria: "(1) an intervention comparison described in the protocol as the primary review comparison; (2) the first intervention comparison mentioned in the title of the protocol; (3) an intervention comparison described in the review as the primary review comparison; (4) the first intervention comparison mentioned in the objectives of the review; and (5) the intervention comparison used in the first meta-analysis presented in the review."

2.5. Methodological quality appraisal

The overall methodological quality of the systematic reviews was assessed using the Assessment of Multiple SysTemAtic Reviews (AMSTAR) tool (Appendix Table B at www.jclinepi.com) [14]. The scores range from 0 to 11, with higher scores indicating superior quality. For our study, a score of 8 or higher was considered higher quality. This assessment was conducted to ascertain the overall quality of completed and published systematic reviews that were registered in PROSPERO.

2.6. Analysis

We explored the association between statistical significance of meta-analysis results and adding, upgrading, or downgrading of outcomes compared to no discrepancies, by calculating a relative risk (RR) and 95% confidence interval (CI), where the meta-analysis results were dichotomized into favorable and statistically significant vs. any of the other four categories. The formula is $RR=[a/(a+b)]\div[c/(c+d)]$, where a is the number of meta-analysis outcomes that are discrepant and have a favorable and statistically significant result, b is the number of meta-analysis outcomes that are not discrepant and have a favorable and statistically significant result, c is the number of meta-analysis outcomes that are discrepant and do not have a favorable and statistically significant result, and d is the number of meta-analysis outcomes that are not discrepant and do not have favorable and statistically significant result. This analysis was similar to those conducted by Page et al. [9] in their Cochrane review of outcome reporting bias. The RR and 95% CI were calculated for outcomes that were explicitly reported as primary outcomes, as well as including those that were derived using the classification scheme reported above. Our hypotheses were that when the meta-analysis result was favorable and statistically significant, adding/upgrading of outcomes would be more likely, whereas downgrading of outcomes would be less likely. A sensitivity analysis was also conducted consistent with the analysis method used by Kirkham et al. [5], to allow comparability of results. For this analysis, the meta-analysis results were dichotomized into statistically significant vs. not statistically significant, and the hypotheses were that new/upgraded outcomes would be more likely to have statistically significant meta-analysis results, whereas downgraded outcomes would be less likely, than if there was no discrepancy.

We also conducted a post hoc analysis for systematic reviews that were funded. Similar to our primary analysis, we explored the association between statistical significance of meta-analysis results and adding, upgrading, or downgrading of outcomes compared to no discrepancies by calculating an RR and 95% CI, where the meta-analysis results were dichotomized into favorable and statistically significant vs. any of the other four categories. This analysis was repeated for systematic reviews that did not have funding. Sensitivity analyses were also conducted using the Kirkham et al. [5] approach.

The RR and 95% CI were calculated for obtaining a positive conclusion for new primary outcomes or upgrades, and downgrades compared to no discrepancies (where conclusions were categorized as positive vs. all other conclusion types). Our hypotheses were that when the conclusion was positive, adding/upgrading of outcomes would be more likely, whereas downgrading of outcomes would be less likely. A sensitivity analysis was also conducted to calculate the RR and 95% CI using a similar approach as to Kirkham et al. [5]. For this sensitivity analysis, our hypothesis was that when outcomes were added or upgraded, a positive conclusion would be more likely, whereas when outcomes were downgraded, a positive conclusion would be less likely.

3. Results

3.1. Sample of PROSPERO records

In November 2013, 2,426 protocol records were registered with PROSPERO and 343 were completed systematic reviews (Fig. 1). Of the completed reviews, 140 were potentially relevant (i.e., published or in press), and of these, 44 were excluded because they were not systematic reviews of interventions or the final review was not written in English (Appendix Table C at www.jclinepi.com). Ninety-six systematic reviews fulfilled the eligibility criteria and were subsequently included (Appendix Table C at www.jclinepi.com).

3.2. Systematic review characteristics

Eighty-nine (92.7%) of the systematic reviews were published between 2012 and 2013, and 4 (4.2%) were published in 2014, as they were in press at the time we downloaded their PROSPERO records. Eighty-one (84.3%) included 2 to 30 studies, 56 (58.3%) limited inclusion to randomized controlled trials, and 67 (68.8%) conducted a meta-analysis (Table 1). In addition, 36 (37.5%) reported no source of funding, 45 (46.9%) were conducted in the United Kingdom or North America, and 5 (5.2%) published their protocol in a journal.

3.3. Methodological quality

Eight of the 11 AMSTAR items were adequately addressed by more than 72 (75%) of the systematic reviews (Fig. 2, Appendix Table D at www.jclinepi.com). However, 72 (75%) of the reviews did not state conflicts of interest for included studies and review authors, 63 (66%) did not provide a list of excluded studies, 39 (41%) did not assess publication bias where it would have been

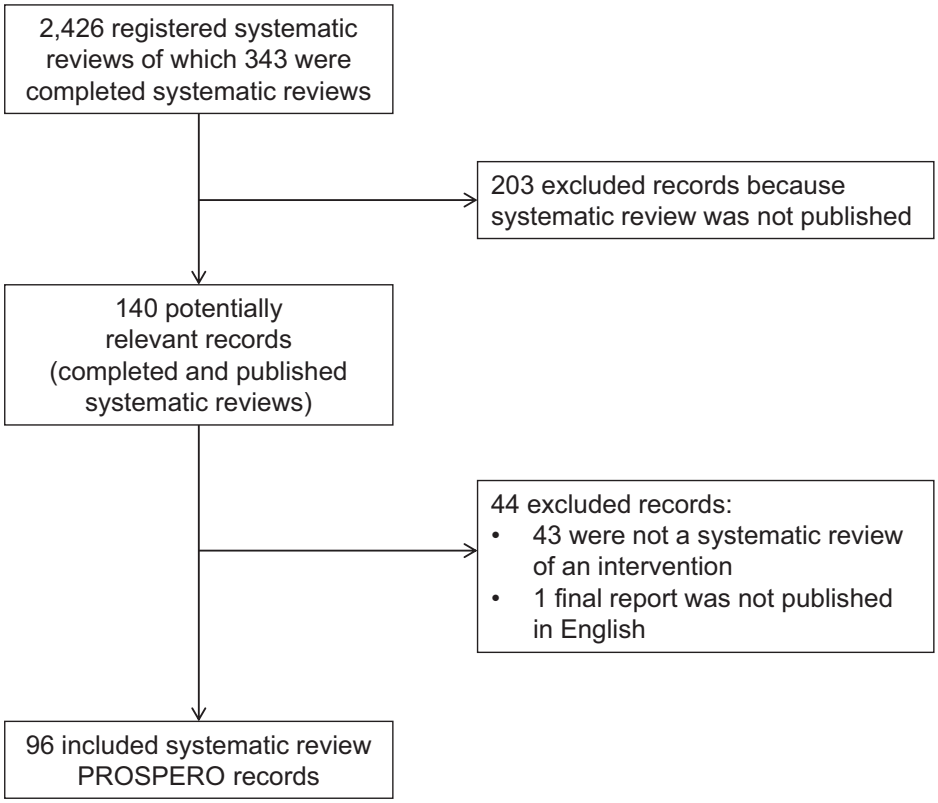


Fig. 1. Flow of systematic reviews through the study.

appropriate to do so, and 14 (15%) did not consider methodological quality or risk of bias results in their conclusion statements.

3.4. Outcome reporting

Although the primary outcome was indicated in PROSPERO, which is structured to separate primary and secondary outcomes, it was not explicitly reported for 37 (38.5%) of the completed systematic reviews, so was derived in this study (Table 2). The primary outcomes were derived using the title (35.2%), objectives (24.3%), or were the most serious outcomes (40.5%). Thirty-one (32.3%) of the systematic reviews had a discrepancy between the primary outcomes reported in the PROSPERO record and final publication, whereas 65 (67.7%) had no discrepancies (Table 3). Of the reviews with discrepancies, 6 (5.9%) had a new primary outcome, 6 (5.9%) excluded a primary outcome, 6 (5.9%) upgraded an outcome, and 22 (21.8%) downgraded a primary outcome. One (1.0%) of the systematic reviews reported a reason for changing their primary outcome. Six (5.9%) systematic reviews reported a change in their primary outcome definition, and 1 (1.0%) changed the measurement method for the primary outcome.

3.5. Meta-analysis results

The results of 139 meta-analyses in 67 systematic reviews are presented in Appendix Table E at www.jclinepi.com. There was no significant increased risk of adding or upgrading an outcome when the meta-analysis result was favorable and statistically significant (RR, 2.14; 95% CI: 0.53, 8.63), which was the same result as found in our sensitivity analysis (Appendix Table F at www.jclinepi.com). This result was unchanged when only the primary outcomes that were explicitly reported were included in our analysis (RR, 2.02; 95%: CI 0.35, 11.56; Appendix Table G at www.jclinepi.com). Furthermore, there was no significant decreased risk of downgrading an outcome when the meta-analysis result was favorable and statistically significant (RR, 0.76; 95% CI: 0.27, 2.17), and the same result was observed in our sensitivity analysis. Similarly, when only the primary outcomes that were explicitly reported were included in our analysis, no statistically significant results were observed for downgrades (RR, 1.37; 95% CI: 0.20, 9.42). Calculations were not possible for excluded primary outcomes because they were absent from the publications (by definition).

A post hoc analysis was conducted for systematic reviews with funding and without funding (Appendix

Table 1. Characteristics of the 96 included systematic reviews

Characteristic	# of systematic reviews (%)
Publication year	
2011	3 (3.1)
2012	29 (30.2)
2013	60 (62.5)
2014	4 (4.2)
Total number of studies included	
0–20	70 (72.9)
21–40	9 (19.8)
>40	7 (7.3)
Total number of participants in included studies	
≤1,000–5,000	48 (50)
5,001–10,000	5 (5.2)
10,001–50,000	7 (7.3)
50,001–100,000	3 (3.1)
>100,000	2 (2.1)
Not reported	31 (32.3)
Study designs included	
All randomized controlled trials	56 (58.3)
Mixed study designs[a]	35 (36.5)
All observational studies	5 (5.2)
Meta-analysis conducted	
Yes	67 (69.8)
No	29 (30.2)
Funding[b]	
Stated no funding received	36 (37.5)
Public funder (e.g., academia, government)	56 (58.4)
Commercial organization	4 (4.2)
Geographic region[c]	
Europe	47 (49)
North America	20 (20.9)
South America	11 (11.4)
Eastern Asia	9 (9.3)
Australia	5 (5.2)
Southern Asia	2 (2.1)
Southern Africa	2 (2.1)
Published protocol in a journal	
Yes	5 (5.2)
No	91 (94.8)
Participant population in publication[d]	
Healthy or presumed healthy	14 (14.6)
Mixed conditions	11 (11.5)
Musculoskeletal conditions	10 (10.4)
Infectious diseases	9 (9.4)
Present/history of cancer	9 (9.4)
Pregnancy-related or reproductive conditions	8 (8.3)
Psychiatric/mental health conditions	7 (7.3)
Cardiovascular conditions	6 (6.3)
Respiratory conditions	6 (6.3)
Autoimmune diseases	3 (3.1)
Gastrointestinal and abdominal conditions	2 (2.1)
Genetic diseases	2 (2.1)
Neurodegenerative/neurologic conditions	2 (2.1)
Oral-related conditions	2 (2.1)
Urinary conditions	2 (2.1)
Auditory conditions	1 (1.0)
Overweight	1 (1.0)
Type 2 diabetes	1 (1.0)

Abbreviation: RCT, randomized controlled trial.

[a] Mixed could indicate, for example, RCT and quasi-RCT (not necessarily mixed with observational studies).

[b] Source: Cochrane EPOC Group. Available at: http://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/datacollectionchecklist.pdf.

[c] If more than one country was listed ($n = 8$), only the first country's geographic region is listed here.

[d] As reported by the review authors.

Tables H–J at www.jclinepi.com). No statistically significant results were observed in our overall analysis or sensitivity analyses.

3.6. Conclusion statements

The categorization of conclusions for all included systematic reviews is presented in Appendix Table K at www.jclinepi.com. There was no significant increased risk of adding or upgrading outcomes when the conclusion was positive (RR, 0.89; 95% CI: 0.31, 2.53). Furthermore, there was no significant decreased risk of downgrading an outcome when the conclusion was positive (RR, 0.56; 95% CI: 0.29, 1.08). Our sensitivity analyses also found no significant risk of a positive conclusion when the outcomes were added/upgraded or downgraded (Appendix Table L at www.jclinepi.com).

4. Discussion

One-third of published systematic reviews that were registered with PROSPERO had a discrepancy between the primary outcome reported in their record and the primary outcome reported in the review publication. Of the discrepancies, downgrading of primary outcomes was most common (22%), and 6% of reviews omitted a protocol-specified primary outcome from the review. In addition, 39% of reviews did not explicitly specify a primary outcome(s) in the review. Although a lot of discrepancies were observed, we did not find statistically significant associations between discrepant outcome reporting and having a favorable and statistically significant meta-analysis result or positive conclusion. However, the small number of reviews within each subgroup of discrepancy classification likely limited the statistical power to detect statistically significant results. PROSPERO has now passed 10,000 records, and repeating this study is likely to yield a larger number of published systematic reviews to examine.

Our study is the first to measure outcome reporting bias of systematic reviews that were registered in PROSPERO. To

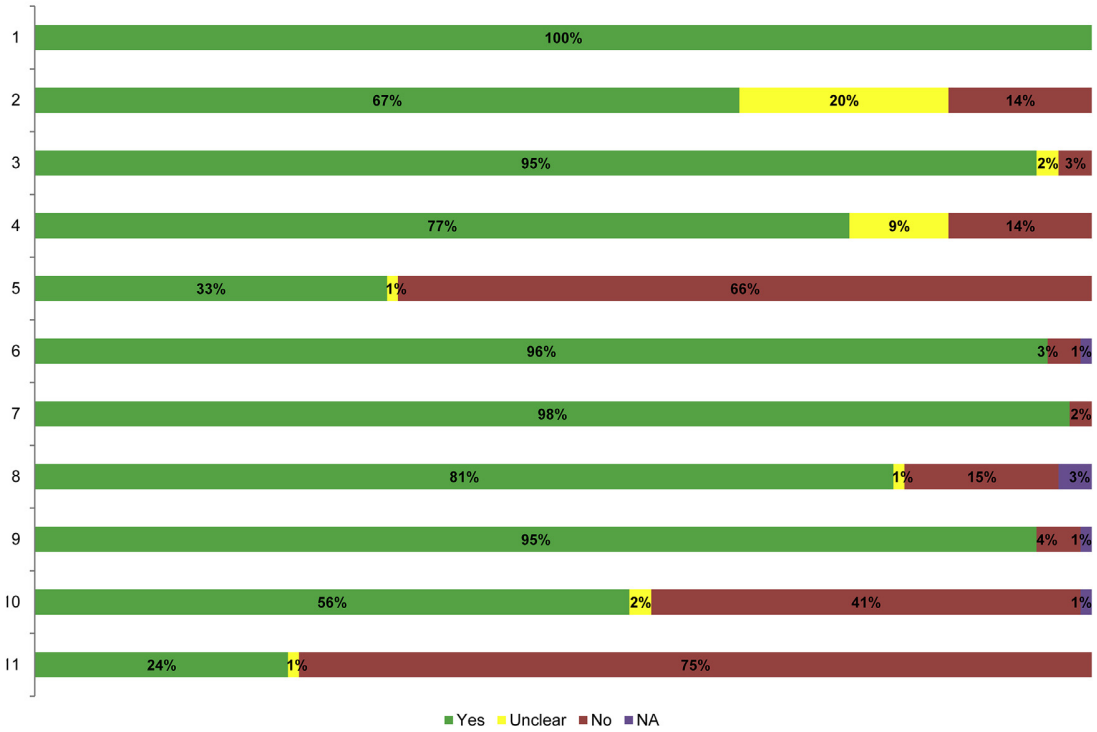


Fig. 2. AMSTAR methodological quality results. Items: 1. a priori design, 2. duplicate selection/DA, 3. literature search, 4. publication status, 5. list of studies, 6. study characteristics, 7. quality assessed, 8. quality used, 9. methods appropriate, 10. publication bias assessed, and 11. conflicts stated. AMSTAR, Assessment of Multiple SysTemAtic Reviews; NA, not applicable.

examine this issue, we systematically searched for 96 systematic reviews published between 2011 and 2014. We abstracted data in duplicate, which were triple checked by a third reviewer, and appraised the included reviews using the AMSTAR tool. The included systematic reviews were of high methodological quality, on average. Areas for improvement included providing a list of excluded studies, assessing publication bias when appropriate (as per the AMSTAR criterion), and reporting conflicts of interest for the systematic review authors, as well as for the included studies.

Our results are only generalizable to intervention reviews, as the risk of outcome reporting bias in other types of reviews (e.g., diagnostic reviews) remains unknown. As well, we only included non-Cochrane reviews. We considered only primary outcomes, which may have underestimated the occurrence of outcome reporting bias for all types of outcomes.

Table 2. Number of primary outcomes in the publications

Outcome details	# of systematic reviews (%)
Number explicit per review	
0	37 (38.5)
1	35 (36.5)
2	10 (10.4)
3	6 (6.3)
4	3 (3.1)
5	1 (1.0)
6	2 (2.1)
7	1 (1.0)
8	1 (1.0)
Number derived per review	
NA (were explicit)	59 (61.5)
1	24 (25.0)
2	6 (6.3)
3	5 (5.2)
4	1 (1.0)
5	0 (0)
6	1 (1.0)
Derived method used	
NA (were explicit)	59 (61.5)
Method 1—from title	13 (13.5)
Method 2—from objectives	9 (9.4)
Method 3—most serious	15 (15.6)

Abbreviation: NA, not applicable.

Table 3. Changes in primary outcomes

Change type	# of systematic reviews with ≥1change(s) (%)[a]
New primary outcome(s)	6 (5.9)
Exclusion of primary outcome(s)	6 (5.9)
Upgrade of primary outcome(s)	6 (5.9)
Downgrade of primary outcome(s)	22 (21.8)
Change in primary outcome definition	6 (5.9)
Change in primary outcome measure	1 (1.0)
No discrepancies	65 (67.7)

[a] Does not add up to 100% because some systematic reviews included more than one primary outcome.

However, this is the same approach to other studies examining outcome reporting bias [4–7]. Limited resources meant that we were unable to contact authors of the discrepant systematic reviews to determine the reason for these inconsistencies. Only one review reported a rationale for changing the outcome, which makes it difficult to provide definitive conclusions as to why these changes may occur [15]. The reason that was reported by the authors was that the clinical experts on their team selected the most clinically important outcomes, which did not align with what was reported in their PROSPERO record. We were unable to include a larger sample of published and completed systematic reviews, due to resource restraints. Because of the small number of included reviews in our analyses, we were unable to examine possible sources of heterogeneity that may have confounded our results or conduct subgroup analysis for outcome reporting bias for systematic reviews with active comparators vs. placebo, ''high'' vs. ''low'' quality as per the AMSTAR tool, and randomized trials vs. nonrandomized studies. As well, there is a chance that there were more completed systematic reviews that were published, but the authors of the review failed to update their PROSPERO record (although they are sent three autoreminders to update their information in PROSPERO). We were only able to include the systematic reviews with meta-analyses in our statistical analysis of outcome reporting bias, which is consistent with previous studies [4–7]. Finally, we calculated risk ratios instead of odds ratios to compare our study with previous studies conducted in this area.

A recent Cochrane review [9] included four previous studies that examined discrepancies in outcome reporting between systematic review protocols and published systematic reviews [4–7]. All these studies included Cochrane reviews that were published between 2000 and 2009, and none appraised the methodological quality of included systematic reviews using the AMSTAR tool. A total of 485 Cochrane reviews were included, and discrepancies were identified in 38% of these. A meta-analysis of two of the studies was conducted, and no statistically significant association between statistical significance of meta-analysis results and discrepant outcome reporting (adding, upgrading, or downgrading) was found. These results are consistent with those observed in our study.

Our results suggest that authors of non-Cochrane reviews are similar to Cochrane review authors in their outcome reporting behaviors. It is possible that systematic review authors are not focused on identifying primary outcomes of interest at the protocol stage and are instead just completing the PROSPERO form. Furthermore, as registration in PROSPERO is voluntary (and is relatively new), it is possible that our sample (as well as studies using samples of Cochrane reviews) underestimated the overall number of primary outcome discrepancies in systematic reviews in general.

Using pre-established methods [16], we estimate that 17,399 systematic reviews were published in 2013. During this time, 1,612 Cochrane reviews were registered and 1,526 non-Cochrane reviews were registered with PROSPERO. This means that only 18% of published systematic review authors registered their protocol. As such, we recommend that all non-Cochrane reviews are registered with PROSPERO. Furthermore, review authors are advised to consider the selection of primary outcomes carefully and report the explanations for protocol modifications in the final review publication. Review authors should think about the importance of outcomes before embarking on their review and limit the number of outcomes to ensure that those selected are both necessary and meaningful. Core outcome sets have been recommended for trials (COMET initiative, http://www.comet-initiative.org/), and it is recommended that systematic review authors are familiar with this guidance when selecting outcomes for inclusion in their review. Peer reviewers should check PROSPERO to see if there are any discrepancies between the record and review publication and ensure that the author explains these. Finally, journals are encouraged to focus acceptance on registered systematic reviews, as we found that these are likely to be of high methodological quality.

Few studies have examined outcome reporting bias in systematic reviews [9]. There has been no study of systematic reviews that are not registered with the Cochrane Collaboration or PROSPERO. This could be done by contacting review authors to obtain their unpublished protocol, if one exists. Future research should examine a larger sample of PROSPERO records as this database matures and examine the discrepancies in primary outcomes reported in the abstract and full text of the published systematic reviews.

Acknowledgments

The authors thank Inthuja Selvaratnam for formatting our article and Judy Tran for assisting with creating the manuscript tables. A.C.T. affirms everyone who contributed significantly to the work in this study has been acknowledged.

Authors' contributions: All authors conceptualized the study. A.C.T. pilot tested the data abstraction form, resolved discrepancies, analyzed the results, interpreted the results, wrote the article, and approved the final article. E.C. coordinated the review, pilot tested the data abstraction form, resolved discrepancies, checked all the cleaned data, helped write the article, and approved the final article. A.B., J.P., T.J.C., K.D., M.J.P., and H.M. pilot tested the data abstraction form, conducted data abstraction, appraised the quality of the articles, edited the article, and approved the final article. M.J.P. also analyzed the data, A.B. screened the records for inclusion, and H.M. helped clean the data and resolve discrepancies. T.J.C., L.A.S., S.E.S., and D.M. edited the article and approved the final article.

Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jclinepi.2016.03.025.

References

[1] Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0. The Cochrane Collaboration; 2011. Available at http://handbook.cochrane.org.

[2] Institute of Medicine. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press; 2011.

[3] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.

[4] Dwan K, Kirkham JJ, Williamson PR, Gamble C. Selective reporting of outcomes in randomised controlled trials in systematic reviews of cystic fibrosis. BMJ Open 2013;3(6). e002709.

[5] Kirkham JJ, Altman DG, Williamson PR. Bias due to changes in specified outcomes during the systematic review process. PLoS One 2010;5:e9810.

[6] Silagy CA, Middleton P, Hopewell S. Publishing protocols of systematic reviews: comparing what was done to what was planned. JAMA 2002;287:2831−4.

[7] Parmelli E, Liberati A, D'Amico R. Reporting of outcomes in systematic reviews: comparison of protocols and published systematic reviews. Sao Paulo: 15th Cochrane Colloquium; 2007.

[8] Tricco AC, Tetzlaff J, Sampson M, Fergusson D, Cogo E, Horsley T, et al. Few systematic reviews exist documenting the extent of bias: a systematic review. J Clin Epidemiol 2008;61:422−34.

[9] Page MJ, McKenzie JE, Kirkham J, Dwan K, Kramer S, Green S, et al. Bias due to selective inclusion and reporting of outcomes and analyses in systematic reviews of randomised trials of healthcare interventions. Cochrane Database Syst Rev 2014;10:MR000035.

[10] PROSPERO. York, England: Centre for Reviews and Dissemination, Univeristy of York; [updated November 2015]. Available at http://www.crd.york.ac.uk/PROSPERO/.

[11] Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. PloS Med 2007;4(3):e78.

[12] Moher D, Dulberg CS, Wells GA. Statistical power, sample size, and their reporting in randomized controlled trials. JAMA 1994;272:122−4.

[13] Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. J Clin Epidemiol 2009;62:380−386.e1.

[14] Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009;62:1013−20.

[15] Mesgarpour B, Griebler U, Glechner A, Kien C, Strobelberger M, Van Noord MG, et al. Extended-release opioids in the management of cancer pain: a systematic review of efficacy and safety. Eur J Pain 2014;18:605−16.

[16] Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PloS Med 2010;7(9):e1000326.

Examining outcome reporting bias in systematic reviews: Appendices

Appendix A. Study protocol

Team: Andrea C. Tricco, Elise Cogo, Alison Booth, David Moher, Sharon E. Straus, Julie Polisena, Tammy Clifford, Lesley Stewart, Kerry Dwan, Matthew Page.

Background and rationale:
A study protocol helps reduce the risk of bias in a systematic review by specifying *a priori* hypotheses and methods. Outcome reporting bias is a recognized problem in clinical trials but has been less studied in systematic reviews. We plan to conduct the first study using the International Prospective Register of Systematic Reviews (PROSERO) to compare systematic review publications to their protocol details. Four similar studies focused their research on Cochrane reviews [4-7] and found a substantial number of changes in outcomes between the protocol and completed reviews. The PROSPERO database is another source of systematic review protocol details, which might be a more generalizable sample of systematic reviews versus those from the Cochrane Collaboration.

As of October 9, 2013, there are 95 completed publications of systematic review protocol details that were registered with the PROSPERO database. We will compare the results generated by this sample of systematic reviews with the previous studies [4-7,17]. If similar results are found, we will submit a paper for publication. However, if we obtain different results, we will use the data to apply for a CIHR open operating grant targeting the spring 2014 competition. The grant will propose to examine the risk of outcome reporting bias using the entire sample of systematic reviews that were registered in the PROSPERO register.

Objectives:
1. To assess whether outcome reporting bias exists, and to what extent, in published systematic reviews registered in PROSPERO.
2. To assess the methodological quality overall in published systematic reviews that are registered in PROSPERO.

Methods:
We will identify all published, completed systematic reviews whose protocol details are registered in the PROSPERO register. We will compare the primary outcomes reported in the published systematic reviews to those reported in the PROSPERO protocol registrations. We will also compare these outcomes with any protocols published in other sources, such as the *Systematic Reviews* journal.

Changes from PROSPERO record to publication will be coded using the following classification scheme, similar to that used by Parmelli et al. 2007 [7] and Kirkham et al. 2010 [5]: Inclusion of a new primary outcome, exclusion of a primary outcome, or change in type of outcome. The latter ('change') will be further classified as either an upgrade (when a secondary outcome was changed to a primary outcome or when not defined in protocol became primary in the systematic review) or a downgrade (vice-versa). If the primary outcome is not stated (e.g., in the title or objectives), a decision-tree approach will be used and the most serious outcome will be chosen [12, 13]. The overall methodological quality of the systematic reviews will be assessed using the AMSTAR tool [14].

Prior to embarking on data abstraction, the teams will pilot-test the data abstraction form using a random sample of 10 of the included systematic reviews. Data abstraction will only commence when high agreement has been achieved (e.g., percent agreement >80%). Subsequently, two members of the research team will abstract each of the systematic reviews and appraise their methodological quality, independently. In addition, if reasons for the changes to primary outcomes from protocol to publication are not indicated in the publication, the corresponding author of the review will be contacted twice, separated by two weeks. All conflicts will be resolved through discussion.

Appendix Table A. Data abstraction explanation and elaboration document

NB:
For all items if either not applicable or not reported, enter NA or NR.
Please do not leave blank spaces.
Please do not abstract non-English publications.
We will only include **intervention** systematic reviews.

Items in white will be data abstracted manually.
Items highlighted in pink will be downloaded from PROSPERO by CRD.

Study Characteristics:

Excel Column	Description
CRD no.	Enter the number in the first column from the PROSPERO download file (registration number).
DA 1	Enter your initials here.
DA 2	(Leave blank).
Publication author	List the last name of the first author of the publication.
Publication year	List the year of the publication.
Contact	Contact author named in the PROSPERO record.
Publication citation	Citation information of the systematic review publication. (Note that scoping reviews are not included).
Registration date	Latest date when protocol details were registered before status changed to Completed. This is the PROSPERO record version that will be used for data abstraction and comparison below.
Other protocol	URL for the PDF or citation information of the full protocol publication. If not applicable, enter NA.
Country of conduct	Country in which the systematic review was conducted (if this is unclear then use the country of origin of the first author).
Funding	Data from PROSPERO record will be categorized for funding source into the following options: - No funding; - Governmental organisation; - Commercial organisation; - Health-care provider organisation; - Voluntary body (e.g., American Medical Association); - Charitable trust; - Research funding body (e.g., Medical Research Council); - Mixed; - Other; - Unclear; - NR.

	[Source: Cochrane EPOC Group. Available at: http://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/datacollectionchecklist.pdf].
No. of studies	Total number of studies included in the systematic review.
Study design	Select from the drop-down menu options below the study designs included in the systematic review: - all RCTs; - all observational; - mixed.
Sample size	Total number of participants captured in the systematic review. If this is not obvious from the report, enter NR (i.e. not necessary to add up studies).
Population in protocol details	Brief description of the systematic review population(s) in the protocol details.
Population in publication	Brief description of the systematic review population(s) in the abstract and publication.
Intervention in protocol details	Brief description of the systematic review intervention(s) in the protocol details. If it is not a therapy review, describe the experimental procedure or exposure that was studied (e.g., diagnostic test, risk factor, etc.).
Intervention in publication	Brief description of the systematic review intervention(s) in the abstract and publication.
Comparator in protocol details	Brief description of the systematic review comparator(s) in the protocol details.
Comparator in publication	Brief description of the systematic review comparator(s) in the abstract and publication.

Primary Outcomes:

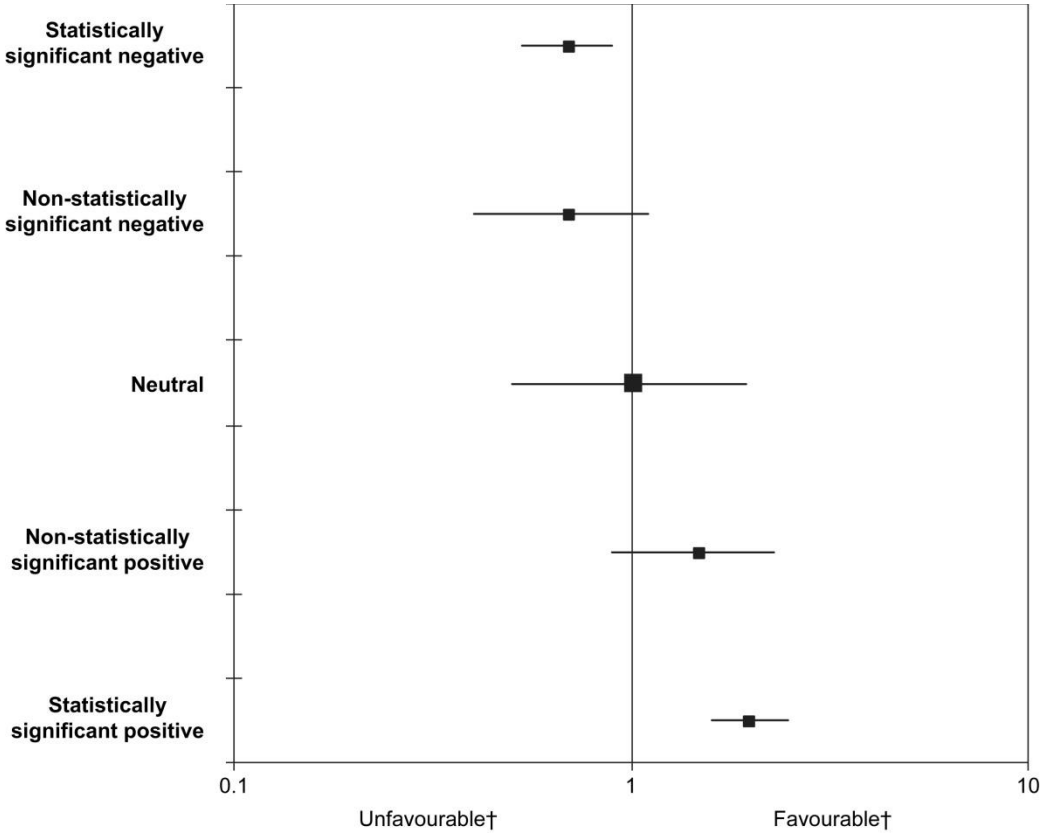
Excel Column	Description
CRD no.	Enter the number in the first column from the PROSPERO download file (registration number).
No. of 1ºoutcomes in protocol details	Data from PROSPERO record will be used to record the number of primary outcomes. (This is a mandatory field in PROSPERO).
No. of 1ºoutcomes in publication- Explicit	Number of primary outcomes in systematic review publication that are explicitly called 'primary' outcomes NB- use the overall domain of the outcome instead of the specific outcome measures. Example: -Mark 'quality of life' as one outcome here instead of adding up the separate scales used to measure this.

Name(s)- Explicit	Enter the names of the explicit primary outcome(s).
No. of 1°outcomes in publication- Derived	Number of primary outcomes in systematic review publication that are derived. If zero was entered above (i.e. no explicit 1° outcome), then use the following order to select the primary outcome for the purpose of comparison with the PROSPERO record: 1) the outcome listed in the title; 2) the outcome listed in the objectives; 3) the most serious outcome (e.g., death); If this row is not applicable, enter NA.
Name(s)- Derived	Enter the name(s) of the derived primary outcome(s).
Derived method	Enter the method used above to derive the primary outcome. If this row is not applicable, enter NA.
2°outcomes in protocol details	Data from PROSPERO record on secondary outcomes. *This will only be used for the primary outcome change categorizations below.* (This is a mandatory field in PROSPERO).
Change – New 1° outcome	For a change in the type of primary outcome from the protocol details to the publication that is the addition of a completely new primary outcome, enter the number of new primary outcomes added. Note: if this is not applicable, enter '0' here.
Name(s)- New	Enter the names of the new primary outcome(s).
Change – Exclusion of1° outcome	For a change in the type of primary outcome from the protocol details to the publication that is the omission of a primary outcome in the publication, enter the number of excluded primary outcomes. Note: if this is not applicable, enter '0' here.
Name(s)- Exclusion	Enter the names of the excluded primary outcome(s).
Change – Upgrade of 1° outcome	For a change in the type of primary outcome from the protocol details to the publication that is an upgrade (i.e. when a secondary or undefined outcome in the protocol details was changed to a primary outcome in the publication), enter the number of upgraded primary outcomes. Note: if this is not applicable, enter '0' here.
Name(s)- Upgrade	Enter the names of the upgraded primary outcome(s).
Change – Downgrade of 1° outcome	For a change in the type of primary outcome from the protocol details to the publication that is a downgrade (i.e. when a primary outcome in the protocol details was changed to a secondary or undefined outcome in publication), enter the number of downgraded primary outcomes. Note: if this is not applicable, enter '0' here.
Name(s)- Downgrade	Enter the names of the downgraded primary outcome(s).
Change in 1°	If there was a change in primary outcome definition between the

outcome definition	protocol details and publication, enter the name of the outcome that was changed. If not applicable, enter NA.
The row above will be repeated for up to 10 changes.	
Change in 1º outcome measure	If there was a change in primary outcome measure between the protocol details and publication, enter the name of the outcome that was changed. If not applicable, enter NA.
The row above will be repeated for up to 10 changes.	
Rationale for change of 1º outcome	If the authors provide a reason for a change in primary outcome in the publication, enter the text here including which outcome(s) they are referring. If none was provided, enter NR here. If not applicable, enter NA.
The row above will be repeated for up to 10 reasons.	
Synthesis strategy	Information provided in the protocol details on the data synthesis strategy.
Meta-analysis conducted	Was a meta-analysis conducted for the primary outcome in the publication (drop-down menu)? - Yes; - No.
Meta-analysis results- Direction	Enter the direction of the results from the following drop-down options (see Fig. 1* below): - Favourable, statistically significant (i.e. effect in favour of the intervention with $p \leq 0.05$); - Favourable, non-statistically significant; - Neutral (effect size between 0.95-1.05 and the confidence interval crosses 1); - Unfavourable, statistically significant (i.e. effect in favour of the nonintervention comparator with $p \leq 0.05$); - Unfavourable, non-statistically significant; - Non-comparative (e.g., review of prevalence); - NA.
Name- MA	Enter a description of the corresponding meta-analysis above. <u>Examples:</u> - intervention vs. control for pain - Tx gp 2 vs. placebo for nausea
The 2 rows above will be repeated for up to 10 results.	
Conclusions	For all the systematic reviews (with or without meta-analysis),choose the categorization of the conclusions (from the Abstract &Discussion sections) from the following drop-down options: - Positive (authors stated that there is evidence of effectiveness); - Neutral (no evidence of effectiveness or they reported no opinion); - Negative (authors advised against the use of the intervention or it was not recommended); - Indeterminate (authors stated that there is insufficient evidence or that

	more research is required); - Non-comparative; - NR; - NA.
Name- Conclusion	Enter a description of the corresponding conclusion above. <u>Examples:</u> - intervention vs. control for pain - Tx gp 2 vs. placebo for nausea
The 2 rows above will be repeated for up to 10 conclusions.	

Appendix Figure A. Non Cochrane vs. Cochrane Reviews' Conclusion Statements



Notes: †"Unfavorable" represents systematic review results favoring the control or comparison intervention, while "favorable" represents systematic review results favoring the intervention of interest.

*From Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. J Clin Epidemiol. 2009 Apr; 62(4): 380-386.e1. PMID: 19128940.

Appendix Table B. Quality Assessment using AMSTAR*

Choose 'YES', 'NO', 'UNCLEAR', or 'NOT APPLICABLE (NA)' for each question below:

Excel Column	Description
1. A priori design	*Was an 'a priori' design provided?* "The research question and inclusion criteria should be established before the conduct of the review". This means that the authors must mention that they worked from a protocol or that they registered their review protocol or that they published their review protocol. All our included reviews will automatically have a YES here.
2. Duplicate selection	*Was there duplicate study selection and data extraction?* "There should be at least two independent data extractors and a consensus procedure for disagreements should be in place". Since this item lumps 2 questions into 1, data can be screened in duplicate and data abstraction verified or vice versa. Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.
3. Literature search	*Was a comprehensive literature search performed?* "At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found". In order to score a YES, at least two electronic sources should be searched. Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).
4. Publication status	*Was the status of publication (i.e. grey literature) used as an inclusion criterion?* "The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review) based on their publication status, language, etc." In order to score a YES, they should include unpublished data. If they only included peer reviewed material, mark 'No' here. Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SINGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this

	purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.
5. List of studies	*Was a list of studies (included and excluded) provided?* "A list of included and excluded studies should be provided". To score a YES, all included AND excluded studies should be provided. Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."
6. Study characteristics	*Were the characteristics of the included studies provided?* "In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed (e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases) should be reported." To score a YES, they must at least report one each of participants, interventions and outcomes. Note: Acceptable if not in table format as long as they are described as above.
7. Quality assessed	*Was the scientific quality of the included studies assessed and documented?* "'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant". To score a YES, they must appraise risk of bias or methodological quality (i.e. assessed quality but detailed reporting of these findings not required here). Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).
8. Quality used	*Was the scientific quality of the included studies used appropriately in formulating conclusions?* "The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations". If quality/risk of bias was not assessed, then this is NA. Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.
9. Methods	*Were the methods used to combine the findings of studies appropriate?*

appropriate	"For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?)". For reviews that do not conduct a meta-analysis, authors should provide a rationale for this (e.g., the results were too heterogeneous so the results were described narratively). Reviews that do not describe their synthesis process should be scored as a NO. Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.
10. Publication bias assessed	*Was the likelihood of publication bias assessed?* "An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken)". If a meta-analysis was not conducted, then the possibility of publication bias should be at least mentioned in the discussion section. Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.
11. Conflicts stated	*Was the conflict of interest stated?* "Potential sources of support should be clearly acknowledged in both the systematic review and the included studies". Score as a YES even if a conflict of interest exists but it is stated. This item is asking whether it was reported (not whether conflicts of interest exist). Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.

*Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007 Feb 15; 7:10. PMID: 17302989.

Appendix Table C. References to Studies

Included Studies (n=96)

1. Abbott RA, Whear R, Thompson-Coon J, Ukoumunne OC, Rogers M, Bethel A, et al. Effectiveness of mealtime interventions on nutritional outcomes for the elderly living in residential care: a systematic review and meta-analysis. Ageing Res Rev. 2013;12(4):967-81.
2. Araghi MH, Chen Y-F, Jagielski A, Choudhury S, Banerjee D, Hussain S, et al. Effectiveness of lifestyle interventions on obstructive sleep apnea (OSA): systematic review and meta-analysis. Sleep. 2013;36(10):1553.
3. Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. Clin Infect Dis. 2013;57 Suppl 2:S80-9.
4. Avery L, Flynn D, van Wersch A, Sniehotta FF, Trenell MI. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. Diabetes Care. 2012;35(12):2681-9.
5. Barnes C, Cauvin E, Duran-Kim M, Montalbano L, Londrigan M. A systematic review of the effectiveness of patient centred care on emergency room visits, hospitalizations, unscheduled sick clinic visits, and missed school days for children with asthma. The JBI Database of Systematic Reviews and Implementation Reports. 2012;10(14):832-94.
6. Beck CR, McKenzie BC, Hashim AB, Harris RC, Zanuzdana A, Agboado G, et al. Influenza vaccination for immunocompromised patients: systematic review and meta-analysis from a public health policy perspective. PLoS ONE. 2011;6(12):e29249.
7. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr. 2013;110(7):1178-87.
8. Castellucci LA, Cameron C, Le Gal G, Rodger MA, Coyle D, Wells PS, et al. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. BMJ. 2013;347:f5133.
9. Castro-Rodriguez JA, Rodrigo GJ. A systematic review of long-acting beta2-agonists versus higher doses of inhaled corticosteroids in asthma. Pediatrics. 2012;130(3):e650-7.
10. Chambrone L, Pannuti CM, Tu YK, Chambrone LA. Evidence-based periodontal plastic surgery. II. An individual data meta-analysis for evaluating factors in achieving complete root coverage. J Periodontol. 2012;83(4):477-90.
11. Cherry MG, Greenhalgh J, Osipenko L, Venkatachalam M, Boland A, Dundar Y, et al. The clinical effectiveness and cost-effectiveness of primary stroke prevention in children with sickle cell disease: a systematic review and economic evaluation. Health Technol Assess. 2012;16(43):1-129.
12. Chua ME, Escusa KG, Luna S, Tapia LC, Dofitas B, Morales M. Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis. Andrology. 2013;1(5):749-57.
13. Cox NS, Alison JA, Rasekaba T, Holland AE. Telehealth in cystic fibrosis: a systematic review. J Telemed Telecare. 2012;18(2):72-8.
14. Cundy TP, Marcus HJ, Clark J, Hughes-Hallett A, Mayer EK, Najmaldin AS, et al. Robot-assisted minimally invasive surgery for pediatric solid tumors: a systematic review of feasibility and current status. Eur J Pediatr Surg. 2014;24(2):127-35.
15. Cunill R, Castells X, Tobias A, Capella D. Atomoxetine for attention deficit hyperactivity disorder in the adulthood: a meta-analysis and meta-regression. Pharmacoepidemiol Drug

Saf. 2013;22(9):961-9.
16. Domingo GRR, Reyes FC, Thompson FV, Johnson PM, Shortridge-Baggett LM. Effectiveness of structured discharge process in reducing hospital readmission of adult patients with community acquired pneumonia: A systematic review. The JBI Database of Systematic Reviews and Implementation Reports. 2012;10(18):1086-121.
17. Easthall C, Song F, Bhattacharya D. A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence. BMJ Open. 2013;3(8).
18. Elazab N, Mendy A, Gasana J, Vieira ER, Quizon A, Forno E. Probiotic administration in early life, atopy, and asthma: a meta-analysis of clinical trials. Pediatrics. 2013;132(3):e666-76.
19. Emdin CA, Chong NJ, Millson PE. Non-physician clinician provided HIV treatment results in equivalent outcomes as physician-provided care: a meta-analysis. J Int AIDS Soc. 2013;16:18445.
20. Figueiredo JB, Nastri CO, Vieira AD, Martins WP. Clomiphene combined with gonadotropins and GnRH antagonist versus conventional controlled ovarian hyperstimulation without clomiphene in women undergoing assisted reproductive techniques: systematic review and meta-analysis. Arch Gynecol Obstet. 2013;287(4):779-90.
21. Ford J, Cummins E, Sharma P, Elders A, Stewart F, Johnston R, et al. Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours. Health Technol Assess. 2013;17(29):1-386.
22. Fretheim A, Odgaard-Jensen J, Brors O, Madsen S, Njolstad I, Norheim OF, et al. Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis. BMC Med. 2012;10:33.
23. Frey AU, Sonksen J, Fode M. Neglected side effects after radical prostatectomy: a systematic review. J Sex Med. 2014;11(2):374-85.
24. Galvao TF, Silva MT, Serruya SJ, Newman LM, Klausner JD, Pereira MG, et al. Safety of benzathine penicillin for preventing congenital syphilis: a systematic review. PLoS ONE. 2013;8(2):e56463.
25. Gupta AA, Yao X, Verma S, Mackay H, Hopkins L, Sarcoma Disease Site G, et al. Systematic chemotherapy for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma: a systematic review. Clin Oncol (R Coll Radiol). 2013;25(6):346-55.
26. Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, et al. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. BMJ. 2013;346:f839.
27. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA. 2012;307(18):1959-69.
28. Henshaw H, Ferguson MA. Efficacy of individual computer-based auditory training for people with hearing loss: a systematic review of the evidence. PLoS ONE. 2013;8(5):e62836.
29. Hobbs N, Godfrey A, Lara J, Errington L, Meyer TD, Rochester L, et al. Are behavioral interventions effective in increasing physical activity at 12 to 36 months in adults aged 55 to 70 years? A systematic review and meta-analysis. BMC Med. 2013;11:75.
30. Hollis JL, Williams LT, Collins CE, Morgan PJ. Effectiveness of interventions using Motivational Interviewing for dietary and physical activity modification in adults: A Systematic Review. The JBI Database of Systematic Reviews and Implementation Reports. 2013;11(5):1-27.
31. Hopkins U, Itty AS, Nazario H, Pinon M, Slyer J, Singleton J. The effectiveness of delegation interventions by the registered nurse to the unlicensed assistive personnel and their impact on quality of care, patient satisfaction, and RN staff satisfaction: a systematic review. The JBI

Database of Systematic Reviews and Implementation Reports. 2012;10(15):895-934.
32. Huang TS, Shyu YC, Chen HY, Lin LM, Lo CY, Yuan SS, et al. Effect of parenteral selenium supplementation in critically ill patients: a systematic review and meta-analysis. PLoS ONE. 2013;8(1):e54431.
33. Huang TS, Shyu YC, Chen HY, Yuan SS, Shih JN, Chen PJ. A systematic review and meta-analysis of adjuvant interferon therapy after curative treatment for patients with viral hepatitis-related hepatocellular carcinoma. J Viral Hepat. 2013;20(10):729-43.
34. Hutton P, Taylor PJ. Cognitive behavioural therapy for psychosis prevention: a systematic review and meta-analysis. Psychol Med. 2014;44(3):449-68.
35. Jacobs WC, Rubinstein SM, Willems PC, Moojen WA, Pellise F, Oner CF, et al. The evidence on surgical interventions for low back disorders, an overview of systematic reviews. Eur Spine J. 2013;22(9):1936-49.
36. Kamioka H, Tsutani K, Yamada M, Park H, Okuizumi H, Honda T, et al. Effectiveness of rehabilitation based on recreational activities: A systematic review. World Journal of Meta-analysis. 2013.
37. Kasawara KT, do Nascimento SL, Costa ML, Surita FG, e Silva JL. Exercise and physical activity in the prevention of pre-eclampsia: systematic review. Acta Obstet Gynecol Scand. 2012;91(10):1147-57.
38. Khatib R, Joseph P, Briel M, Yusuf S, Healey J. Blockade of the renin-angiotensin-aldosterone system (RAAS) for primary prevention of non-valvular atrial fibrillation: a systematic review and meta analysis of randomized controlled trials. Int J Cardiol. 2013;165(1):17-24.
39. Krag M, Perner A, Wetterslev J, Wise MP, Hylander Moller M. Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Intensive Care Med. 2014;40(1):11-22.
40. Kunath F, Keck B, Antes G, Wullich B, Meerpohl JJ. Tamoxifen for the management of breast events induced by non-steroidal antiandrogens in patients with prostate cancer: a systematic review. BMC Med. 2012;10:96.
41. Kunath F, Keck B, Rucker G, Motschall E, Wullich B, Antes G, et al. Early versus deferred androgen suppression therapy for patients with lymph node-positive prostate cancer after local therapy with curative intent: a systematic review. BMC Cancer. 2013;13:131.
42. Li XX, Han M, Wang YY, Liu JP. Chinese herbal medicine for gout: a systematic review of randomized clinical trials. Clin Rheumatol. 2013;32(7):943-59.
43. Malafarina V, Uriz-Otano F, Iniesta R, Gil-Guerrero L. Effectiveness of nutritional supplementation on muscle mass in treatment of sarcopenia in old age: a systematic review. J Am Med Dir Assoc. 2013;14(1):10-7.
44. Mariani J, Doval HC, Nul D, Varini S, Grancelli H, Ferrante D, et al. N-3 polyunsaturated fatty acids to prevent atrial fibrillation: updated systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2013;2(1):e005033.
45. Mesgarpour B, Griebler U, Glechner A, Kien C, Strobelberger M, Van Noord MG, et al. Extended-release opioids in the management of cancer pain: a systematic review of efficacy and safety. Eur J Pain. 2014;18(5):605-16.
46. Mickenautsch S, Yengopal V. Failure rate of atraumatic restorative treatment using high-viscosity glass-ionomer cement compared to that of conventional amalgam restorative treatment in primary and permanent teeth: a systematic review update. Journal of Minimum Intervention in Dentistry. 2012;5:63-124.
47. Mills SD, Tanner LM, Adams J. Systematic literature review of the effects of food and drink advertising on food and drink-related behaviour, attitudes and beliefs in adult populations. Obes Rev. 2013;14(4):303-14.
48. Morici N, Moja L, Rosato V, Oreglia JA, Sacco A, De Marco F, et al. Time from adenosine di-

phosphate receptor antagonist discontinuation to coronary bypass surgery in patients with acute coronary syndrome: meta-analysis and meta-regression. Int J Cardiol. 2013;168(3):1955-64.
49. Munn Z, Jordan Z. The effectiveness of interventions to reduce anxiety, claustrophobia, sedation and non-completion rates of patients undergoing high technology medical imaging. The JBI Database of Systematic Reviews and Implementation Reports. 2012;10(19):1122-85.
50. National Collaborating Centre for Mental Health. *Antisocial Behaviour and Conduct Disorders in Children and Young People: The NICE Guideline on Recognition, Intervention and Management (NICE Clinical Guideline 158)*. Leicester & London: The British Psychological Society and the Royal College of Psychiatrists; 2013.
51. Nurmatov U, Buckingham S, Kendall M, Murray SA, White P, Sheikh A, et al. Effectiveness of holistic interventions for people with severe chronic obstructive pulmonary disease: systematic review of controlled clinical trials. PLoS ONE. 2012;7(10):e46433.
52. O'Neill SM, Kearney PM, Kenny LC, Henriksen TB, Lutomski JE, Greene RA, et al. Caesarean delivery and subsequent pregnancy interval: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2013;13:165.
53. O'Sullivan K, McAuliffe S, Deburca N. The effects of eccentric training on lower limb flexibility: a systematic review. Br J Sports Med. 2012;46(12):838-45.
54. O'Sullivan K, O'Keeffe M, O'Sullivan L, O'Sullivan P, Dankaerts W. The effect of dynamic sitting on the prevention and management of low back pain and low back discomfort: a systematic review. Ergonomics. 2012;55(8):898-908.
55. Pandor A, Thokala P, Gomersall T, Baalbaki H, Stevens JW, Wang J, et al. Home telemonitoring or structured telephone support programmes after recent discharge in patients with heart failure: systematic review and economic evaluation. Health Technol Assess. 2013;17(32):1-207, v-vi.
56. Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach JF, et al. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. Epidemiology. 2012;23(3):402-14.
57. Pham A, Liu G. Dexamethasone for antiemesis in laparoscopic gynecologic surgery: a systematic review and meta-analysis. Obstet Gynecol. 2012;120(6):1451-8.
58. Polanski LT, Barbosa MA, Martins WP, Baumgarten MN, Campbell B, Brosens J, et al. Interventions to improve reproductive outcomes in women with elevated natural killer cells undergoing assisted reproduction techniques: a systematic review of literature. Hum Reprod. 2014;29(1):65-75.
59. Rodrigo GJ, Castro-Rodriguez JA. Daily vs. intermittent inhaled corticosteroids for recurrent wheezing and mild persistent asthma: a systematic review with meta-analysis. Respir Med. 2013;107(8):1133-40.
60. Rodrigo GJ, Neffen H. Comparison of indacaterol with tiotropium or twice-daily long-acting beta -agonists for stable COPD: a systematic review. Chest. 2012;142(5):1104-10.
61. Saha S, Koley M. Homeopathic treatment of headaches and migraine: a meta-analysis of the randomized controlled trials. Asian Journal of Pharmaceutical and Clinical Research. 2013;6(3).
62. Saha S, Koley M, Medhurst R. A meta-analysis of the randomized controlled trials of individualized homeopathy in rheumatoid arthritis. World Journal of Pharmacy and Pharmaceutical Sciences. 2013;2(4):2097-117.
63. Santomassino M, Costantini GD, McDermott M, Primiano D, Slyer JT, Singleton JK. A systematic review on the effectiveness of continuity of care and its role in patient satisfaction and decreased hospital readmissions in the adult patient receiving home care services. The JBI Database of Systematic Reviews and Implementation Reports. 2012;10(21):1214-59.
64. Sawh SC, Newman JJ, Deshpande S, Jones PM. Lacosamide adjunctive therapy for partial-

onset seizures: a meta-analysis. PeerJ. 2013;1:e114.
65. Schwingshackl L, Hoffmann G. Long-term effects of low-fat diets either low or high in protein on cardiovascular and metabolic risk factors: a systematic review and meta-analysis. Nutr J. 2013;12:48.
66. Selk A, Kroft J. Misoprostol in operative hysteroscopy: a systematic review and meta-analysis. Obstet Gynecol. 2011;118(4):941-9.
67. Shneerson C, Taskila T, Gale N, Greenfield S, Chen YF. The effect of complementary and alternative medicine on the quality of life of cancer survivors: a systematic review and meta-analyses. Complement Ther Med. 2013;21(4):417-29.
68. Silva MT, Galvao TF, Zimmerman IR, Pereira MG, Lopes LC. Non-aspirin non-steroidal anti-inflammatory drugs for the primary chemoprevention of non-gastrointestinal cancer: summary of evidence. Curr Pharm Des. 2012;18(26):4047-70.
69. Silva MT, Zimmermann IR, Galvao TF, Pereira MG. Olanzapine plus fluoxetine for bipolar disorder: a systematic review and meta-analysis. J Affect Disord. 2013;146(3):310-8.
70. Singh B, Parsaik AK, Mielke MM, Erwin PJ, Knopman DS, Petersen RC, et al. Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2014;39(2):271-82.
71. Singh B, Parsaik AK, Prokop LJ, Mittal MK. Endovascular therapy for acute ischemic stroke: a systematic review and meta-analysis. Mayo Clin Proc. 2013;88(10):1056-65.
72. Smith T, Kirby E, Davies L. A systematic review to determine the optimal type and dosage of land-based exercises for treating knee osteoarthritis. Physical Therapy Reviews. 2014;19(2):105-13.
73. Smith TO, Bacon H, Jerman E, Easton V, Armon K, Poland F, et al. Physiotherapy and occupational therapy interventions for people with benign joint hypermobility syndrome: a systematic review of clinical trials. Disabil Rehabil. 2014;36(10):797-803.
74. Smith TO, Postle K, Penny F, McNamara I, Mann CJ. Is reconstruction the best management strategy for anterior cruciate ligament rupture? A systematic review and meta-analysis comparing anterior cruciate ligament reconstruction versus non-operative treatment. Knee. 2014;21(2):462-70.
75. Sonuga-Barke EJ, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiatry. 2013;170(3):275-89.
76. Stradling C, Chen YF, Russell T, Connock M, Thomas GN, Taheri S. The effects of dietary intervention on HIV dyslipidaemia: a systematic review and meta-analysis. PLoS ONE. 2012;7(6):e38121.
77. Suchdev PS, De-Regil LM, Walleser S, Vist GE, Peña-Rosas P, Organization WH. Multiple micronutrient powders for home (point of use) fortification of foods in pregnant women: a systematic review. 2011.
78. Sukhodolsky DG, Bloch MH, Panza KE, Reichow B. Cognitive-behavioral therapy for anxiety in children with high-functioning autism: a meta-analysis. Pediatrics. 2013;132(5):e1341-50.
79. Sunguya BF, Poudel KC, Mlunde LB, Urassa DP, Yasuoka J, Jimba M. Nutrition training improves health workers' nutrition knowledge and competence to manage child undernutrition: a systematic review. Front Public Health. 2013;1:37.
80. Tarp S, Bartels EM, Bliddal H, Furst DE, Boers M, Danneskiold-Samsoe B, et al. Effect of nonsteroidal antiinflammatory drugs on the C-reactive protein level in rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis Rheum. 2012;64(11):3511-21.
81. Tatla SK, Sauve K, Virji-Babul N, Holsti L, Butler C, Van Der Loos HF. Evidence for outcomes of motivational rehabilitation interventions for children and adolescents with cerebral palsy: an American Academy for Cerebral Palsy and Developmental Medicine systematic review. Dev Med Child Neurol. 2013;55(7):593-601.

82. Tefikow S, Barth J, Maichrowitz S, Beelmann A, Strauss B, Rosendahl J. Efficacy of hypnosis in adults undergoing surgery or medical procedures: a meta-analysis of randomized controlled trials. Clin Psychol Rev. 2013;33(5):623-36.
83. ten Broek RPG, Stommel MWJ, Strik C, van Laarhoven CJHM, Keus F, van Goor H. Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis. The Lancet. 2014;383(9911):48-59.
84. Thiele M, Gluud LL, Dahl EK, Krag A. Antiviral therapy for prevention of hepatocellular carcinoma and mortality in chronic hepatitis B: systematic review and meta-analysis. BMJ open. 2013;3(8).
85. Timmons BW, Leblanc AG, Carson V, Connor Gorber S, Dillman C, Janssen I, et al. Systematic review of physical activity and health in the early years (aged 0-4 years). Appl Physiol Nutr Metab. 2012;37(4):773-92.
86. Tirlapur SA, Vlismas A, Ball E, Khan KS. Nerve stimulation for chronic pelvic pain and bladder pain syndrome: a systematic review. Acta Obstet Gynecol Scand. 2013;92(8):881-7.
87. Tohira H, Williams TA, Jacobs I, Bremner A, Finn J. The impact of new prehospital practitioners on ambulance transportation to the emergency department: a systematic review and meta-analysis. Emerg Med J. 2014;31(e1):e88-e94.
88. Tricco AC, Chit A, Soobiah C, Hallett D, Meier G, Chen MH, et al. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. BMC Med. 2013;11:153.
89. van Middendorp JJ, Hosman AJ, Doi SA. The effects of the timing of spinal surgery after traumatic spinal cord injury: a systematic review and meta-analysis. J Neurotrauma. 2013;30(21):1781-94.
90. Viljoen E. A Systematic Review of the effect and safety of Ginger in the treatment of pregnancy associated nausea and vomiting [Master's Thesis]. Stellenbosch University; 2012.
91. Vonthein R, Heimerl T, Schwandner T, Ziegler A. Electrical stimulation and biofeedback for the treatment of fecal incontinence: a systematic review. Int J Colorectal Dis. 2013;28(11):1567-77.
92. Wang XQ, Zheng JJ, Yu ZW, Bi X, Lou SJ, Liu J, et al. A meta-analysis of core stability exercise versus general exercise for chronic low back pain. PLoS ONE. 2012;7(12):e52082.
93. Whitelock G, Aromataris E. Effectiveness of mealtime interventions to improve nutritional intake of adult patients in the acute care setting: a systematic review. The JBI Database of Systematic Reviews and Implementation Reports. 2013;11(3):263-305.
94. Wu MY, Hsu YH, Bai CH, Lin YF, Wu CH, Tam KW. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy: a meta-analysis of randomized controlled trials. Am J Kidney Dis. 2012;59(6):810-8.
95. Yang G, Wang Y, Tian J, Liu JP. Huperzine A for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials. PLoS ONE. 2013;8(9):e74916.
96. Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA. 2013;309(7):678-88.

Included Systematic Reviews with a Meta-analysis (n=67)

1. Abbott RA, Whear R, Thompson-Coon J, Ukoumunne OC, Rogers M, Bethel A, et al. Effectiveness of mealtime interventions on nutritional outcomes for the elderly living in residential care: a systematic review and meta-analysis. Ageing Res Rev. 2013;12(4):967-81.
2. Araghi MH, Chen Y-F, Jagielski A, Choudhury S, Banerjee D, Hussain S, et al. Effectiveness of lifestyle interventions on obstructive sleep apnea (OSA): systematic review and meta-

analysis. Sleep. 2013;36(10):1553.
3. Avery L, Flynn D, van Wersch A, Sniehotta FF, Trenell MI. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. Diabetes Care. 2012;35(12):2681-9.
4. Beck CR, McKenzie BC, Hashim AB, Harris RC, Zanuzdana A, Agboado G, et al. Influenza vaccination for immunocompromised patients: systematic review and meta-analysis from a public health policy perspective. PLoS ONE. 2011;6(12):e29249.
5. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr. 2013;110(7):1178-87.
6. Castellucci LA, Cameron C, Le Gal G, Rodger MA, Coyle D, Wells PS, et al. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. BMJ. 2013;347:f5133.
7. Castro-Rodriguez JA, Rodrigo GJ. A systematic review of long-acting beta2-agonists versus higher doses of inhaled corticosteroids in asthma. Pediatrics. 2012;130(3):e650-7.
8. Chambrone L, Pannuti CM, Tu YK, Chambrone LA. Evidence-based periodontal plastic surgery. II. An individual data meta-analysis for evaluating factors in achieving complete root coverage. J Periodontol. 2012;83(4):477-90.
9. Chua ME, Escusa KG, Luna S, Tapia LC, Dofitas B, Morales M. Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis. Andrology. 2013;1(5):749-57.
10. Cunill R, Castells X, Tobias A, Capella D. Atomoxetine for attention deficit hyperactivity disorder in the adulthood: a meta-analysis and meta-regression. Pharmacoepidemiol Drug Saf. 2013;22(9):961-9.
11. Easthall C, Song F, Bhattacharya D. A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence. BMJ Open. 2013;3(8).
12. Elazab N, Mendy A, Gasana J, Vieira ER, Quizon A, Forno E. Probiotic administration in early life, atopy, and asthma: a meta-analysis of clinical trials. Pediatrics. 2013;132(3):e666-76.
13. Emdin CA, Chong NJ, Millson PE. Non-physician clinician provided HIV treatment results in equivalent outcomes as physician-provided care: a meta-analysis. J Int AIDS Soc. 2013;16:18445.
14. Figueiredo JB, Nastri CO, Vieira AD, Martins WP. Clomiphene combined with gonadotropins and GnRH antagonist versus conventional controlled ovarian hyperstimulation without clomiphene in women undergoing assisted reproductive techniques: systematic review and meta-analysis. Arch Gynecol Obstet. 2013;287(4):779-90.
15. Ford J, Cummins E, Sharma P, Elders A, Stewart F, Johnston R, et al. Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours. Health Technol Assess. 2013;17(29):1-386.
16. Fretheim A, Odgaard-Jensen J, Brors O, Madsen S, Njolstad I, Norheim OF, et al. Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis. BMC Med. 2012;10:33.
17. Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, et al. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. BMJ. 2013;346:f839.
18. National Collaborating Centre for Mental Health. *Antisocial Behaviour and Conduct Disorders in Children and Young People: The NICE Guideline on Recognition, Intervention and Management (NICE Clinical Guideline 158)*. Leicester & London: The British Psychological

Society and the Royal College of Psychiatrists; 2013.
19. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA. 2012;307(18):1959-69.
20. Hobbs N, Godfrey A, Lara J, Errington L, Meyer TD, Rochester L, et al. Are behavioral interventions effective in increasing physical activity at 12 to 36 months in adults aged 55 to 70 years? A systematic review and meta-analysis. BMC Med. 2013;11:75.
21. Huang TS, Shyu YC, Chen HY, Lin LM, Lo CY, Yuan SS, et al. Effect of parenteral selenium supplementation in critically ill patients: a systematic review and meta-analysis. PLoS ONE. 2013;8(1):e54431.
22. Huang TS, Shyu YC, Chen HY, Yuan SS, Shih JN, Chen PJ. A systematic review and meta-analysis of adjuvant interferon therapy after curative treatment for patients with viral hepatitis-related hepatocellular carcinoma. J Viral Hepat. 2013;20(10):729-43.
23. Hutton P, Taylor PJ. Cognitive behavioural therapy for psychosis prevention: a systematic review and meta-analysis. Psychol Med. 2014;44(3):449-68.
24. Kamioka H, Tsutani K, Yamada M, Park H, Okuizumi H, Honda T, et al. Effectiveness of rehabilitation based on recreational activities: A systematic review. World Journal of Meta-analysis. 2013.
25. Kasawara KT, do Nascimento SL, Costa ML, Surita FG, e Silva JL. Exercise and physical activity in the prevention of pre-eclampsia: systematic review. Acta Obstet Gynecol Scand. 2012;91(10):1147-57.
26. Khatib R, Joseph P, Briel M, Yusuf S, Healey J. Blockade of the renin-angiotensin-aldosterone system (RAAS) for primary prevention of non-valvular atrial fibrillation: a systematic review and meta analysis of randomized controlled trials. Int J Cardiol. 2013;165(1):17-24.
27. Krag M, Perner A, Wetterslev J, Wise MP, Hylander Moller M. Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Intensive Care Med. 2014;40(1):11-22.
28. Kunath F, Keck B, Antes G, Wullich B, Meerpohl JJ. Tamoxifen for the management of breast events induced by non-steroidal antiandrogens in patients with prostate cancer: a systematic review. BMC Med. 2012;10:96.
29. Kunath F, Keck B, Rucker G, Motschall E, Wullich B, Antes G, et al. Early versus deferred androgen suppression therapy for patients with lymph node-positive prostate cancer after local therapy with curative intent: a systematic review. BMC Cancer. 2013;13:131.
30. Li XX, Han M, Wang YY, Liu JP. Chinese herbal medicine for gout: a systematic review of randomized clinical trials. Clin Rheumatol. 2013;32(7):943-59.
31. Mariani J, Doval HC, Nul D, Varini S, Grancelli H, Ferrante D, et al. N-3 polyunsaturated fatty acids to prevent atrial fibrillation: updated systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2013;2(1):e005033.
32. Mickenautsch S, Yengopal V. Failure rate of atraumatic restorative treatment using high-viscosity glass-ionomer cement compared to that of conventional amalgam restorative treatment in primary and permanent teeth: a systematic review update. Journal of Minimum Intervention in Dentistry. 2012;5:63-124.
33. Morici N, Moja L, Rosato V, Oreglia JA, Sacco A, De Marco F, et al. Time from adenosine di-phosphate receptor antagonist discontinuation to coronary bypass surgery in patients with acute coronary syndrome: meta-analysis and meta-regression. Int J Cardiol. 2013;168(3):1955-64.
34. Munn Z, Jordan Z. The effectiveness of interventions to reduce anxiety, claustrophobia, sedation and non-completion rates of patients undergoing high technology medical imaging. The JBI Database of Systematic Reviews and Implementation Reports. 2012;10(19):1122-

85.
35. O'Neill SM, Kearney PM, Kenny LC, Henriksen TB, Lutomski JE, Greene RA, et al. Caesarean delivery and subsequent pregnancy interval: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2013;13:165.
36. Pandor A, Thokala P, Gomersall T, Baalbaki H, Stevens JW, Wang J, et al. Home telemonitoring or structured telephone support programmes after recent discharge in patients with heart failure: systematic review and economic evaluation. Health Technol Assess. 2013;17(32):1-207, v-vi.
37. Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach JF, et al. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. Epidemiology. 2012;23(3):402-14.
38. Pham A, Liu G. Dexamethasone for antiemesis in laparoscopic gynecologic surgery: a systematic review and meta-analysis. Obstet Gynecol. 2012;120(6):1451-8.
39. Polanski LT, Barbosa MA, Martins WP, Baumgarten MN, Campbell B, Brosens J, et al. Interventions to improve reproductive outcomes in women with elevated natural killer cells undergoing assisted reproduction techniques: a systematic review of literature. Hum Reprod. 2014;29(1):65-75.
40. Rodrigo GJ, Castro-Rodriguez JA. Daily vs. intermittent inhaled corticosteroids for recurrent wheezing and mild persistent asthma: a systematic review with meta-analysis. Respir Med. 2013;107(8):1133-40.
41. Rodrigo GJ, Neffen H. Comparison of indacaterol with tiotropium or twice-daily long-acting beta -agonists for stable COPD: a systematic review. Chest. 2012;142(5):1104-10.
42. Saha S, Koley M. Homeopathic treatment of headaches and migraine: a meta-analysis of the randomized controlled trials. Asian Journal of Pharmaceutical and Clinical Research. 2013;6(3).
43. Saha S, Koley M, Medhurst R. A meta-analysis of the randomized controlled trials of individualized homeopathy in rheumatoid arthritis. World Journal of Pharmacy and Pharmaceutical Sciences. 2013;2(4):2097-117.
44. Sawh SC, Newman JJ, Deshpande S, Jones PM. Lacosamide adjunctive therapy for partial-onset seizures: a meta-analysis. PeerJ. 2013;1:e114.
45. Schwingshackl L, Hoffmann G. Long-term effects of low-fat diets either low or high in protein on cardiovascular and metabolic risk factors: a systematic review and meta-analysis. Nutr J. 2013;12:48.
46. Selk A, Kroft J. Misoprostol in operative hysteroscopy: a systematic review and meta-analysis. Obstet Gynecol. 2011;118(4):941-9.
47. Shneerson C, Taskila T, Gale N, Greenfield S, Chen YF. The effect of complementary and alternative medicine on the quality of life of cancer survivors: a systematic review and meta-analyses. Complement Ther Med. 2013;21(4):417-29.
48. Silva MT, Zimmermann IR, Galvao TF, Pereira MG. Olanzapine plus fluoxetine for bipolar disorder: a systematic review and meta-analysis. J Affect Disord. 2013;146(3):310-8.
49. Singh B, Parsaik AK, Mielke MM, Erwin PJ, Knopman DS, Petersen RC, et al. Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2014;39(2):271-82.
50. Singh B, Parsaik AK, Prokop LJ, Mittal MK. Endovascular therapy for acute ischemic stroke: a systematic review and meta-analysis. Mayo Clin Proc. 2013;88(10):1056-65.
51. Smith TO, Postle K, Penny F, McNamara I, Mann CJ. Is reconstruction the best management strategy for anterior cruciate ligament rupture? A systematic review and meta-analysis comparing anterior cruciate ligament reconstruction versus non-operative treatment. Knee. 2014;21(2):462-70.
52. Sonuga-Barke EJ, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of

randomized controlled trials of dietary and psychological treatments. Am J Psychiatry. 2013;170(3):275-89.
53. Stradling C, Chen YF, Russell T, Connock M, Thomas GN, Taheri S. The effects of dietary intervention on HIV dyslipidaemia: a systematic review and meta-analysis. PLoS ONE. 2012;7(6):e38121.
54. Sukhodolsky DG, Bloch MH, Panza KE, Reichow B. Cognitive-behavioral therapy for anxiety in children with high-functioning autism: a meta-analysis. Pediatrics. 2013;132(5):e1341-50.
55. Tarp S, Bartels EM, Bliddal H, Furst DE, Boers M, Danneskiold-Samsoe B, et al. Effect of nonsteroidal antiinflammatory drugs on the C-reactive protein level in rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis Rheum. 2012;64(11):3511-21.
56. Tefikow S, Barth J, Maichrowitz S, Beelmann A, Strauss B, Rosendahl J. Efficacy of hypnosis in adults undergoing surgery or medical procedures: a meta-analysis of randomized controlled trials. Clin Psychol Rev. 2013;33(5):623-36.
57. ten Broek RPG, Stommel MWJ, Strik C, van Laarhoven CJHM, Keus F, van Goor H. Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis. The Lancet. 2014;383(9911):48-59.
58. Thiele M, Gluud LL, Dahl EK, Krag A. Antiviral therapy for prevention of hepatocellular carcinoma and mortality in chronic hepatitis B: systematic review and meta-analysis. BMJ open. 2013;3(8).
59. Tohira H, Williams TA, Jacobs I, Bremner A, Finn J. The impact of new prehospital practitioners on ambulance transportation to the emergency department: a systematic review and meta-analysis. Emerg Med J. 2014;31(e1):e88-e94.
60. Tricco AC, Chit A, Soobiah C, Hallett D, Meier G, Chen MH, et al. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. BMC Med. 2013;11:153.
61. van Middendorp JJ, Hosman AJ, Doi SA. The effects of the timing of spinal surgery after traumatic spinal cord injury: a systematic review and meta-analysis. J Neurotrauma. 2013;30(21):1781-94.
62. Viljoen E. A Systematic Review of the effect and safety of Ginger in the treatment of pregnancy associated nausea and vomiting [Master's Thesis]. Stellenbosch University; 2012.
63. Vonthein R, Heimerl T, Schwandner T, Ziegler A. Electrical stimulation and biofeedback for the treatment of fecal incontinence: a systematic review. Int J Colorectal Dis. 2013;28(11):1567-77.
64. Wang XQ, Zheng JJ, Yu ZW, Bi X, Lou SJ, Liu J, et al. A meta-analysis of core stability exercise versus general exercise for chronic low back pain. PLoS ONE. 2012;7(12):e52082.
65. Wu MY, Hsu YH, Bai CH, Lin YF, Wu CH, Tam KW. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy: a meta-analysis of randomized controlled trials. Am J Kidney Dis. 2012;59(6):810-8.
66. Yang G, Wang Y, Tian J, Liu JP. Huperzine A for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials. PLoS ONE. 2013;8(9):e74916.
67. Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA. 2013;309(7):678-88.

PROSPERO records excluded from the study (n=44)

PROSPERO No.	Title
CRD42011001123	Identifying treatment burden in stroke patients, a systematic review
CRD42011001241	Systematic review of the prevalence and risk of domestic violence victimisation amongst people with mental disorders.

CRD42011001280	Systematic review of sedentary behaviour and health indicators in preschool aged children
CRD42011001281	Systematic review of the prevalence and risk of domestic violence victimisation amongst mental health service users
CRD42011001283	The diagnostic accuracy of MRI for rotator cuff tears: a systematic review and meta-analysis
CRD42011001342	The diagnostic test accuracy of radiological imaging (Magnetic Resonance Imaging / Magnetic Resonance Arthrography / Computer Tomography) for chondral lesions of the tibiofemoral and patellofemoral joint
CRD42011001352	The diagnostic test accuracy of magnetic resonance imaging, magnetic resonance arthrography and multidetection array computer tomography in the detection of chondral lesions of the hip joint
CRD42011001364	General and geriatric pharmacology education for health professionals and students: a systematic review
CRD42011001376	Systematic review of the diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy
CRD42011001380	The role of host genetic factors in human susceptibility to influenza infection and disease: a systematic review
CRD42011001417	Protocol to guide the assessment of genetic testing for hereditary mutations in the VHL gene that cause von Hippel-Lindau syndrome
CRD42011001431	The relationship between prolonged sedentary behaviour lasting 7 days or less on markers of metabolic risk
CRD42011001441	Epidemiology and outcomes of biliary atresia: a systematic review
CRD42011001455	Interferon-gamma release assays for the diagnosis of active tuberculosis in HIV-infected patients: a systematic review and meta-analysis
CRD42011001526	The experience of long term maintenance and barriers to recovery systematic review
CRD42011001591	Effekt av tiltak for å redusere tvangsbruk i psykisk helsevern for voksne [Interventions for reducing seclusion and restraint in mental health for adults]
CRD42011001610	Systematic review of the contribution of peripheral blood culture, in addition to central line culture, in adults and children with cancer with central venous lines and suspected infection
CRD42011001614	Adjunctive colposcopy technologies for examination of the uterine cervix - Dysis, LuViva Advanced Cervical Scan, Niris Imaging System and APX 100
CRD42011001654	Care seeking for neonatal illness in low- and middle-income countries: a systematic review
CRD42011001670	Depression screening and patient outcomes in cardiovascular care: an updated systematic review
CRD42011001752	A systematic review to determine the reliability of knee joint position sense assessment measures
CRD42011001810	Association of incident type-2 diabetes with glycemic load: dose-response meta-analyses of prospective cohort studies and sources of heterogeneity
CRD42011001818	Chlamydia screening interventions from community pharmacies: a systematic review
CRD42011001834	Depth of anaesthesia monitoring (E-Entropy, Bispectral Index and Narcotrend)
CRD42011001856	Evidence grade associating periodontitis to chronic renal disease: a systematic review evaluating exposure and effects of periodontal treatment
CRD42011001872	A systematic review of the drug induced Stevens Johnson syndrome and toxic epidermal necrolysis in Indian population
CRD42012001891	Socioeconomic and behavioural risk factors for adverse winter health and social outcomes in economically developed countries: a systematic review of quantitative observational studies

CRD42012001911	A systematic review and economic evaluation of SeHCAT (Tauroselcholic [75Selenium] acid) for the investigation of bile acid malabsorption (BAM) and measurement of bile acid pool loss
CRD42012001961	Burden and support needs of carers of persons with personality disorder: a systematic review
CRD42012001977	Factors facilitating and constraining the delivery of effective teacher training to promote health and well-being in schools: a survey of current practice and systematic review
CRD42012002049	The assessment of dementia for people admitted with a fractured neck of the femur (FNoF): a systematic review and meta-analysis
CRD42012002056	Demand-side financing measures to increase maternal health service utilisation and improve health outcomes: a systematic review of evidence from low- and middle-income countries
CRD42012002247	Shift work and the development of breast cancer: protocol for a systematic review
CRD42012002342	Does magnetic resonance imaging predict future low back pain? A systematic review
CRD42012002370	Do people with joint hypermobility really have reduced joint proprioception? A systematic review
CRD42012002372	The relationship between joint hypermobility syndrome and anxiety and depression: a systematic review of the literature
CRD42012002485	What is the rate of radiologist error when interpreting computed tomography: systematic review and meta-analysis
CRD42012002767	Does intravascular ultrasound provide clinical benefits for bare-metal stenting? A meta-analysis of randomized controlled trials
CRD42012002833	Systematic review of economic evaluations for enhanced recovery after surgery (ERAS) pathways for patients undergoing elective colorectal surgery
CRD42012002893	The anorexia of ageing: physiopathology, prevalence, associated comorbidity and mortality. A systematic review
CRD42012002908	Pets exposure and risk of atopic dermatitis in the paediatric age
CRD42012002960	Risk factors for incident delirium in acute medical in-patients. a systematic review
CRD42012003203	Assessing the quality of information about bladder pain syndrome available on the Internet: a systematic review
CRD42013004221	Malaria and soil-transmitted intestinal helminth co-infections and it's impact on anemia: a systematic review and meta-analysis

Appendix Table D. AMSTAR results for included systematic reviews (N=96)												
First author, Year	**A Priori Design**	**Duplicate Selection/ DA**	**Literature Search**	**Publication Status**	**List of Studies**	**Study Characteristics**	**Quality Assessed**	**Quality Used**	**Methods Appropriate**	**Publication Bias Assessed**	**Conflicts Stated**	**AMSTAR Rating**
Fretheim, 2012	Y	Y	Y	N	Y	Y	Y	Y	Y	U	N	8
Selk, 2011	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Khatib, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Tarp, 2012	Y	Y	Y	Y	N	Y	Y	N	Y	N	N	7
Kunath, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	8
Cox, 2012	Y	Y	Y	N	N	Y	Y	N	Y	N	N	6
Beck, 2011	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	8
Viljoen, 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Timmons, 2012	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	8
Avery, 2012	Y	Y	Y	U	N	Y	Y	Y	Y	Y	N	8
Chambrone, 2012	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10
Hempel, 2012	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10
Pelucchi, 2012	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	9
Kunath, 2012	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	10
Stradling, 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Vontein, 2013	Y	U	Y	Y	Y	Y	Y	Y	Y	U	N	8
Pandor, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Sonuga-Burke, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Henshaw,	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	7

2013												
Ford, 2013	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	9
Castro-Rodrigo, 2012	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10
Hobbs, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Tefikow, 2013	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	9
Cherry, 2012	Y	Y	U	N	N	Y	Y	N	Y	N	N	5
Araghi, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Rodrigo, 2012	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Suchdev, 2011	Y	Y	Y	Y	Y	NA	Y	NA	NA	NA	U	6
Gupta, 2013	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	8
Whitelock, 2013	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	8
Hollis, 2013	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	N	9
Munn, 2012	Y	U	Y	Y	Y	N	Y	Y	Y	N	N	7
Hopkins, 2012	Y	U	Y	Y	Y	N	Y	Y	Y	N	N	7
Wu, 2012	Y	N	Y	Y	N	Y	Y	Y	Y	N	N	7
O'Sullivan, 2012	Y	U	Y	N	N	Y	Y	Y	Y	N	N	6
O'Sullivan, 2012	Y	U	Y	N	N	Y	Y	Y	Y	N	N	6
Wang, 2012	Y	Y	Y	U	N	Y	Y	Y	Y	N	N	7
Easthall, 2013	Y	Y	U	N	N	Y	Y	N	Y	Y	N	6
NCCMH, 2013	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	N	9
Domingo,	Y	N	Y	Y	Y	Y	Y	N	Y	N	N	7

2012												
Santomassino, 2012	Y	N	Y	Y	Y	Y	Y	N	Y	N	N	7
Barnes, 2012	Y	U	Y	Y	Y	Y	Y	Y	Y	N	N	8
Haase, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	9
Huang, 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Jacobs, 2013	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	7
Morici, 2013	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	8
Mickenautsch, 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Aspinall, 2013	Y	U	Y	Y	U	Y	Y	Y	Y	Y	N	8
Tricco, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10
Emdin, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Silva, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Kasawara, 2012	Y	Y	Y	N	N	Y	N	NA	N	N	N	4
Shneerson, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Cunill, 2013	Y	U	Y	Y	N	Y	Y	Y	Y	Y	N	8
Silva, 2012	Y	Y	Y	U	N	Y	Y	Y	Y	N	N	7
Galvao, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	9
Sawh, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Mesgarpour, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Pham,	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9

2012												
Mariani, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10
Hutton, 2013	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	9
Mills, 2013	Y	N	Y	Y	N	Y	Y	Y	Y	N	N	7
Figueiredo ,2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Zarychanski, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Smith, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Kamioka, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Bueno, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Huang, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Nurmatov, 2012	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	8
Tirlapur, 2012	Y	U	Y	Y	N	Y	Y	Y	Y	N	Y	8
Malafarina, 2013	Y	U	Y	U	N	Y	Y	N	N	N	N	4
Sukhodolsky, 2013	Y	U	Y	Y	N	Y	Y	N	Y	Y	N	7
Abbott, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	8
Schwingshackl, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Smith, 2014	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	8
Tohira, 2013	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	7
Frey, 2013	Y	N	Y	U	N	Y	Y	N	Y	N	N	5
O'Neill, 2013	Y	Y	Y	U	N	Y	Y	Y	Y	Y	N	8
Chua,	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10

2013												
Middendorp, 2013	Y	U	N	N	N	Y	Y	Y	Y	Y	Y	7
Polanski, 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	9
Rodrigo, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Yang, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Tatla, 2013	Y	U	Y	N	N	Y	Y	Y	N	N	N	5
Smith, 2013	Y	Y	N	Y	N	Y	Y	Y	Y	N	N	7
ten Broek, 2014	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10
Catellucci, 2013	Y	N	Y	Y	N	Y	Y	U	Y	N	N	6
Cundy, 2013	Y	U	Y	Y	N	Y	N	NA	N	N	N	4
Sunguya, 2013	Y	U	Y	Y	N	Y	Y	N	Y	N	N	6
Singh, 2013	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	8
Balwinder, 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Thiele, 2013	Y	U	Y	Y	N	Y	Y	Y	Y	Y	N	8
Li, 2013	Y	N	Y	U	N	Y	Y	Y	Y	Y	N	7
Krag, 2014	Y	Y	Y	U	N	Y	Y	Y	Y	Y	Y	9
Elazab, 2013	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	9
Subhranil, 2013	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	N	9
Saha, 2013	Y	U	N	Y	N	Y	Y	Y	Y	Y	N	7
Abbreviations: NA = not applicable, N = no, U = unclear, Y = yes.												

Appendix Table E. Meta-analysis results

	Direction & Significance of Meta-analysis Result				
Type of Discrepancy	**Favourable Significant result (p<0.05) n=72 (43)***	**Favourable Non-significant result (p>0.05) n=45 (30)**	**Neutral n=28 (19)**	**Unfavourable Significant result (p<0.05) n=11 (9)**	**Unfavourable Non-significant result (p>0.05) n=11 (6)**
New Primary Outcome (all)	2 (2)	2 (2)	0	0	0
"True" New Primary Outcome	1 (1)	1 (1)	0	0	0
Upgrade of Primary Outcome (all)	3 (3)	1 (1)	0	0	0
"True" Upgrade of Primary Outcome	2 (2)	1 (1)	0	0	0
Downgrade of Primary Outcome (all)	5 (3)	3 (2)	5 (3)	1 (1)	0
"True" Downgrade of Primary Outcome	2 (1)	0	1 (1)	1 (1)	0
No Discrepancy (all)	62 (40)	39 (27)	23 (17)	10 (8)	11 (6)
"True" No Discrepancy	49 (31)	33 (23)	20 (14)	10 (8)	5 (3)

Notes: *Parentheses indicate the number of systematic reviews affected, which do not add up to 67 because some systematic reviews had multiple meta-analyses, "True" primary outcome means that the outcome was explicitly reported as a primary outcome versus derived.

Appendix Table F. Sensitivity analyses results, meta-analysis results by overall statistical significance: All primary outcomes (both explicit and derived)

Type of Discrepancy	Significant MA result ($p<0.05$)	Non-significant MA result ($p>0.05$)
New Primary Outcome	2 (2)*	2 (2)
Upgrade of Primary Outcome	3 (3)	1 (1)
Downgrade of Primary Outcome	6 (4)	3 (2)
No Discrepancy	72 (46)	50 (29)
New or upgrades (5/3 versus 72/50): Relative risk 1.06, 95 % CI 0.61 to 1.85 New alone (2/2 versus 72/50): Relative risk 0.85, 95 % CI 0.31 to 2.28 Upgrade alone (3/1 versus 72/50): Relative risk 1.27, 95 % CI 0.71 to 2.28 Downgrade (6/3 versus 72/50): Relative risk 1.13, 95 % CI 0.70 to 1.83		

*Parentheses indicate the number of reviews affected.

Appendix Table G. Sensitivity analyses results, meta-analysis results by overall statistical significance: Explicitly reported primary outcomes alone

Type of Discrepancy	Significant MA result (p<0.05)	Non-significant MA result (p>0.05)
"True" New Primary Outcome	1 (1)*	1 (1)
"True" Upgrade of Primary Outcome	2 (2)	1 (1)
"True" Downgrade of Primary Outcome	3 (2)	0
"True" No Discrepancies	59 (37)	38 (25)
New or upgrades (3/2 versus 59/38): Relative risk 0.99, 95 % CI 0.47 to 2.05 New alone (1/1 versus 59/38): Relative risk 0.82, 95 % CI 0.20 to 3.32 Upgrade alone (2/1 versus 59/38): Relative risk 1.10, 95 % CI 0.48 to 2.48 Downgrade (3/0 versus 59/38): Relative risk 1.44, 95 % CI 0.96 to 2.16		

*Parentheses indicate the number of reviews affected.

Appendix Table H. Meta-analysis results for systematic reviews with funding and without funding

	Direction & Significance of Meta-analysis Result				
Type of Discrepancy	**Favourable Significant result (p<0.05) n=72 (43)***	**Favourable Non-significant result (p>0.05) n=45 (30)**	**Neutral n=28 (19)**	**Unfavourable Significant result (p<0.05) n=11 (9)**	**Unfavourable Non-significant result (p>0.05) n=11 (6)**
New 1º Outcomes- with ANY funding	2 (2)	0	0	0	0
New 1º Outcomes- with NO funding	0	2 (2)	0	0	0
Upgrades of 1º Outcomes- with ANY funding	2 (2)	1 (1)	0	0	0
Upgrades of 1º Outcomes- with NO funding	1 (1)	0	0	0	0
Downgrades of 1º Outcome- with ANY funding	4 (2)	0	3 (1)	0	0
Downgrades of 1º Outcome- with NO funding	1 (1)	3 (2)	2 (2)	1 (1)	0
No Discrepancies- with ANY funding	45 (26)	21 (15)	11 (9)	6 (4)	2 (2)
No Discrepancies- with NO funding	17 (14)	18 (11)	12 (8)	4 (4)	9 (4)

Any funding:
New or upgrades: 4/45 versus 1/40 = Relative risk 3.35, 95 % CI 0.39 to 28.78
Downgrades: 4/45 versus 3/40 = Relative risk 1.17, 95 % CI 0.28 to 4.94

No funding:
New or upgrades: 1/17 versus 2/43 = Relative risk 1.25, 95 % CI 0.12 to 12.94
Downgrades: 1/17 versus 6/43 = Relative risk 0.45, 95 % CI 0.06 to 3.51

Notes: *Parentheses indicate the number of systematic reviews affected, which do not add up to 67 because some systematic reviews had multiple meta-analyses.

Appendix Table I. Sensitivity analyses, meta-analysis results by funding: All primary outcomes (both explicit and derived)

Type of Discrepancy	Significant MA result (p<0.05)	Non-significant MA result (p>0.05)
New 1º Outcomes- with ANY funding	2 (2)*	0
New 1º Outcomes- with NO funding	0	2 (2)
Upgrades of 1º Outcomes- with ANY funding	2 (2)	1 (1)
Upgrades of 1º Outcomes- with NO funding	1 (1)	0
Downgrades of 1º Outcome- with ANY funding	4 (2)*	0
Downgrades of 1º Outcome- with NO funding	2 (2)	3 (2)
No Discrepancies- with ANY funding	51 (29)	22 (16)
No Discrepancies- with NO funding	21 (17)	28 (13)

Any funding:
New or upgrades (4/1 versus 51/22): Relative risk 1.15, 95 % CI 0.72 to 1.82
New alone (2/0 versus 51/22): Relative risk 1.20, 95 % CI 0.71 to 2.03
Upgrade alone (2/1 versus 51/22): Relative risk 0.95, 95 % CI 0.42 to 2.15
Downgrade (4/0 versus 51/22): Relative risk 1.29, 95 % CI 0.93 to 1.80

No funding:
New or upgrades (1/2 versus 21/28): Relative risk 0.78, 95 % CI 0.15 to 3.98
New alone (0/2 versus 21/28): Relative risk 0.39, 95 % CI 0.03 to 4.97
Upgrade alone (1/0 versus 21/28): Relative risk 1.74, 95 % CI 0.74 to 4.13
Downgrade (2/3 versus 21/28): Relative risk 0.93, 95 % CI 0.30 to 2.86

*Parentheses indicate the number of reviews affected.

Appendix Table J: Sensitivity analyses, meta-analysis results by funding: Explicitly reported primary outcomes alone

Type of Discrepancy	Significant MA result (p<0.05)	Non-significant MA result (p>0.05)
"True" New 1º Outcomes- with ANY funding	1 (1)*	0
"True" New 1º Outcomes- with NO funding	0	1 (1)
"True" Upgrades of 1º Outcomes- with ANY funding	2 (2)	1 (1)
"True" Upgrades of 1º Outcomes- with NO funding	0	0
"True" Downgrades of 1º Outcome- with ANY funding	2 (1)	0
"True" Downgrades of 1º Outcome- with NO funding	1 (1)	0
"True" No Discrepancies- with ANY funding	40 (22)	19 (13)
"True" No Discrepancies- with NO funding	9 (7)	19 (12)

Any funding:
New or upgrades (3/1 versus 40/19): Relative risk 1.07, 95 % CI 0.66 to 1.74
New alone (1/0 versus 40/19): Relative risk 0.96, 95 % CI 0.46 to 2.00
Upgrade alone (2/1 versus 40/19): Relative risk 1.20, 95 % CI 0.67 to 2.16
Downgrade (2/0 versus 40/19): Relative risk 1.04, 95 % CI 0.71 to 1.52

No funding:
New or upgrades (0/1 versus 9/19): Relative risk 0.76, 95 % CI 0.07 to 8.90
New alone (0/1 versus 9/19): Relative risk 0.76, 95 % CI 0.07 to 8.90
Upgrade alone (0/0 versus 9/19): Relative risk 1.53, 95 % CI 0.20 to 11.60
Downgrade (1/0 versus 9/19): Relative risk 2.29, 95 % CI 0.88 to 5.95

*Parentheses indicate the number of reviews affected.

Appendix Table K. Conclusion results for all included systematic reviews

	Categorization of Conclusions			
Type of Discrepancy	**Positive**	**Neutral**	**Negative**	**Indeterminate**
New Primary Outcome	3 (3)*	1 (1)	1 (1)	2 (2)
Upgrade of Primary Outcome	3 (3)	1 (1)	0	2 (2)
Downgrade of Primary Outcome	11 (7)	5 (3)	1 (1)	17 (9)
No Discrepancy	71 (46)	33 (26)	10 (9)	30 (24)

*Parentheses indicate the number of systematic reviews affected, which do not add up to 96 because some systematic reviews had multiple conclusions.

Appendix Table L. Sensitivity Analyses results, Conclusions Statements:

Type of Discrepancy	Positive	Negative, Neutral, or Indeterminate
New Primary Outcome	3 (3)*	4 (4)
Upgrade of Primary Outcome	3 (3)	3 (3)
Downgrade of Primary Outcome	11 (7)	23 (13)
No Discrepancy	71 (46)	73 (59)
New or upgrades (6/7 versus 71/73): Relative risk 0.94, 95% CI 0.51 to 1.72 Downgrade (11/23 versus 71/73): Relative risk 0.66, 95% CI 0.39 to 1.10		

*Parentheses indicate the number of reviews affected.

17. Appendix 6

Booth A, Mitchell AS, Mott A et al. **An assessment of the extent to which the contents of PROSPERO records meet the systematic review protocol reporting items in PRISMA-P** [version 2; peer review: 2 approved]. *F1000Research* 2020, 9:773 (https://doi.org/10.12688/f1000research.25181.2)
https://f1000research.com/articles/9-773/v2

- Published paper
- Open Peer Review
- Appendix 1 items, scoring options and guidance/rules for assessment of PROSPERO records compared to PRISMA-P reporting requirements
- Study protocol
- Items, scoring options and guidance/rules for assessment of PROSPERO records compared to PRISMA-P reporting requirements
- PRISMA-P scoring sheet for PROSPERO records
- Scores for all sub-group analyses

RESEARCH ARTICLE

REVISED An assessment of the extent to which the contents of PROSPERO records meet the systematic review protocol reporting items in PRISMA-P [version 2; peer review: 2 approved]

Alison Booth, Alex S. Mitchell, Andrew Mott, Sophie James, Sarah Cockayne, Samantha Gascoyne, Catriona McDaid

Department of Health Sciences, York Trials Unit, University of York, York, YO10 5DD, UK

v2 **First published:** 27 Jul 2020, **9**:773
https://doi.org/10.12688/f1000research.25181.1
Latest published: 10 Sep 2020, **9**:773
https://doi.org/10.12688/f1000research.25181.2

Abstract

Background: PROSPERO is an international prospective register for systematic review protocols. Many of the registrations are the only available source of information about planned methods. This study investigated the extent to which records in PROSPERO contained the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).

Methods: A random sample of 439 single entry PROSPERO records of reviews of health interventions registered in 2018 was identified. Using a piloted list of 19 PRISMA-P items, divided into 63 elements, two researchers independently assessed the registration records. Where the information was present or not applicable to the review, a score of 1 was assigned. Overall scores were calculated and comparisons made by stage of review at registration, whether or not a meta-analysis was planned and whether or not funding/sponsorship was reported.

Results: Some key methodological details, such as eligibility criteria, were relatively frequently reported, but much of the information recommended in PRISMA-P was not stated in PROSPERO registrations. Considering the 19 items, the mean score was 4.8 (SD 1.8; median 4; range 2-11) and across all the assessed records only 25% (2081/8227) of the items were scored as reported. Considering the 63 elements, the mean score was 33.4 (SD 5.8; median 33; range 18-47) and overall, 53% (14,469/27,279) of the elements were assessed as reported. Reporting was more frequent for items required in PROSPERO than optional items. The planned comparisons showed no meaningful differences between groups.

Conclusions: PROSPERO provides reviewers with the opportunity to be transparent in their planned methods and demonstrate efforts to reduce bias. However, where the PROSPERO record is the only

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 2 (revision) 10 Sep 2020		
version 1 27 Jul 2020	✓ report	✓ report

1. **Dawid Pieper**, University Witten/Herdecke, Cologne, Germany

2. **Xin Sun**, Sichuan University, Chengdu, China

Any reports and responses or comments on the article can be found at the end of the article.

available source of *a priori* reporting, there is a significant shortfall in the items reported, compared to those recommended. This presents challenges in interpretation for those wishing to assess the validity of the final review.

Keywords
Systematic review, protocol, reporting, registration

Corresponding author: Alison Booth (alison.booth@york.ac.uk)

Author roles: Booth A: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Mitchell AS**: Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – Review & Editing; **Mott A**: Data Curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – Review & Editing; **James S**: Formal Analysis, Investigation, Methodology, Visualization, Writing – Review & Editing; **Cockayne S**: Investigation, Methodology, Writing – Review & Editing; **Gascoyne S**: Investigation, Methodology, Writing – Review & Editing; **McDaid C**: Methodology, Writing – Review & Editing

Competing interests: AB led on the development of PROSPERO and is a group author of the PRISMA-P reporting guidelines papers. AB has not been involved in the management of PROSPERO since 2015. SC, SJ, SG, ASM, AM and CM declare they have no conflicts of interest.

Grant information: The author(s) declared that no grants were involved in supporting this work.

How to cite this article: Booth A, Mitchell AS, Mott A *et al.* **An assessment of the extent to which the contents of PROSPERO records meet the systematic review protocol reporting items in PRISMA-P [version 2; peer review: 2 approved]** F1000Research 2020, **9**:773 https://doi.org/10.12688/f1000research.25181.2

First published: 27 Jul 2020, **9**:773 https://doi.org/10.12688/f1000research.25181.1

REVISED **Amendments from Version 1**

In the discussion we have addressed the differences between a systematic review protocol and registration of key details, and explained the use of PRISMA-P guidelines, even though they do not align with PROSPERO fields. We have also added the use of a scoring system as a potential limitation of the study. Other minor issues raised in peer review have also been addressed.

Any further responses from the reviewers can be found at the end of the article

Introduction

Detailing the planned methods for conducting a systematic review in advance of commencing the review is essential in order to minimise a range of potential biases[1,2]. The plan, set out in a protocol, should ideally be made available in the public domain to facilitate transparency[3,4]. In addition, registration of key protocol details is encouraged as best practice in reporting guidelines[5,6] by publishers like the British Medical Journal (BMJ), Public Library of Science (PLoS), and BioMed Central (BMC), and is mandated in their instructions to authors by journals such as BMC Systematic Reviews, BMJ, BMJ Open, PLoS One, and National Institute for Health Research (NIHR) journals.

There are a number of options for putting systematic review protocols into the public domain, such as publication in open access journals like BMC Systematic Reviews and uploading to open data repositories like the Open Science Framework (OSF) (https://osf.io/registries/discover?q=protocols). PROSPERO (https://www.crd.york.ac.uk/prospero/) is a facility for registering key methodological details in advance of carrying out a review. Registration on PROSPERO requires completion of an internationally agreed minimum dataset for a systematic review protocol[7,8]. Registrants also have the option of uploading their protocol or providing a hyperlink to it.

PROSPERO remains the only free, open access registry of systematic review protocols, making it a single searchable source of the protocols of on-going and completed reviews. Uptake of registration has increased exponentially and by the end of 2019 there were over 60,000 registrations in PROSPERO. There is evidence that considerably more systematic reviews are registered in PROSPERO than have peer-reviewed protocols published. In 2016, 1058 records were accepted by PROSPERO; in the same time period, only 404 published systematic review protocols were identified[3]. Another study reported identifying 20,814 non-Cochrane systematic review protocols from web scraping PROSPERO and bibliographic database searches. Of these, 924 were only published in journals, 807 were published in journals and registered in PROSPERO and 19,890 were only available as a record in PROSPERO[9]. There is further evidence from Ge *et al.* (2018) that of the non-Cochrane reviews registered in PROSPERO, only 3% or 4% have a published protocol[9,10]. This means that for a large number of reviews a PROSPERO record is likely to be the only source providing details of the planned methods.

Published protocols and registration records aim to provide transparency in the review process by allowing public access to the key pre-specified elements for the conduct of a review. One of the stated aims of PROSPERO is to facilitate comparison between planned review methods and reported results[8]. Such a comparison enables peer reviewers and other readers of the final review to assess for themselves the potential for bias in the findings. There is also a steadily growing body of research using PROSPERO records to assess the risk of biases in final review reports[10–15]. Given this reliance on the information provided in PROSPERO records, it is important to understand the level of detail provided in records. The focus of this study was on the stated aim of PROSPERO to reduce the opportunity for bias by enabling comparison of the completed review with what was planned in the protocol[8].

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Protocols (PRISMA-P) were developed through expert consensus using internationally compiled datasets such as PROSPERO and SPIRIT[4,6].

Key methodological aspects of a protocol are mandated for registration in PROSPERO; other items, mainly administrative fields, are optional[7,8]. Submissions for registration are not subject to any form of peer review or critical appraisal, they are simply checked for sense but not methodological rigor. Therefore, there is the possibility that PROSPERO records do not provide all the necessary information identified by the PRISMA-P guidelines to enable comparison with the completed systematic review. The registration record may be the only place where *a priori* methods are available for users, in particular peer reviewers, to check for potential issues such as selection, outcome reporting and publication biases. This study investigated the extent to which records in PROSPERO, where no protocol or other information was available, comply with each of the items for reporting of protocols set out in the PRISMA-P guidelines.

Methods

A random sample of PROSPERO registration records were assessed against the systematic review protocol reporting criteria set out in the PRISMA-P 2015 checklist[4]. Key methods are provided here with further details available in the protocol for this study, which was prepared and made publicly available on the OSF, 17 March 2020 (*Extended data*[16]).

Study sample of PROSPERO records

A dataset of non-Cochrane PROSPERO records was provided by Metaxis, the software managers of PROSPERO. Records of reviews defined by the record holder as a health intervention registered on or between 1 January 2018 and 31 December 2018, were identified.

Cochrane reviews, reviews of animal studies, non-intervention reviews as identified in PROSPERO, i.e. Diagnostic accuracy, Prognostic factors, Prevention, Epidemiological reviews relevant to health and social care, Public health, Service delivery in health and social care, Methodological reviews, reviews of reviews, and synthesis of qualitative studies, were all

excluded as PROSPERO and PRISMA-P were developed for reviews of interventions. Only records with no evidence from the registration record of other protocol related information, for example in a published protocol or other links in the PROSPERO record, were included and we restricted the data set to those records with a single registry entry.

Records from the calendar year 2018 were used to allow time for dissemination and adoption of the PRISMA-P guidelines published in 2015. A sample of 20% of these records was randomly selected using simple random sampling for assessment against the PRISMA-P reporting criteria.

Assessment tool and scoring

The PRISMA-P checklist recommends 17 numbered items, with nine subdivisions, totalling 26 items be reported in a systematic review protocol[4]. Seven of the 26 items were excluded from the assessment as they would always or never meet registration requirements in PROSPERO. For example, registration is implicit for a record accepted in PROSPERO, and there is no field for author contributions or sponsor role so these would never be reported. The study assessment tool, developed specifically for this study as a Google Form, therefore contained 19 of the PRISMA-P items. Where the PRISMA-P description for an item specified more than one piece of information, the individual elements were listed as subsets of the items[4,6]. For example, item 14. Risk of bias in individual studies, says: "Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis." Scoring for this item was for each of the following separate elements: No risk of bias assessment planned and justification provided; Risk of bias tools named for all study types included; Outcome or study level or both; Domains/outcomes for risk of bias assessment stated; Risk of bias assessment process described; How risk of bias findings will be used in synthesis. Applying this approach to the 19 items resulted in a list containing 63 elements to be reported.

Where an item was reported or not applicable, a score of 1 was assigned. Where the information was not reported this scored 0. The maximum possible overall score for the PRISMA-P listed items was 19 per record. Scores for the breakdown of individual elements within the items was also reported, the maximum possible score was 63 per record.

Assessment procedure

The researchers undertaking the assessments (AB, ASM, AM, SJ, SC, SG) familiarised themselves with both PRISMA-P papers[4,6]. All had previously received training in systematic review methods and/or authored at least one systematic review. The draft assessment form and accompanying guidance notes were revised and finalised during a training session and piloted with the aim of achieving greater than 90% agreement.

Two researchers independently compared the information provided in each PROSPERO record with the relevant items in the study assessment tool. Options for decisions were: Reported (information provided as per PRISMA-P requirements); Not reported (some or all information not provided); and, Not applicable (where an item was not relevant to an individual record, e.g. a meta-analysis was not planned).

Records were randomly assigned to assessors by first creating a list of the sampled record unique identification numbers and dividing the list into 14 blocks of approximately equal size, with each block being assigned a colour. A copy of this list together with the block configuration was then placed alongside the original list. Seven sub-lists were then created by randomly selecting a block from the first list and a block from the second list, such that blocks of the same colour were not in the same sub-list, and each colour appeared in two sub-lists. Each sub-list was then randomly assigned to an assessor.

It was not feasible to blind the researchers to the authors of registrations in PROSPERO. None of the assessors were authors of included registrations. On completion of the pilot assessments and the full set of records, disagreements were resolved through discussion or recourse to a third researcher.

The assessment form and the guidance notes are available on the OSF (*Extended data*[16]).

Analysis

The primary outcome for this study was the compliance of PROSPERO registration records to PRISMA-P reporting items. This was measured by the total mean score allocated by the two independent assessors to each of the 19 items assessed (maximum possible score 19) for each record and by the total mean score for the individual elements within items (maximum possible score 63). Overall scores for the assessed dataset, scores by the 19 PRISMA-P items and by the 63 elements were the planned outcome measures.

For the eligible 2018 records that were assessed and those not assessed, demographic data for month of registration, funding/sponsor, planned meta-analysis, number of authors, stage of review at registration, topic and country of review were to be reported. Comparisons to identify any association between records registered before or after screening started; whether a meta-analysis was planned or not; and whether a review was funded/sponsored or not and completeness of reporting of items were planned.

Deviations from protocol

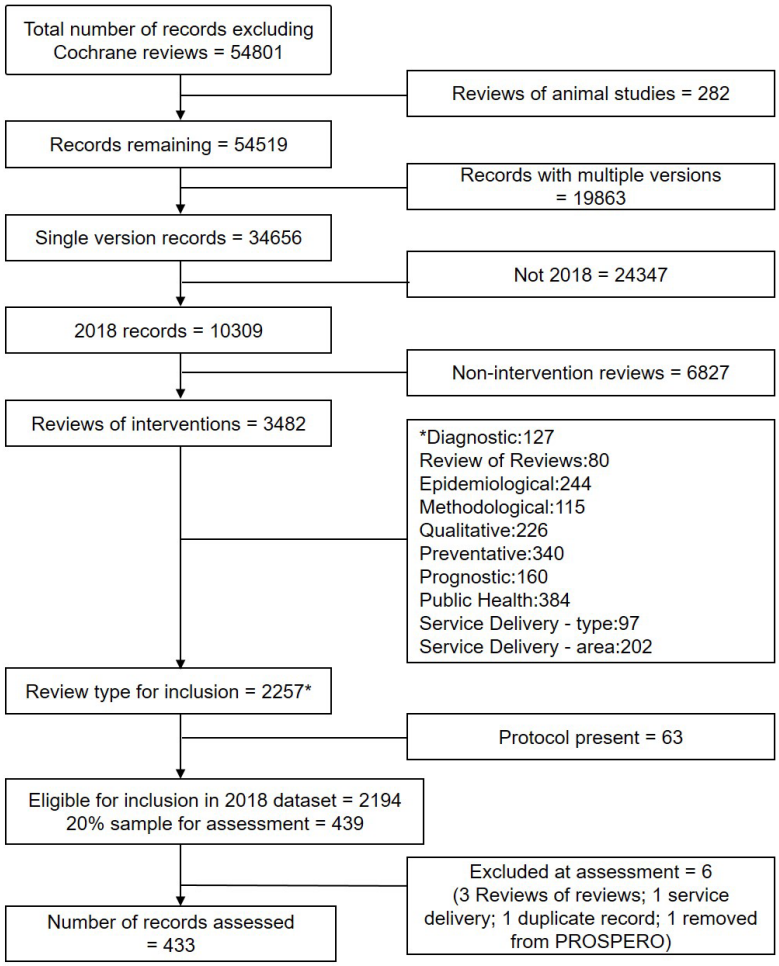
During piloting of the assessment form, it became clear that it would not be possible to assess records for PRISMA-P item 5a Sources and 5b Sponsor. This would have required separating sources of financial support from sponsorship or any other form of support as reported in the single PROSPERO field, which was not possible. This item was therefore removed from the assessment form. Instead, a series of regular expression patterns was compared to the list of eligible records to identify those where the record contained any indication of funding/sponsorship/support or indicated there was none. These data were used in the presentation of demographics and subgroup comparison.

Results

The PROSPERO dataset contained 5,313 records for reviews of health interventions first accepted in 2018 (excluding Cochrane and reviews of animal studies). Applying the other study inclusion/exclusion criteria resulted in 2,194 eligible registration records. The randomly selected sample of 20% for assessment included 439 records. During assessment, six records were excluded, for not meeting the inclusion criteria (4), being a duplicate (1) or no longer available on PROSPERO (1). Assessments were therefore carried out on 433 PROSPERO records. A flow chart of record selection is shown in Figure 1.

Agreement following initial piloting of the assessment form was 87%; after further discussions and revision of the assessment guidance notes and form a second pilot achieved 92% agreement. For all the records assessed, agreement between researchers was 90%, all differences were resolved through discussion or referral to a third researcher.

Demographic details of the sample of PROSPERO records selected for assessment and those not assessed are provided in Table 1. The number of authors listed ranged between one and 17, with the exception of a single record, included in the assessed sample, where 47 authors were listed. The eligible sample for 2018 included records from 67 different countries: 20 records listed two countries and 15 listed between three and nine countries involved in the review. There were no substantial differences between the data sets in the month of registration; whether any details of funding and/or sponsorship were provided; whether a meta-analysis was planned or not; the number of authors listed per record; stage of review at registration; topic of review or country involved in undertaking the review.



**A registration record may have multiple record types, hence discrepancy in numbers*

Figure 1. Flow chart of record sample identification.

None of the PROSPERO records assessed against the eligibility criteria reported on all elements in each of the items recommended for a systematic review protocol in the PRISMA-P guidelines. The mean total score for individual PROSPERO records, where 1 point was gained for each of the 19 items in the PRISMA-P checklist, was 4.8, the standard deviation 1.8, the median 4, and range 2 to 11. Considering all items across all the assessed records, only 25% (2081/8227) of the items were scored as reported.

The mean total score for individual PROSPERO records where 1 point was gained for each of the 63 elements of the PRISMA-P reporting guidelines was 33.4, the standard deviation 5.8, the median 33 and the range 18–47. Overall, 53% (14,469/27,279) of the elements were considered as reported.

Scoring for 19 PRISMA-P items

The highest scoring item was PRISMA-P 1b which requires the protocol to be identified as to whether it is an update of a review; the high score was the result of this being a not-applicable item for 423 (98%) of the 433 records (Table 2). Eligibility criteria (study design, setting, population, intervention, comparator, outcomes) was the next highest scoring item with 386 (89%) reporting all of these elements. Selection process (214, 49%), describing the criteria under which study data will be quantitatively synthesized (200, 46%), and describing the type of summary planned if quantitative synthesis is not appropriate (227, 52%) were the next highest scoring of the 19 items assessed.

The scores by PRISMA-P item and by breakdown of items are presented in Table 2. The full dataset with assessment outcomes and scores for individual records, and the subgroup analyses scoring are available on the OSF (*Underlying data*[16]).

Scoring for 63 elements of the PRISMA-P items

The score for some of the 19 items was reduced as a result of just one or two of the constituent elements being omitted from reports while others were relatively regularly identified.

Table 1. Demographic details of non-sample set and sample set of the eligible 2018 PROSPERO records.

Demographic		Records for assessment (n = 439)	Records not assessed (n = 1755)
Month of registration n (%)	*January*	45 (10)	168 (10)
	February	32 (7)	141 (8)
	March	25 (6)	100 (6)
	April	35 (8)	122 (7)
	May	16 (4)	110 (6)
	June	36 (8)	151 (8)
	July	54 (12)	188 (11)
	August	56(12)	200 (11)
	September	31 (7)	151 (9)
	October	37 (8)	138 (8)
	November	37 (8)	160 (9)
	December	35 (8)	126 (7)
Funding/support indicated n (%)		386 (88)	1572 (90)
Meta-analysis planned n (%)		253 (58)	1064 (61)
Number of listed authors (mean, range)		4.1 (0 – 47*)	3.9 (0 – 17)
Stage of review n (%)**	*Not Started*	96 (22)	385 (22)
	Searches Start	65(15)	283 (16)
	Searches Complete	12 (3)	57 (3)
	Pilot Selection Start	56 (13)	252 (14)
	Pilot Selection Complete	16 (4)	50 (3)
	Screening Start	80 (19)	285 (16)
	Screening Complete	13 (3)	56 (3)
	Extraction Start	93 (21)	376 (21)
	Extraction complete	2 (0)	8 (1)

Demographic		Records for assessment (n = 439)	Records not assessed (n = 1755)
Topic of review* n (%)**	*Alcohol/substance misuse/ abuse*	12 (3)	28 (2)
	Blood and immune system	13 (3)	90 (5)
	Cancer	42 (10)	182 (10)
	Cardiovascular	61 (14)	220 (13)
	Care of the elderly	16 (4)	72 (4)
	Child health	31 (7)	139 (8)
	Complementary therapies	43 (10)	178 (10)
	Crime and justice	0 (0)	2 (0)
	Dental	30 (7)	138 (8)
	Digestive system	34 8)	127 (7)
	Ear, nose and throat	7 (2)	27 (2)
	Education	10 (2)	23 (1)
	Endocrine and metabolic disorders	35 (8)	144 (8)
	Eye disorders	3 (1)	16 (1)
	General interest	5 (1)	29 (2)
	Genetics	3 (1)	5 (0)
	Health inequalities/health equity	3 (1)	8 (1)
	Infections and infestations	22 (5)	97 (6)
	International development	0 (0)	2 (0)
	Mental health and behavioural conditions	51 (12)	129 (7)
	Musculoskeletal	70 (16)	253 (14)
	Neurological	44 (10)	208 (12)
	Nursing	11 (3)	45 (3)
	Obstetrics and gynaecology	23 (5)	101 (6)
	Oral health	21 (5)	100 (6)
	Palliative	4 (1)	16 (1)
	Perioperative care	14 (3)	81 (5)
	Physiotherapy	36 (8)	129 (7)
	Pregnancy and childbirth	13 (3)	60 (3)
	Public Health	0 (0)	0 (0)
	Rehabilitation	43 (10)	173 (10)
	Respiratory disorders	16 (4)	87 (5)
	Service delivery	0 (0)	0 (0)
	Skin disorders	12 (3)	40 (2)
	Social care	0 (0)	2 (0)
	Surgery	49 (11)	209 (12)
	Tropical medicine	0 (0)	0 (0)
	Urological	20 (5)	71 (4)
	Wounds, injuries and accidents	11 (3)	70 (4)
	Violence and abuse	3 (1)	10 (1)

Demographic		Records for assessment (n = 439)	Records not assessed (n = 1755)
Country of review* n (%)**	*Australia*	33 (8)	143 (8)
	Brazil	53 (12)	224 (13)
	Canada	38 (9)	121 (7)
	China	100 (23)	414 (24)
	England	46 (10)	163 (9)
	Germany	13 (3)	40 (2)
	Italy	14 (3)	62 (4)
	Netherlands	13 (3)	51 (3)
	Spain	13 (3)	39 (2)
	USA	48 (11)	160 (9)
	57 other countries	127 (29)	562 (32)

* *the record with 47 authors was a single outlier: range excluding this record was 0–15*

** *details for three records were not available on PROSPERO*

*** *all items reported by authors included; therefore totals are more than the number of records*

Table 2. Assessment scores by item and breakdown for 433 PROSPERO records.

PRISMA-P reporting item	Reported or not applicable n (%)	Not reported n (%)	Breakdown of items	Reported n (%)	Not reported n (%)	Not applicable n (%)
Section 1 Administrative information						
1a. Identification in the title: Identify the report as a protocol of a systematic review	22 (5)	411 (95)	Identify the report as a protocol	22 (5)	411 (95)	/
			Identify the report as a systematic review	342 (79)	91 (21)	/
1b. Update: If the protocol is for an update of a previous systematic review	424 (98)	9 (2)	Identify the report as an update	1 (0)	9 (2)	423 (98)
Section 2 Introduction						
6. Rationale: Describe the rationale for the review in the context of what is already known	38 (9)	395 (91)	Rationale described	44 (10)	389 (90)	/
			Context provided**	108 (25)	325 (75)	/
7. Objectives: Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)*	134 (31)	299 (69)	Population	397 (92)	36 (8)	/
			Intervention	416 (96)	17 (4)	/
			Comparator	142 (33)	264 (61)	27 (6)
			Outcomes	237 (55)	196 (45)	/
Section 3 Methods						
8. Eligibility criteria: Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review*	386 (89)	47 (11)	Study design specified*	427 (99)	6 (1)	/
			Setting (condition or domain) specified*	410 (95)	23 (5)	/
			Population*	429 (99)	4 (1)	/
			Intervention*	428 (99)	5 (1)	/
			Comparator*	392 (91)	14 (3)	27 (6)
			Outcome(s)*	424 (98)	9 (2)	/

PRISMA-P reporting item	Reported or not applicable n (%)	Not reported n (%)	Breakdown of items	Reported n (%)	Not reported n (%)	Not applicable n (%)
9. Information sources: Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage*	2 (1)	431 (99)	Electronic database(s) named	431 (99)	2 (1)	/
			Grey literature sources	100 (23)	333 (77)	/
			Study registries	289 (67)	144 (33)	/
			Contact with study authors planned or statement that contact not planned	27 (6)	406 (94)	/
			Other: e.g. hand searching reference lists of included studies	152 (35)	281 (65)	/
			Planned search dates	238 (55)	195 (45)	/
10. Search strategy: Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	75 (17)	358 (83)	Draft search strategy provided	91 (21)	342 (79)	/
			Search terms given alone	100 (23)	242 (56)	91 (21)
			Approach to limits/ restrictions reported e.g. language or dates/ statement of no limits*	332 (77)	101 (23)	/
11a. Data management: Describe the mechanism(s) that will be used to manage records and data throughout the review	17 (4)	416 (96)	Software named/type indicated**	56 (13)	377 (87)	/
			De-duplication planned	42 (9)	391 (91)	/
11b. Selection process: State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	214 (49)	219 (51)	Initial screening process described**	232 (54)	201 (46)	/
			Full paper screening process described**	219 (51)	214 (49)	/
11c. Data collection process: Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators*	50 (12)	383 (88)	Data extraction form	169 (39)	264 (61)	/
			Data extraction process described	258 (60)	175 (40)	/
			Obtain missing data	76 (18)	357 (82)	/
12. Data items: List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	6 (1)	427 (99)	List of data for extraction**	219 (51)	214 (49)	/
			Variables defined**	29 (7)	404 (93)	/
			Any data assumptions reported	17 (4)	416 (96)	/
13. Outcomes and prioritisation: List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale	3 (1)	430 (99)	Primary/main outcome(s)* specified as such	418 (97)	15 (3)	/
			Primary/main outcome(s) measure specified**	235 (54)	198 (46)	/
			Additional outcomes specified/ state None*	430 (99)	3 (1)	/
			Additional outcomes: measures specified**	131 (30)	180 (42)	122 (28)
			Rationale for choice of outcome(s)	8 (2)	425 (98)	/

PRISMA-P reporting item	Reported or not applicable n (%)	Not reported n (%)	Breakdown of items	Reported n (%)	Not reported n (%)	Not applicable n (%)
14. Risk of bias in individual studies: Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis*	41 (9)	392 (91)	No risk of bias assessment planned, and justification provided	4 (1)	3 (1)	426 (98)
			Risk of bias tools named for all study types included	362 (84)	67 (16)	4 (1)
			Outcome or study level or both	310 (71)	119 (28)	4 (1)
			Domains/outcomes for risk of bias assessment stated	342 (79)	87 (20)	4 (1)
			Risk of bias assessment process described	296 (68)	133 (31)	4 (1)
			How risk of bias findings will be used in the synthesis	64 (15)	365 (84)	4 (1)
15a. Synthesis: Describe criteria under which study data will be quantitatively synthesized	200 (46)	233 (54)	Criteria for doing a quantitative synthesis/ meta-analysis described*	131 (30)	233 (54)	69 (16)
15b. If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	70 (16)	363 (84)	Summary measures*	202 (46)	163 (38)	68 (16)
			Statistical method*	89 (20)	276 (64)	68 (16)
			Use of fixed or random effects or both*	194 (44)	171 (40)	68 (16)
			Data handling: conversion to same format	106 (24)	259 (60)	68 (16)
			Data handling: missing data	14 (3)	351 (81)	68 (16)
			Combining data/ exploration of consistency	179 (41)	186 (43)	68 (16)
			Name of software to be used for meta-analysis	204 (47)	161 (37)	68 (16)
15c. Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	84 (19)	349 (81)	Subgroup analyses planned: co-variants named*	344 (79)	21 (5)	68 (16)
			Methods for subgroup analyses reported	25 (6)	280 (65)	128 (29)
			Sensitivity analyses planned	85 (19)	280 (65)	68 (16)
15d. If quantitative synthesis is not appropriate, describe the type of summary planned*	227 (52)	206 (48)	Descriptive, narrative, or qualitative synthesis planned	194 (45)	55 (12)	184 (43)
			Descriptive, narrative or qualitative synthesis methods described	49 (11)	200 (46)	184 (43)
			Other analyses planned	3 (1)	11 (3)	419 (96)
16. Meta-bias(es): Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	72 (17)	361 (83)	Publication bias to be assessed	94 (21)	271 (63)	68 (16)
			Outcome reporting bias to be assessed	4 (1)	361 (83)	68 (16)
17. Confidence in cumulative evidence: Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	37 (9)	396 (91)	Overall assessment of included studies planned	40 (9)	393 (91)	/
			Methods specified	38 (9)	395 (91)	/

** Item/element required in PROSPERO **Item/element identified in PROSPERO but as optional*

Although overall the review question (item 7) was not found to contain all the expected elements, most did specify the elements of population (397, 92%) and the intervention (416, 96%) and just over half included the outcomes (237, 55%). The comparator was less frequently included (142, 33%); this may have been because of the intention of the review but where this was clear, the item was scored as not applicable (6%).

Information sources (item 9) was scored as completed in only two records (1%) overall; however, for the individual elements 431 (99%) did name the electronic databases to be searched, 289 (67%) said whether they planned to search study registries, and 238 (55%) indicated search dates. In item 10, provision of a draft search strategy (91, 21%) or search terms (100, 23%) was poor; but restrictions such as to English language papers were reported in 332 (77%).

Reporting of item 13, outcomes, scored badly overall (3, 1%) as, although the outcomes were included in most records (Primary 418, 97%; Secondary 430, 99%) only 8 (2%) were assessed as having provided a rationale for their choice of outcomes. Similarly, in item 14, the absence of information on how the risk of bias would be used in the synthesis, detracted from the high rate of inclusion of risk of bias tools and use. Reporting of the details for a quantitative synthesis, item 15b, had one element with a very low score (handling missing data, 14, 3%), the other six elements scored between 89 (20%) and 204 (47%).

In three items, the overall score reflected the general picture from the included elements. In item 6, rationale, both the reason for undertaking the review and the context were infrequently identified. PRIMSA-P items 16, meta-bias(es) and 17, confidence in cumulative evidence, were rarely reported. Only context is classified as optional information in PROSPERO, the remainder of these elements are not explicitly requested.

There appears to be a trend towards higher frequency of reporting of elements that are mandatory in PROSPERO, for example, in the eligibility criteria (item 8) and risk of bias (item 14). The trend is also seen in item 13, the required specification of primary and secondary outcomes, both frequently reported, but with a drop in specifying measures, which was optional.

Subgroup comparisons

The subgroup comparisons, which were all pre-defined, investigated the stage of review at registration; whether or not information was reported on source of funding, sponsorship or support and where none was indicated; and whether or not the relevant box in the registration form had been ticked to indicate a meta-analysis was planned.

There were no differences in total scores for the 19 PRISMA-P items or the 63 elements, between those records registered before screening against eligibility criteria had started and those records registered after screening had commenced. This held true for the mean, standard deviation, median and range of scores.

A 6% difference was seen in the total score achieved for the meta-analysis (23%) vs no meta-analysis (29%) groups in the assessment of the 19 PRISMA-P items. The difference was reduced to 2% when considering the breakdown of 63 elements within the reported items (52% vs 54%). At both item and element level, the group of records with no planned meta-analysis scored slightly higher, but with a higher standard deviation from the mean and wider range of scores achieved.

Across all results for both the 19 items and 63 elements, the group with funding, sponsorship or support, scored slightly higher than those not receiving funding, sponsorship or support.

The results of the subgroups investigated are presented in Table 3. The subgroup scores by individual PRISMA-P reporting item are available on the OSF (*Underlying data*[16]).

We present the scores by the 19 PRISMA-P items and by the breakdown of 63 elements for the ten countries and topics with the highest number of assessed records, and for number of authors listed in Table 4. None of these factors appear to have a marked influence on the number of PRISMA-P items or elements reported in PROSPERO records.

Discussion

Publication and registration of a systematic review protocol provides transparency in the review process, allowing readers to see the efforts made to minimise biases and where biases may still have influenced the final review findings. There is empirical evidence that few of the protocol registrations in PROSPERO have a corresponding published report[9]. Where there is no protocol, the registration provides the only public record of what was originally planned. This study set out to establish to what extent PROSPERO registrations of systematic review protocols of healthcare interventions reported on items in the PRISMA-P reporting guidelines.

Using a random sample of 433 PROSPERO records from 2018, two researchers independently assessed the frequency of reporting of 19 PRISMA-P items, with 63 individual elements. The results show that while some key methodological details are relatively frequently reported, much of the information recommended in PRISMA-P is missing. Reporting was unsurprisingly more frequent for items that are mandatory in PROSPERO than those that are optional. Comparisons by stage of review at registration, whether meta-analysis was planned and whether funding or sponsorship was reported showed no meaningful differences between groups. The slight difference between groups with a planned meta-analysis or none may be because in PRISMA-P more details are specified for the reporting of a meta-analysis than for a descriptive, narrative or qualitative analysis.

The review protocol is a detailed record of the planned methods developed through an iterative process[5]. Once finalised or close to finalising, the key methodological details should be registered in PROSPERO[8]. These are two separate but

Table 3. **Subgroup comparisons.**

Subgroup	Variable	No. of records	Total possible score	Total score achieved N (%)	Mean score (SD)	Median score	Range of scores
For 19 PRISMA-P reporting items							
Stage of review at registration	Before screening started	245	4655	1181 (25)	4.8 (1.9)	5	2–11
	After screening started	188	3572	900 (25)	4.8 (1.8)	4	2–10
Meta-analysis planned	M-A	250	4750	1088 (23)	4.4 (1.5)	4	2–9
	No M-A	183	3477	993 (29)	5.4 (2.1)	5	2–11
Funded / Sponsored / Supported	Funded etc.	381	7239	1841 (25)	4.8 (1.9)	4	2–11
	Not funded etc.	52	988	240 (24)	4.6 (1.6)	4	2–8
For 63 PRISMA-P reporting elements							
Stage of review at registration	Before screening started	245	15435	8214 (53)	33.5 (5.9)	33	18–47
	After screening started	188	11844	6255 (53)	33.3 (5.8)	33	21–47
Meta-analysis	M-A	250	15750	8244 (52)	33.0 (5.2)	32	21–45
	No M-A	183	11529	6225 (54)	34.0 (6.6)	34	18–47
Funded / Sponsored / Supported	Funded etc.	381	24003	12804 (53)	33.6 (5.9)	33	18–47
	Not funded etc.	52	3276	1665 (51)	32.0 (5.3)	31	22–46

Table 4. **Overall scores by country, number of authors and topic of review.**

	No of records	For the 19 PRISMA-P items assessed				For the 63 elements assessed			
		Overall score (% of possible score)	Mean score (SD)	Median score	Range of scores	Overall score (% of possible score)	Mean score (SD)	Median score	Range of scores
Country (10 with most assessed records)									
Australia	33	179 (28)	5.4 (2.1)	5	2–11	1115 (54)	33.8 (6.2)	32	21–47
Brazil	53	272 (27)	5.1 (1.9)	5	2–9	1826 (55)	34.5 (6.0)	35	18–46
Canada	37*	197 (28)	5.3 (2.1)	5	2–9	1301 (56)	35.2 (6.7)	35	21–45
China	101	418 (22)	4.1 (1.3)	4	2–10	3385 (54)	33.5 (4.5)	34	23–45
England	46	259 (29)	5.6 (2.2)	5	2–10	1620 (55)	35.2 (6.9)	35.5	22–47
Germany	11*	59 (28)	5.4 (2.3)	4	3–10	380 (55)	34.5 (6.2)	33	26–47
Italy	15	71 (27)	4.7 (1.8)	4	3–9	499 (57)	33.3 (6.2)	32	24–47
Netherlands	13	68 (28)	5.2 (2.1)	5	2–9	439 (53)	33.8 (7.0)	33	23–47
Spain	13	64 (26)	4.9 (1.8)	4	2–7	426 (52)	32.8 (5.6)	33	22–42
USA	48	242 (27)	5.0 (2.2)	4	2–10	1526 (51)	31.8 (6.4)	31	21–47
Number of authors									
0–3	202	956 (25)	4.7 (1.8)	4	2–10	6648 (52)	32.9 (5.9)	32	18–47
4–6	179	867 (25)	4.8 (1.9)	5	2–11	6008 (53)	33.6 (5.7)	34	21–47
7+	52	258 (27)	5.0 (1.9)	4	2–9	1813 (56)	34.9 (5.9)	34	21–47

	No of records	For the 19 PRISMA-P items assessed				For the 63 elements assessed			
		Overall score (% of possible score)	Mean score (SD)	Median score	Range of scores	Overall score (% of possible score)	Mean score (SD)	Median score	Range of scores
Topic of review (10 with most assessed records)									
Cancer	42	184 (23)	4.4 (1.8)	4	2–10	1326 (50)	31.6 (5.6)	31	21–47
Cardiovascular	58*	278 (25)	4.8 (1.8)	4	2–10	1952 (53)	33.7 (5.5)	33	21–46
Complementary therapies	43	211 (26)	4.9 (1.8)	5	2–9	1511 (56)	35.1 (6.0)	36	22–44
Endocrine and metabolic disorders	34*	175 (27)	5.1 (2.1)	5	2–10	1204 (56)	35.4 (6.1)	36	21–47
Mental health and behavioural conditions	51	266 (27)	5.2 (2.0)	5	2–10	1762 (55)	34.5 (5.7)	33	21–44
Musculoskeletal	70	335 (25)	4.8 (2.0)	4	2–11	2295 (52)	32.8 (6.2)	32	18–47
Neurological	42*	221 (28)	5.3 (1.9)	5	2–11	1443 (55)	34.4 (6.1)	33.5	23–47
Physiotherapy	36	174 (25)	4.8 (1.8)	4	2–8	1194 (53)	33.2 (5.8)	32.5	18–43
Rehabilitation	42*	201 (25)	4.8 (2.1)	4	2–11	1393 (53)	33.2 (5.7)	32.5	23–47
Surgery	49	251 (27)	5.1 (1.8)	5	2–10	1644 (53)	33.6 (5.2)	33	23–47

**numbers differ from Table 1 because of the record(s) excluded at assessment*

inter-related activities. PROSPERO was launched in 2011, a time when there were few opportunities to publish protocols, however, registration is not meant to be a substitute for preparation of a protocol. PROSPERO and PRISMA-P 2015 requirements are not aligned as they serve different purposes. However, a stated aim of registration is to facilitate comparison of what was planned with what is reported. Even if limited information were registered, we would expect the mandatory fields in PROSPERO to be fully completed. This was not the case, particularly for details related to outcome measures, assessment of risk of bias and quantitative analysis methods. It would not be reasonable to expect that PROSPERO records meet all the PRISMA-P recommended items, given the differences in purpose between a protocol and registration, but it is important to understand what information is available where registration is the only public source.

Eligibility criteria and type of analysis planned were most frequently reported and are all separate required fields in PROSPERO. However, study selection process, which is optional, was also a higher frequency reported item. This may be explained by considering that some elements of items, such as eligibility criteria, study selection and risk of bias have what might be considered a standard, recognisable format that facilitates reporting. Other items need a more nuanced approach underpinned by a clear understanding of systematic review methods, and therefore may be associated with being less frequently reported due to a lack of confidence or experience with these aspects of review methods. For example, how risk of bias will be used in the synthesis, data handling in a meta-analysis, meta-biases and confidence in cumulative evidence, all had low scores. Part of the problem may be the uncertainty of what the searches will find when designing a systematic review but needing to know so the design is appropriate. For example, the intention may be to perform a meta-analysis, this may not be possible once the studies for inclusion have been identified. While, both PROSPERO and PRISMA-P acknowledge that protocols are iterative documents and may need to be amended, changes should be documented, justified and the stage of review at the time of the amendment made clear. Therefore, it is better to record alternative options for activities such as how data will be analysed and the conditions for selection of option when finalising the protocol.

Differences in frequency of reporting may also reflect where researchers considered items to be less or more important than others. For example, naming the software used for data management may not be seen as crucial, whereas the eligibility criteria and approach to synthesis are.

There are strengths and limitations to this study. The assessed sample of 433 records was representative of all the eligible 2018 non-Cochrane intervention reviews registered in PROSPERO. As a result, the findings may reasonably be generalised to other registrations of healthcare interventions, but not necessarily other types of registered reviews excluded from our sample.

PRISMA-P is a reporting guideline and not a rating scale, so judgements about whether sufficient information had been provided for some items carried a degree of subjectivity. The assessment guide and form developed for the study aimed to maximise

objectivity but in accordance with PRISMA-P did not weight importance of items. Although two researchers independently carried out the assessments, achieving an overall agreement rate of 90%, subjectivity was minimised but not eliminated.

PROSPERO was developed in 2011 to record key protocol details and does not necessarily accord with everything subsequently recommended in the 2015 PRISMA-P reporting guidelines. Some registration items are mandatory and others optional. However, this study looked at records that had no other protocol output and arguably should therefore have provided PRISMA-P level detail. The evidence that protocol details are only available in PROSPERO for around 96% of non-Cochrane reviews makes the infrequency of reporting of items a concern[9,10]. Based on the findings of other studies, promoting improved reporting of protocol details may help increase the quality of systematic reviews[17,18].

Protocols are iterative documents and even after a review has started there may be legitimate reasons for amendments. Such changes should and can be reported in a registration record, with their justification and timing. Just over two thirds of PROSPERO records have more than one version (Figure 1). While focussing on single entry records to be certain that any changes were not made after completion of the review this may have excluded records where more complete information was added to the record over time at key points in the review process.

This study simply looked at whether items were reported and not at the level of detail or suitability/appropriateness of the planned methods. Use of a scoring system giving equal weight to all items and elements as PRISMA-P does, is a limitation of this study because PROSPERO identifies information as either mandatory or optional. However, the scoring used in this study only relates to the presence or absence of information, and we have indicated the mandatory/optional fields in Table 2. The option of 'partially reported' could have been used at assessment but was avoided to minimise subjectivity. The focus was on simply establishing whether items were reported or not. The assessors focussed on whether the information was reported or could reasonably be inferred from what was reported. Assessing the quality of planned methods inprotocol registrations needs to be the subject of further research.

This study shows that there is work to be done to promote the complete reporting of items recommended in the guidelines for systematic review protocols when the registration in PROSPERO is the only place they can be accessed. This is in line with other research that has identified issues with the quality of reporting, publication and outcome reporting biases in systematic review protocols in general[3,9,11,13,19,20]. As proposed in the PRISMA-P statement paper, actions and potential benefits to encourage adherence to PRISMA-P will take a joint effort on the part of a host of stakeholders, including reviewers, registries, and journal editors[5,21].

Conclusions

PROSPERO provides reviewers with the opportunity to be transparent in their planned methods and demonstrate efforts to reduce bias. However, where the PROSPERO record is the only available source of *a priori* reporting, there is a significant shortfall in the items reported, compared to those recommended in PRISMA-P. This presents peer reviewers and others wishing to assess the validity of the final review with challenges in interpretation. PROSPERO records are not peer reviewed or assessed for methodological quality, it is the responsibility of those registering their review to complete the registration form fully or provide access to a complete protocol. There are several areas requiring particular attention when completing the registration form. These include explaining the rationale for undertaking the review in the context of what is known; providing information sources beyond a list of databases to be searched; and reporting reproducible process methods for data management, study selection and risk of bias assessment. In addition, defining variables for data extraction, how specified outcomes will be measured, and the planned analyses, with criteria for undertaking a quantitative synthesis should all be included in detail.

This study only looked at whether recommended items were reported or not in PROSPERO records. Further research is needed to assess the quality of the planned methods in systematic review protocol registrations.

Data availability

Underlying data

Open Science Framework: PROSPERO and PRISMA-P, https://doi.org/10.17605/OSF.IO/7PW4G[16].

Extended data

Open Science Framework: PROSPERO and PRISMA-P, https://doi.org/10.17605/OSF.IO/7PW4G[16].

This project contains the following underlying data:

- Study protocol
- Items, scoring options and guidance/rules for assessment of PROSPERO records compared to PRISMA-P reporting requirements

Acknowledgements

The authors would like to thank Fiona Rose for her assistance with the assessment of records.

References

1. Centre for Reviews and Dissemination: **Systematic reviews: CRD's guidance for undertaking reviews in health care**. University of York, 2009.
Reference Source

2. Higgins JPT, Thomas J, Chandler J, *et al.*: **Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated September 2019)**. 2nd ed.: Wiley-Blackwell, 2019.
Publisher Full Text

3. Allers K, Hoffmann F, Mathes T, *et al.*: **Systematic reviews with published protocols compared to those without: more effort, older search.** *J Clin Epidemiol.* 2018; **95**: 102–110.
PubMed Abstract | Publisher Full Text

4. Shamseer L, Moher D, Clarke M, *et al.*: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation.** *BMJ.* 2015; **350**: g7647.
PubMed Abstract | Publisher Full Text

5. Moher D, Liberati A, Tetzlaff J, *et al.*: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.** *PLoS Med.* 2009; **6**(7): e1000097.
PubMed Abstract | Publisher Full Text | Free Full Text

6. Moher D, Shamseer L, Clarke M, *et al.*: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.** *Syst Rev.* 2015; **4**(1): 1.
PubMed Abstract | Publisher Full Text | Free Full Text

7. Booth A, Clarke M, Dooley G, *et al.*: **The nuts and bolts of PROSPERO: an international prospective register of systematic reviews.** *Syst Rev.* 2012; **1**: 2.
PubMed Abstract | Publisher Full Text | Free Full Text

8. Booth A, Clarke M, Ghersi D, *et al.*: **Establishing a minimum dataset for prospective registration of systematic reviews: an international consultation.** *PLoS One.* 2011; **6**(11): e27319.
PubMed Abstract | Publisher Full Text | Free Full Text

9. Viguera-Guerra I, Ruano J, Aguilar-Luque M, *et al.*: **Evolution of international collaborative research efforts to develop non-Cochrane systematic reviews.** *PLoS One.* 2019; **14**(2): e0211919.
PubMed Abstract | Publisher Full Text | Free Full Text

10. Ge L, Tian JH, Li YN, *et al.*: **Association between prospective registration and overall reporting and methodological quality of systematic reviews: a meta-epidemiological study.** *J Clin Epidemiol.* 2018; **93**: 45–55.
PubMed Abstract | Publisher Full Text

11. Khaleel S, Sathianathen N, Balaji P, *et al.*: **Quality of urological systematic reviews registered in PROSPERO.** *BJU Int.* 2019; **124**(2): 195–196.
PubMed Abstract | Publisher Full Text

12. Parsons R, Golder S, Watt I: **More than one-third of systematic reviews did not fully report the adverse events outcome.** *J Clin Epidemiol.* 2019; **108**: 95–101.
PubMed Abstract | Publisher Full Text

13. Tricco AC, Cogo E, Page MJ, *et al.*: **A third of systematic reviews changed or did not specify the primary outcome: a PROSPERO register study.** *J Clin Epidemiol.* 2016; **79**: 46–54.
PubMed Abstract | Publisher Full Text

14. Kelly SE, Moher D, Clifford TJ: **Quality of conduct and reporting in rapid reviews: an exploration of compliance with PRISMA and AMSTAR guidelines.** *Syst Rev.* 2016; **5**: 79.
PubMed Abstract | Publisher Full Text | Free Full Text

15. Peters JPM, Hooft L, Grolman W, *et al.*: **Reporting Quality of Systematic Reviews and Meta-Analyses of Otorhinolaryngologic Articles Based on the PRISMA Statement.** *PLoS One.* 2015; **10**(8): e0136540.
PubMed Abstract | Publisher Full Text | Free Full Text

16. Booth A, James S, Cockayne S, *et al.*: **PROSPERO and PRISMA-P**. 2020.
http://www.doi.org/10.17605/OSF.IO/7PW4G

17. Page MJ, Moher D: **Evaluations of the uptake and impact of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement and extensions: a scoping review.** *Syst Rev.* 2017; **6**(1): 263.
PubMed Abstract | Publisher Full Text | Free Full Text

18. Sideri S, Papageorgiou SN, Eliades T: **Registration in the international prospective register of systematic reviews (PROSPERO) of systematic review protocols was associated with increased review quality.** *J Clin Epidemiol.* 2018; **100**: 103–110.
PubMed Abstract | Publisher Full Text

19. Ruano J, Gomez-Garcia F, Gay-Mimbrera J, *et al.*: **Evaluating characteristics of PROSPERO records as predictors of eventual publication of non-Cochrane systematic reviews: a meta-epidemiological study protocol.** *Syst Rev.* 2018; **7**(1): 43.
PubMed Abstract | Publisher Full Text | Free Full Text

20. Runjic E, Rombey T, Pieper D, *et al.*: **Half of systematic reviews about pain registered in PROSPERO were not published and the majority had inaccurate status.** *J Clin Epidemiol.* 2019; **116**: 114–121.
PubMed Abstract | Publisher Full Text

21. Moher D, Stewart L, Shekelle P: **Implementing PRISMA-P: recommendations for prospective authors.** *Syst Rev.* 2016; **5**: 15.
PubMed Abstract | Publisher Full Text | Free Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 1

Reviewer Report 17 August 2020

https://doi.org/10.5256/f1000research.27788.r68890

✔ **Xin Sun**
Chinese Evidence-Based Medicine Center and Cochrane China Center, West China Hospital, Sichuan University, Chengdu, China

This study conducted a methodological survey to assess the extent to which the contents of PROSPERO records meet the systematic review protocol reporting items in PRISMA-P. This paper addresses an important research question, and the findings may have implications for the reporting of systematic review protocols. However, there are a few issues for authors to consider:

1. One aim of PRISMA-P is to aid authors in transitioning their systematic review protocols prepared in accordance with PRISMA-P into full text, while the authors used records from PROSPERO (i.e., not full-text) to assess the compliance to PRISMA-P reporting items, which may be a limitation that should be discussed in this paper.

2. In the methods part, it could be desirable that the authors could clearly report how the 17 numbered items of PRISMA-P were broken down into 63 elements.

3. The author should clearly report whether the subgroup analyses reported in table 3 were pre-planned.

4. The use of a scoring scheme for PRISMA-P and the 63 elements may not be optimal, given the potential difference in item importance, which should be added to the discussion part as a limitation.

5. In table 2, values in parentheses are percentages, which should be indicated in the table.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 01 Sep 2020

Alison Booth, University of York, UK, York, UK

We thank you for your peer review and give our responses as follows:

1. One aim of PRISMA-P is to aid authors in transitioning their systematic review protocols prepared in accordance with PRISMA-P into full text, while the authors used records from PROSPERO (i.e., not full-text) to assess the compliance to PRISMA-P reporting items, which may be a limitation that should be discussed in this paper.

Thank you for raising this point. We agree and have addressed this point in the addition of the following to the discussion:

PROSPERO and PRISMA-P 2015 requirements are not aligned as they serve different purposes. However, a stated aim of registration is to facilitate comparison of what was planned with what is reported. Even if limited information were registered, we would expect the mandatory fields in PROSPERO to be fully completed. This was not the case, particularly for details related to outcome measures, assessment of risk of bias and quantitative analysis methods. It would not be reasonable to expect that PROSPERO records meet all the PRISMA-P recommended items, given the differences in purpose between a protocol and registration, but it is important to understand what information is available where registration is the only public source.

2. In the methods part, it could be desirable that the authors could clearly report how the 17 numbered items of PRISMA-P were broken down into 63 elements.

We have added an example from the study protocol to illustrate the description of how the elements were derived from the 19 PRISMA-P items, as follows:

Where the PRISMA-P description for an item specified more than one piece of information, the individual elements were listed as subsets of the items. For example, item 14. Risk of bias in individual studies, says: "Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis." Scoring for this item will be for each of the following separate elements: No risk of bias assessment planned and justification provided; Risk of bias tools named for all study types included; Outcome or study level or both; Domains/outcomes for risk of bias assessment stated; Risk of bias assessment process described; How risk of bias findings will be used in synthesis. Applying this approach to the 19 items resulted in a list containing 63 elements to be reported.

3. The author should clearly report whether the subgroup analyses reported in table 3 were pre-planned.

We can confirm they were all included in the study protocol, available at https://doi.org/10.17605/OSF.IO/7PW4G. We have added 'which were all pre-defined' to the section on Subgroup comparisons in the manuscript.

4.The use of a scoring scheme for PRISMA-P and the 63 elements may not be optimal, given the potential difference in item importance, which should be added to the discussion part as a limitation.

This is an important point thank you, which we have incorporated into the discussion as follows:

This study simply looked at whether items were reported and not at the level of detail or suitability/appropriateness of the planned methods. Use of a scoring system particularly as all items and elements carried the same weight is a limitation of this study. The scoring does not accord with the PROSPERO dataset which identifies information as either mandatory or optional. For this reason we have indicated the mandatory/optional fields in Table 2. The scoring only relates to the presence or absence of information. The option of 'partially reported' could have been used at assessment but was avoided to minimise subjectivity. The focus was on simply establishing whether items were reported or not. The assessors focussed on whether the information was reported or could reasonably be inferred from what was reported. Assessing the quality of planned methods in protocol registrations needs to be the subject of further research.

We have also amended how the mandatory/optional fields are indicated in Table 2 so the difference is clearer.

5. In table 2, values in parentheses are percentages, which should be indicated in the table.

Apologies for this omission, this has been corrected in the revised version.

Competing Interests: No competing interests were disclosed.

Reviewer Report 31 July 2020

https://doi.org/10.5256/f1000research.27788.r68072

Dawid Pieper
Faculty of Health, Department of Medicine, University Witten/Herdecke, Cologne, Germany

This article is an analysis of how PROSPERO records adhere to the PRISMA-P guideline. The Analysis is based on a random sample of 439 PROSPERO records published in 2018. The authors conclude that reporting in PROSPERO should be improved given the fact that the PROSPERO record is often the only available source of a priori reporting.

The manuscript is methodologically sound and well written. What I think can be improved is the discussion. I wonder what is the implication of this study. Do the authors want to make the point that PROSPERO records should follow PRISMA-P? To the best of my knowledge PRISMA-P is even not mentioned in the PROSPERO guidance. If this would be the intention then wy not allign PROSPERO with the PRISMA-P items. I admit that PRISMA-P has been primarily designed for SRs of healthcare interventions, but most items are General and would be applicable to other review types as well. I do not want to make the point that this is a great idea, but it is somehow a logical question resulting from your manuscript and this should be mentioned in the discussion. Registries and protocols should be seen as different entities, and thus I think that a perfect result of all PROSPERO records meeting all PRISMA-P items cannot be what we aiming for. If this would be the case, this would probably dilute the difference between a PROSPERO record and a protocol.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Research methods, clinical epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 01 Sep 2020

Alison Booth, University of York, UK, York, UK

We thank you for your peer comments and agree this is an important point. We have added the following paragraph to the discussion section:

The review protocol is a detailed record of the planned methods developed through an iterative process. Once finalised or close to finalising, the key methodological details should be registered in PROSPERO. These are two separate but inter-related activities. PROSPERO was launched in 2011, a time when there were few opportunities to publish protocols, however, registration is not meant to be a substitute for preparation of a protocol. PROSPERO and PRISMA-P 2015 requirements are not aligned as they serve different purposes. However, a stated aim of registration is to facilitate comparison of what was planned with what is reported. Even if limited information were registered, we would expect the mandatory fields in PROSPERO to be fully completed. This was not the case, particularly for details related to outcome measures, assessment of risk of bias and quantitative analysis methods. It would not be reasonable to expect that PROSPERO records meet all the PRISMA-P recommended items, given the differences in purpose between a protocol and registration, but it is important to understand what information is available where registration is the only public source.

Competing Interests: No competing interests were disclosed.

Appendix 1

Items, scoring options and guidance/rules for assessment of PROSPERO records compared to PRISMA-P reporting requirements

PILOT Version1 15 March 2020

The assessment form contains a breakdown of PRISMA-P reporting items re-organised to match the order in which information is presented in PROSPERO. Numbering of items matches the numbering in PRISMA-P for ease of referral to the field in the E&E paper.

A number of fields have been excluded: details of these and the reasons for exclusion are documented in the study protocol.

Sub-questions have been included for sections as not all the information for PRISMA-P is required/requested in PROSPERO. These elements will be included in the total scoring for each item, and then reported in the detailed breakdown of items in the context of what PROSPERO requires.

Information required by PRISMA-P may be contained in any field within PROSPERO – it does not have to be in the expected field. E.g. Context may be indicated in the research question, or objectives fields. The exceptions are Q1 where the information must be in the title and Q7 where the information must be included in the objectives (see below).

If you are really unsure about something, don't let it hold you up – make a decision and remember we are double assessing and discrepancies will be discussed.

Rules for specific fields

Item	Options	Scoring rules
1a. Identification in the title: Identify the report as a protocol	Yes/No	Refers to information in the title only. If it does not state in the title that it is a protocol, the score is 'No'
1a. Identification in the title: Identify the report as a systematic review / meta-analysis / or other form of systematic review such as a rapid review	Yes/No	Refers to information in the title only. If it does not state in the title that it is a systematic review or meta-analysis or variation on a systematic review such as a rapid review, the score is 'No'
1b. Update: If the protocol is for an update of a previous systematic review, identify as such in the title	Yes/No/Not applicable	Refers to information in the title only. If it says Update in the title then clearly the score is Yes. Updates are rare therefore most frequent response is likely to be N/A. However, if in the course of completing the assessment it becomes clear that the reviewers are in fact updating an existing review, this should be revisited and scored as 'No'. PROSPERO contains the field "Details of any existing review

		of the same topic by the same authors", which if completed appears in the record and will indicate that this is an update (unless of course they indicate 'none'!) Looking for pre-existing reviews is an essential part of avoiding duplication of reviews; this does not count as them planning to update a review. Updates of reviews are still rare in PROSPERO registered non-Cochrane review
INTRODUCTION		
7. Objectives: Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes/No/Not applicable	Refers to the information given in the research question, which should include reference to participants, interventions, comparators, and outcomes (PICO) – score Yes/No/ Not applicable for each element. N.B while PROSPERO then asks for each of these elements separately, PRISMA-P guidance for this is specific to the research question
Participants		
Intervention		
Comparator		
Outcome(s)		
METHODS		
9. Information sources: Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage		
Electronic database(s) named	Yes/No [unclear]	'Yes' if any bibliographic database(s) are named e.g. PubMed, MedLine, Embase, CENTRAL, LILACS
Grey literature sources named or statement of no grey lit searches planned		e.g. databases of theses, conference abstracts, OpenGrey, System for Information on Grey Literature in Europe (Sigle)
Study registries		e.g. PROSPERO, clinicaltrials.gov
Contact with study authors planned or statement that contact not planned		Will they be contacting authors, leaders in the field to ask them to identify studies/provide information on unpublished work?
Other: e.g. hand searching reference lists of included studies		Anything not included above that relates to getting hold of study papers or data relevant to the review
Planned search dates		'Yes' if they say e.g. databases to be searched from inception or a date (July 2000) or they indicate a date when the searches will be carried out. Don't give either = 'No'
10. Search strategy: Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated		
Draft search strategy provided	Yes/No/Not applicable	e.g. list of search terms and how they will be combined for a specific database e.g. PubMed This may or may not include

		combining results to arrive at a final dataset: some topics are so niche they only require a simple search
Search terms given alone i.e. not formal strategy for a database		List of words with no information about how they will be combined or where they will be used
Approach to limits/restrictions reported e.g. dates; statement of no limits		Any mention of limiting the searches by date, language or any other parameter. A statement that there will be no limitations/restrictions used should score a 'Yes' as they have reported on this item
6. Rationale: Describe the rationale for the review in the context of what is already known		
Rationale described (e.g. existing evidence base)	Yes/No	Statement about why this review is needed. E.g. unanswered question - no existing review; to inform guideline development; new studies since last review = update or new review
Context provided (e.g. scale of problem/condition)		Background on clinical condition
8. Eligibility criteria: Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review		
Study design specified	Yes/No/Not applicable	Types of study designs to be included are listed, or if no restriction on type of design, statement saying so
Setting (condition or domain) specified		Should be in specific PROSPERO field: Condition or domain being studied. There may be more info in the non-mandatory 'Context' field
Population detailed		Population identified in sufficient detail to enable data extraction
Intervention specified		Intervention described in sufficient detail to enable data extraction
Comparator specified		This may be an alternate specific intervention, usual care or for network M-A interventions are compared with each other
Outcome(s) specified		Outcome(s) listed
13. Outcomes and prioritisation: List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale		
Primary/main outcome(s) specified as such	Yes/No/Not applicable	Primary/main outcome(s) described and identified as such
Primary/main outcome measure(s) specified		Measure(s) specified / included in description of outcome(s)
Additional outcomes specified as such		Other outcomes specified
Additional outcome(s): measure(s) specified		Measure(s) specified / included in description of outcome(s)
Study records		
11a. Data management: Describe the mechanism(s) that will be used to manage records and data throughout the review		

Software named/type indicated	Yes/No [Unclear]	Details of how the search results will be handled e.g RevMan, Covidence, Eppi-reviewer, or unspecified 'software'
De-duplication planned		A statement anywhere to say that search results will be de-duplicated or how multiple reports of the same study will be handled
11b. Selection process: State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)		
Initial screening process detailed	Yes/No [Unclear]	Title and abstract screening – number of reviewers/ resolution of disagreements
Full paper screening process detailed		Description of how the eligibility criteria will be applied to the records from initial screening – number of reviewers/resolution of disagreements
11c. Data collection process: Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators		
Pilot extraction form	Yes/No [Unclear]	Mechanism for consistent recording of extracted data, e.g. form to be developed and piloted
Data extraction process described		How data extraction be performed, e.g. double blind with disagreements resolved by discussion/third reviewer
Obtain missing data		Statement about how missing data will be dealt with: e.g. contact study authors/account for in statistical analyses
12. Data items: List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications		
List of data for extraction	Yes/No [Unclear]	Items to be included in data extraction listed
Variables defined		Definitions for the items for extraction
Any data assumptions reported		Statement of any pre-specified assumptions e.g. what they will do with unclear information or missing data
14. Risk of bias in individual studies: Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis		
No risk of bias assessment planned and justification provided	Yes/No/Not applicable	Statement to say the authors are not going to carry out a risk of bias assessment and provide an explanation to justify this = Yes. Anything less = No
Risk of bias tools named for all study types included		Risk of Bias tool named for assessment of each study design to be included in the review
Outcome or study level or both		Statement to indicate if ROB results will be used at study level or specifically at outcome level or both. N.B. identifying a ROB tool that is designed to assess both study and outcome levels (e.g. Cochrane RoB or Newcastle Ottawa Scale (NOS) = Yes

Domains/outcomes for risk of bias assessment stated		The constructs for assessment are listed, defined and judgment options (e.g. high low unclear) reported If constructs listed and defined but judgement options not specifically given – consider if tool to be used has pre-specified judgement options if so = Yes
Risk of bias assessment process described		Statement of how risk of bias will be undertaken e.g. two reviewers independently/blinded – method for resolution of disagreements
How risk of bias findings will be used in synthesis		Statement of whether studies will/will not be excluded based on risk of bias score. Or include all studies meeting criteria but account for risk of bias in statistical analyses (sub-group/sensitivity analyses)
Data		
15a. Synthesis: Describe criteria under which study data will be quantitatively synthesized		
Criteria for doing a quantitative synthesis planned / statement that quantitative synthesis not planned	Yes/No/Not applicable	Statement to say under what circumstances a meta-analysis (M-A) will be undertaken or that a M-A will not be undertaken Statement that descriptive stats only/narrative synthesis planned = Yes
15b. If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)		
Summary measures	Yes/No/Not applicable	Details of measure of treatment effects / statistical method / use of fixed or random effects or both / assessment of heterogeneity. Any of these = Yes
Data handling		Details of how data will be handled to ensure measures are converted/presented in the same format. Approach to handling of rare events and imputation of missing data. Any of these = Yes
Combining data/ exploration of consistency		Plans for how data will be combined and how they will evaluate between study inconsistency (heterogeneity)
Name of software to be used for meta-analysis		Type or name of software to be used for performing the M-A e.g. Stata, R, RevMan
15c. Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)		
Subgroup analyses planned: co-variants named	Yes/No/Not applicable	Statement that sub-group analyses are planned - must include the co-variants. Statement that no-subgroup analyses are planned = yes
Methods for subgroup analyses reported		How groups will be divided, use of fixed or random effects
Sensitivity analyses planned		Statement that sensitivity analyses are planned or not planned, to include items to be examined
15d. If quantitative synthesis is not appropriate, describe the type of summary planned		
Descriptive synthesis planned	Yes/No/Not applicable/	Usually performed along with a M-A or a Narrative synthesis: literally a plan to describe the included studies

Narrative or qualitative synthesis	None stated	For a narrative synthesis details of how studies/findings will be combined/stratified narratively (in text or tables): i.e. some form of synthesis beyond providing a description of the studies and data extracted For reviews of qualitative studies, plans how the synthesis will be carried out e.g. thematic analysis or framework development etc should be provided
Other analyses planned		Details of any other analyses such as cost effectiveness are provided. If no mention in record of data being collected for other analyses = Not applicable. If e.g. cost data collected but no analysis planned = No
16. Meta-bias(es): Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)		
Publication bias to be assessed	Yes/No/Not applicable	Methods for testing for publication bias should be given e.g. funnel plot; Egger's test
Outcome reporting bias to be assessed		Methods for assessing potential for outcome reporting bias should be given, e.g. ORBIT system; sensitivity analysis
17. Confidence in cumulative evidence: Describe how the strength of the body of evidence will be assessed (e.g., GRADE)		
Overall assessment of included studies planned or statement that no overall assessment will be made	Yes/No/Not applicable	Is there a plan to look at overall study quality in addition to the ROB assessment of individual studies?
Methods specified (eg GRADE)		If an overall assessment is planned, are the methods specified? (Not applicable if not planned – Score No if No to previous question)
Support		
5a. Sources: Indicate sources of financial or other support for the review **5b. Sponsor: Provide name for the review funder and/or sponsor**		
Source of financial/ other support provided or statement of no financial/other support	Yes/No	Straightforward Yes they make a statement about funding/no funding = Yes or no statement = No
Name of sponsor given or statement of no sponsorship		Straightforward Yes they make a statement about sponsor/no sponsor = Yes or no statement = No
Comment or observations on this record		For any observations you may have about this record or any issue you may want to raise. Please also feel free to make use of the questions sheet in the shared drive

An assessment of the extent to which the contents of PROSPERO records meet the systematic review protocol reporting items in PRISMA-P: study protocol

Alison Booth*, Sarah Cockayne, Sophie James, Samantha Gascoyne, Alex S Mitchell, Andrew Mott. York Trials Unit, Department of Health Sciences, University of York.
*Corresponding author email: alison.booth@york.ac.uk

Background

High quality systematic reviews start with the preparation of a protocol. The methods for conducting the review should be identified and recorded in the protocol in advance of commencing the review in order to minimise a range of potential biases.[1 2] Ideally protocols should be made available in the public domain to facilitate transparency.[3 4] In addition, registration of key protocol details is encouraged as best practice in reporting guidelines, [5 6] by publishers like the British Medical Journal (BMJ), Public Library of Science (PLoS), and BioMed Central (BMC) and is mandated in their instructions to authors by journals such as BMC Systematic Reviews, BMJ, BMJ Open, PLoS One, British Journal of Radiology and National Institute for Health Research (NIHR) journals.

PROSPERO is a facility for making key methodological details publicly available in advance of carrying out a systematic review. Registration on PROSPERO requires completion of an internationally agreed minimum dataset from a systematic review protocol.[7 8]

The database was launched in 2011, at a time when there were few options for publishing protocols outside of major organisations such as the Cochrane and Campbell Collaborations, Joanna Briggs Institute, or on the websites of major funders and commissioners of research such as the NIHR in the UK and the Agency for Healthcare Research and Quality (AHRQ) in the USA. There are now more options for publication of systematic review protocols, such as open access journals like Systematic Reviews and open data repositories like the Open Science Framework (https://osf.io/registries/discover?q=protocols). PROSPERO remains the only free, open access registry of systematic review protocols, making it a single searchable source of on-going and completed reviews. Uptake of registration has increased exponentially and by the end of 2019 there were over 60,000 registrations in PROSPERO. There is evidence that considerably more systematic reviews are registered in PROSPERO than have peer-reviewed protocols published. In 2016, 1058 records were accepted by PROSPERO, in the same time period, only 404 published systematic review protocols were identified.[3] Another study reported identifying 20,814 [sic] non-Cochrane systematic review protocols from web scraping PROSPERO and bibliographic database searches. Of these, 924 were only published in journals, 807 were published in journals and registered in PROSPERO and 19,890 were only available as a record in PROSPERO.[9] There is further evidence from Ge et al (2018) that of the non-Cochrane reviews registered in PROSPERO, only 3% or 4% have a published protocol.[9 10] This means that

for a large number of reviews a PROSPERO record is likely to be the only source providing details of the planned methods.

Published protocols and registration records aim to provide transparency in the review process by allowing public access to the key pre-specified elements for the conduct of a review. One of the stated aims of PROSPERO is to facilitate comparison between planned review methods and reported results.[8] Such a comparison enables peer reviewers and other readers of the final review to assess for themselves the potential for bias in the findings. There is also a steadily growing body of research using PROSPERO records to assess the risk of biases in final review reports.[10-15] Given this reliance on the information provided in PROSPERO records, it is important to know whether the level of detail in the records is sufficient. Our focus in this study is on the stated aim of PROSPERO to reduce opportunity for bias by enabling comparison of the completed review with what was planned in the protocol. [8]

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Protocols (PRISMA-P) were informed by the international consultation research that established the PROSPERO dataset.[4 6] Key methodological aspects of a protocol are mandated for registration in PROSPERO; other items, mainly administrative fields, are optional.[7 8] Submissions for registration are checked to make sure information makes literal sense and is in the appropriate field, but they are not subject to any form of peer review or critical appraisal. There is therefore the possibility that PROSPERO records do not provide all the necessary information identified by the reporting guidelines to enable comparison with the completed systematic review. The registration record may be the only place where a priori methods are available for users, in particular peer reviewers, to check for potential issues such as selection, outcome reporting and publication biases. This study will investigate the extent to which records in PROSPERO comply with each of the items for reporting of protocols set out in the PRISMA-P guidelines, when no protocol or other information is available.

There is evidence from studies of compliance with the PRISMA statement that the demographics of reviews can vary considerably. Characteristics of reviews included in methodological studies of reporting include; type of journal, year of publication, article word count, country, number of authors, funding, topic, planned meta-analysis and registration.[9 14 16-18] We therefore also aim to examine the same characteristics where the data are available in our sample. We will explore whether country, number of authors, funding, topic, and planned meta-analysis have any association with the completeness or otherwise of reporting specific items.

Methods

This study protocol has been prepared and agreed in advance of commencing the study. There are no reporting guidelines for protocols of methodological research studies as far as we are aware. We have aimed to provide as much information about our planned methods in this protocol as possible. There is also a lack of a single point of registration for protocols of methods studies. However, the protocol will be made available on the open access platform

Open Science Framework prior to identification of the study sample and the assessment process.

We will assess a random sample of PROSPERO registration records against the protocol reporting criteria set out in the PRISMA-P 2015 checklist. PRISMA-P will be used as it is the only reporting guideline specifically for systematic review protocols and meta-analyses and was developed in line with guideline development methods.[19] A dataset of PROSPERO records for reviews of health interventions from 2018, where no additional information about the planned methods are available in a publicly available protocol (e.g. published paper or additional documents attached to the PROSPERO record) will be analysed to give an overview of the register content and the extent to which the information recommended in PRISMA-P is reported.

The study will focus on reviews of health care interventions as this is the type of review for which the PROSPERO minimum dataset was originally designed.[8] As was the long term aim for the register, it now contains records for a wide range of types of reviews. The sample size required to assess all of these is beyond the capacity of this un-funded study. In addition, the PRISMA-P reporting guidelines were written primarily for reviews of health care interventions.

Records from the calendar year 2018 will be used to allow time for dissemination and adoption following publication of the PRISMA-P papers in 2015. A complete dataset for 2018 will be obtained. This will be used to provide the contextual overview and from which a random sample of records will be taken for assessment.

Peer review is an important part of the publication process and compliance with reporting guidelines and protocols are expected as part of peer review of a completed systematic review. The focus of this study is therefore the large body of registrations where the registered record is the sole source of publicly available information about the pre-planned methods. PROSPERO registrations with an associated protocol will be excluded. Included records will have indicated that the planned methods were agreed at some point prior to the completion of data extraction in order to have met the PROSPERO acceptance criteria in 2018.

We will exclude records with multiple versions as these are registrations where changes have been made. By only including single version records we will be assessing the version a peer reviewer would use and excluding any potential post-hoc amendments, that is, changes to the initial registration information following work on the review commencing/being complete/having peer reviewer feedback. Accounting for changes in planned methods within different versions in relation to the timing of the changes within the review process is a topic for a different study.

The implications of the chosen inclusion and exclusion criteria on external validity of the study will be explored in the results paper.

Outcomes

The primary outcome for this study will be the compliance between registration records and PRISMA-P reporting items. Each of the 21 items will carry a score of 1 where reporting is complete, making the maximum possible score 21.

We will also report on the number of elements within PRISMA-P items assessed as completely reported in PROSPERO.

Demographic data for both the full set of eligible 2018 registrations and the sample set of records assessed will be reported, to include: month of registration, funding, country, number of authors, topic of review, stage of review, meta-analysis planned. The following definitions will be used.

Funding: Field 12. Funding sources/sponsors in PROSPERO is a single free text field which prohibits consistent differentiation between funder/funding and sponsor/sponsorship for the full 2018 dataset. We will therefore categorise the information provided as either 'no listed funder or sponsor' or 'listed sponsor or funder'.

Topic of review: will be reported as self-defined by authors in PROSPERO. The PROSPERO topic of review options are based on the Health Research Classification system (https://hrcsonline.net/health-categories/). Additional codes are included in PROSPERO to accommodate the broad nature of the inclusion criteria.

Stage of review: authors are required to indicate the stage of their review at the time of registration in a matrix as below. We will define stage of review as the furthest point in the review process indicated by authors of records. This could be either an activity started or completed. For example, the following record would be counted as 'Started Data extraction'.

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	**Yes**	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Meta-analysis planned: assessor responses to PRISMA-P item 15b, sub-question about whether a meta-analysis is planned will be used.

Sample size and selection

Using a PROSPERO dataset made available to us for research purposes, [we are grateful to Professor Lesley Stewart, Director of CRD and Gordon Dooley of METAXIS] we will apply the inclusion and exclusion criteria to generate a set of eligible records for 2018. A 20% random sample will be drawn from all eligible records, using simple random sampling without replacement. This will be done using the sample function in the base functionality of R.[20]

The PROSPERO dataset contains 5,313 records for reviews of interventions first accepted in 2018 (excluding Cochrane and reviews of animal studies). Applying the other study inclusion/ exclusion criteria results in 2,194 eligible registration records. We will assess the reporting of information in the random sample of 439 (20%) of these records.

Inclusion criteria

- Registration published in PROSPERO on or between 1 January 2018 and 31 December 2018
- Systematic review of a health care intervention (as self-defined by authors in PROSPERO)
- Single registration record (i.e. no amendments have been made)
- PROSPERO record does not state there is a peer reviewed published protocol or provide information about or access to a protocol

Exclusion criteria

- Cochrane reviews
- Reviews of animal studies
- Non-intervention reviews as identified in PROSPERO i.e. Diagnostic accuracy, Prognostic factors, Prevention, Epidemiological reviews relevant to health and social care, Public health, Service delivery in health and social care, Methodological
- Reviews of reviews
- Synthesis of qualitative studies
- Provides any files, question response, or reference to a protocol

Data assessment:

Two researchers will independently compare the information provided in the public interface of the PROSPERO register with the relevant items in the PRISMA-P checklist. Disagreements will be resolved through discussion or recourse to a third researcher.

For each PROSPERO record, assessment will involve the researchers completing an assessment form containing the PRISMA-P items as set out in the 'fields for assessment' below, but ordered to match PROSPERO public record items. Options for decisions will be: Yes (information provided as per PRISMA-P requirements); No (some or all information not provided); and, where relevant, Not applicable/None Stated. The option of [Unclear] will be available for some items, but use discouraged at training. Where PRISMA-P items specify more than one piece of information, the individual elements will be listed separately and scored as above. The items as listed are from the summary checklist; the breakdown elements are informed by the information presented in the expansion and explanation paper.[4 6] For example, item 14. Risk of

bias in individual studies, says: “Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis.” Scoring for this item will be for each of the following separate elements: No risk of bias assessment planned and justification provided; Risk of bias tools named for all study types included; Outcome or study level or both; Domains/outcomes for risk of bias assessment stated; Risk of bias assessment process described; How risk of bias findings will be used in synthesis.

Where the required information is present (Yes) the score for an item will be 1; if the information is not reported (No) the score for the item will be 0. Where an item is sub-divided, scoring will be assigned on the basis that if any of the responses are No the overall score for the item will be 0; if all the responses to the elements are Yes, the item score is 1. The maximum possible overall score will be 21. The scores for the individual elements of items will also be presented to demonstrate where registration information partially meets the PRISMA-P requirements and whether there are any persistent gaps in reporting.

The assessment tool has been developed as a Google Form for: ease of access by multiple users at the same or different times; accuracy of recording decisions; and ability to export the data in a Microsoft Excel spreadsheet for identifying discrepancies, recording the final decision and producing the study results.

The researchers undertaking the assessment have familiarised themselves with the PRISMA-P checklist and the detailed information provided in the Explanation and Elaboration paper.[4 6] Prior to identification of the dataset and starting the study, the lead author (AB) developed the pilot assessment form. All the authors met for a training session where all the items and elements were discussed. Potential issues were resolved and all authors agreed the content of the revised pilot form. The agreed items, elements, scoring and assessment guidance are set out in Appendix 1 of this protocol. The form contains a link to the PRISMA-P explanation and elaboration paper for ease of access at any time during the assessment phase. The assessment Google Form will be piloted with all researchers assessing the same 10 PROSPERO records from the study data set. Level of agreement, setup of the form and consistency of use will be reviewed and discussed with the assessors until a high level of agreement is achieved (>90%). The form will be amended as necessary following piloting, additional training or support materials supplied as required and assessment of the study dataset undertaken.

Each assessor will be given a list of allocated records containing a hyperlink to the record in the PROSPERO database. Allocation will be random as will pairings of researchers for dual independent assessment. It will not be possible to blind the researchers to the authors of registrations in PROSPERO. Should any of the researchers be authors of included registrations, they will not assess their own records.

PRISMA-P fields for assessment

ADMINISTRATIVE INFORMATION
Title

1a. Identification as a protocol
1b. Update
Support
5a. Sources
5b. Sponsor
INTRODUCTION
6. Rationale
7. Objectives
METHODS
8. Eligibility criteria
9. Information sources
10. Search strategy
Study records
11a. Data management
11b. Selection process
11c. Data collection process
12. Data items
13. Outcomes and prioritization
14. Risk of bias in individual studies
Data
15a. (criteria for synthesis)
15b. (summary measures and data handling)
15c. (additional analyses)
15d. (alternative to quantitative synthesis)
16. Meta-bias(es)
17. Confidence in cumulative evidence

PRISMA-P fields excluded from assessment

The following reporting requirements will be excluded for the reasons given.

- 2. Registration: as the study only includes records registered in PROSPERO the answer to this will always be 'Yes'
- Authors: 3a. Contact: only the person registering the protocol is required to give their name and email address: postal address is optional, so the answer to this would always be 'No'.
- Authors: 3b. Contributions: this is not information that is collected anywhere in the PROSPERO record so the answer to this would always be 'No'.
- 4. Amendments: Amended versions of records are automatically displayed with dates in the public interface of PROSPERO, but what the changes are is unclear as the revision notes explaining the changes are not currently made publicly available. We are excluding records with amendments for other reasons, but the assumption would be that 'Yes' amendments have been identified but the justification probably 'Unclear'.

Results

The numbers and process used to identify the registrations assessed will be reported in the results.

For the complete set of all eligible registration records for 2018, we will present descriptive statistics of demographic information on country, number of authors, topic of review, stage of review at registration, funding and sponsorship status, and whether a meta-analysis is planned.

We will present the same demographic information for the sample of assessed records to set them in the context of the whole dataset to demonstrate the representativeness of the sample used. Month of publication of the record will be reported as an indicator that the sample records were randomly selected.

For compliance between registration record entry and PRISMA-P reporting item we will tabulate the number of records scoring 1 in response to the PRISMA-P reporting items. Where items have been broken down into separate elements, we will also tabulate the result for each element to demonstrate were information has been assessed as missing. For each individual item (and sub item), we will present the number and percentage to score 1.

For the overall total score for records (maximum possible 21) we will present the mean, standard deviation, median, and inter-quartile range.

The influence of the following variables on compliance with reporting guidelines will be presented as number and percentage to score 1: country; number of authors; topic of review; stage of review at the time of registration. Number and percentage to score 1 for assessed items will be reported for: no listed funder or sponsor vs listed sponsor or funder; and whether authors indicate a meta-analysis is planned or not. Graphical representation of results will be used where appropriate.

Dissemination

The results paper will be submitted for publication in a peer reviewed journal. The paper is intended for inclusion in AB's thesis for PhD by publication. The findings will be shared and discussed with the team at CRD who produce and manage PROSPERO. All relevant data and outputs from the study will also be placed with the protocol in the Open Science Framework.

Conflicts of interest

AB lead on the development of PROSPERO and is a group author of the PRISMA-P reporting guidelines papers. AB has not been involved in the management of PROSPERO since 2015. SC, SJ, SG, ASM, and AM declare they have no conflicts of interest.

Funding and sponsorship

The authors have not received any funding, sponsorship or other support in undertaking this study.

Research ethics

Research ethics is not required for this analysis of research methods data in the public domain.

References

1. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care University of York 2009.

2. Higgins J, Thomas J, Eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated September 2019). 2nd ed: Wiley-Blackwell 2019:728.
3. Allers K, Hoffmann F, Mathes T, et al. Systematic reviews with published protocols compared to those without: more effort, older search. Journal of clinical epidemiology 2018;95:102-10. doi: https://doi.org/10.1016/j.jclinepi.2017.12.005
4. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration & explanation. BMJ (Clinical research ed) 2015;350 doi: 10.1136/bmj.g7647
5. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097 [published Online First: 2009/07/22]
6. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews 2015;4(1):1-9. doi: 10.1186/2046-4053-4-1
7. Booth A, Clarke M, Dooley G, et al. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. Systematic reviews 2012;1:2. doi: 10.1186/2046-4053-1-2 [published Online First: 2012/05/17]
8. Booth A, Clarke M, Ghersi D, et al. Establishing a minimum dataset for prospective registration of systematic reviews: an international consultation. PLoS ONE 2011;6 doi: 10.1371/journal.pone.0027319
9. Viguera-Guerra I, Ruano J, Aguilar-Luque M, et al. Evolution of international collaborative research efforts to develop non-Cochrane systematic reviews. PLOS ONE 2019;14(2):e0211919. doi: 10.1371/journal.pone.0211919
10. Ge L, Tian JH, Li YN, et al. Association between prospective registration and overall reporting and methodological quality of systematic reviews: a meta-epidemiological study. Journal of clinical epidemiology 2018;93:45-55. doi: 10.1016/j.jclinepi.2017.10.012 [published Online First: 2017/11/08]
11. Khaleel S, Sathianathen N, Balaji P, et al. Quality of urological systematic reviews registered in PROSPERO. BJU international 2019;124(2):195-96. doi: 10.1111/bju.14742 [published Online First: 2019/03/14]
12. Parsons R, Golder S, Watt I. More than one-third of systematic reviews did not fully report the adverse events outcome. Journal of clinical epidemiology 2019;108:95-101. doi: https://doi.org/10.1016/j.jclinepi.2018.12.007
13. Tricco AC, Cogo E, Page MJ, et al. A third of systematic reviews changed or did not specify the primary outcome: a PROSPERO register study. Journal of clinical epidemiology 2016;79:46-54. doi: 10.1016/j.jclinepi.2016.03.025 [published Online First: 2016/04/16]
14. Kelly SE, Moher D, Clifford TJ. Quality of conduct and reporting in rapid reviews: an exploration of compliance with PRISMA and AMSTAR guidelines. Systematic reviews 2016;5(1):79. doi: 10.1186/s13643-016-0258-9
15. Peters JPM, Hooft L, Grolman W, et al. Reporting Quality of Systematic Reviews and Meta-Analyses of Otorhinolaryngologic Articles Based on the PRISMA Statement. PLOS ONE 2015;10(8):e0136540. doi: 10.1371/journal.pone.0136540
16. Page MJ, Moher D. Evaluations of the uptake and impact of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement and extensions: a scoping review. Systematic reviews 2017;6(1):263. doi: 10.1186/s13643-017-0663-8 [published Online First: 2017/12/21]
17. Sideri S, Papageorgiou SN, Eliades T. Registration in the international prospective register of systematic reviews (PROSPERO) of systematic review protocols was associated with

increased review quality. Journal of clinical epidemiology 2018;100:103-10. doi: 10.1016/j.jclinepi.2018.01.003 [published Online First: 2018/01/18]
18. Nawijn F, Ham WHW, Houwert RM, et al. Quality of reporting of systematic reviews and meta-analyses in emergency medicine based on the PRISMA statement. BMC Emergency Medicine 2019;19(1):19. doi: 10.1186/s12873-019-0233-6
19. Moher D, Schulz KF, Simera I, et al. Guidance for developers of health research reporting guidelines. PLoS Med 2010;7 doi: 10.1371/journal.pmed.1000217
20. R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Items, scoring options and guidance/rules for assessment of PROSPERO records compared to PRISMA-P reporting requirements

FINAL Version1.1 8 April 2020

The assessment form contains a breakdown of PRISMA-P reporting items re-organised to match as far as possible the order in which information is presented in PROSPERO. Numbering of items matches the numbering in PRISMA-P for ease of referral to the field in the E&E paper.

A number of fields have been excluded: details of these and the reasons for exclusion are documented in the study protocol.

Sub-questions (items) have been included for sections as not all the information for PRISMA-P is required/requested in PROSPERO. These elements will be included in the total scoring for each item, and then reported in the detailed breakdown of items in the context of what PROSPERO requires.

Information required by PRISMA-P may be contained in any field within PROSPERO – it does not have to be in the expected field. E.g. Context may be indicated in the Context, Condition or domain, Research question, or Objectives fields. The exceptions are: Q1 where the information must be in the Title; and Q7 where the information must be included in the Review question (see below).

If you are really unsure about something, remember we are assessing whether they have reported how they are approaching something, not judging the quality of their methods. You can make a comment in the final text box and we are doing a blind assessment and any discrepancies will be discussed.

Rules for specific fields

Item	Options	Scoring rules
1a. Identification in the title: Identify the report as a protocol	Reported /Not reported	Refers to information in the title only. If it does not state in the title that it is a protocol, the score is 'Not reported'.
1a. Identification in the title: Identify the report as a systematic review / meta-analysis / or other form of systematic review such as a rapid review	Reported /Not reported	Refers to information in the title only. If it does not state in the title that it is a systematic review or meta-analysis or variation on a systematic review such as a rapid review, the score is 'Not reported'.
1b. Update: If the protocol is for an update of a previous systematic review, identify as such in the title	Reported /Not reported /**Not an update**	Refers to information in the title only. If it says Update in the title then clearly the score is Yes**. Updates are rare therefore most frequent/default response is likely to be Not an update.** However, if in the course of completing the assessment it becomes clear that the reviewers are in fact updating an existing review, this should be revisited and

		scored as 'Not reported'. PROSPERO contains the field "Details of any existing review of the same topic by the same authors", which if completed appears in the record and may indicate that this is an update (unless of course they just say 'none'!). Looking for pre-existing reviews is an essential part of avoiding duplication of reviews; this does not count as them planning to update a review. Updates of reviews are still rare in PROSPERO registered non-Cochrane review.
INTRODUCTION		
7. Objectives: Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Reported /Not reported /Not applicable	Refers to the information given in the research question, which should include reference to participants, interventions, comparators, and outcomes (PICO) – score Reported/ Not reported/Not applicable for each element. N.B while PROSPERO then asks for each of these elements separately, PRISMA-P guidance for this is specific to the research question. We will accept anything that alludes to an element as = Reported (e.g. P: "aging individuals", I "which treatment is most likely to be effective", C: "other interventions" O: "manage uncertainty" = Reported. However, something like "effective and safe" as an outcome here is too vague = Not reported. For non-comparative reviews (e.g. efficacy and safety), Comparator should = Not applicable.
Participants		
Intervention		
Comparator		
Outcome(s)		
METHODS		
9. Information sources: Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage		
Electronic database(s) named	Reported /Not reported	'Reported' if any bibliographic database(s) are named e.g. PubMed, MedLine, Embase, CENTRAL, LILACS
Grey literature sources named or statement of no grey lit searches planned		e.g. databases of theses, conference abstracts, OpenGrey, System for Information on Grey Literature in Europe (Sigle)
Study registries (inc. CENTRAL)		e.g. PROSPERO, clinicaltrials.gov. N.B. CENTRAL includes details of on-going trials from clinicaltrials.gov and the WHO registries platform = Reported. Likewise, searching Cochrane Library includes CENTRAL.
Contact with study authors planned or statement that contact not planned		Will they be contacting authors, leaders in the field to ask them to identify studies/provide information on unpublished work?
Other: e.g. hand searching reference lists of included studies		Anything not included above that relates to getting hold of study papers or data relevant to the review

Planned search dates		'Reported' if they say e.g. databases to be searched from inception or a date (July 2000) or they indicate a date when the searches will be carried out. Plan to update searches before final analysis = Reported. Don't give any indication = 'Not reported'
10. Search strategy: Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated		
Draft search strategy provided	Reported /Not reported /Not applicable	e.g. list of search terms and how they will be combined for a specific database e.g. PubMed This may or may not include combining results to arrive at a final dataset: some topics are so niche they only require a simple search. If 'strategy attached' = Reported even if not accessible.
Search terms given alone i.e. not formal strategy for a database		List of words with no information about how they will be combined or where they will be used (Not applicable if full search strategy provided)
Approach to limits/restrictions reported e.g. dates; statement of no limits		Any mention of limiting the searches by one or more items such as date, language or any other parameter(s). A statement that there will be no limitations/restrictions used should score a 'Reported' as they have reported on this item. This item should never = Not applicable.
6. Rationale: Describe the rationale for the review in the context of what is already known		
Rationale described (e.g. existing evidence base)	Reported /Not reported	Statement about why this review is needed. E.g. unanswered question - no existing review; to inform guideline development; new studies since last review = update or new review. The focus for this item is more on how the findings will be used.
Context provided (e.g. scale of problem/condition)		Background on clinical condition; thinking behind the planned review eligibility criteria e.g. informed by PPI work. Focus for context is more on how important the issue is. NB. The rationale and context are often presented as a single statement rather than separate elements so may need unpicking.
8. Eligibility criteria: Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review		
Study design specified	Reported /Not reported /Not applicable	Types of study designs to be included are listed, or if no restriction on type of design, statement saying so
Setting (condition or domain) specified		Should be in specific PROSPERO field: Condition or domain being studied. There may be more info in the non-mandatory 'Context' field
Population detailed		Population identified in sufficient detail to enable data extraction
Intervention specified		Intervention described in sufficient detail to enable data extraction
Comparator specified		This may be an alternate specific intervention, usual care or for network M-A interventions are compared with each other

Outcome(s) specified		Outcome(s) listed
13. Outcomes and prioritisation: List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale		
Primary/main outcome(s) specified as such	Reported /Not reported /Not applicable	Primary/main outcome(s) described and identified as such. Where a list of outcomes is presented under the Primary outcome heading = Reported
Primary/main outcome measure(s) specified		Any measure(s) specified / included in description of outcome(s) = Reported.
Additional outcomes specified as such		Other outcomes specified = Reported None = Reported
Additional outcome(s): measure(s) specified		Any measure(s) specified / included in description of outcome(s) = Reported. If No additional outcomes stated = Not applicable
Rationale for choice of outcome(s)		Do they say why the outcomes are appropriate, give reason for choice?
Study records		
11a. Data management: Describe the mechanism(s) that will be used to manage records and data throughout the review		
Software named/type indicated	Reported /Not reported	Details of how the search results will be handled e.g RevMan, Covidence, Eppi-reviewer, or unspecified 'software'.
De-duplication planned		A statement anywhere to say that search results will be de-duplicated or how multiple reports of the same study will be handled.
11b. Selection process: State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)		
Initial screening process described	Reported /Not reported	Title and abstract screening – number of reviewers/ resolution of disagreements: if any elements of the process described = Reported.
Full paper screening process described		Description of how the eligibility criteria will be applied to the records from initial screening – e.g. number of reviewers/resolution of disagreements: if any elements of the process described = Reported.
11c. Data collection process: Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators		
Data extraction form (develop own/use template/pilot)	Reported /Not reported	Mechanism for consistent recording of extracted data, e.g. form to be developed or use of standardised form such as Cochrane data extraction – ideally piloted but not essential.
Data extraction process described		How data extraction to be performed, e.g. double blind/ disagreements resolved by discussion/third reviewer. N.B. data extraction and risk of bias assessment may be undertaken at the same time i.e. as part of a single process.
Obtain missing data		Statement about how missing data will be dealt with: e.g. contact study authors/account for in statistical analyses
12. Data items: List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications		

List of data for extraction	Reported /Not reported	Items to be included in data extraction listed
Variables defined		Definitions for the items for extraction e.g. unit of measurement for items presented such as time points for the review outcomes
Any data assumptions reported		Statement of any pre-specified assumptions e.g. what they will do with unclear information or missing data
14. Risk of bias in individual studies: Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis		
No risk of bias assessment planned and justification provided	Reported /Not reported /Not applicable	If risk of bias details are provided, this item = Not applicable. A statement to say the authors are not going to carry out a risk of bias assessment and provide an explanation to justify this = Reported (and following items would be Not applicable). Anything less = Not reported.
Risk of bias tools named for all study types included		Risk of Bias tool named for assessment of each study design to be included in the review. If just one tool named but implication is same tool used for different study designs included = Reported. If specifically say using a named tool for type of study but then don't name tools for other study designs to be included = Not reported. If clearly using a recognised tool but do not actually name it = Reported. [Examples of tools for study designs other than RCTs: Cochrane has ROBINS-I, SIGN, CASP, JBI, Newcastle Ottawa Scale (NOS), Down and Blacks, PEDRo. N.B. There are probably about 200 such tools – *if in doubt do a quick google search*]
Outcome or study level or both		RoB should look at assessing the potential for bias: a) in specific domains within each of the included studies such as incomplete outcome data, selective outcome reporting, and/or b) the overall risk of bias for each study. N.B. some RoB tools are designed to assess at both study and outcome levels (e.g. Cochrane RoB/RoB2, NOS, ROBINS-I, ROBINS-E, QUADAS, JBI, Downs and Black) If one of these is used or the authors state they will assess at either or both levels = Reported. N.B Jadad, PEDRo and Drummond are not RoB tools but assess methodological quality of RCTs/Economic evaluations = Not reported.
Domains/outcomes for risk of bias assessment stated		The constructs for assessment are listed, defined and judgment options (e.g. high low unclear) given = reported If constructs listed and defined but judgement options not specifically given – consider if tool to be used has pre-specified constructs and judgement options if so = Reported

		[Those listed above have judgement options assigned – including Jadad and PEDRo].
Risk of bias assessment process described		Any statement of how risk of bias will be undertaken e.g. two reviewers independently/blinded +/- method for resolution of disagreements
How risk of bias findings will be used in the synthesis		Statement of whether studies will/will not be excluded based on risk of bias score. Or include all studies meeting criteria but account for risk of bias in statistical analyses (sub-group/sensitivity analyses)
Data		
15a. Synthesis: Describe criteria under which study data will be quantitatively synthesized		
Criteria for doing a quantitative synthesis/ M-A described	Reported /Not reported /Not applicable	Statement to say under what circumstances a quantitative synthesis/ meta-analysis (M-A) will be undertaken (e.g. if studies are sufficiently homogeneous) = Reported Quant/M-A planned but no mention of criteria for going ahead = Not reported M-A will not be undertaken (e.g. narrative or qualitative synthesis planned = Not applicable
15b. If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)		
Summary measures	Reported /Not reported /Not applicable	Details of effect measures; e.g. RR or mean difference
Statistical method		Method to be used should be stated e.g. inverse variance, DerSimonian-Laired, Mantel-Haenszel, Baysian
Use of fixed or random effects or both		Statement about which model(s) they will apply = Reported
Data handling: conversion to same format		Details of how data will be handled to ensure measures are converted/presented in the same format. E.g. plan to calculate standardised mean difference
Data handling: missing data		Approach to handling of rare events; imputation of missing data.
Combining data/ exploration of consistency		Plans for how data will be combined and how they will evaluate between study inconsistency (heterogeneity)
Name of software to be used for meta-analysis		Type or name of software to be used for performing the meta-analysis e.g. Stata, R, RevMan
15c. Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)		
Subgroup analyses planned: co-variants named	Reported /Not reported /Not applicable	Statement that sub-group analyses are planned - must include the co-variants. Statement that no-subgroup analyses are planned = Reported Post-hoc analyses planned without co-variants = Reported
Methods for subgroup analyses reported		How groups will be divided, use of fixed or random effects. Statement that no subgroup analyses planned = Not applicable
Sensitivity analyses planned		Statement that sensitivity analyses are planned or not planned, to include items to be examined

15d. If quantitative synthesis is not appropriate, describe the type of summary planned		
Descriptive, Narrative or Qualitative synthesis planned	Reported /Not reported /Not applicable	Statement of how data not suitable for reporting in the M-A will be presented. Where no M-A, description of method for data synthesis e.g. narrative or qualitative. If all data to be presented in M-A = Not applicable
Narrative or qualitative synthesis methods described		For a narrative synthesis details of how studies/findings will be combined/stratified/prioritised narratively (in text or tables): i.e. some form of synthesis beyond providing a description of the studies and data extracted, may reference method e.g. CRD guidance. Any methods information beyond statement of type = Reported. For reviews of qualitative studies, plans how the synthesis will be carried out e.g. thematic analysis or framework development etc should be provided. Either reported or Not reported
Other analyses planned e.g. cost data		Details of any other analyses such as cost effectiveness are provided = Reported. If no mention in record of data being collected for other analyses = Not applicable. If e.g. cost data collected but no analysis planned = Not reported
16. Meta-bias(es): Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)		
Publication bias to be assessed	Reported /Not reported /Not applicable	Methods for testing for publication bias should be given e.g. funnel plot; Egger's test. NB Not applicable for Narrative Synthesis
Outcome reporting bias to be assessed		Methods for assessing potential for outcome reporting bias should be given, e.g. ORBIT system; sensitivity analysis. NB Not applicable for Narrative Synthesis
17. Confidence in cumulative evidence: Describe how the strength of the body of evidence will be assessed (e.g., GRADE)		
Overall assessment of included studies planned or statement that no overall assessment will be made	Reported /Not reported /Not applicable	Is there a plan to look at overall study quality in addition to the ROB assessment of individual studies?
Methods specified (e.g. GRADE)		If an overall assessment is planned, are the methods specified? (Not applicable if not planned – Score Not reported if previous question is Not reported)
Comment or observations on this record		For any observations you may have about this record or any issue you may want to raise. Please also feel free to make use of the questions sheet in the shared drive

PRISMA-P scoring sheet for PROSPERO records

Assessment form Version 1.1 08 April 2020

*Required

1. PROSPERO RECORD UNIQUE ID: 11 digit number only *

_____

2. RESEARCHER ID *

Tick all that apply.

- [ ] Alex
- [ ] Alison
- [ ] Andrew
- [ ] Fiona
- [ ] Sam
- [ ] Sarah
- [ ] Sophie

ADMINISTRATION

Elaboration and explanation paper: https://www.bmj.com/content/349/bmj.g7647

3. 1a. Identification in the title: Identify the report as a protocol *

Tick all that apply.

- [ ] Reported
- [ ] Not reported

4. 1a. Identification in the title: Identify the report as a systematic review / meta-analysis / or other form of systematic review such as a rapid review *

Tick all that apply.

- [ ] Reported
- [ ] Not reported

5. 1b. Update: If the protocol is for an update of a previous systematic review, identify it as su in the title *

Tick all that apply.

- [ ] Reported
- [ ] Not reported
- [ ] Not an update

INTRODUCTION

Elaboration and explanation paper: https://www.bmj.com/content/349/bmj.g7647

6. 7. Objectives: Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) *

This should be in the Review Question field.

Mark only one oval per row.

	Reported	Not reported	Not applicable
Population	◯	◯	◯
Intervention	◯	◯	◯
Comparator	◯	◯	◯
Outcomes	◯	◯	◯

METHODS

Elaboration and explanation paper: https://www.bmj.com/content/349/bmj.g7647

7. 9. Information sources: Describe all intended information sources (e.g., electronic database contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage *

Mark only one oval per row.

	Reported	Not reported
Electronic database(s) named	◯	◯
Grey literature sources named or statement of no grey lit searches planned	◯	◯
Study registries (inc. CENTRAL)	◯	◯
Contact with study authors planned or statement that contact not planned	◯	◯
Other: e.g. hand searching reference lists of included studies	◯	◯
Planned search dates	◯	◯

8. 10. Search strategy: Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated *

Mark only one oval per row.

	Reported	Not reported	Not applicable
Draft search strategy provided	◯	◯	◯
Search terms given alone i.e. not formal strategy for a database	◯	◯	◯
Approach to limits/restrictions reported e.g. language or dates/statement of no limits	◯	◯	◯

9. 6. Rationale: Describe the rationale for the review in the context of what is already known *

Do they explain why the review is needed and refer to what is already know? This information may be in the context fie or provided elsewhere.

Mark only one oval per row.

	Reported	Not reported
Rationale described (e.g. existing evidence base)		
Context provided (e.g. scale of problem/condition)		

10. 8. Eligibility criteria: Specify the study characteristics (e.g., PICO, study design, setting, tir frame) and report characteristics (e.g., years considered, language, publication status) to used as criteria for eligibility for the review *

Mark only one oval per row.

	Reported	Not reported	Not applicable
Study design specified			
Setting (condition or domain) specified			
Population detailed			
Intervention specified			
Comparator specified			
Outcome(s) specified			

11. 13. Outcomes and prioritisation: List and define all outcomes for which data will be sough including prioritisation of main and additional outcomes, with rationale *

Mark only one oval per row.

	Reported	Not reported	Not applicable
Primary/main outcome(s) specified as such			
Primary/main outcome(s) measure specified			
Additional outcomes specified/ state None			
Additional outcomes: measures specified			
Rationale for choice of outcome(s)			

STUDY RECORDS

Elaboration and explanation paper: https://www.bmj.com/content/349/bmj.g7647

12. 11a. Data management: Describe the mechanism(s) that will be used to manage records a data throughout the review *

Mark only one oval per row.

	Reported	Not reported
Software named/type indicated		
De-duplication planned		

13. 11b. Selection process: State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) *

Mark only one oval per row.

	Reported	Not reported
Initial screening process described		
Full paper screening process described		

14. 11c. Data collection process: Describe planned method of extracting data from reports (e. piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators *

Mark only one oval per row.

	Reported	Not reported
Data extraction form (develop own/use template/pilot)		
Data extraction process described		
Obtain missing data		

15. 12. Data items: List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications *

Mark only one oval per row.

	Reported	Not reported
List of data for extraction		
Variables defined		
Any data assumptions reported		

16. 14. Risk of bias in individual studies: Describe anticipated methods for assessing risk of bi of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis *

Mark only one oval per row.

	Reported	Not reported	Not applicable
No risk of bias assessment planned and justification provided			
Risk of bias tools named for all study types included			
Outcome or study level or both			
Domains/outcomes for risk of bias assessment stated			
Risk of bias assessment process described			
How risk of bias findings will be used in the synthesis			

DATA

Elaboration and explanation paper: https://www.bmj.com/content/349/bmj.g7647

17. 15a. Synthesis: Describe criteria under which study data will be quantitatively synthesized

Mark only one oval per row.

	Reported	Not reported	Not applicable
Criteria for doing a quantitative synthesis/M-A described			

18. 15b. If data are appropriate for quantitative synthesis, describe planned summary measur methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I squared, Kendall's tau)

Mark only one oval per row.

	Reported	Not reported	Not applicable
Summary measures			
Statistical method			
Use of fixed or random effects or both			
Data handling: conversion to same format			
Data handling: missing data			
Combining data/ exploration of consistency			
Name of software to be used for meta-analysis			

19. 15c. Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)

Mark only one oval per row.

	Reported	Not reported	Not applicable
Subgroup analyses planned: co-variants named			
Methods for subgroup analyses reported			
Sensitivity analyses planned			

20. 15d. If quantitative synthesis is not appropriate, describe the type of summary planned *

Mark only one oval per row.

	Reported	Not reported	Not applicable
Descriptive, Narrative, or Qualitative synthesis planned			
Narrative or qualitative synthesis methods described			
Other analyses planned			

21. 16. Meta-bias(es): Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) *

Mark only one oval per row.

	Reported	Not reported	Not applicable
Publication bias to be assessed			
Outcome reporting bias to be assessed			

22. 17. Confidence in cumulative evidence: Describe how the strength of the body of evidenc will be assessed (e.g., GRADE) *

Mark only one oval per row.

	Reported	Not reported	Not applicable
Overall assessment of included studies planned or statement that no overall assessment will be made			
Methods specified (e.g. GRADE)			

23. Comment or observations on this record

Please add anything

Scores for all sub-group analyses

PRISMA-P REPORTING ITEM	Stage of review at registration:		Meta-analysis planed or not		Lead country for the review	
	Before screening started (245)	After screening started (188)	Meta-analysis planned (250)	No meta-analysis planned (183)	OECD member (237)	Not an OECD member (196)
1a. Identification in the title: Identify the report as a protocol of a systematic review	14	8	11	11	15	7
1b. Update: If the protocol is for an update of a previous systematic review	241	183	242	182	234	190
6. Rationale	24	14	22	16	15	23
7. Objectives: Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	60	45	67	38	68	37
8. Eligibility criteria: Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	218	168	223	163	206	180
9. Information sources: Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	1	1	2	0	2	0
10. Search strategy: Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	34	42	40	36	37	39
11a. Data management: Describe the mechanism(s) that will be used to manage records and data throughout the review	11	6	8	9	11	6
11b. Selection process: State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	128	88	119	97	131	85
11c. Data collection process: Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	33	19	32	20	37	15
12. Data items: List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	3	3	3	3	3	3
13. Outcomes and prioritisation: List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale	2	1	3	0	3	0
14. Risk of bias in individual studies: Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	24	19	30	13	25	18
15a. Synthesis: Describe criteria under which study data will be quantitatively synthesized	122	78	91	109	127	73
15b. If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	36	34	5	65	45	25
15c. Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	40	45	12	73	56	29
15d. If quantitative synthesis is not appropriate, describe the type of summary planned	127	100	146	81	109	118
16. Meta-bias(es): Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	38	34	6	66	46	26
17. Confidence in cumulative evidence: Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	25	12	26	11	20	17