Jennifer Marie McCaig Tetzlaff
AUTEUR DE LA THÈSE / AUTHOR OF THESIS

M.Sc. (Epidemiology)
GRADE / DEGREE

Department of Epidemiology and Community Medicine
FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

Developing an Evidence-Based Reporting Guideline for Randomized Controlled Trial Protocols: The SPIRIT Initiative

TITRE DE LA THÈSE / TITLE OF THESIS

David Moher
DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

Lucie Brosseau

Brendon Wilson

Gary W. Slater
Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies
Developing an evidence-based reporting guideline for randomized controlled trial protocols: The SPIRIT Initiative

Jennifer Marie Tetzlaff

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies
In partial fulfillment of the requirements
For the MSc degree in Epidemiology and Community Medicine

Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa

© Jennifer Tetzlaff, Ottawa, Canada, 2010
Abstract

Protocols of randomized controlled trials (RCT) are important for many stakeholders including trialists, consumers, ethics boards, funding agencies and journal editors. However, RCT protocols often incompletely describe important trial details or describe inadequate methods. Biased methodological changes are also prevalent. This thesis’ objective was to provide the evidence-base for the SPIRIT (Standard Protocol Items for Randomized Trials) Initiative, which aims to increase transparency by developing a reporting guideline for RCT protocols. Guideline content was developed and refined by: 1) a Delphi survey of key stakeholders and 2) a systematic review of empirical evidence. These two components yielded divergent yet complementary perspectives for concepts that RCT protocols should address. Cumulatively, 41 concepts related to trial methodology, administration/organization, ethics and dissemination were recommended for inclusion and 24 concepts for further discussion. These findings inform the SPIRIT guideline content and may ultimately help to improve protocol transparency and the validity of healthcare literature.
Acknowledgements

Many people have helped make this thesis possible. First and very importantly, I extend a sincere thank you to my supervisors, Drs. David Moher and An-Wen Chan. They devoted countless hours to guiding and supporting this work by helping develop the methodology; pilot testing and participating in the Delphi survey; screening and performing data extraction for the systematic review; and providing exceptional feedback on this thesis. Most importantly, they inspired, encouraged and motivated me. I thank them wholeheartedly for the opportunity to contribute to this very important initiative.

I am also grateful to other colleagues. Dr. Andrea Tricco helped develop the methods for the systematic review and validated early screening. Dr. Margaret Sampson helped develop the search strategies for the systematic review. Dr. Sally Hopewell provided guidance on the Delphi technique.

I thank the SPIRIT Steering group and Delphi panellists for nominating additional participants, pilot testing Delphi rounds and, mostly, for their dedication to seeing this process succeed. Their substantive feedback and support was very much appreciated given the significant request for their time.

I thank the Department of Epidemiology and Community Medicine for allowing my participation in this program. I feel extremely fortunate to have had this fantastic learning experience.

Finally, I am indebted to my immediate and extended family; from your encouraging words to the many cumulative hours helping care for Aiden – thank you. To Aiden, my beautiful baby boy, for providing additional motivation to complete this work and many moments to stop and laugh when the thesis might have otherwise consumed me! Most importantly, to my husband Jeff who, due to his patience, understanding and unfailing support even given the absences and difficulties that a tremendous effort like this brings, is truly one of the main reasons this work is actually complete - I am forever grateful.
# Table of contents

ABSTRACT .......................................................................................................................... II

ACKNOWLEDGEMENTS ....................................................................................................... III

LIST OF TABLES .................................................................................................................. VI

LIST OF FIGURES ............................................................................................................... VII

LIST OF ABBREVIATIONS ................................................................................................... VIII

1.0 INTRODUCTION ........................................................................................................... 1

2.0 AIMS AND OBJECTIVES ............................................................................................. 12

3.0 DEVELOPMENT AND REFINEMENT OF GUIDELINE CONTENT VIA DELPHI CONSENSUS
........................................................................................................................................... 13

3.1 OBJECTIVE ................................................................................................................ 13

3.2 METHODS .................................................................................................................... 13

3.2.1 Overview – Delphi methodology ............................................................................ 13

3.2.2 Selection of participants ....................................................................................... 13

3.2.3 Selection of preliminary items ............................................................................. 15

3.2.4 Delphi ................................................................................................................... 16

3.2.5 Analysis .................................................................................................................. 20

3.3 RESULTS ..................................................................................................................... 20

3.3.1 Delphi participants ............................................................................................... 20

3.3.2 Delphi results ........................................................................................................ 22

4.0 IDENTIFICATION AND SYNTHESIS OF EVIDENCE INFORMING GUIDELINE CONTENT .. 38

4.1 OBJECTIVE ................................................................................................................ 38

4.2 METHODS .................................................................................................................... 38

4.2.1 Criteria for considering studies for review ............................................................. 38

4.2.2 Search strategy for identification of studies .......................................................... 40

4.2.3 Methods of the review .......................................................................................... 41

4.3 RESULTS ..................................................................................................................... 44

4.3.1 Study selection ...................................................................................................... 44

4.3.2 Study characteristics ............................................................................................ 46

4.3.3 Synthesis of results .............................................................................................. 49

5.0 SYNTHESIS OF EVIDENCE FROM DELPHI CONSENSUS SURVEY AND SYSTEMATIC
REVIEW ................................................................................................................................ 56

5.1 OBJECTIVE ................................................................................................................ 56

5.2 METHODS .................................................................................................................... 56

5.3 RESULTS ..................................................................................................................... 57

5.3.1 Overview ................................................................................................................ 57

5.3.2 Item-specific recommendations ........................................................................... 58

5.3.3 Summary of recommendations ............................................................................ 79

6.0 DISCUSSION ................................................................................................................. 80

6.1 SUMMARY OF MAIN FINDINGS ............................................................................. 80

6.2 RELEVANCE TO KEY GROUPS ............................................................................... 81

6.3 COMPARISON WITH OTHER EXISTING GUIDELINES ................................................. 88

6.4 LIMITATIONS OF APPROACHES .............................................................................. 92
List of Tables

TABLE 1: CHARACTERISTICS OF DELPHI SURVEY PANELLISTS (N = 96) ......................................................... 22
TABLE 2: INITIAL SET OF CHECKLIST ITEMS: RESULTS FROM DELPHI SURVEY ROUNDS 1 AND 2 ...... 24
TABLE 3: NEW ITEMS SUGGESTED BY PANELLISTS IN DELPHI ROUND 1: RESULTS FROM DELPHI SURVEY ROUNDS 2 AND 3 ................................................................. 31
TABLE 4: ITEMS RATED ‘MILD’ IN DELPHI ROUND 2: RESULTS FROM DELPHI SURVEY ROUND 3 ................................................................. 34
TABLE 5: ITEMS REQUIRING ADDITIONAL DELINEATION/CLARIFICATION: RESULTS FROM DELPHI SURVEY ROUND 3 ................................................................. 35
TABLE 6: CRITERIA FOR GRADING STRENGTH OF EVIDENCE FROM THE SYSTEMATIC REVIEW FOR EACH CANDIDATE CHECKLIST ITEM ................................................................. 44
TABLE 7: CHARACTERISTICS OF STUDIES INCLUDED IN SYSTEMATIC REVIEW ................................................................. 48
TABLE 8: SYSTEMATIC REVIEW RESULTS ................................................................. 50
TABLE 9: SYNTHESIS OF DELPHI SURVEY AND SYSTEMATIC REVIEW RESULTS: RECOMMENDATIONS FOR THE SPIRIT CHECKLIST - SECTION 1: GENERAL INFORMATION ................................................................. 59
TABLE 10: SYNTHESIS OF DELPHI SURVEY AND SYSTEMATIC REVIEW RESULTS: RECOMMENDATIONS FOR THE SPIRIT CHECKLIST - SECTION 2: INTRODUCTION ................................................................. 60
TABLE 11: SYNTHESIS OF DELPHI SURVEY AND SYSTEMATIC REVIEW RESULTS: RECOMMENDATIONS FOR THE SPIRIT CHECKLIST - SECTION 3: METHODS ................................................................. 62
TABLE 12: SYNTHESIS OF DELPHI SURVEY AND SYSTEMATIC REVIEW RESULTS: RECOMMENDATIONS FOR THE SPIRIT CHECKLIST - SECTION 4: TRIAL ORGANIZATION AND ADMINISTRATION 71
TABLE 13: SYNTHESIS OF DELPHI SURVEY AND SYSTEMATIC REVIEW RESULTS: RECOMMENDATIONS FOR THE SPIRIT CHECKLIST - SECTION 5: ETHICAL CONSIDERATIONS ................................................................. 75
TABLE 14: SYNTHESIS OF DELPHI SURVEY AND SYSTEMATIC REVIEW RESULTS: RECOMMENDATIONS FOR THE SPIRIT CHECKLIST - SECTION 6: REPORTING AND DISSEMINATION ................................................................. 77
TABLE 15: SYNTHESIS OF DELPHI SURVEY AND SYSTEMATIC REVIEW RESULTS: RECOMMENDATIONS FOR THE SPIRIT CHECKLIST - SECTION 7: OTHER ................................................................. 79
TABLE 16: ITEMS INCLUDED IN PREVIOUS PROTOCOL GUIDELINES ................................................................. 130
TABLE 17: EXAMPLE OF ITEM-SPECIFIC SYSTEMATIC REVIEW DATA EXTRACTION TABLE ................................................................. 168
TABLE 18: COMPARISON OF RECOMMENDATIONS WITH SELECT PROMINENT GUIDELINES ................................................................. 170
List of Figures

FIGURE 1: EXAMPLE OF QUESTIONNAIRE LAYOUT FROM DELPHI ROUND 1 ........................................ 17
FIGURE 2: EXAMPLE OF QUESTIONNAIRE LAYOUT FROM DELPHI ROUND 2 .................................. 19
FIGURE 3: EXAMPLE OF QUESTIONNAIRE LAYOUT FROM DELPHI ROUND 3: A) ITEMS IN PART 4, B) ITEMS IN PART 5 .................................................................................. 20
FIGURE 4: FLOW OF ITEMS THROUGH DELPHI CONSENSUS SURVEY ........................................... 23
FIGURE 5: SYSTEMATIC REVIEW FLOW-DIAGRAM ........................................................................... 46
FIGURE 6: EXAMPLES OF DELPHI FREQUENCY DISTRIBUTIONS ...................................................... 166
FIGURE 7: EXAMPLES OF ITEM-SPECIFIC DELPHI COMMENTS ....................................................... 167
**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDSR</td>
<td>Cochrane Database of Systematic Reviews</td>
</tr>
<tr>
<td>CMR</td>
<td>Cochrane Methodology Register</td>
</tr>
<tr>
<td>CONSORT</td>
<td>CONsolidated Standards Of Reporting Trials</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
</tr>
<tr>
<td>EQUATOR</td>
<td>Enhancing the QUAlity and Transparency Of health Research</td>
</tr>
<tr>
<td>ICH E6</td>
<td>International Conference on Harmonization Tripartite Guideline for Good Clinical Practice E6</td>
</tr>
<tr>
<td>IQR</td>
<td>Inter-Quartile Range</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>REC/IRB</td>
<td>Research Ethics Committee/Institutional Review Board</td>
</tr>
<tr>
<td>SPIRIT</td>
<td>Standard Protocol Items for Randomized Trials</td>
</tr>
</tbody>
</table>
1.0 Introduction

Every randomized controlled trial (RCT) requires a protocol, a document describing its rationale, methods, proposed analyses, and organizational/administrative details. Protocols should be a comprehensive account of the proposed trial methodology, from trial inception to publication of the research results. They provide investigators with a document to guide trial conduct; trial participants with a detailed description of trial methodology; research ethics committees/institutional review boards (REC/IRBs) with a foreknowledge of predefined safeguards to protect participants’ interest; and research funders with a means of accountability for adherence to proposed methods. Protocol review is essential to ensure that trials meet scientific and ethical standards to protect all participants and future patients. As such, RCT protocol content is extremely important.

Protocols must be clear, detailed and transparent, not only for practical reasons as outlined above, but also to protect the trial from sources of bias. Bias may affect a trial throughout the period of its conduct, such as during recruitment, interim analyses or early stopping, and at completion, such as during analysis and preparation for publication. For example, the absence of concealed patient allocation, lack of blinding/masking and inappropriate randomization methods have been shown to bias treatment effect estimates. Protocol development is an opportune time to identify design deficiencies and reduce such potentially avoidable biases. Therefore, clearly written trial protocols are imperative so researchers, funding agencies and REC/IRBs can accurately assess trial methodology.

Explicitly describing methods and analyses in protocols prior to trial inception also facilitates external monitoring of whether biased changes are made based on the interim or final trial results. Comparisons of trial protocols with corresponding journal publications
have consistently shown important, unacknowledged and biased differences between them. For example, surveys have shown modifications of primary outcomes between the protocol and the final report in approximately half of all trials examined\textsuperscript{3, 5, 11}. A recent systematic review of such studies suggests that between 13 and 31% of protocol-defined primary outcomes are omitted from journal publications of trial results, and between 10 and 18% of final publications report primary outcomes not mentioned in the protocol\textsuperscript{5}. Furthermore, outcomes reported in final publications were significantly more likely to be statistically significant than those omitted. Potentially biased changes to or reporting of trial methods has also recently been noted for sample size calculations\textsuperscript{12} and analysis methods including planned subgroup analyses\textsuperscript{13}. While valid reasons may exist for changing trial methods, these changes should be made explicit, approved by REC/IRBs and acknowledged in trial reports, allowing readers the opportunity to assess the potential for bias.

In an attempt to monitor such problems, some journals now require submission of protocols with manuscripts of trial results for peer review\textsuperscript{14-18}. However, even with such initiatives, the absence of complete reporting in clinical trial protocols makes comparing protocols and final reports difficult. A high proportion of trial protocols do not adequately describe important methodological details. For example, incomplete reporting in protocols has been shown for factors such as primary outcomes (25%)\textsuperscript{11}, allocation concealment (59-83%, depending on stringency of definition)\textsuperscript{19}, power calculations (27%)\textsuperscript{12} and sponsor and investigators roles in aspects of trial conduct\textsuperscript{20}.

Incomplete reporting is not specific to clinical trial protocols. Numerous studies have provided evidence for such inadequacies in final research publications in many specialties and in trials of various study designs\textsuperscript{21-26}. Whereas some research suggests that inadequate
reporting does not necessarily indicate poor trial conduct, the lack of transparency makes critical assessment of trials difficult.

As a result, a number of evidence-based initiatives have set out to improve the quality of journal publications to guide recommendations. For example, the well-endorsed CONSORT (CONsolidated Standards Of Reporting Trials) Statement, a guideline aimed at increasing the transparency of publications of parallel-group RCTs, has prompted the development of extensions for other trial designs, such as cluster RCTs, pragmatic trials and equivalence and non-inferiority trials; for specific intervention types, such as non-pharmacologic treatments and herbal interventions; and for other types of RCT reports, such as abstracts. Additionally, following the motivation for CONSORT, other independent initiatives have been developed. Some of the initiatives, such as CONSORT and STARD (STAndards for the Reporting of Diagnostic accuracy studies), have been empirically shown to improve report quality. As in the case of CONSORT, some have also become endorsed by major editorial groups such as the International Committee of Medical Journal Editors, the World Association of Medical Editors, the Council of Science Editors and editorial boards of major healthcare journals.

As a consequence of some of these initiatives, the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network, an international collaboration consisting of reporting guideline developers, journal editors, peer reviewers, medical writers and funding agencies, was launched. The Network aims to increase the transparency, and hence enhance the reliability of healthcare literature. Two recent projects conducted by this group, a survey of guideline developers and a systematic review of reporting guidelines for healthcare research publications indicate that most existing guidelines have been developed using informal consensus methods (77 and 53%, respectively) and many do not describe
systematic methods for collating the empirical research to inform guideline content. A few exceptions, including many of the initiatives mentioned above, were developed using evidence-based approaches.

Despite the many reporting guidelines for publications, similar evidence-based guidance is not available for protocols of RCTs. At least one funding agency refers applicants to CONSORT, asking them to consider how they dealt with CONSORT items in their protocols\textsuperscript{46}. While commendable, incomplete overlap exists between RCT protocols and final publications. For example, trial protocols require a detailed account of administrative/trial management issues not generally covered in reports of trial results. Protocols are also often not limited by space constraints, allowing for more detailed descriptions of important trial components.

Guidelines for trial protocol content are available from many sources such as textbooks, funding applications and institutional guidelines. As no systematic assessment of the development and content of these guidelines is known to exist, the background to this thesis included a systematic review of existing recommendations.

1.1 Existing reporting guidelines for RCT protocols: a systematic review\textsuperscript{1}

1.1.1 Objectives. The objectives of this systematic review were to identify guidelines for reporting RCT protocols, assess the methods and levels of evidence used for guideline development, and review the recommendations. The methods and results of this study are reported briefly here; full details are available from the author.

\textsuperscript{1} The systematic review described in this section was completed in partial fulfillment of the requirements for course EPI 6188 Systematic reviews and meta-analysis completed for the MSc degree in Epidemiology and Community Medicine
1.1.2 Methods. Studies were eligible for inclusion in this review if they described an itemized guideline explicitly informing the content or major headings for RCT protocols. Guidelines needed to pertain to, but needed not be limited to, protocols for RCTs (any type including parallel-group, cluster RCTs), for research in humans. Tools were excluded if they were intended solely to guide the reporting of non-randomized, non-controlled clinical trials; guide the reporting of protocols of a narrow area of health care research, such as a specific medical procedure, condition or laboratory test; or assess the quality of clinical trials described in protocols, as this concept is not synonymous with reporting.

Searches were conducted in MEDLINE (1950 to April 18th 2007, Ovid Interface), EMBASE (1980 to April 16th, 2007, Ovid Interface) and the Cochrane Methodology Register (CMR; The Cochrane Library 2007, Issue 1). Additional records were identified using reference lists, book chapters, related article features and citation snowballing. The final subset was limited to English or French records due to practical limitations. One reviewer screened records and extracted data using a pilot tested form; a second reviewer validated a random sample at each level of screening (Level 1: 5%, Level 2: 25%) and extraction (10%). Disagreements were resolved by consensus. In the case of multiple publications, all related reports were consulted for additional information.

The following data were extracted from the included studies: report characteristics (number of authors, country of corresponding author, year of publication, source); guideline characteristics (format, intended scope); accountability (authors, date/version, contact information); guideline development process (types of methods, number, country and role of participants, time-frame of process); internal/external validity (using evidence in development process, circulating document for expert validation within or outside working group); dissemination, uptake, impact and funding; and recommended items (number and
content of items, supporting evidence, if applicable). The results were combined qualitatively. Pre-specified sub-group comparisons were guidelines limited to RCT protocols versus those with a broader scope; guidelines with and without development methods described; guidelines citing evidence for included items versus those without evidence; and guidelines with versus those without described funding sources.

1.1.3 Results. A total of 7148 records were identified by electronic searches (1903 MEDLINE, 5011 EMBASE and 234 CMR). After removal of duplicates and screening of titles and abstracts, 119 were classified as potentially relevant. One-hundred-and-thirty-one full-text reports were retrieved (119 from the database search and 12 from books/personal files), of which 30 reports, corresponding to 27 unique guidelines for clinical trial protocols, were included in the review.

The guidelines were published between 1977 and 2006 (78% from 1995-2006) as journal articles (n = 13), book chapters (n = 11) and government/agency reports (n = 3). Two were published in French and one in Spanish (with an English translation). The corresponding authors/agencies were located in Belgium (1), Canada, (1), France (2), India (1), Turkey (1), UK (9) and USA (10); locations of corresponding authors were not stated in two reports. One document did not list any authors, a version date or contact information; 25/27 (93%) included at least authors’ names or contact information.

Three guidelines pertained only to RCT protocols, while the remainder also included non-randomized trials and other healthcare research. The guidelines were presented mostly as checklists, bullet-lists or tables with accompanying text (12/27; 44%) or flow-diagram (5; 19%); others included only a checklist/bullet-list/table (5; 19%) or text (5; 19%).
Types of recommended flowcharts/diagrams differed and included a flow of patients through the study, trial design/procedures and organizational flowcharts.

1.1.3.1 Guideline development. Only four guidelines (15%) described development methods: one report (the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice E6 [ICH E6]) and three journal articles. Of these four, one was RCT-specific. Methods described for guideline development included consensus meetings, informal consensus procedures, field testing/pilot testing and soliciting feedback from a broader group (e.g. public/stakeholders). No reports indicated performing either a systematic or non-systematic search of major research databases for relevant literature or a formal (e.g. Delphi consensus) process for guideline development.

One guideline described methods meeting a broad definition of tool validation: the tool was pilot tested, shared with a broad community including consumers/experts, and modified in response to these methods. One additional guideline author reported soliciting comments from the general public and indicated future plans to pilot test their tool.

The total number of countries represented by members contributing to each guideline ranged from one (in 21/27 cases; 78%) to 11. Contributors’ disciplines/backgrounds were reported for a minority of guidelines (9; 33%), and included clinical researchers (8 guidelines; 30%), bioethicists, biostatisticians, trial managers and information technology personnel (1 guideline each). Only one report stated the time from inception of guideline development to publication (4 years).

1.1.3.2 Items. Guidelines contained a median of 22 items (inter-quartile range [IQR] = 17, 29) with a range of 8 - 96 items. The 3 guidelines presented as institutional/collaborative reports overall contained more items (median (IQR) = 54 (53, 56)) than those in the 11 books.
(median (IQR) = 25 (20, 29)) or 13 journal articles (median (IQR) = 19 (14, 21)). No differences were observed between other subgroups.

There were over 200 distinct items/concepts in the 27 reporting guidelines. Many items overlapped in content but contained distinguishing features; very little consistency existed across guidelines. Appendix 1 includes concepts addressed in at least five guidelines.

1.1.3.3 Evidence. Three reports (11%) cited evidence supporting at least one guideline item. The methods of identifying evidence were unclear in two cases while one, intended as a software application for preparing protocols for pragmatic RCTs, reported searching the Internet, reference lists, and contacting experts for evidence and previous guidelines.

Cited evidence supporting items was nearly non-existent, with the exception of informal expert consensus between colleagues and authors. Where empirical or theoretical evidence was cited for specific items, it was considerably outdated. For example, allocation concealment has been shown to affect RCT results; thus plans to conceal allocation (e.g. sealed envelopes, centralized allocation center), if any, should be detailed in the protocol. Only one guideline cited evidence for this item which was limited to work by Schulz and colleagues published in 1995, whereas other relevant evidence has since been published. Similarly, the most recent evidence cited for sample size description was by Freiman and colleagues published in 1978, despite the subsequent publication of many other relevant studies. This failure to cite evidence that had been published by the time of development and publication of these guidelines suggests that comprehensive literature searches were not performed.

Additionally, guidelines often did not recommend components with recent supporting empirical evidence and, when recommended, often did not cite relevant evidence. For
example, none of the six studies published after pivotal research showing biased
modifications of primary outcomes specifically requested primary outcomes. Only two
guidelines requested this information; both were published before this research. Empirical
evidence also suggests that published trials with competing interests related to industry and
trials funded by industry are more likely to report positive results than other trials,
however conflicts of interest and roles of the sponsor were only requested in two guidelines.

Another recent advance not evident in existing guidelines is the need for a thorough
literature search to provide rationale for the trial. While almost all of the reviewed
guidelines request background information and trial rationale, none specified the importance
of a systematic review for this purpose, a new requirement for some granting agencies.
Empirical evidence has highlighted the deficiencies and bias associated with non-systematic
literature searches. In the context of granting approval for human research, substantiation
of the need for a trial warrants considerable attention to ensure that patients are not being
subjected to treatments previously shown to be inferior or deprived of treatments previously
shown to be superior.

1.1.4 Limitations. This review had some limitations. Firstly, the assessment of evidence or
methods informing guideline development may not be complete as data were extracted solely
from the final report. Secondly, not all guidelines were located and included in this review.
As this was a course component, the review focused on database-indexed material, while
books and institutional/international collaboration reports were searched systematically but
not comprehensively. Books were identified via local libraries and the Internet (e.g.
www.amazon.com) using keywords, and reports were identified via reference lists; as such
they are only a sample of eligible reports. For example, only reports drafted or utilized by
the USA government\textsuperscript{47, 50, 73} were referenced in included studies and thus included in this review. An update of this work will include a more comprehensive assessment of funding/regulatory agency/governmental documents as well other relevant references not available at the time of this review.

1.1.5. Conclusion. This review identified a number of reporting guidelines applicable to RCT protocols. Despite very liberal definitions of ‘methods’, ‘evidence’ and ‘validity’, very few guidelines could be considered up-to-date or evidence-based as determined by their report. Evidence cited for guideline items mostly related to previous guidelines and expert consensus.

The review highlighted the deficiencies of and inconsistencies between existing guidelines, having implications for researchers preparing clinical trial protocols and REC/IRBs, granting agencies and peer-reviewers who review research protocols. Special attention should be paid not only to guidelines set forth by agencies, but also to the increasing evidence-base informing the content RCT protocols.

Only one guideline described methods for tool development and included some evidence for inclusion of items\textsuperscript{76}. This tool was not intended specifically as a reporting guideline, but rather as a computer software program for RCT protocol development. While it appears very useful, its content was developed by informal consensus of five investigators guided by a non-systematic internet search for previous guidelines. Other than this tool, no concise, evidence-based guideline for reporting RCT protocols was identified.

Given the importance of RCT protocols, the evidence of protocol deficiencies, the lack of evidence-based guidelines for RCT protocol and calls for greater access to RCT protocols\textsuperscript{83} and clinical trial registration\textsuperscript{84}, this is an opportune time to review the evidence
informing the content in RCT protocols and use it to develop recommendations for protocol content. As a result, an international group of researchers have united for the SPIRIT (Standard Protocol Items for Randomized Trials) Initiative, with the primary aim of producing a guideline for reporting protocols of RCTs. This thesis identifies the key evidence informing the SPIRIT Initiative guideline.
2.0 Aims and Objectives

The overall objective of this thesis is to provide the evidence-base for developing a reporting guideline for RCT protocols. The specific aims are to identify the evidence for a checklist of key protocol items using the following two systematic approaches:

1. Development and refinement of checklist content based on consensus of key expert stakeholders in clinical trials research
2. Identification and synthesis of evidence informing checklist content via systematic review of the literature
3.0 Development and Refinement of Guideline Content via Delphi Consensus

3.1 Objective

The objective of this portion of the thesis was to generate and refine items for a guideline for reporting RCT protocols using consensus among experts.

3.2 Methods

3.2.1 Overview – Delphi methodology

The Delphi method is “a structured process for collecting and distilling knowledge from a group of experts by means of a series of questionnaires interspersed with controlled opinion feedback”\textsuperscript{85}. The Delphi method is useful when: 1) the research problem may benefit from subjective judgments on a collective basis (i.e., little empirical evidence); 2) the research population has diverse backgrounds; 3) more subjects are needed than can effectively interact face-to-face; and 4) when conservation of anonymity of participants is beneficial.

3.2.2 Selection of participants

One of the most important features for the validity of a Delphi consensus survey is the selection of panel experts. We attempted to make this selection unbiased by having pre-defined criteria for invited participants. As described by Adler and Ziglio\textsuperscript{85}, experts had to meet all of the following criteria: (1) knowledge and experience with the issues under investigation; (2) capacity and willingness to participate; (3) sufficient time to participate; and (4) effective communication skills. To meet this last requirement, participants were required to be fluent in English.
We selected a varied group of participants for our panel to incorporate the interests of the SPIRIT checklist’s many potential consumers and stakeholders. We targeted experts in various aspects of clinical trial conduct, including trialists/clinicians, methodologists, statisticians and senior study coordinators from each area of academia, industry and government, where possible; REC/IRB members; members of funding and regulatory agencies; and major healthcare journal editors. This diverse group was selected to increase checklist generalizability and ideally increase endorsement and adherence.

Following the suggestions of Delbecq et al., we identified our potential panellists using a multi-step, iterative approach: 1) nomination of experts by steering group members; 2) identification of experts by authorship on relevant guidelines or methodological research; 3) snowballing; and 4) supplemental methods to increase geographical/cultural diversity and identify unique experts.

Firstly, SPIRIT steering group members - seven researchers with extensive experience in clinical trial methodology and/or the development of reporting guidelines - were asked to nominate a core set of individuals likely meeting the criteria stated above. Where possible, experts were ranked according to objective criteria. For example, clinical trialists/clinicians were required to be an author on a minimum of five English-language RCT publications over the past 10 years. High-ranking nominees were contacted and those expressing willingness to participate (or interested in the project but unable to participate) were asked for additional nominations (i.e., snowballing).

We then identified additional participants from specific groups by purposive sampling, with emphasis on increasing the geographical distribution and areas of panellist expertise. For example, additional clinical trialists were identified from the “ISI highly cited researchers in clinical medicine” and specific location-based PubMed searches, while
adhering to minimum expertise criteria as stated above. Study coordinators were identified by trialists’ nominations. Expert methodologists, ethics board members and funding agency representatives were identified by searching relevant guidelines, existing empirical research and targeted internet searches, again, requiring evidence for expertise this field (e.g. via relevant publications and/or available biographical information).

Our objective was to include approximately 100 panellists to be able to detect divergent opinions between respondent types, if present. We planned to recruit approximately 40 trialists/clinicians, 20 methodologists, 15 study coordinators, 10 ethics board heads/members, 10 funding agency representatives and 5 healthcare journal editors. Although panellists were selected for expertise in one category, several met minimum criteria for multiple areas of expertise (e.g., methodologist and journal editor).

3.2.3 Selection of preliminary items

An initial set of potential checklist items was collated based on *a priori* knowledge of existing empirical evidence and previous protocol reporting guidance as reviewed in the background to this thesis. Concepts present in a minimum of three existing guidelines were included and similar concepts were combined. Each item included a heading and description; wording and structure were kept similar to existing guidelines, where possible. This list was circulated to the SPIRIT executive group members and one item (how the results will be displayed such as planned tables and figures) was subsequently excluded. The initial checklist contained 59 items grouped under the following broad headings: a) General information; b) Introduction; c) Methods; d) Trial organization and administration; e) Ethical considerations; f) Reporting and dissemination; and g) Other.
3.2.4 Delphi

Ethics approval was obtained for the Delphi survey through the Children’s Hospital of Eastern Ontario.

Once the lists of potential participants and initial candidate items were finalized, a three-round electronic Delphi survey was conducted to modify and refine the checklist. Prior to survey inception, potential participants were informed electronically about the upcoming survey and the background and objectives of the SPIRIT initiative, and their participation was requested. They were informed of the anticipated study timeline, the expected time commitment of participation and the methods used to collate their responses, to select items for inclusion and to ensure confidentiality. They were informed that consent to participate did not require participation in all rounds, but were encouraged to contribute to each round to ensure the validity of the research. Where invitees declined participation, we requested reasons for declining, where possible, providing the following response options: 1) lack of time, 2) disagreement with survey purpose, 3) disagreement with the Delphi process or 4) other (please specify). Approximately two weeks later, Round 1 of the survey was administered electronically (by e-mail).

Each survey round was conducted over 5-6 weeks. In the first week, the questionnaire was pilot tested. Pilot testing was conducted by 5-10 participants, depending on the round, including steering group members and three additional panellists identified to represent views of groups not represented in the steering group (e.g. Director of ethics board). Pilot testers were asked to respond within one week of questionnaire receipt.

The survey was then administered and data collected over three weeks. Panellists were sent the questionnaire electronically and asked to respond either by email or by
facsimile by the deadline for the round (approximately three weeks later). Reminders were
sent to non-respondents approximately one week and a few days prior to the deadline for
each round. The final week of each round was reserved for collating the results and preparing
the succeeding round. This survey was conducted between July and November 2007.

Round 1 of the survey included each candidate item and description and requested
that participants rate, on a 10-point discrete visual analogue scale, the suitability of each item
for inclusion in a checklist for RCT protocols (Figure 1 and Appendix B). A rating of ‘1’
corresponded to ‘unimportant - should be dropped as an item to consider’ and ‘10’
corresponded to ‘very important – must be included’. Respondents were also given the
choice of selecting ‘no judgment’ if they did not feel comfortable rating a particular item.
Participants were provided with space for comments, edits and nominations of items not
included in this preliminary list. Additionally, Round 1 requested demographic information
including occupation/field and place of employment (university, hospital, government, non-
profit organization, for-profit organization, self-employed, other). Finally, we requested
respondents’ perceived level of expertise in participating in this process.

<table>
<thead>
<tr>
<th>Section and Topic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Section 1: General Information</strong></td>
<td></td>
</tr>
<tr>
<td>1 Title</td>
<td>Provide a descriptive title (e.g. population intervention main outcome) identifying the study as a randomized controlled trial</td>
</tr>
<tr>
<td></td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10 □ No judgment</td>
</tr>
<tr>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td>Very important</td>
</tr>
<tr>
<td>2 Trial Identifier</td>
<td>Unique trial identification number or name (e.g. trial registration number protocol number) and where registered (i.e. name of trial register)</td>
</tr>
<tr>
<td></td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10 □ No judgment</td>
</tr>
<tr>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td>Very important</td>
</tr>
<tr>
<td>3 Protocol Version</td>
<td>Include a version or amendment number and date</td>
</tr>
<tr>
<td></td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10 □ No judgment</td>
</tr>
<tr>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

**Figure 1:** Example of questionnaire layout from Delphi Round 1
Following Round 1, the moderator (student) collated all results, calculated medians and IQRs for the scores for each item and combined text comments, where relevant. Participant anonymity and confidentiality of responses were ensured; individual responses were known only to the moderator.

Round 2 of the survey (Appendix B) contained all Round 1 items; however, they were grouped categorically by collated Round 1 median scores rounded to the nearest whole number (high importance – median ≥ 8; moderate importance - 6 ≤ median ≥ 7; low importance - median ≤ 5). No changes were made to checklist wording. Respondents were provided with summarized ratings (medians, IQRs and frequency distributions), their previous rating and anonymous free text comments from all panellists for each item (Figure 2). Panellists were asked to read the comments provided by other panellists and to re-rate each item (on a scale of 1-10 or ‘no-judgment’) in light of the previous rounds’ ratings and comments, and to respond to existing comments, if desired. The final section of Round 2 contained new checklist items suggested by respondents from Round 1.

For items circulated in both Rounds 1 and 2, respondents were notified that, following Round 2, original items with a median of ≥ 8 would be considered ‘included’ in the first draft of the SPIRIT Checklist and items with a median of ≤ 5 would be considered ‘excluded’; these items would not be re-rated in Delphi Round 3. Newly introduced items would be re-circulated. Analysis for Round 2 was similar to Round 1.
The third, and final, round of the Delphi survey (Appendix B) contained five parts: Part 1: Items rated of high importance (‘included’ - median ≥ 8); Part 2: Items rated of low importance (‘excluded’ - median ≤ 5); Part 3: Items introduced in Round 2; Part 4: Items rated of moderate importance (6 ≤ median ≥ 7); and Part 5: ‘Included’ items requiring additional feedback. Respondents were not asked to rate items where consensus had already been reached (Parts 1 and 2). Consensus was defined by a median rating of eight or greater or five or less after two rounds, stability of the ratings between rounds and no additional significant issues noted from text comments. Panellists were asked to re-rate items in Part 3 as described previously, on a scale of 1-10 (see Figure 2).

In part 4 (items circulated for two rounds but where no clear consensus had been established), respondents were asked to select ‘include’, ‘exclude’ or ‘unsure’, to indicate their opinion on including the item in this reporting guideline (Figure 3a). Part 5 addressed items where comments suggested that separate concepts in some items were of differing importance, making rating difficult. Where possible, concepts were delineated and sub-items were created; respondents were asked to rate each sub-item separately (Figure 3b).

Figure 2: Example of questionnaire layout from Delphi Round 2.
3.2.5 Analysis

Medians and IQRs of group ratings were calculated for each item. For items where a large range of responses or clear bimodal results were noted after two rounds, results were explored by visual analysis of subgroup responses by respondents’ occupation and self-rated expertise.

3.3 Results

3.3.1 Delphi participants

One hundred and sixty seven experts in various aspects of clinical trials were invited to participate in the Delphi survey. Invitees were identified as follows: SPIRIT steering group members (n = 7), steering group nominations (n = 87) snowballing (n = 42) and targeted searches (by expertise) of the Internet, PubMed and ISI highly cited list (n = 37). One-hundred-and-four potential participants (62%) accepted the invitation and no responses were received from 44 (26%). Those declining participation (n = 19; 11%) were either too busy/unable (15), not interested (1), or did not provide a reason (3). Of the panellists
agreeing to participate, eight (8%) did not respond to either Round 1 or 2 and were not invited to participate in Round 3. Thus, 96 experts comprised the final panel (Appendix C). Seventy-four (77%) panellists responded to all three rounds, 15 (16%) responded to two rounds and 7 (7%) responded to one round of the Delphi.

Panellists represented various groups involved in the development and assessment of clinical trial protocols, meeting our *a priori* goals for proportions of profession/expertise representation (Table 1). Most respondents were employed at least in part by a university, hospital or governmental organization (90%), while a minority (4%) was employed solely by for-profit organizations (e.g. pharmaceutical companies) and none were self-employed.

Most panellists (90%) reported high or mid-high levels of self-perceived expertise in responding to this survey. The respondent selecting low-mid level of expertise had been invited to participate due their expertise in guideline development/analysis; their responses did not skew the results so they continued to be invited to participate on the panel.
### Table 1: Characteristics of Delphi survey panellists (N = 96)

<table>
<thead>
<tr>
<th>Question</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Profession</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical trialists</td>
<td>30 (32)</td>
</tr>
<tr>
<td>Healthcare professional</td>
<td>28 (30)</td>
</tr>
<tr>
<td>Methodologist</td>
<td>28 (30)</td>
</tr>
<tr>
<td>Statistician</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Trial coordinator</td>
<td>12 (13)</td>
</tr>
<tr>
<td>REC/IRB head/member</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Journal editor</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Funding agency representative</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Regulator/regulatory board member</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (8)</td>
</tr>
<tr>
<td><strong>Place of employment</strong></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>58 (62)</td>
</tr>
<tr>
<td>Hospital</td>
<td>30 (32)</td>
</tr>
<tr>
<td>Government</td>
<td>13 (14)</td>
</tr>
<tr>
<td>Non-profit organization</td>
<td>9 (10)</td>
</tr>
<tr>
<td>For-profit organization</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (5)</td>
</tr>
<tr>
<td><strong>Self-perceived level of expertise</strong></td>
<td></td>
</tr>
<tr>
<td>High level</td>
<td>49 (54)</td>
</tr>
<tr>
<td>Mid-high level</td>
<td>33 (36)</td>
</tr>
<tr>
<td>Mid level</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Low-mid level</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Low-level/no expertise</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*aSome panellists selected more than one relevant category*

### 3.3.2 Delphi results

Figure 4 presents the flow of items and Tables 2 to 5 present the numerical results obtained from the SPIRIT Initiative Delphi survey. Fifty-nine initial items were circulated in Rounds 1 and 2 (Table 2). Fifteen additional items were suggested by respondents and were circulated in Rounds 2 and 3 (Table 3). Initial items requiring a third assessment or clarification in Round 3 are presented in Tables 4 and 5. Additional details are included below. Frequency distributions may be found in Appendix D.
3.3.2.1 **Round 1.** Eighty-nine (95%) panellists from 17 countries responded to Round 1 of the Delphi survey. Of the initial 59 items circulated for this round, respondents collectively rated 56 items with a median of eight or greater, three with a median of 6 or 7, none with a median of five or less (Table 2). All three items rated of moderate importance (Personnel [Item 44], Logistics [Item 45] and Budget [Item 47]) were in Section 4: Trial organization and administration. Fifteen new items were suggested by panellists (Table 3).
<table>
<thead>
<tr>
<th>Section and Topic</th>
<th>Description</th>
<th>Round 1</th>
<th>Round 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Section 1: General Information</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Title</td>
<td>Provide a descriptive title (e.g., population, intervention, main outcome) identifying the study as a randomized controlled trial</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>2. Trial identifier</td>
<td>Unique trial identification number or name (e.g., trial registration number, protocol number) and where registered (i.e., name of trial register)</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>3. Protocol Version</td>
<td>Include a version or amendment number and date</td>
<td>10 (7, 10)</td>
<td>10 (8, 10)</td>
</tr>
<tr>
<td>4. Protocol Summary</td>
<td>Provide a short summary of the proposed research. Where required, include appropriate lay/non-technical language</td>
<td>9 (7, 10)</td>
<td>9 (7, 10)</td>
</tr>
<tr>
<td>5. Names and addresses</td>
<td>Provide names and addresses (i.e., affiliated institution, company) of the primary investigators and sponsors</td>
<td>10 (9, 10)</td>
<td>10 (8, 10)</td>
</tr>
<tr>
<td>6. Table of contents</td>
<td>Provide a list of the contents of the protocol and associated page numbers</td>
<td>8 (6, 10)</td>
<td>8 (5, 9)</td>
</tr>
<tr>
<td>7. List of abbreviations</td>
<td>List and descriptors of abbreviations used throughout the protocol</td>
<td>8 (6, 10)</td>
<td>7 (5, 8)</td>
</tr>
<tr>
<td><strong>Section 2: Introduction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Rationale</td>
<td>Outline the research topic and provide justification for undertaking the study</td>
<td>10 (9, 10)</td>
<td>10 (9, 5, 10)</td>
</tr>
<tr>
<td>9. Background of the study</td>
<td>Summarize previous studies on the topic, including unpublished studies known to the investigators and sponsors, and animal studies or other preclinical data, where relevant. Ideally, a relevant up-to-date systematic review should be referenced or reported, supporting the need for the current trial (e.g., clinical equipoise)</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>10. Preliminary data</td>
<td>Describe any results of preliminary studies already obtained in the area of the proposed study (e.g., by investigators)</td>
<td>9 (8, 10)</td>
<td>9 (8, 10)</td>
</tr>
<tr>
<td>11. Objectives</td>
<td>State the specific objectives and hypotheses of the study</td>
<td>10 (10, 10)</td>
<td>10 (10, 10)</td>
</tr>
<tr>
<td>12. General approach</td>
<td>Outline the general approach to address the research question</td>
<td>8 (6, 10)</td>
<td>7 (5, 9)</td>
</tr>
<tr>
<td>13. Study location(s)</td>
<td>Briefly describe and justify the site(s) where the research is to be conducted, including relevant demographic and epidemiological information about the country or region concerned</td>
<td>9 (7, 10)</td>
<td>8 (7, 9)</td>
</tr>
<tr>
<td><strong>Section 3: Methods</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Population</td>
<td>Describe the target and study population and the source (e.g., catchment area) of the study population</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>Section and Topic</td>
<td>Description</td>
<td>Round 1</td>
<td>Round 2</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
</tbody>
</table>
| 15. Eligibility criteria       | Describe the criteria for inclusion and exclusion of potential participants, and justification for the exclusion of any subgroup.                                                                          | 10 (10, 10) | 10 (10, 10)
| 16. Sample size                | The estimated number of research participants needed to achieve the study objective, and how this was determined, including any assumptions and calculations used.                                                    | 10 (10, 10) | 10 (10, 10)
| 17. Recruitment                | Describe the process of recruitment (e.g., advertisements, physician contacts) and enrolment.                                                                                                                   | 9 (8, 10) | 9 (8, 10)
| 18. Type of study              | A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and trial framework (e.g., exploratory, superiority, equivalence, non-inferiority)     | 10 (10, 10) | 10 (10, 10)
| 19. Study timeline             | Schematic diagram of study timetable and organizational chart including design, procedures and stages of trial.                                                                                               | 9 (8, 10) | 9 (8, 10)
| 20. Randomization:             | Describe the method to be used to generate the random sequence list, including details of any restriction (e.g., blocking, stratification).                                                                    | 10 (9, 10) | 10 (9, 10)
| Sequence generation            |                                                                                                                                                                                                            |        |        |
| 21. Randomization:             | Describe the method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence will be concealed until interventions are assigned.                     | 10 (9, 10) | 10 (10, 10)
| Allocation concealment         |                                                                                                                                                                                                            |        |        |
| 22. Randomization:             | Describe who will generate the allocation sequence, who will enrol participants, and who will assign participants to their group.                                                                              | 10 (8, 10) | 10 (8, 10)
| Implementation                 |                                                                                                                                                                                                            |        |        |
| 23. Blinding (masking)         | State whether or not participants, those administering the interventions, and those assessing the outcomes will be aware of group assignment. If relevant, how the success of blinding will be assessed.          | 10 (9, 10) | 10 (10, 10)
| 24. Interventions              | Provide precise details of the interventions intended for each group how they will be administered (e.g., dosage and dosage form, device), where applicable. Justify the control interventions used (e.g., no treatment, placebo or active control). | 10 (10, 10) | 10 (10, 10)
| 25. Schedule(s) of Intervention(s) | State the number and duration of treatment periods including run-in and washouts, where applicable.                                                                                                         | 10 (9, 10) | 10 (10, 10)
| 26. Concomitant interventions  | List relevant treatment(s)/intervention(s) that are permitted or not, prior to and/or during the study                                                                                                       | 10 (9, 10) | 10 (9, 10)
| 27. Risks To become "Harms"    | State the known or potential risks and adverse reactions for each study intervention                                                                                                                       | 10 (9, 10) | 10 (10, 10)
| 28. Outcomes                   | Describe and define primary and secondary outcome measures.                                                                                                                                                 | 10 (10, 10) | 10 (10, 10)
<table>
<thead>
<tr>
<th>Section and Topic</th>
<th>Description</th>
<th>Round 1</th>
<th>Round 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>29. Data collection</td>
<td>Describe methods, including study instruments (e.g. questionnaires, laboratory measurements) and time point(s), of data collection, outcome measurement and recording</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>30. Follow-up</td>
<td>State follow-up plans including description and schedule of visits and logistics, if relevant</td>
<td>10 (8, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>31. Data management</td>
<td>Describe plans for data entry, editing and management, including handling data collection forms and different versions of data, data coding, and data storage</td>
<td>8 (7, 10)</td>
<td>8 (7, 9)</td>
</tr>
<tr>
<td>32. Quality control</td>
<td>State any methods used to enhance the quality of outcome assessment (e.g., duplicate observations, training of assessors, pilot testing, validation etc.) and data records to ensure the completeness and accuracy of information</td>
<td>9 (8, 10)</td>
<td>9 (8, 10)</td>
</tr>
<tr>
<td>33. Compliance</td>
<td>Describe procedures and measures proposed to monitor participant compliance (e.g. tablet return), if relevant</td>
<td>9 (8, 10)</td>
<td>9 (8, 10)</td>
</tr>
<tr>
<td>34. Safety Evaluations</td>
<td>State plans for monitoring the continuing safety of interventions administered for purposes of the trial, including specification of methods and timing of measuring safety parameters</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>35. Statistical methods</td>
<td>Describe statistical methods to be employed to compare groups for primary outcome(s) and secondary outcome(s) as well as methods for additional analyses, such as subgroup analyses and adjusted analyses. State whether intention-to-treat or other analysis will be used for the primary comparison(s)</td>
<td>10 (10, 10)</td>
<td>10 (10, 10)</td>
</tr>
<tr>
<td>36. Withdrawals</td>
<td>State criteria that will be used to withdraw or exclude participants from the trial (e.g. compliance requirements), and specify the data to be collected from withdrawn participants and follow-up, in a multi-centre study state when a centre may be discontinued from the trial</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>37. Missing data</td>
<td>Describe the methods to account for missing data or erroneous data</td>
<td>9 (8, 10)</td>
<td>9 (8, 10)</td>
</tr>
<tr>
<td>38. Data and Safety Monitoring Board</td>
<td>If relevant, describe the composition and role of the data and safety monitoring board</td>
<td>9 (8, 10)</td>
<td>9 (9, 10)</td>
</tr>
<tr>
<td>39. Interim trial monitoring</td>
<td>Describe the process and timing of any planned interim analyses</td>
<td>10 (8, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>40. Stopping guidelines</td>
<td>State the criteria for the premature termination of the trial</td>
<td>10 (8, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>41. Adverse event reporting</td>
<td>Describe methods for recording and reporting both solicited and spontaneous adverse events, and provisions for dealing with them</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>42. Emergency code-breaking procedure</td>
<td>Information about how the code, if any, for the participants' identity is established, where it will be kept and when, how and by whom it can be broken in the event of an emergency</td>
<td>10 (8, 10)</td>
<td>10 (8, 10)</td>
</tr>
<tr>
<td>43. Limitations</td>
<td>Describe the limitations of the proposed study, including possible bias in data collection, measurement and analysis</td>
<td>9 (7, 10)</td>
<td>8 (6, 10)</td>
</tr>
<tr>
<td>Section and Topic</td>
<td>Description</td>
<td>Round 1</td>
<td>Round 2</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Section 4: Trial organization and administration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44. Personnel</td>
<td>Provide names, affiliations, contact details, qualifications, time commitment and job descriptions of trial personnel including investigators, statisticians, and other relevant staff, including consultants</td>
<td>7 (5, 9)</td>
<td>6 (4, 7)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>45. Logistics</td>
<td>Describe the availability of resources and logistics of the trial including administrative responsibilities (e.g., how they will be shared), equipment, and physical facilities</td>
<td>7 (5, 8)</td>
<td>6 (4, 7)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>46. Monetary and material support</td>
<td>Name the source(s) of financial and material support, type of support provided, amount, and how (e.g., to a research account or as an honorarium)</td>
<td>9 (7, 10)</td>
<td>9 (7, 10)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>47. Budget</td>
<td>Provide the budget for personnel, equipment, facilities and supplies</td>
<td>6 (3, 9)</td>
<td>5 (2, 6)</td>
</tr>
<tr>
<td><strong>Section 5: Ethical considerations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48. Potential benefits and risks</td>
<td>The potential benefits and risks of the research to study participants and to society</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>49. Agreement and consent</td>
<td>Describe the method to obtain individual informed consent, information provided to the patient and the name and position of the person responsible for obtaining consent. Provide a copy of the consent form and patient information leaflet</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>50. Surrogate Consent or Assent</td>
<td>If a prospective participant is not capable of informed consent, provide information on how permission will be obtained from an authorized individual. In the case of individuals below legal consenting age, provide information on how assent and permission from a legal guardian or other authorized individual will be obtained</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>51. Confidentiality and Anonymity</td>
<td>The provisions for protecting the confidentiality and anonymity of personal data and respecting the privacy of participants</td>
<td>10 (8, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>52. Ethics approval</td>
<td>State whether ethics approval has been obtained, if so, provide the name of the committee(s)</td>
<td>10 (9, 10)</td>
<td>10 (8, 10)</td>
</tr>
<tr>
<td>53. Role of Sponsor</td>
<td>Describe the role of the sponsor in the trial design, data collection, access to trial data (including interim data, audits and regulatory inspections), data analysis and interpretation, and manuscript preparation</td>
<td>10 (8, 10)</td>
<td>10 (8, 10)</td>
</tr>
<tr>
<td>54. Conflict of Interest</td>
<td>Disclose financial or other real or perceived conflicts of interest</td>
<td>10 (9, 10)</td>
<td>10 (8, 10)</td>
</tr>
<tr>
<td><strong>Section 6: Reporting and Dissemination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55. Protocol Amendments</td>
<td>Describe how changes to the original protocol, including the statistical plan, will be communicated to investigators and ethics committees and how these will be reported and justified in subsequent amendments of the protocol and/or the final report, as appropriate</td>
<td>9 (7, 10)</td>
<td>9 (7, 10)</td>
</tr>
<tr>
<td>Section and Topic</td>
<td>Description</td>
<td>Round 1</td>
<td>Round 2</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>56. Dissemination</td>
<td>Describe how the researcher(s) or sponsor(s) will disseminate the results to participants, health care professionals, the public, or other relevant groups.</td>
<td>8 (7, 10)</td>
<td>8 (7, 10)</td>
</tr>
<tr>
<td>57. Publication Policy</td>
<td>Details on who has the right to publish the study results or modify the manuscript (i.e., principal investigator(s), co-investigator(s), sponsor), including publication restrictions and authorship guidelines.</td>
<td>9 (8, 10)</td>
<td>9 (7, 10)</td>
</tr>
</tbody>
</table>

**Section 7: Other**

| 58. References | Provide a list of the references cited in the protocol | 10 (9, 10) | 10 (9, 10) |
| 59. Appendix Materials | Provide relevant materials including samples of the standardized case-report forms or other data collection forms (e.g., questionnaires) and consent/assent forms | 9 (7, 10) | 8 (7, 10)* |

*Items re-circulated in Round 3 for final assessment and/or clarification. All other items were circulated in Round 3 only to present results.*

Many additional comments, both general and item-specific, were received in Round 1 of the survey. Only general comments are highlighted here; item-specific comments are discussed in Chapter 5.

Many respondents stated that, although there were many items, most were important and hence rated highly. Although there must be a ‘balance between guiding researchers and being too prescriptive’ as suggested by a few respondents, some respondents stated that a comprehensive list is more useful in light of the evidence for poor reporting in protocols (6 respondents) and due to the ‘serious business’ of clinical trials which ‘deserve[s] a detailed reporting at any stage’ (1 respondent). Two respondents were concerned, however, about the possible increased burden on trialists and one believed that, while all were potentially important elements, it ‘depends on the length of the protocol’. Two panellists suggested that some items could be available through sources other than the protocol (e.g., websites).

Other general comments related to the scope of the checklist including study designs it should address and who the end user of the protocol or checklist will be. Originally, the goal of the SPIRIT Initiative was to develop a reporting guideline for protocols of 2-group
parallel design RCTs. Some insightful comments prompted us to consider the relevance of this checklist to trials with more than 2-groups (2 respondents) and to clarify our intent to target trials with individuals as the unit of randomization.

For some items, many respondents felt their ratings would likely differ depending where the protocol was being submitted. For example, some ethical considerations are important for a funded study submitted for ethics approval, but possibly excessive for a funding application. Alternatively, “items such as logistics/management would be differently appreciated by a funding body (who would like as much detail as possible…) than by others (publishers always have space constraints…).” As an alternative, one respondent suggested considering separately “which items should be recommended as the minimal for an ethical committee, a granting agency, or for publication in a clinical trial register”. In general, the proposed checklist was intended for all RCT protocols regardless of the ultimate user (trialists, granting agency, REC/IRB, journal) and this was reiterated in Round 2.

Finally, three respondents commented on the ambiguity of the term protocol. For example, one panellist viewed the protocol “as the ‘clinical’ guidance document for the study, while things like the Statistical Charter and the contract deal with issues related to data management/analysis and remuneration and publication.” Another stated, “currently, the research application we receive as a funder and the final protocol is not one and the same.” We conveyed that we consider a protocol to be a document written prior to participant enrolment to describe the objective(s), design, methodology, statistical considerations, and organizational or administrative aspects of a clinical trial. We provided these comments to panellists in the introduction to Round 2 and attempted to clarify ambiguities where possible.
3.3.2.2 Round 2. Eighty-six (91%) panellists from 17 countries responded to Round 2 of the Delphi survey. This round included all existing and the fifteen new items. Respondents were given the opportunity to re-rate each original item considering the results of Round 1 (median, IQR, frequency distribution, text comments and previous individual response for each item).

Overall, results suggested consensus was achieved for the majority of items circulated in Round 1 and Round 2 (Table 2). Forty-five (76%) of the original items were considered ‘Included’ in (median ≥ 8) and one item was considered ‘Excluded’ from (median ≤ 5; Budget) the draft checklist. Consensus was also confirmed for most items related to trial methodology by the narrowing of score ranges (Appendix D). Interestingly, score ranges widened slightly for many items classified under Section 4: Trial organization and administration, Section 5: Ethical considerations and Section 6: Reporting and Dissemination although this did not significantly affect medians or IQRs. Four items (List of abbreviations, General Approach, Personnel and Logistics) were considered of ‘moderate’ importance. Of the fifteen new items rated for the first time in this round (Items 60-72; Table 3), nine were rated with a median ≥ 8, 6 with a median of 6 or 7 and none with a median ≤ 5.
### Table 3: New items suggested by panellists in Delphi Round 1 Results from Delphi survey Rounds 2 and 3

<table>
<thead>
<tr>
<th>Section and Topic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>60. Signatures</strong></td>
<td>Provide appropriate signatures including principal investigator(s) or chief medical officer</td>
</tr>
<tr>
<td><strong>61. Co-enrolment in studies</strong></td>
<td>State regulations pertaining to co-enrolment of participants into other research studies</td>
</tr>
<tr>
<td><strong>62. Investigational product(s)</strong></td>
<td>If relevant, describe the formulation, packaging, labelling and supply of the investigational product and accountability procedures</td>
</tr>
<tr>
<td><strong>63. Biological specimens</strong></td>
<td>If relevant, describe plans for laboratory evaluation, specimen collection, storage and shipping to central laboratories</td>
</tr>
<tr>
<td><strong>64. Data collection forms</strong></td>
<td>Provide a summary table (e.g. matrix) of all forms to be collected at each time point</td>
</tr>
<tr>
<td><strong>65. Validation of instrumentation</strong></td>
<td>Describe reliability and validity of instruments to be used, including questionnaires, laboratory instruments, and analytic tests, if known, or plans to establish such validation</td>
</tr>
<tr>
<td><strong>66. Trial Monitoring</strong></td>
<td>Describe the plans for trial monitoring (e.g. by a Clinical Research Associate) including if the monitoring process was independent from the principal investigator and sponsor and how often trial sites will be monitored</td>
</tr>
<tr>
<td><strong>67. Reporting of early stopping</strong></td>
<td>Describe how the researcher(s) or sponsor(s) of trials will disseminate the results of trials that were stopped early (for benefits, harms or futility)</td>
</tr>
<tr>
<td><strong>68. Ancillary and sub-studies</strong></td>
<td>Describe any foreseen further uses of personal data or biological materials for related sub-studies or ancillary studies <em>and whether consent was obtained for these studies</em></td>
</tr>
<tr>
<td><strong>69. Pregnancy</strong></td>
<td>For research on pregnant women, specify plans for monitoring the health of the woman and the short-term and long-term health of the child</td>
</tr>
<tr>
<td><strong>70. Post-trial care</strong></td>
<td>State plans for post-trial follow-up and access to investigational treatment, if relevant, specifying the means of implementation, the duration of care and the individual or organization responsible for financially supporting this care</td>
</tr>
<tr>
<td><strong>71. Post-trial data/materials storage</strong></td>
<td>Describe plan to store data/materials after the trial is complete including the location(s), required length of storage period and who will be responsible for the data</td>
</tr>
<tr>
<td><strong>72. Feasibility</strong></td>
<td>Justify the feasibility of the trial including the acceptability of the protocol for both participants and physicians and the capacity of recruitment</td>
</tr>
<tr>
<td><strong>73. Insurance</strong></td>
<td>Details of plans including insurance coverage, to provide treatment (including the funding of treatment) and compensation for research-related disability or death</td>
</tr>
<tr>
<td><strong>74. Data ownership</strong></td>
<td>State who has ownership of data and disclose any agreement or contract with sponsor that limits principal investigators ownership of data</td>
</tr>
</tbody>
</table>

### Median (IQR)

<table>
<thead>
<tr>
<th></th>
<th>Round 2</th>
<th>Round 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>60. Signatures</strong></td>
<td>6 (3, 9)</td>
<td>5 (2, 8)</td>
</tr>
<tr>
<td><strong>61. Co-enrolment in studies</strong></td>
<td>7 (5, 9)</td>
<td>7 (5, 9)</td>
</tr>
<tr>
<td><strong>62. Investigational product(s)</strong></td>
<td>8 (5, 9)</td>
<td>7 (5, 9)</td>
</tr>
<tr>
<td><strong>63. Biological specimens</strong></td>
<td>8 (6, 10)</td>
<td>8 (6, 9)</td>
</tr>
<tr>
<td><strong>64. Data collection forms</strong></td>
<td>8 (5, 9)</td>
<td>8 (6, 9)</td>
</tr>
<tr>
<td><strong>65. Validation of instrumentation</strong></td>
<td>8 (6, 9)</td>
<td>8 (6, 9)</td>
</tr>
<tr>
<td><strong>66. Trial Monitoring</strong></td>
<td>8 (7, 9)</td>
<td>8 (6, 9)</td>
</tr>
<tr>
<td><strong>67. Reporting of early stopping</strong></td>
<td>8 (5, 10)</td>
<td>8 (5, 10)</td>
</tr>
<tr>
<td><strong>68. Ancillary and sub-studies</strong></td>
<td>7 (4, 9)</td>
<td>7 (5, 9)</td>
</tr>
<tr>
<td><strong>69. Pregnancy</strong></td>
<td>8 (6, 10)</td>
<td>7 (4, 10)</td>
</tr>
<tr>
<td><strong>70. Post-trial care</strong></td>
<td>8 (6, 9)</td>
<td>8 (6, 9)</td>
</tr>
<tr>
<td><strong>71. Post-trial data/materials storage</strong></td>
<td>7 (5, 9)</td>
<td>7 (4, 8)</td>
</tr>
<tr>
<td><strong>72. Feasibility</strong></td>
<td>7 (4, 9)</td>
<td>6 (3, 8)</td>
</tr>
<tr>
<td><strong>73. Insurance</strong></td>
<td>6 (3, 8)</td>
<td>5 (2, 7)</td>
</tr>
<tr>
<td><strong>74. Data ownership</strong></td>
<td>8 (7, 10)</td>
<td>8 (7, 10)</td>
</tr>
</tbody>
</table>
General comments received in Round 2 echoed those from Round 1. A number of respondents again stated that the importance of some items was relative to the target end-user and that other associated documents (e.g. contracts, statistical and Data and Safety Monitoring Board (DSMB) charters, investigational brochures and laboratory or pharmacy manuals) may address some concepts, with some panellists suggesting that the protocol then reference all related documents. A few respondents also expressed concern about the length and number of requirements, stating, for example, “academic clinical trials are already seriously under resourced” and “presenting a protocol with all the information listed [may give] an overwhelming amount of data with possible counter productive consequences.”

One new point was raised: a suggestion to exclude items requiring repeated protocol amendments (e.g. Personnel, Study sites, REC/IRB approval) as the need for official amendments and protocol resubmissions could potentially jeopardize trial progress.

3.3.2.3 Round 3. Eighty-four (89%) panellists from 16 countries responded to Round 3 of the Delphi survey. As previously mentioned, items considered ‘Included’ or ‘Excluded’ following Round 2 were circulated (Parts 1 and 2, respectively) but not re-rated in Round 3.

The results for the 15 new items suggested by respondents in Round 1 (Part 3) are presented in Table 3. Following Round 3, seven of these items were considered ‘Included’, six were rated of moderate importance and two were considered ‘Excluded’ from the draft checklist. Collectively, there was less conviction for including these items than for many existing items, with eight being the highest median and most items having wide IQRs. The seven ‘Included’ items and those considered of moderate importance were retained in the draft checklist for further consideration and discussion at subsequent consensus meetings.
Initial items receiving moderate support after Rounds 1 and 2 (Part 4) were re-circulated in Round 3 (Table 4), when a further two items were excluded (Personnel [Item 44] and Logistics [Item 45]). A slim majority (52%) felt the item General approach (Item 12) should be included, but many comments (n = 28) stated it was addressed in existing items such as objectives, type of study or protocol/summary. The remaining item (List of abbreviations) was retained for further discussion.
Table 4: Items rated ‘Moderate’ in Delphi Round 2: results from Delphi survey Round 3

<table>
<thead>
<tr>
<th>Section and Topic</th>
<th>Description</th>
<th>Round 3</th>
</tr>
</thead>
</table>
| 7. List of abbreviations | List and descriptors of abbreviations used throughout the protocol.       | I: 59 (74)  
E: 15 (19)  
U: 6 (8) |
| 12. General approach | Outline the general approach to address the research question.            | I: 43 (52)  
E: 35 (42)  
U: 5 (6) |
| 44. Personnel | Provide names, affiliations and contact details of key trial personnel including investigators, statisticians, and other relevant staff, (e.g. consultants). a | I: 33 (40)  
E: 42 (51)  
U: 7 (9) |
| 45. Logistics | Describe the availability of resources and logistics of the trial including administrative responsibilities (e.g. how they will be shared), equipment, and physical facilities. | I: 22 (27)  
E: 53 (64)  
U: 8 (10) |

aText modified in Round 3 as a result of panellists’ comments

The final section of Round 3 of the Delphi (Part 5) addressed items where comments indicated clarification of subcomponents was required for the validity of the results (even where numerical results showed consensus). As shown in Table 5, delineating these items more clearly demonstrated the specific sub-components of importance to panellists. For example, in general, where items requested specific information plus a justification, respondents were much more strongly in favour of requesting the main concept but not the justification (e.g. study locations [I = 87%, justification: I = 46%] and eligibility criteria [I = 99%, justification: I = 66%]). Differing levels of support were also received for the four components of the item Monetary and material support (source of support: I = 95%; type of support - material, financial: I = 70%; amount of support: I = 30%; how support is provided: I = 35%).
<table>
<thead>
<tr>
<th>Section and Topic</th>
<th>Initial description</th>
<th>Sub-items</th>
<th>Round 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Protocol Summary</td>
<td>Provide a short summary of the proposed research Where required, include appropriate lay/non-technical language</td>
<td><strong>A.</strong> Provide a short summary of the proposed research</td>
<td>I 78 (94)  E 4 (5)  U 1 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>B.</strong> Where required, include appropriate lay/non-technical language</td>
<td>I 50 (63)  E 21 (27)  U 8 (10)</td>
</tr>
<tr>
<td>13. Study location(s)</td>
<td>Briefly describe and justify the site(s) where the research is to be conducted, including relevant demographic and epidemiological information about the country or region concerned</td>
<td><strong>A.</strong> Briefly describe the site(s) where the research is to be conducted</td>
<td>I 71 (87)  E 9 (11)  U 2 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>B.</strong> Briefly justify the site(s) where the research is to be conducted</td>
<td>I 38 (46)  E 38 (46)  U 6 (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>C.</strong> Briefly describe relevant demographic and epidemiological information about the country or region where the research is to be conducted</td>
<td>I 38 (46)  E 29 (47)  U 6 (8)</td>
</tr>
<tr>
<td>15. Eligibility criteria</td>
<td>Describe the criteria for inclusion and exclusion of potential participants, and justification for the exclusion of any subgroup</td>
<td><strong>A.</strong> Describe the criteria for inclusion and exclusion of potential participants</td>
<td>I 81 (99)  E 1 (1)  U 0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>B.</strong> Justify the exclusion of any subgroup</td>
<td>I 55 (66)  E 23 (28)  U 5 (6)</td>
</tr>
<tr>
<td>19. Study timeline</td>
<td>Schematic diagram of study timetable and organizational chart including design, procedures and stages of trial</td>
<td><strong>A.</strong> Schematic diagram of schedule of procedures and visits for participants through each stage of the trial</td>
<td>I 69 (84)  E 8 (10)  U 5 (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>B.</strong> Schematic diagram of the study timeline, specifying dates at which stages of the study are expected to be completed</td>
<td>I 48 (58)  E 25 (30)  U 10 (12)</td>
</tr>
<tr>
<td>24. Interventions</td>
<td>Provide precise details of the interventions intended for each group how they will be administered (e.g. dosage and dosage form, device), where applicable Justify the control interventions used (e.g. no treatment, placebo or active control)</td>
<td><strong>A.</strong> Provide precise details of the interventions intended for each group how they will be administered (e.g. dosage and dosage form, device), where applicable</td>
<td>I 82 (99)  E 1 (1)  U 0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>B.</strong> Justify the control interventions used (e.g. no treatment, placebo or active control)</td>
<td>I 72 (87)  E 7 (8)  U 4 (5)</td>
</tr>
<tr>
<td>36. Withdrawals</td>
<td>State criteria that will be used to withdraw or exclude participants from the trial (e.g. compliance requirements), and specify the data to be collected from withdrawn participants and follow-up, in a multi-centre study state when a centre may be discontinued from the trial</td>
<td><strong>A.</strong> State criteria that will be used to withdraw or exclude participants from the intervention (e.g. compliance requirements, safety concerns)</td>
<td>I 78 (95)  E 2 (2)  U 2 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>B.</strong> Specify the data to be collected from withdrawn participants and how enrolled participants will be followed-up</td>
<td>I 70 (85)  E 4 (5)  U 8 (10)</td>
</tr>
</tbody>
</table>
C. In a multi-centre study state when a centre may be discontinued from the trial

<table>
<thead>
<tr>
<th>40. Stopping guidelines</th>
<th>State the criteria for the premature termination of the trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. If relevant, state the predefined statistical stopping boundaries for the early termination of the trial</td>
<td></td>
</tr>
<tr>
<td>B. If relevant, state any non-statistical predefined criteria for the early termination of the trial</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>46. Monetary and material support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name the source(s) of financial and material support, type of support provided, amount, and how (e.g., to a research account or as an honorarium)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A. Name the source(s) of financial and material support</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. List the type(s) of support provided</td>
</tr>
<tr>
<td>C. State the amount of support provided</td>
</tr>
<tr>
<td>D. State how source(s) of support are provided (e.g., to a research account or as an honorarium)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>59. Appendix Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide relevant materials including samples of the standardized case-report forms or other data collection forms (e.g., questionnaires) and consent/assent forms</td>
</tr>
</tbody>
</table>

| A. Provide relevant materials including samples of the standardized case-report forms |
| B. other data collection forms (e.g., questionnaires) |
| C. consent/assent forms |

The results also showed that some respondents differentially interpreted the item requesting a schematic diagram of study timeline as a) a schematic of the schedule of procedures and visits for participants through trial stages and b) a schematic of the study timeline including expected completion dates for trial stages. Results from Round 3 clearly showed respondents favouring the former over the latter (I = 84% vs. 58%, respectively) as items for the SPIRIT Statement.

Subgroup analysis of item-specific results showed some differences between respondents by profession and level of self-perceived expertise, although these variables were not independent; trial coordinators were significantly more likely to rate their perceived level of expertise as mid-level or mid-high level and methodologists more likely to rate their
expertise as high level. Subgroup comparisons and item-specific comments are presented and discussed in Chapter 5 of this thesis for the synthesis of the Delphi and systematic review results.
4.0 Identification and Synthesis of Evidence Informing Guideline Content

4.1 Objective

The objective of this portion of the thesis is to identify and synthesize the empirical evidence supporting the importance of reporting particular concepts in RCT protocols via a systematic review of the research literature.

4.2 Methods

4.2.1 Criteria for considering studies for review

Wherever possible, methods were pre-specified. Any changes between the protocol and the final systematic review are distinguished in this report.

4.2.1.1 Types of studies. Reports were eligible for inclusion if they described an empirical study examining trial elements of possible importance for inclusion in a reporting guideline for RCT protocols. An empirical study was defined as an experimental or observational study using the scientific method (e.g. has an objective, methods and results) and based on verifiable facts (i.e., could be replicated). Eligible study designs included cohort, cross-sectional and case-control studies or other unbiased samples of RCT protocols and/or publications; systematic reviews of trial protocols, publications or methodological studies; or experimental studies, such as RCTs or quasi-RCTs assessing relevant trial components, nested within existing RCTs. Case reports, case series, simulation studies and studies relating to hypothetical trials were excluded.

Reports had to describe, but needed not be limited to, studies examining protocols or publications of RCTs of healthcare interventions. If results for RCTs were not reported
separately from other study designs, a minimum of 80% RCTs was required (post-hoc addition). Research on non-randomized studies alone was not considered.

Studies were eligible if they assessed one of the following: 1) reporting in RCT protocols; 2) methodological, organizational or ethical aspects of RCTs described in protocols or other reports and the study was deemed relevant to inform the development of RCTs protocols; or 3) the association between specific RCT characteristics and trial outcomes, such as efficacy, recruitment or retention. Studies assessing methodological quality of trials as described in publications or protocols (point 2) were limited (post-hoc) to RCTs conducted or published from 1992 to the present; studies of earlier cohorts were excluded. Studies reviewing only final publication reporting quality were not eligible. Reports could be descriptive, but had to include quantitative data subject to the eligibility criteria previously described.

For practical reasons, only studies published in English or French were eligible. There were no limits based on publication status of studies or date of publication.

4.2.1.2 Types of comparisons. Comparisons were as described in the included studies. Broadly, these included the association between specific characteristics of RCTs (e.g. as stated in protocols or final reports) and trial outcomes.

4.2.1.3 Outcomes. The primary outcomes of interest were:

1) Estimates of the association between specific characteristics of RCTs (e.g., in protocols or published reports) and trial outcomes (e.g. effect sizes, recruitment, and cost). Estimates, such as odds ratios or relative risks were recorded as described in the original study report, including confidence intervals, where provided.
2) Prevalence of particular elements/concepts in protocols. Prevalence was reported using both counts and relative measures, where possible.
3) Prevalence of deficiencies in RCT methodology, administration or ethical aspects as assessed, for example, from trial protocols, final reports or audits.
Other relevant empirical evidence was eligible, but was not pre-specified.

4.2.2 Search strategy for identification of studies

The initial electronic search was conducted in the following databases:

- MEDLINE (From 1950 to August 9th, 2007, Ovid interface)
- EMBASE (1980 to August 1st, 2007, Ovid interface)
- CDSR, limited to Cochrane Methodology Reviews (The Cochrane Library 2008, Issue 3, Wiley interface)

Search strategies were developed in consult with an experienced information specialist (Margaret Sampson, MLIS, PhD). No limits were included on publication language in the search strategies. The MEDLINE search strategy excluded editorials, comments and news articles and the EMBASE search strategy excluded editorials. The final MEDLINE search strategy (Appendix E) was modified for EMBASE and the Cochrane Library to account for indexing differences. To account for lack of indexing specificity in EMBASE for this type of research, we electronically eliminated MEDLINE-indexed EMBASE citations prior to combining citations across databases.

Based on initial screening results, the MEDLINE and EMBASE searches had low precision, while the CMR, which is populated by MEDLINE- and hand-searching, had higher precision, included additional relevant records including conference abstracts, and did not compromise sensitivity. However, there is a significant indexing lag in the CMR. Therefore, the updated search was conducted as follows:

- MEDLINE (September 18th, 2009, Ovid interface) using a variation of previous search strategy in response to indexing changes effective 2008
- The CMR and CDSR (limited to Methodology Reviews) (The Cochrane Library 2009, Issue 3, Wiley interface)
Other methods of identifying relevant literature included the following:

- Citation snowballing - SCOPUS was used to identify publications from 2006 to present citing included studies
- PubMed 'related articles' feature - top 40 related articles were searched for each included study
- Scanning reference lists of included studies
- Searching previously identified reporting guidelines (as described in Chapter 1)

### 4.2.3 Methods of the review

#### 4.2.3.1 Identifying relevant studies.

All records were downloaded and imported into Reference Manager 11 where duplicate records were removed. Screening forms were pilot-tested by two reviewers. Titles and abstracts were screened by one reviewer using broad criteria, and a second reviewer verified a 20% sample of the excluded studies. One reviewer then screened the title and abstract of all remaining records; a second reviewer independently screened a 10% random sample. The full-text of studies meeting predefined eligibility criteria or those where eligibility remained unclear were screened by one reviewer; a second reviewer independently screened a random sample of 100 records. Where eligibility remained unclear after full-text screening, a second reviewer independently screened reports and corresponding authors were contacted if necessary. Screening questions are included in Appendix F.

All disagreements were resolved by consensus or, if necessary, by the involvement of a third reviewer. Reviewers were not blinded to any report characteristics. One reviewer searched reference lists, book chapters, related articles features and previous guidelines.

#### 4.2.3.2 Data extraction.

The data extraction form was pilot-tested by two reviewers on five included studies. One reviewer extracted all remaining data and a second reviewer
independently extracted a random sample of five articles, although initially they were to verify a 10% sample; this change was due to logistical constraints.

The types of data extracted depended on the study design and the topic. In general, the following data were extracted from the included studies, where relevant:

- Report characteristics (authors, publication status, journal, year of publication);
- Study characteristics (study design, country of corresponding author, objectives, methods, selection criteria [e.g. source of trials], number of included studies/reports, funding source);
- Characteristics of included studies/reports;
- Interventions (if relevant); and
- Number of, and evidence for, potential checklist items to which the study pertained. If study pertained to additional concepts not previously considered, this was also noted.

Duplicate information, such as primary data included in more than one secondary publication, was extracted only once. Missing information or clarifications were obtained by e-mail contact with corresponding authors, where possible.

4.2.3.4. Data analysis and synthesis. Quantitative data were extracted from each included study and relative measures were calculated from count data (e.g. percentages from fractions), where relevant. Data were first organized by included study and then all data relevant to specific candidate checklist items were collated.

Although initially intended, we did not perform a formal risk of bias assessment (i.e., ‘quality assessment’) of the included studies or a formal assessment of the level and consistency of the evidence (e.g. GRADE approach\textsuperscript{90}) due to the heterogeneous nature of the studies and the lack of evidence to guide this synthesis for the types of studies included. Rather, information indicative of internal (methodology of studies) and external (generalizability) validity was extracted. Studies were defined as having a narrow or broad scope based on study design and narrow or broad topic based on clinical content area.
The overall strength of the evidence derived from the results of the systematic review was rated for each candidate checklist item (Strong, Moderate, Weak/None) to provide an overview of the evidence. These ratings were based on a structured qualitative assessment of the available empirical evidence for each potential checklist item, and in addition to the results of the included studies, accounted for issues of directness, generalizability, and consistency of the results, based on objective criteria where possible (Table 6).

One reviewer rated the strength of the evidence for all items and two additional reviewers each independently rated a random sample of 10 items/sub-items (approx. 12%).

No sub-group analyses, formal assessment of heterogeneity, publication or other reporting biases were planned for this review.
### Table 6
Criteria for grading strength of evidence from the systematic review for each candidate checklist item

<table>
<thead>
<tr>
<th>Strength of evidence</th>
<th>Study design</th>
<th>Study objective for relevant item</th>
<th>Scope of study topic</th>
</tr>
</thead>
</table>
| **Strong**           | Systematic review of methodological studies | - association between trial characteristic and outcome  
                        - prevalence of trial characteristic or reporting in protocols | N/A generally broad topic scope |
|                      | Systematic review of RCTs (protocols or reports) | - association between trial characteristic and outcome  
                        - prevalence of trial characteristic or reporting in protocols | - broad  
                        - narrow if examples are across various ranges of specialties |
|                      | Cohort/cross-section of RCTs (protocols or reports) | - association between trial characteristic and outcome  
                        - prevalence of trial characteristic or reporting in protocols | - broad  
                        - narrow if examples are across various ranges of specialties |
| **Moderate**         | Systematic review of RCTs (protocols or reports) | - association between trial characteristic and outcome  
                        - prevalence of trial characteristic or reporting in protocols | - narrow if only one or two examples in narrow fields (i.e., possibly confounded by topic)  
                        - broad if supported by a strong theoretical rationale  
                        - narrow if supported by strong theoretical rationale and examples are across various ranges of specialties |
|                      | Cohort outcome/cross-section of RCTs | - association between trial characteristic and outcome  
                        - prevalence of trial characteristic or reporting in protocols | - narrow if only one or two examples in narrow fields (i.e., possibly confounded by topic)  
                        - broad if supported by a strong theoretical rationale |
|                      | Three or more experimental studies within RCTs | - association between trial characteristic and outcome | - if examples are across various ranges of specialties |
| **Weak**             | Systematic review of RCTs (protocols or reports) | - prevalence of trial characteristic or reporting in protocols | - narrow if only one or two examples in narrow fields (i.e., possibly confounded by topic) |
|                      | Cohort outcome/cross-section of RCTs | - prevalence of trial characteristic or reporting in protocols | - narrow if only one or two examples in narrow fields (i.e., possibly confounded by topic) |
|                      | One or two experimental studies within RCTs | - association between trial characteristic and outcome | - narrow if only one or two examples in narrow fields (i.e., possibly confounded by topic) |
| **None or Other**    | N/A | N/A | N/A |

E: Exclude, I: Include, Q1: lower 25% quartile, N/A: not applicable, RCT: randomized controlled trial

#### 4.3 Results

##### 4.3.1 Study selection

The search of MEDLINE, EMBASE, the Cochrane Library (CMR and CDSR) and additional methods retrieved 7166, 6449, 2784 and 533 citations, respectively (Figure 5). MEDLINE-indexed EMBASE citations (n = 5454) and duplicate citations (n = 753) were
removed as described by Sampson and colleagues\textsuperscript{88} and Reference Manager 11\textsuperscript{89}, respectively. After screening the titles and abstracts of the remaining 10,725 citations, 8292 were excluded and 2433 were retrieved in full text. Authors were contacted for additional data to assess eligibility for 135 studies. Kappa was not calculated as screening criteria were modified after screening validation and discussion was required between reviewers for approximately 15\% of studies. Where uncertainty remained (n = 385), a second or third reviewer screened records independently and all disagreements were resolved by discussion.

Studies were excluded for failing to meet the following criteria: 1) assessment of methodological, organizational or ethical characteristics of RCTs or reporting in protocols (44\%); 2) assessment of characteristics relevant to RCT protocol content (6\%); 3) empirical study (29\%); or 4) use of an eligible study design (10\%). Another 12\% of studies were excluded for other reasons (less than 80\% RCTs and results for RCTs not reported separately, trials before 1992, results too specific/not generalizable, language other than English or French, unable to contact author to determine eligibility).

Four-hundred-and-fifty-five reports were eligible for inclusion in this review (337 from database searches and 118 from additional methods). Following removal of overlapping records (multiple and previous publications [including abstracts]) data were ultimately extracted from 396 studies. Twenty-one studies were subsequently found to be included in relevant methodological reviews, thus, although extracted data was retained, the following section refers to the 375 most comprehensive reports.
4.3.2 Study characteristics

Of the included studies, most (n = 344; 92%) were published in full; 28 were conference proceedings or published abstracts (7%), and four were unpublished or other (Table 7). Most reports were presented or published recently: 2000-2009 (n = 315; 84%); 1990-1999 (n = 50; 13%); 1980-1989 (n = 9; 2%). Studies were published in 169 different journals, most frequently in the *Journal of Clinical Epidemiology* (n = 23; 6%), *British Medical Journal* (n = 19; 5%), *Journal of the American Medical Association* (n = 16; 4%)}
and *Controlled Clinical trials* (n = 13; 3%). Corresponding authors were most frequently based in North America (n = 190; 51%) or Europe (n = 143; 38%) and were from 28 countries, most frequently the USA, UK and Canada.

Two-hundred-and-one studies (54%) reported funding for their research: 171 (46%) from not-for-profit agencies (e.g. government, charities), 10 (3%) from for-profit agencies, 11 (3%) from both and in 9 (2%) the type of funding source was unclear. The remainder reported no funding (n = 19; 5%) or did not indicate whether the study was funded (n = 155; 41%, including 127/344 (37%) full-text articles and 28/28 (100%) abstracts).

Studies were classified as systematic reviews of methodological research (n = 39; 10%); systematic reviews (n = 96; 26%) or cohorts, case-control or cross-sections (n = 148; 39%) of RCT protocols or full text reports; experimental studies (e.g. RCTs) within RCTs (n = 29; 8%) or other (e.g. other unbiased samples, relevant experimental case-reports; n = 63; 17%). Studies were most often relevant to only a few checklist items (median (IQR): 2 (1,3)) while 7 studies were relevant to 10 or more potential items\(^91-97\).

Approximately 40% of studies had a narrow scope and narrow topic (e.g. cross-section in select journals of RCTs in a particular topic). Another 28% of studies had a broad scope and narrow topic (e.g. SR of RCTs in a particular topic), 21% a narrow scope and broad topic (e.g. cross-section in select journals on any topic), and 11% a broad scope and broad topic (e.g. systematic review of RCTs in any topic).
Table 7  Characteristics of studies included in systematic review

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 375</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Report</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conference or published abstract</td>
<td>28</td>
<td>(7)</td>
</tr>
<tr>
<td>Published – full text</td>
<td>344</td>
<td>(92)</td>
</tr>
<tr>
<td>Other (1 unpublished, 1 report, 1 conference abstract and additional unpublished manuscript, 1 published correspondence)</td>
<td>4</td>
<td>(1)</td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980-1984</td>
<td>2</td>
<td>(0.5)</td>
</tr>
<tr>
<td>1985-1989</td>
<td>7</td>
<td>(2)</td>
</tr>
<tr>
<td>1990-1994</td>
<td>9</td>
<td>(2)</td>
</tr>
<tr>
<td>1995-1999</td>
<td>41</td>
<td>(11)</td>
</tr>
<tr>
<td>2000-2004</td>
<td>117</td>
<td>(31)</td>
</tr>
<tr>
<td>2005-2009</td>
<td>198</td>
<td>(53)</td>
</tr>
<tr>
<td><strong>Journals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 169</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Country of corresponding author</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>140</td>
<td>(37)</td>
</tr>
<tr>
<td>UK</td>
<td>63</td>
<td>(17)</td>
</tr>
<tr>
<td>Canada</td>
<td>50</td>
<td>(13)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>19</td>
<td>(5)</td>
</tr>
<tr>
<td>Denmark</td>
<td>12</td>
<td>(3)</td>
</tr>
<tr>
<td>Australia</td>
<td>9</td>
<td>(2)</td>
</tr>
<tr>
<td>Not reported</td>
<td>12</td>
<td>(3)</td>
</tr>
<tr>
<td>Other</td>
<td>70</td>
<td>(19)</td>
</tr>
<tr>
<td><strong>Funding sources</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>155</td>
<td>(41)</td>
</tr>
<tr>
<td>Reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-profit</td>
<td>171</td>
<td>(46)</td>
</tr>
<tr>
<td>For profit (pharmaceutical company)</td>
<td>10</td>
<td>(3)</td>
</tr>
<tr>
<td>Both for-profit and not-for profit</td>
<td>11</td>
<td>(3)</td>
</tr>
<tr>
<td>Unclear</td>
<td>9</td>
<td>(2)</td>
</tr>
<tr>
<td>Reported no funding</td>
<td>19</td>
<td>(5)</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR of methodological research</td>
<td>39</td>
<td>(10)</td>
</tr>
<tr>
<td>SR of RCTs (protocols or full-text)</td>
<td>96</td>
<td>(26)</td>
</tr>
<tr>
<td>Cohort/Cross-section/case-control RCTs</td>
<td>148</td>
<td>(39)</td>
</tr>
<tr>
<td>Experimental (e.g. nested RCT in RCT)</td>
<td>29</td>
<td>(8)</td>
</tr>
<tr>
<td>Other</td>
<td>63</td>
<td>(17)</td>
</tr>
<tr>
<td><strong>Number of relevant items/study, Median (I.Q.R.)</strong></td>
<td>2</td>
<td>(1, 3)</td>
</tr>
<tr>
<td>Range</td>
<td>1 - 32</td>
<td></td>
</tr>
</tbody>
</table>

RCT randomized controlled trial, SR systematic Review, UK United Kingdom, USA United States of America

Data extraction validation showed minor differences between reviewers, mostly limited to the quantity of information extracted (e.g. extent of details of methodology of included studies). In one instance, reviewers did not have 100% agreement on the candidate checklist items to which the reference was relevant as the items' sub-concepts overlapped.
(Monetary and material support, Role of sponsor and Conflict of interest). The primary reviewer was more liberal in this instance and the discrepancy was resolved by discussion. An example of data extraction results is included in Appendix G (Table 17); full data extraction tables are available from the author.

4.3.3 Synthesis of results

Table 8 presents references to relevant empirical research and the results of the assessment of the strength of the evidence for each potential checklist item. Validation of the rating of the strength of the evidence showed good agreement (Reviewers 1&2: 80% agreement, weighted kappa = 0.787, n = 10 items; Reviewers 1&3: 80% agreement, weighted kappa = 0.681, n = 10 items).

Two new concepts not previously captured in the Delphi were identified from the systematic review. The first addresses the importance of including the names of protocol authors and the second addresses planned methods of increasing adherence and retention. These concepts received Weak and Moderate support from the systematic review, respectively.

Overall, the results of the systematic review provide strong support for 23 items/sub-items, moderate support for 23 and weak/no support for 44 items/sub-items. Further details of these results are discussed in Chapter 5.
<table>
<thead>
<tr>
<th>Section/Topic (^a)</th>
<th>SR</th>
<th>References (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Section 1: General Information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Title</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
<tr>
<td>2. Trial identifier</td>
<td>Moderate</td>
<td>SR methods (^97) Sample RCTs - prev (^98)</td>
</tr>
<tr>
<td>3. Protocol Version</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
<tr>
<td>4. Protocol Summary A.</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
<tr>
<td>4. Protocol Summary B. Lay summary</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
<tr>
<td>5. Names and addresses</td>
<td>Weak/None</td>
<td>Sample RCT - prev (^99,100)</td>
</tr>
<tr>
<td>6. Table of contents</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
<tr>
<td>7. List of abbreviations</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Section 2: Introduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Rationale</td>
<td>Moderate</td>
<td>SR methods (^97/101,102-104) Sample RCTs - other (^81,82) Sample RCTs - prev (^96,105)</td>
</tr>
<tr>
<td>9. Background of the study</td>
<td>Moderate</td>
<td>Sample RCTs - other (^81,82) Sample RCTs - prev (^96,105-110) incl. (^111,112)</td>
</tr>
<tr>
<td>10. Preliminary data</td>
<td>Weak/None</td>
<td>SR methods (^97/101) Sample RCTs - outcome (^113) Sample RCTs - prev (^114,115) other (^116)</td>
</tr>
<tr>
<td>11. Objectives</td>
<td>Weak/None</td>
<td>SR methods (^97/101,102-104) Sample RCTs - prev (^117-119)</td>
</tr>
<tr>
<td>12. General approach</td>
<td>Weak/None</td>
<td>SR methods (^104)</td>
</tr>
<tr>
<td>13. Study location(s): A. Description of sites(s)</td>
<td>Strong</td>
<td>SR methods (^97/101,95,104,120-123) Sample RCTs - outcome (^91)</td>
</tr>
<tr>
<td>13. Study location(s): B. Justification of sites(s)</td>
<td>Moderate</td>
<td>Sample RCTs - prev (^21,133) other (^134/135) incl. (^136,137)</td>
</tr>
<tr>
<td>13. Study locations C. Relevant demographic and epidemiological information</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td><strong>Section 3: Methods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Population</td>
<td>Moderate</td>
<td>Sample RCTs - outcome (^94,138) Sample RCTs - prev (^92,139) (and others in Eligibility criteria)</td>
</tr>
<tr>
<td>15. Eligibility criteria A. Describe criteria</td>
<td>Strong</td>
<td>SR methods (^97,102,122,140,141) Sample RCTs - outcome (^91,94,124,127,138,142,143) Sample RCTs - prev (^96,139,144-150) Sample RCTs vs. target population (^139,145,151-173) other (^116) incl. (^174)</td>
</tr>
<tr>
<td>Section/ Topic(^a)</td>
<td>SR</td>
<td>References(^b)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------</td>
<td>------------------</td>
</tr>
<tr>
<td>61. Co-enrolment in studies</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| 16. Sample size       | Strong  | SR methods\(^{93, 97, 120}\)  
|                       |         | Other MA of method. SR\(^{10}\)  
|                       |         | Sample RCTs – outcome\(^{99, 175-177}\)  
|                       |         | Sample RCTs – prev\(^{12, 21, 92, 98, 114, 115, 117, 153, 178-232}\)  
| 17. Recruitment       | Strong  | SR methods\(^{93, 95, 97, 104, 140, 233-239}\)  
|                       |         | Sample RCTs - outcome\(^{113, 240-242}\)  
|                       |         | Experimental in ≥ 1 RCT\(^{243-249}\)  
|                       |         | Sample RCTs - prev\(^{195}\)  
|                       |         | Other\(^{250}\)  
|                       |         | Incl.\(^{251-256}\)  
|                       |         | 116, 257  
| 18. Type of study     | Strong  | SR methods\(^{234}\)  
|                       |         | Sample RCTs - outcome\(^{113, 259-262}\)  
|                       |         | Sample RCTs - prev\(^{210, 215}\)  
| 19. Study timeline: A. | Weak/None | SR methods\(^{101}\)  
|                       |         | Sample RCTs - outcome\(^{94}\)  
|                       |         | 127, 130, 263  
|                       |         | 264  
|                       |         | See note  
| 19. Study timeline B: | Weak/None | N/A  
| Schematic diagram of  |         |  
| procedures and visits |         |  
| 20. Randomization:    | Strong  | SR methods\(^{93, 97}\)  
| Sequence generation   |         | Other MA of method. SR\(^{10}\)  
|                       |         | Sample RCTs - outcome\(^{128, 175, 197, 214, 240, 260, 264 273}\)  
|                       |         | Sample RCTs - prev\(^{19, 21, 190, 191, 195, 196, 207, 211, 219 222, 231, 274-285}\)  
|                       |         | Other\(^{134} / 135 / 286, 287\)  
|                       |         | Incl.\(^{288}\)  
| 21. Randomization:    | Strong  | SR methods\(^{93, 97, 289}\)  
| Allocation concealment|         | Other MA of method. SR\(^{7, 10, 290}\)  
|                       |         | Sample RCTs - outcome\(^{132, 176, 186, 197, 214, 240, 260, 266-273, 291-297}\)  
|                       |         | Sample RCTs – prev\(^{19, 118, 133, 149, 179, 185, 187, 188, 190, 196, 201, 204, 207, 211, 219, 222, 224, 225, 231, 274, 275, 278-281, 283-286, 298-309\)  
|                       |         | Incl.\(^{8, 9, 91, 175, 265, 268, 269, 310, 314}\)  
| 22. Randomization:    | Weak/None | SR methods\(^{97}\)  
| Implementation        |         | Sample RCTs - outcome\(^{91}\)  
|                       |         | 272  
|                       |         | Sample RCTs - prev\(^{188}\)  
|                       |         | 274, 301  
|                       |         | Other\(^{116}\)  
| 23. Blinding (masking)| Strong  | SR methods\(^{93, 97, 233}\)  
|                       |         | Other MA of method. SRs\(^{7, 10, 290}\)  
|                       |         | Sample RCTs - outcome\(^{94, 132, 176, 186, 214, 240, 260, 266-268, 270-273, 292, 293, 296, 297, 315-319}\)  
|                       |         | Sample RCTs - prev\(^{92, 114, 118, 133, 149, 150, 179, 182, 185, 187, 188, 190-193, 196, 202, 204, 207, 211, 219, 221, 222, 225, 229, 231, 269, 274-286, 298-304, 305-309, 320-329\)  
|                       |         | Other (sample / survey)\(^{330, 331}\)  

\(^a\) Section/Topic

\(^b\) References
<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>SR</th>
<th>References&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| 24. Interventions A. Details of the interventions | Strong | SR methods<sup>93, 97, 104, 123</sup>  
Sample RCTs - outcome<sup>91, 94, 107, 111-113, 127, 129, 130, 132, 263, 264, 286, 291, 336-341</sup> |
| 24. Interventions B. Justify the control interventions | Strong | Sample RCTs - other<sup>82</sup>  
Sample RCTs - prev<sup>92, 96, 105, 133, 138, 202, 221, 323, 327, 342-345</sup>  
Experimental in ≥ 1 RCT<sup>346-348</sup> |
| 62. Investigational product(s) | Moderate | SR methods<sup>349</sup>  
Sample RCTs - outcome<sup>337</sup> |
| 25. Schedule(s) of Intervention(s) | Moderate | SR methods<sup>97</sup>  
Sample RCTs - outcome<sup>127, 350</sup>  
<sup>See note</sup> |
| 26. Concomitant interventions | Weak/None | SR methods<sup>93</sup>  
Sample RCTs - prev<sup>92, 222</sup> |
| 27. Risks/Harms | Weak/None | Sample RCTs - prev<sup>221</sup> |
| 28. Outcomes | Strong | SR methods<sup>5, 93, 97, 290</sup>  
Sample RCTs - outcome<sup>4, 98, 129, 183, 214, 293, 344, 351-354</sup>  
Sample RCTs - prev<sup>91, 92, 182, 185, 192, 209, 220, 222, 232, 271, 279</sup>  
Experimental in ≥ 1 RCT<sup>346-370</sup> |
| 29. Data collection | Strong | SR methods<sup>97/101, 123, 290, 359-363</sup>  
Sample RCT - outcome<sup>352, 364</sup>  
Sample RCT - prev<sup>92, 117, 185, 202, 222, 288, 322, 356</sup>  
Experimental in ≥ 1 RCT<sup>365-370</sup> |
| 65. Validation of instrumentation | Strong | SR methods<sup>290, 361, 363</sup>  
Sample RCTs - outcome<sup>364</sup>  
Sample RCTs - prev<sup>92, 117, 296, 322, 356</sup>  
Experimental in ≥ 1 RCT<sup>365</sup> |
| 64. Data collection forms | Weak/None | N/A |
| 63. Biological specimens | Weak/None | N/A |
| 30. Follow-up | Strong | SR methods<sup>93, 95, 97</sup>  
Sample RCTs - outcome<sup>94, 128, 260, 265, 270, 315, 339, 352</sup>  
Sample RCTs - prev<sup>d133, 222</sup>  
Experimental in ≥ 1 RCT<sup>371, 370, 372, 373</sup> |
| 31. Data management | Moderate | SR methods<sup>359, 361</sup>  
Experimental in ≥ 1 RCT<sup>366, 368, 374</sup> |
| 32. Quality control | Moderate | SR methods<sup>95, 97, 359</sup>  
Sample RCTs - prev<sup>117, 198, 221</sup>  
Experimental in ≥ 1 RCT<sup>375</sup>  
<sup>Incl.</sup><sup>374</sup> |
| 33. Compliance | Moderate | SR methods<sup>97, 361</sup>  
Sample RCTs - prev<sup>221</sup>  
Experimental in ≥ 1 RCT<sup>346</sup> |
<p>| 34. Safety Evaluations | Weak/None | Experimental in ≥ 1 RCT&lt;sup&gt;365&lt;/sup&gt; |
| 35. Statistical methods | Strong | SR methods&lt;sup&gt;97, 93&lt;/sup&gt; |</p>
<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>SR</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>36. Withdrawals A. Criteria for withdrawal</td>
<td>Weak/None</td>
<td>Sample RCTs - outcome 266</td>
</tr>
<tr>
<td>36. Withdrawals B. Data from withdrawals</td>
<td>Weak/None</td>
<td>Sample RCTs - prev 92</td>
</tr>
<tr>
<td>36. Withdrawals C. Centre withdrawal</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
<tr>
<td>37. Missing data</td>
<td>Moderate</td>
<td>Sample RCTs - outcome 362, 387</td>
</tr>
<tr>
<td>38. Data and Safety Monitoring Board (DSMB)</td>
<td>Weak/None</td>
<td>SR methods 97</td>
</tr>
<tr>
<td>39. Interim trial monitoring</td>
<td>Moderate</td>
<td>SR methods 97</td>
</tr>
<tr>
<td>40. Stopping guidelines A. Statistical stopping guidelines</td>
<td>Moderate</td>
<td>SR methods 97</td>
</tr>
<tr>
<td>40. Stopping guidelines B. Non-statistical stopping guidelines</td>
<td>Moderate</td>
<td>SR methods 96, 413, 416</td>
</tr>
<tr>
<td>41. Adverse event reporting</td>
<td>Weak/None</td>
<td>Experimental in ≥ 1 RCT 365</td>
</tr>
<tr>
<td>42. Emergency code-breaking procedure</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
<tr>
<td>43. Limitations</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Section 4: Trial organization and administration

| 44. Personnel | Strong | SR methods 97/101, 95, 102, 120 |
| 45. Logistics | Weak/None | SR methods 96 |
| 46. Monetary and material support A. Source(s) of financial and material support. | Strong | SR methods 6, 78, 120, 419, 420 |

Other MA of method. SR

Sample RCTs - outcome 91, 138, 175, 266-269, 271, 273, 293, 294, 322, 376-387


Other 399-410

Incl. 282, 288, 310, 311, 333

Sample RCTs - outcome 376-387


Other 399-410

Incl. 282, 288, 310, 311, 333

Sample RCTs - outcome 369

Sample RCTs - prev 375

Sample RCTs - prev Q. 177, 399, 401, 403, 404, 411, 412

Sample RCTs - outcome 92

Sample RCTs - prev N/A

Experimental in ≥ 1 RCT 375

Additional studies (not included) 414, 415

Sample RCTs - outcome 92

Sample RCTs - prev 12, 96, 229, 413

Sample RCTs - outcome 96, 413, 416

Sample RCTs - prev 96, 413, 416

Sample RCTs - prev 96

Sample RCTs - outcome 116, 368

Sample RCTs - outcome 91, 113, 126, 188, 310, 417, 418

Sample RCTs - outcome 116, 368


Sample RCTs – prev 110, 118, 285, 297, 310, 320, 438, 439

Incl. 79, 105, 106, 319, 343, 440-443
<table>
<thead>
<tr>
<th>Section/ Topic</th>
<th>SR</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monetary and material support B. Type(s) of support</td>
<td>Moderate</td>
<td>Sample RCTs - outcome[^294^, ^439^, ^442^] Other[^116^]</td>
</tr>
<tr>
<td>Monetary and material support C. Amount of support</td>
<td>Weak/None</td>
<td>Sample RCTs - outcome[^113^]</td>
</tr>
<tr>
<td>Monetary and material support D. How support is provided</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
<tr>
<td>Budget</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
<tr>
<td>Signatures</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
<tr>
<td>Trial monitoring</td>
<td>Weak/None</td>
<td>SR methods[^97^]</td>
</tr>
<tr>
<td>Post-trial care</td>
<td>Weak/None</td>
<td>SR methods[^95^] Experimental in ≥ 1 RCT[^370^]</td>
</tr>
<tr>
<td>Post-trial data/materials storage</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Moderate</td>
<td>SR methods[^97^, ^103^, ^104^, ^122^, ^123^, ^238^, ^360^] See note</td>
</tr>
<tr>
<td>Insurance</td>
<td>Weak/None</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Section 5: Ethical considerations**

| Potential benefits and risks | Moderate | SR methods[^95^, ^101^, ^123^] See note |
| Surrogate consent or assent | Weak/None | N/A |
| Confidentiality and Anonymity | Weak/None | N/A |
| Ethics approval | Weak/None | Sample RCTs - prev[^96^, ^100^, ^454^] |
| Ancillary and sub-studies | Weak/None | N/A |
| Pregnancy | Weak/None | N/A |

**Section 6: Reporting and Dissemination**


[^116^]: Other sources of support not specified.
[^97^]: Sample RCTs - outcome.
[^103^]: Other methods not specified.
[^95^]: Sample RCTs – prev.
[^444^]: Further methods specified.
[^453^]: See note for details.
[^456-462^]: Experimental in ≥ 1 RCT.
[^463-469^]: Further methods specified.
[Incl.]: Inclusion criteria.
[^116^]: Sample RCTs - prev.
<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>SR</th>
<th>References</th>
</tr>
</thead>
</table>
| 56. Dissemination | Strong | SR methods<sup>5</sup> 97 120 121 438  
Sample RCTs – outcome<sup>99</sup> 129 353 386 471 473  
Incl 136 137 428 474 476 |
| 67. Reporting of early stopping | Weak/None | Sample RCTs - prev<sup>476</sup> |
| 57. Publication Policy | Moderate | SR of methods<sup>78</sup> 438  
Sample RCTs - outcome<sup>386</sup>  
Sample RCTs - prev<sup>444</sup> 470  
Incl 79 105 442 |

Section 7: Other

| 58. References | Weak/None | N/A |
| 59. Appendix materials A. Case-report forms | Weak/None | N/A |
| 59. Appendix materials B. Other data collection forms (e.g. questionnaires) | Moderate | SR methods<sup>363</sup>  
Sample RCTs – outcome<sup>364</sup>  
Sample RCTs – prev<sup>296</sup>  
Experment in ≥ 1 RCT<sup>365</sup> |
| 59. Appendix materials C. Consent/assent forms | Strong | SR methods<sup>104</sup> / 445, 95 123 238 360 449-452, 446 / 448  
Sample RCTs - prev<sup>100</sup> 455  
Incl 463 467-469 |

Section 6: Reporting and Dissemination

| Protocol Authors | Weak/None | Sample RCT - prev<sup>470</sup> |
| Methods of increasing Adherence and retention | Moderate | SR methods<sup>96</sup> 373  
Experment in ≥ 1 RCT<sup>346</sup> |

<sup>a</sup> Item numbers are based on Delphi survey, see Chapter 3  
<sup>b</sup> SR methods = Systematic review of methodological studies, Sample RCTs – outcome = Sample of RCTS (e.g. SR, cohort, cross-section) examining the association between trial characteristic and trial outcome, Sample RCTs – prev = Sample of RCTS (e.g. SR, cohort, cross-section) examining the prevalence of trial characteristic (e.g. adequacy of methods), incl = studies extracted but included in subsequent methodological reviews (Note not all studies included methodological reviews were independently extracted and thus not all are included here)  
<sup>c</sup> Studies may be indirectly relevant to item and additional indirect evidence may be included in other items  
<sup>d</sup> Other potentially relevant studies not included if adequacy of follow-up was not clearly in control of the investigator  
<sup>e</sup> Some references more relevant to possible new item on methods to increase adherence/retention
5.0 Synthesis of Evidence from Delphi Consensus Survey and Systematic Review

5.1 Objective

The objective of this chapter of the thesis is to provide an overview and a comparison between the results of the Delphi consensus survey (Chapter 3) and systematic review (Chapter 4) for each candidate item.

5.2 Methods

To facilitate the comparison of the Delphi consensus survey and systematic results, the strength of the evidence from the Delphi numerical results was rated using the same categorization as the systematic review (Strong, Moderate or Weak/None). The criteria used to make these assessments were modified from those used during the Delphi rounds to account for the spread of the results and corresponding criteria were developed for items rated using the categories ‘Include’, ‘Exclude’ and ‘Unsure’ in Round 3. To be rated as Strong, the lower quartile (Q1) was required to be greater than or equal to 8; correspondingly a minimum of 75% of respondents had to have indicated that the item should be ‘Included’. Items receiving a Median score of 6 or 7 were considered to have Moderate support, as were items with a Median score greater than or equal to 8 but with a Q1 < 8 and items where 50-74% of respondents indicated the item should be ‘Included’. Finally, items receiving a Median score of 5 or less, or where less than 50% of respondents indicated ‘Include’, were considered to have Weak/No support. This categorization was based on objective criteria and was done by one researcher. For details on the strength of the evidence from the systematic review, please see Chapter 4.
Final recommendations were then made based on this evidence for each potential item for the SPIRIT Initiative. These recommendations were derived from a combined assessment of the strength of the Delphi evidence, visual analysis of the Delphi subgroup results by profession and self-rated expertise, Delphi panellists’ item-specific comments, and the strength of the systematic review evidence.

The recommendation options were as follows:

- Include item (with or without further discussion),
- Include concept but further discussion or consideration of overlap needed
- Further discussion (no explicit recommendation made), or
- Exclude item (with or without further discussion).

These recommendations were not validated and should be viewed as an overall interpretation of the evidence rather than part of the scientific content of this thesis.

Three examples of the synthesis process and the information used to derive recommendations are included in Appendix G.

### 5.3 Results

#### 5.3.1 Overview

Overall, the Delphi provided strong support for 50 items/sub-items, moderate support for 29 items/sub-items and weak/no support for 9 items/sub-items. Agreement between the Delphi and systematic review results was poor (Weighted kappa = 0.123), due mostly to the lack of empirical evidence for certain items with strong pragmatic or ethical relevance.

Tables 9 to 15 present the results of the assessment of the strength of the evidence for each potential checklist item. Additional notes in these tables include common item-specific comments from Delphi panellists (and suggestions derived from these comments) and sub-
group differences, which were noted where they opposed recommendations or where they informed items warranting further discussion.

The results are discussed under the eight sub-headings used to draft the SPIRIT checklist. The text does not address all items or included studies; rather, the results are tabular and examples are highlighted. Full item descriptions are available in Chapter 3 and all included studies are listed in Chapter 4.

5.3.2 Item-specific recommendations

Section 1: General information. Little supporting empirical evidence was found for items in Section 1 of the checklist (Table 9). Many items, however, received strong Delphi support, highlighting the practical rationale for their inclusion (Title, Trial identifier, Protocol version and Names and addresses). The Delphi also provided strong support for the item Protocol summary, although not for a specific request for a lay summary (Protocol summary [B]). The items Table of contents and List of abbreviations received only moderate support from the Delphi. Although some subgroups favoured including such structural components, the evidence does not support including them in the SPIRIT checklist; further discussion may be required.

Five of eight items in this section were recommended for inclusion and the remainder for exclusion.
Table 9: Synthesis of Delphi survey and systematic review results: recommendations for the SPIRIT checklist -
Section 1: General Information

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Delphi</th>
<th>SR</th>
<th>Recommendation</th>
<th>Additional considerations based on Delphi comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Title</td>
<td>Strong</td>
<td>Weak/None</td>
<td>Include</td>
<td>• Consider revising based on Delphi comments</td>
</tr>
<tr>
<td>2. Trial identifier</td>
<td>Strong</td>
<td>Moderate</td>
<td>Include</td>
<td>• Not relevant at all protocol stages (e.g. before funding). Suggest to add, “if applicable”</td>
</tr>
<tr>
<td>3. Protocol Version</td>
<td>Strong</td>
<td>Weak/None</td>
<td>Include</td>
<td>-</td>
</tr>
<tr>
<td>4. Protocol Summary A</td>
<td>Strong</td>
<td>Weak/None</td>
<td>Include</td>
<td>-</td>
</tr>
<tr>
<td>4. Protocol Summary B. Lay summary</td>
<td>Moderate</td>
<td>Weak/None</td>
<td>Exclude</td>
<td>• Subgroup analysis showed more support from REC/IRB representatives and journal editors (I = 75% each) than other groups (I = 62%) and by those with lower levels of self-rated expertise. • Could be requested separately by relevant groups</td>
</tr>
<tr>
<td>5. Names and addresses</td>
<td>Strong</td>
<td>Weak/None</td>
<td>Include</td>
<td>• Addresses should be changed to “affiliations” or clarified as institutional addresses.</td>
</tr>
<tr>
<td>6. Table of contents</td>
<td>Moderate</td>
<td>Weak/None</td>
<td>Exclude</td>
<td>-</td>
</tr>
<tr>
<td>7. List of abbreviations</td>
<td>Moderate</td>
<td>Weak/None</td>
<td>Exclude, further discussion</td>
<td>• Subgroup analysis showed more support by REC/IRB representatives (I = 75%), funders/regulators (I = 86%) and journal editors (I = 78%) than other groups (I = 73%).</td>
</tr>
</tbody>
</table>

I = Include

*Item numbers are based on Delphi survey; see Chapter 3

Section 2: Introduction. Many items in Section 2 also received strong support from the Delphi; however, some items were also supported by empirical evidence (Table 10). For example, the Delphi provided strong support for the items Rationale, Background of the study and Preliminary data. The empirical support overlapped between Rationale and Background of the study (both received moderate support from the systematic review) while the support for Preliminary data was weak. As recommended by many Delphi respondents, consideration to merge these three items is recommended.
Table 10: Synthesis of Delphi survey and systematic review results: recommendations for the SPIRIT checklist - Section 2: Introduction

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Delphi</th>
<th>SR</th>
<th>Recommendation</th>
<th>Additional considerations based on Delphi comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Rationale</td>
<td>Strong</td>
<td>Moderate</td>
<td>Include concept, consider overlap</td>
<td>Consider merging with &quot;Background of the study&quot;</td>
</tr>
<tr>
<td>9. Background of the study</td>
<td>Strong</td>
<td>Moderate</td>
<td>Include concept, consider overlap</td>
<td>Consider merging with &quot;Rationale&quot;; Re-examine rationale for &quot;equipoise/uncertainty&quot; and &quot;systematic review&quot; (conflicting comments); Re-consider wording of &quot;ideally&quot; (RE: systematic review) (conflicting comments)</td>
</tr>
<tr>
<td>10. Preliminary data</td>
<td>Strong</td>
<td>Weak/None</td>
<td>Include concept, consider overlap</td>
<td>Consider merging with &quot;Background of the study&quot; (and also, possibly &quot;Rationale&quot; as per previous comments)</td>
</tr>
<tr>
<td>11. Objectives</td>
<td>Strong</td>
<td>Weak/None</td>
<td>Include</td>
<td>-</td>
</tr>
<tr>
<td>12. General approach</td>
<td>Moderate</td>
<td>Weak/None</td>
<td>Exclude</td>
<td>Wording/concept too vague. Concept already captured/should be combined with other items: e.g. &quot;Type of Study&quot; or &quot;Background of the study/Rationale&quot;</td>
</tr>
<tr>
<td>13. Study location(s): A. Description of sites(s)</td>
<td>Strong</td>
<td>Strong</td>
<td>Include</td>
<td>Clarification needed; some comments suggest this should be a general description of country or region but not sites. Others support a general description of sites but not a list of all sites as this might change, requiring protocol amendments. Still others support a list of actual known sites as it speaks to the ability to meet recruitment targets. Many panellists do not support &quot;justification&quot; of sites, although others find it important in certain situations. Emphasize &quot;briefly describe&quot; (already included in description). Sub-group analyses suggested REC/IRB members and journal editors (JE) were more in favour of including sub-items B and C (Sub-item B, REC/IRB: I = 63%, JE: I = 78%; Sub-item C, REC/IRB: I = 75%, JE: I = 78%) than other groups (I = 43% for both) Consider discussing additional points in the E&amp;E</td>
</tr>
<tr>
<td>13. Study location(s): B. Justification of sites(s)</td>
<td>Weak/None</td>
<td>Moderate</td>
<td>Exclude</td>
<td></td>
</tr>
<tr>
<td>13. Study locations C. Relevant demographic and epidemiological information</td>
<td>Weak/None</td>
<td>Moderate</td>
<td>Exclude</td>
<td></td>
</tr>
</tbody>
</table>

E&E = Explanation and elaboration document; I = Include

*Item numbers are based on Delphi survey; see Chapter 3

Two concepts included in the item Background generated substantial debate from Delphi panellists: 1) requiring evidence of trial adherence to the ethical principle of 'equipoise'/clinical uncertainty and 2) the conduct or reference of an up-to-date systematic review supporting the need for the trial. Empirical evidence supported...
including both of these concepts in the SPIRIT checklist, highlighting the importance of justifying trial merit in the context of current evidence.

The item *Objectives*, on the other hand, did not receive strong empirical support but was recommended for inclusion. Although lacking direct empirical evidence, it was among the most strongly supported in the Delphi (Median (IQR) = 10 (10, 10)) and is supported by logical argument and indirect evidence.

The three Delphi-derived sub-components of *Study location(s)* received conflicting support. Trial location (e.g. countries/cities and types of setting such as primary care or community) and the total number of trials sites have both been associated with recruitment success\(^{101, 104, 122-124}\) (albeit not consistently\(^{94, 131}\)) and attrition\(^{127, 128}\). Trial location has also been associated with trial outcome\(^{125}\), trial quality aspects (e.g., authenticity of randomization\(^{134}\)) and trial generalizability\(^{133}\). The evidence therefore suggests the SPIRIT checklist include at a minimum, the location and potential number of study sites (i.e. Study location(s) [A]). The results did not support including Study locations [B] or [C] in SPIRIT checklist.

Overall, five of the eight concepts in this section were recommended for inclusion (three for possible merging) and three for exclusion from the SPIRIT checklist

*Section 3: Methods.* The level of support for the items in Section 3 varied substantially (Table 11); 13 of 41 concepts received strong support from the both the Delphi and systematic review, one received weak support from both, and the remainder received differing support.
<table>
<thead>
<tr>
<th>Section/ Topic*</th>
<th>Delphi</th>
<th>SR</th>
<th>Recommendation</th>
<th>Additional considerations based on Delphi comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. Population</td>
<td>Strong</td>
<td>Moderate</td>
<td>Include item, consider overlap</td>
<td><strong>Consider overlap with “Eligibility criteria” and of last concept (describe “catchment area”) with “Study location(s)”</strong>&lt;br&gt;<strong>Consider if this is less relevant/too burdensome for multi-centre studies</strong>&lt;br&gt;<strong>Despite considerations above, recommended for inclusion</strong></td>
</tr>
<tr>
<td>15. Eligibility criteria A.</td>
<td>Strong</td>
<td>Strong</td>
<td>Include</td>
<td><strong>Consider revising sub-item (“justification”) so as not to suggest all (e.g. obvious) exclusions need to be justified</strong>&lt;br&gt;<strong>Consider concern with term ‘obvious’ (subjective), reiteration may be needed</strong>&lt;br&gt;<strong>Subgroup analysis showed REC/IRB members (I = 75%), trial coordinators (I = 80%) and Journal editors (I = 89%) supporting sub-item B than other groups (61%)</strong></td>
</tr>
<tr>
<td>15. Eligibility criteria B.</td>
<td>Moderate</td>
<td>Strong</td>
<td>Include</td>
<td><strong>Consider revising sub-item (“justification”) so as not to suggest all (e.g. obvious) exclusions need to be justified</strong>&lt;br&gt;<strong>Consider concern with term ‘obvious’ (subjective), reiteration may be needed</strong>&lt;br&gt;<strong>Subgroup analysis showed REC/IRB members (I = 75%), trial coordinators (I = 80%) and Journal editors (I = 89%) supporting sub-item B than other groups (61%)</strong></td>
</tr>
<tr>
<td>16. Sample size</td>
<td>Strong</td>
<td>Strong</td>
<td>Include</td>
<td><strong>Consider revising to address comments (e.g. include explicit request for assumptions such as minimum clinically important difference/non-inferiority margins etc and the source of data for these assumptions, with citations, if relevant)</strong></td>
</tr>
<tr>
<td>17. Recruitment</td>
<td>Strong</td>
<td>Strong</td>
<td>Include</td>
<td><strong>Comments suggest that recruitment methods may be site-specific, and thus difficult to describe in the protocol</strong>&lt;br&gt;<strong>Many panelists felt a general overview including a description of where patients will be recruited from (e.g. Study location(s)) and by whom (e.g. clinician) is appropriate, but not how (e.g. newspaper advertisements, mailing strategies, when patients are approached) However, the data from the systematic review support including this information</strong></td>
</tr>
<tr>
<td>18. Type of study</td>
<td>Strong</td>
<td>Strong</td>
<td>Include</td>
<td><strong>Consider revising based on Delphi comments</strong></td>
</tr>
<tr>
<td>19. Study timeline: A. Schematic diagram of procedures and visits</td>
<td>Strong</td>
<td>Weak/ None</td>
<td>Include concept, consider overlap</td>
<td><strong>Many Delphi panelists found the requirement for a “Schematic diagram” too prescriptive and not often necessary as this information could be presented in other formats, particularly for ‘simple’ trials</strong>&lt;br&gt;<strong>Consider addressing the concept (e.g. an overview of participant-level treatments, visits and follow-up throughout the trial) in checklist, possibly combining it with another existing item (e.g. “Schedule(s) of intervention(s)”)</strong>&lt;br&gt;<strong>Consider including a suggestion, not a requirement, for a ‘Schematic diagram’</strong>&lt;br&gt;<strong>Sub-group analysis showed funding agency representatives less supportive for inclusion (I = 40%) than other groups (85%)</strong></td>
</tr>
<tr>
<td>19. Study timeline B: Schematic diagram of trial calendar dates</td>
<td>Moderate</td>
<td>Weak/ None</td>
<td>Exclude</td>
<td>-</td>
</tr>
<tr>
<td>Section/ Topic*</td>
<td>Delphi</td>
<td>SR</td>
<td>Recommendation</td>
<td>Additional considerations based on Delphi comments</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------</td>
<td>----</td>
<td>---------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>20. Randomization: Sequence generation</td>
<td>Strong</td>
<td>Strong</td>
<td>Include</td>
<td>▪ Consider excluding request for block size and possibly specifically requesting such information be omitted from protocol</td>
</tr>
<tr>
<td>21. Randomization: Allocation concealment</td>
<td>Strong</td>
<td>Strong</td>
<td>Include</td>
<td>-</td>
</tr>
</tbody>
</table>
| 22. Randomization: Implementation | Strong | Weak/ None | Include item, consider overlap | ▪ Consider conceptual overlap with “Randomization sequence generation” (‘who’ generated it), “Recruitment” (“who will enrol participants”) and “Randomization – allocation concealment” (“who will assign participants to their group”)  
▪ If kept, consider refocusing this to address “how” the randomization sequence is implemented rather than “who” implemented it |
| 23. Blinding (masking) | Strong | Strong | Include | ▪ Consider revising to address blinding of other relevant groups (i.e., more than the three currently mentioned)  
▪ Consider removing final statement (e.g. assessing success of blinding) to match new CONSORT statement |
| 24. Interventions A. Details of the interventions | Strong | Strong | Include | - |
| 24. Interventions B. Justify the control interventions | Strong | Strong | Include | ▪ Consider if this belongs in different section (e.g. Background) as suggested by a few panelists |
| 62. Investigational product(s) | Moderate | Moderate | Exclude | - |
| 25. Schedule(s) of Intervention(s) | Strong | Moderate | Include concept, consider overlap | ▪ Consider overlap with concept in “Study timeline A”  
▪ As above, consider suggesting, not a requiring, a ‘Schematic diagram’ |
| 26. Concomitant interventions | Strong | Weak/ None | Include | ▪ Supporting evidence is likely topic-specific thus not included in review  
▪ Suggested for inclusion based on theoretical/logical argument (pragmatism and safety) |
| 27. Risks/Harms | Strong | Weak/ None | Include concept, consider overlap | ▪ Supporting evidence is likely topic-specific thus not included in review  
▪ Suggested for inclusion based on theoretical/logical argument (pragmatism and safety)  
▪ Consider potential overlap (and possible merging) with “Safety evaluations” and “Adverse event reporting”  
▪ If not merged, consider if more suitable for Section 5. Ethical considerations  
▪ Revise based on Delphi comments |
<p>| 28. Outcomes | Strong | Strong | Include | - |
| 29. Data collection | Strong | Strong | Include | - |
| 65. Validation of instrumentation | Moderate | Strong | Include concept, consider | ▪ Consider merging concept within (or as sub-item to) “Background”, “Outcomes” [most frequently suggested], &quot;Data collection&quot; or |</p>
<table>
<thead>
<tr>
<th>Section/ Topic</th>
<th>Delphi</th>
<th>SR</th>
<th>Recommendation</th>
<th>Additional considerations based on Delphi comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3. Delphi</strong></td>
<td></td>
<td></td>
<td></td>
<td>&quot;Quality control&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Consider explicitly asking for citations for instruments, if relevant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Consider requesting forms as an appendix</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Sub-group analysis showed this was less strongly supported by funding and regulatory agency representatives (Median [IQR] = 5 [2, 7]) than other groups (8 [6, 9])</td>
</tr>
</tbody>
</table>

| **64. Data collection forms** | Moderate | Weak/ None | Exclude | Comments strongly support the importance of having a list of data collection forms including when they will be used, however the mandated table was not strongly supported, nor was a distinct checklist item |
|                              |          |            |         | - Consider addressing this concept in “Study timeline” (and “Schedule of Interventions”, if combined), information could be presented as part of ‘schematic diagram’ |
|                              |          |            |         | - Consider requesting forms as an appendix, not in protocol, could require extensive amendments to the protocol as forms are drafted and amended |

| **63. Biological specimens** | Moderate | Weak/ None | Exclude, further discussion | Comments state this is very important if relevant, but not always relevant and needs only a high level description |
|                            |          |            |                          | - Some included concepts (e.g. shipping) were deemed relevant for an Operations Manual while others (e.g. specimen collection) should be kept with the protocol |
|                            |          |            |                          | - Consider as a suggested appendix to protocol, if relevant |
|                            |          |            |                          | - Sub-group analysis suggests that this is less important to funding and regulator agency representatives (Median [IQR] = 4 [2, 6]) than to other groups (8 [6, 9]) |
|                            |          |            |                          | - Further discussion may be warranted due to borderline Delphi results (Median [IQR] = 8 [6, 9]) and potential logistical rationale |

| **30. Follow-up** | Strong | Strong | Include | - |
| **31. Data management** | Moderate | Moderate | Further discussion | Many panelists felt a high-level view of some concepts (data entry, data retention/storage) is appropriate but most others should be detailed elsewhere |
|                        |          |          |          | - If included, consider modifying to “Briefly describe “ or “Summance “ and revising concepts |
|                        |          |          |          | - If excluded, consider capturing important concepts (e.g. data entry) in other items (e.g. “Data collection”, “Quality control”) |

| **32. Quality control** | Strong | Moderate | Include concept, further discussion | Some panelists felt this belonged in a separate document (Operations manual, Standard operating procedures) or was already included in separate items (e.g. “Data collection”, “Statistical analysis”) |
|                        |          |          |          | - Consider overlap with other items |
|                        |          |          |          | - Consider revising |

<p>| <strong>33. Compliance</strong> | Strong | Moderate | Further discussion | Some panelists felt this was less important in trials with intention to treat analyses |</p>
<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Delphi</th>
<th>SR</th>
<th>Recommendation</th>
<th>Additional considerations based on Delphi comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>34. Safety Evaluations</td>
<td>Strong</td>
<td>Weak/None</td>
<td>Include concept, consider overlap</td>
<td>- Consider refocusing to capture planned methods to increase compliance (and possibly retention) – concepts not explicitly addressed in checklist – rather than plans to measure it.</td>
</tr>
<tr>
<td>35. Statistical methods</td>
<td>Strong</td>
<td>Strong</td>
<td>Include</td>
<td>- Consider revising to state that if details are elsewhere (e.g., Statistical analysis plan) an overview of methods and reference for details is appropriate.</td>
</tr>
<tr>
<td>36. Withdrawals A. Criteria for withdrawal</td>
<td>Strong</td>
<td>Weak/None</td>
<td>Include</td>
<td>- Description needs to be revised to address concerns of terminology and phrasing.</td>
</tr>
<tr>
<td>36. Withdrawals B. Data from withdrawals</td>
<td>Strong</td>
<td>Weak/None</td>
<td>Include concept</td>
<td>- Consider keeping concepts A and B as one item.</td>
</tr>
<tr>
<td>36. Withdrawals C. Centre withdrawal</td>
<td>Moderate</td>
<td>Weak/None</td>
<td>Exclude</td>
<td>- Sub-group analysis suggest that journal editors are more in favour of including sub-item C (I = 78%) than other groups (55%).</td>
</tr>
<tr>
<td>37. Missing data</td>
<td>Strong</td>
<td>Moderate</td>
<td>Include item, further discussion</td>
<td>- Some panellists preferred including this in a separate document (e.g., analysis plan).</td>
</tr>
<tr>
<td>38. Data and Safety Monitoring Board (DSMB)</td>
<td>Strong</td>
<td>Weak/None</td>
<td>Further discussion</td>
<td>- Consider requesting only presence/absence of DSMB, details (e.g., composition) are suggested to be more appropriate for DSMB charter.</td>
</tr>
<tr>
<td>39. Interim trial monitoring</td>
<td>Strong</td>
<td>Moderate</td>
<td>Include</td>
<td>- Consider revising to address most important concepts and request where further details may be found (e.g., DSMB charter or analysis plan).</td>
</tr>
<tr>
<td>40. Stopping guidelines A. Statistical stopping guidelines</td>
<td>Strong</td>
<td>Moderate</td>
<td>Include</td>
<td>- Consider emphasizing that these are guidelines, not boundaries/rules.</td>
</tr>
<tr>
<td>40. Stopping guidelines B. Non-</td>
<td>Strong</td>
<td>Moderate</td>
<td>Include</td>
<td>- Consider modifying description to state “early termination of trial” rather than “premature termination of trial.”</td>
</tr>
</tbody>
</table>

*Delphi SR Recommendation*
<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Delphi</th>
<th>SR</th>
<th>Recommendation</th>
<th>Additional considerations based on Delphi comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>statistical stopping guidelines</td>
<td></td>
<td></td>
<td></td>
<td>DSMB-, Sponsor-, REC/IRB- or Steering committee- governed stopping guidelines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Consider guiding expected level of detail</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Sub-group analysis suggested that funding and regulatory agency representatives (I = 57%) and trial coordinators (I = 60%) were less supportive of sub-item B than other groups (I = 78%)</td>
</tr>
<tr>
<td>41. Adverse event reporting</td>
<td>Strong</td>
<td>Weak/ None</td>
<td>Include concept, consider overlap</td>
<td>- Supporting evidence is likely topic-specific thus not included in review</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Consider overlap with “Risks/Harms” and “Safety evaluations” and consider merging into one or two items</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Methods of collecting ‘solicited adverse events’ and spontaneous adverse events may be distinct issues. The first may conceivably be part of “Outcomes” and “Data collection”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Some panellists felt that aspects of reporting adverse events (particularly serious adverse events) are governed by regulatory requirements and thus not needed in every protocol. Others supported including this for the same reasons (to ensure regulatory requirements are met).</td>
</tr>
<tr>
<td>42. Emergency code-breaking procedure</td>
<td>Strong</td>
<td>Weak/ None</td>
<td>Include concept, consider overlap</td>
<td>- Consider requesting only a higher-level description or within an existing item (e.g. Blinding, Safety evaluations/Adverse event reporting).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Consider requesting where details of these procedures may be found (e.g. Standard operating procedures, Operations manual).</td>
</tr>
<tr>
<td>43. Limitations</td>
<td>Moderate</td>
<td>Weak/ None</td>
<td>Exclude</td>
<td>-</td>
</tr>
</tbody>
</table>

I – Include; IQR – Inter-quartile range

*Item numbers are based on Delphi survey; see Chapter 3

For instance, data supporting Eligibility criteria complement obvious pragmatic reasons for clearly delineating eligibility criteria in protocols. Eligibility criteria are associated with recruitment and attrition\(^{94, 97, 102, 122; 124, 127, 140, 141}\), generalizability of trial results\(^{154, 158}\) and trial outcome\(^{138, 143}\), although some studies show differing results\(^{91, 147}\). Studies in many disciplines also show eligibility of less than 50% of with-need or on-treatment populations for relevant trials\(^{139, 141, 151-156, 158, 159, 164, 165, 165-170, 172}\), suggesting ‘evidence-based’ treatment decisions are often based on trials of highly selected participant samples, thus questioning their applicability. Evidence also suggests that many eligibility
criteria are not appropriate or are poorly justified\textsuperscript{96, 145, 146, 149} and that excluding certain subgroups may inadvertently exclude other seemingly independent subgroups\textsuperscript{142, 161, 163}. Finally, eligibility criteria may be changed or selectively reported in different publications\textsuperscript{148, 159}. Both components related to this item ([A]: criteria and [B]: justification of criteria) are recommended for the SPIRIT checklist.

Other extensively studied items include \textit{Randomization: Sequence generation}, \textit{Allocation concealment}, \textit{Blinding (masking)} and \textit{Statistical methods}. Although individual study results conflict, methodological studies across a range of disciplines and methodological reviews\textsuperscript{7, 10, 289, 290} have associated these concepts with trial outcome, recruitment efficiency and subsequent publication, and demonstrated inadequate methodology related to these factors (see Table 8, Chapter 4). Studies also show trial protocols lacking or insufficiently describing trial methods\textsuperscript{7, 12, 19, 325, 344} and inconsistent descriptions of trial methods between protocols and subsequent publications, often without justification or mention of protocol amendments\textsuperscript{7, 12, 325}. Thus, these items have been recommended for inclusion. Evidence also suggests that SPIRIT request clear delineation of trial methodology rather than rely on terminology such as ‘randomized’, ‘double-blind’ or ‘intention-to-treat analysis’ as these terms have been used to represent, sometimes inaccurately, a multitude of trial methods\textsuperscript{12, 134, 206, 207, 232, 324, 330, 331, 390, 391}.

The Delphi and review results also informed changes to existing descriptions of items strongly supported for inclusion. For example, the description of \textit{Sequence Generation} should arguably not include block-sizes, where relevant, as this may jeopardize allocation concealment integrity\textsuperscript{19}. Pre-specifying all statistical methods may also be difficult, and possibly inappropriate, as some require understanding of the data, such as patterns of or reasons for missing data; thus, the item \textit{Statistical methods} may need revision to capture this.
Similarly, many Delphi panellists suggested modifying the description of the item *Recruitment*, arguing that recruitment strategies might be site-specific and hence impractical or cumbersome to state in the protocol. Some felt knowing the setting (*Study locations*) and who recruited participants (e.g., physician, nurse, consultant) was important but not the recruitment methods (e.g. advertisements, paid incentives). However, empirical evidence suggests that different recruitment methods and trial characteristics can not only affect the number of participants eventually recruited\textsuperscript{95, 113, 116, 233-239, 241, 243-250} but also the type of participants recruited, and subsequently the generalizability of the trial results\textsuperscript{241, 245, 250}. Therefore, the request for these details in the checklist is supported.

In other instances, Delphi panellists suggested merging overlapping concepts. For example, some panellists suggested combining *Data collection forms* (summary matrix of forms used at specific time-points) with *Study timeline [A]* (schematic diagram of procedures and visits throughout the trial), which, in turn, was suggested to overlap with *Schedule(s) of Intervention(s)*. The systematic review provided at most moderate support for these three items; as such, merging them in some form was recommended. For example, one item requesting a schematic diagram detailing each visit’s administered interventions and collected data (with which forms) could capture all of these concepts. Similar overlap was noted for the items *Data collection, Validation of instrumentation, Data management* and *Quality control*, and for *Risks, Safety evaluations* and *Adverse event reporting*, yielding similar recommendations.

In some cases, the systematic review provided lack of support because existing item-specific empirical support would be mostly topic-specific (i.e., not generalizable to most RCTs) and hence was excluded from the review. Where Delphi results captured strong supporting pragmatic or ethical rationale, such as for *Risks/Safety evaluations/Adverse event*
reporting, Concomitant interventions, Withdrawals, Interim trial monitoring and Stopping guidelines, these items were recommended for inclusion.

Only three items in this section were recommended for exclusion based on the results without further consideration for merging or capturing them within existing items: Limitations, Study timeline [B] (schematic diagram of trial calendar dates), and Withdrawals [C] (criteria to withdraw a study centre).

Section 4: Trial organization and administration. In contrast to Section 3, most items in Section 4 received at most moderate or weak support from the Delphi and systematic review and were recommended for exclusion (8 of 14 items) or for further discussion (no explicit recommendation; 3 items) (Table 12).

Sub-item [A] of Monetary and material support (sources of support), however, received strong support from both the Delphi and the systematic review. Many studies report an increased proportion of positive results (or results otherwise favouring trial funders, such as decreased adverse events) in pharmaceutically funded trials compared to trials funded by non-profit organizations or trials with mixed or no funding (see Table 8, Chapter 4). Hypotheses for this bias’ source include greater use of inactive or poorly absorbed controls, differential dosing, selective reporting (of outcomes and full studies), biased interpretation of results and lack of adherence to the ethical principle of equipoise in industry-funded trials. A number of studies also assessed the role of trial quality but found industry funded trials to be of equal or greater quality than non-industry funded trials. Monetary and material support sub-item [B] (type of support) received moderate support and sub-items [C] (amount of support) and [D] (how support is provided)
received weak/no support and thus were recommended for further discussion and exclusion, respectively.

The suggested exclusion of one item based on Delphi results, *Personnel* (I = 40%, E = 51%, U = 9%), was refuted by the evidence from the systematic review. Characteristics of trial personnel have been associated with trial recruitment, retention and data collection. Specifically, studies have found an association between statistician/biostatistician/epidemiologist participation and aspects of trial methodological quality such as the presence of *a priori* sample size calculations, the use of objectively assessed outcomes and appropriate statistical analyses, although not all results were statistically significant. This item was thus recommended for inclusion. However, in congruence with Delphi panellists’ comments, empirical evidence did not support some components of this item (e.g. job descriptions), while other components (e.g., names and affiliations/contact details) may be captured in existing checklist items. Thus, further discussion regarding the item’s scope and description is recommended.
<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Delphi</th>
<th>SR</th>
<th>Recommendation</th>
<th>Additional considerations based on Delphi comments</th>
</tr>
</thead>
</table>
| **44. Personnel** | Weak/None | Strong | Include item, further discussion | - Item, as written, is not supported for inclusion  
- Some panellists felt a detailed list of names and roles of personnel requires burdensome protocol amendments  
- Some of the components of this item appear to have some empirical support (e.g., knowledge of roles of key trial personnel and some of the qualifications of those individuals, such as the presence of a trial statistician) as they indicate the personnel support and expertise available to the trial, while others do not appear to be empirically supported (e.g., time commitment and job descriptions)  
- Some components are captured in current item “Names and addresses” (names and affiliations/contact details)  
- Further discussion required but consider including with substantial modifications to scope and description |
| **45. Logistics** | Weak/None | Weak/None | Exclude | - Subject to change requiring many protocol amendments  
- Others state this demonstrates adequate infrastructure for trial; thus important for funding applications. Subgroup analysis by profession (Round 3) does not show increased support by funding agency representatives (I = 0%, E = 80%, U = 20%) compared to all other groups combined (I = 29%, E = 62%, U = 9%).  
- If included in some capacity, consider requesting only general information with reference to location of details (e.g., Operations Manual) |
| **46. Monetary and material support A.**  
Source(s) of financial and material support | Strong | Strong | Include | - Will not be known at all protocol stages (e.g., application for funding), consider including “if relevant” |
| **46. Monetary and material support B.**  
Type(s) of support | Moderate | Moderate | Further discussion | - Consider overlap with “Role or sponsor” and “Conflict of interest”  
- Subgroup analysis by profession shows greater support from methodologists, REC/IRB members, funding agency representatives and journal editors (I = 79, 75, 100, 100%, respectively) than from other groups (I = 60%, E = 30%, U = 10%)  
- Trend for increased support with higher self-perceived expertise |
| **46. Monetary and material support C.**  
Amount of support | Weak/None | Weak/None | Exclude | - Subgroup analysis by profession shows greater support from journal editors (I = 78%, E = 22%, U = 0%) than other groups (I = 24%, E = 61%, U = 15%), could be requested in journals’ instructions to authors  
- Trend for increased support with lower self-perceived expertise |
<p>| <strong>46. Monetary and</strong> | Weak/None | Weak/None | Exclude | - Subgroup analysis by profession shows |</p>
<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Delphi</th>
<th>SR</th>
<th>Recommendation</th>
<th>Additional considerations based on Delphi comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>material support D.</td>
<td>None</td>
<td>None</td>
<td>Exclude</td>
<td>greater support from journal editors (I = 89%, E = 11%, U = 0%) than other groups (I = 26%, E = 60%, U = 14%); could be requested in journals' instructions to authors.</td>
</tr>
<tr>
<td>How support is provided</td>
<td></td>
<td></td>
<td></td>
<td>Trend for increased support with lower self-perceived expertise.</td>
</tr>
<tr>
<td>47. Budget</td>
<td>Weak/None</td>
<td>Weak/None</td>
<td>Exclude</td>
<td>Funding may be unknown at outset; budgets may differ from site-to-site; budgets may change requiring many amendments to protocol; issues of privacy.</td>
</tr>
<tr>
<td>60. Signatures</td>
<td>Weak/None</td>
<td>Weak/None</td>
<td>Exclude</td>
<td>Consider addressing concept in “Quality control” (or possibly “Data and Safety Monitoring Board”, depending on intended scope).</td>
</tr>
<tr>
<td>66. Trial monitoring</td>
<td>Moderate</td>
<td>Weak/None</td>
<td>Further discussion</td>
<td>Important for ethical reasons, if relevant; most obviously in trials without widespread access to standard treatments.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conclusions included feasibility of knowing this at outset of trial (before demonstrating intervention efficacy).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>If included, request only high level description, where relevant.</td>
</tr>
<tr>
<td>70. Post-trial care</td>
<td>Moderate</td>
<td>Weak/None</td>
<td>Further discussion</td>
<td>Although not unanimous, the prevailing view was that this information belongs elsewhere (e.g., Manual of Operations, Standard Operating Procedures) or as part of an existing item (e.g., “Data management” or “Biological materials”).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Often governed locally by the sponsor or by regulatory bodies, making it difficult to specify in protocol.</td>
</tr>
<tr>
<td>71. Post-trial data/materials storage</td>
<td>Moderate</td>
<td>Weak/None</td>
<td>Exclude, further discussion</td>
<td>Important but covered elsewhere in protocol (e.g., “Preliminary data”, “Study locations(s)”, “Recruitment”, “Sample Size”, “Agreement and Consent” and “Ethics approval”).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Some panellists also noted the importance of this information for funding agencies but not for other protocol forms. However, subgroup analysis by profession (Round 3) does not show increased support from funding agency representatives over other groups ((IQR) = 3 (1, 6)) vs. 6 (3, 8)).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Subgroup analysis showed more support by trial coordinators (Median [IQR] = 9 [7, 10]) than other groups (5 [3, 8]).</td>
</tr>
<tr>
<td>72. Feasibility</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Exclude</td>
<td>Unclear where this item belongs (e.g. Trial organization and administration, Ethical considerations or Reporting and Dissemination).</td>
</tr>
<tr>
<td>73. Insurance</td>
<td>Weak/None</td>
<td>Weak/None</td>
<td>Exclude</td>
<td>-</td>
</tr>
<tr>
<td>74. Data ownership</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Include concept, further discussion</td>
<td>-</td>
</tr>
</tbody>
</table>
Section 5: Ethical considerations. Seven of nine items in this section were recommended for inclusion (Table 13). Similar to Section 1 (General information), many items in this section received strong support from the Delphi but moderate or weak/no support from the systematic review. While practical rationale superseded the lack of empirical evidence for many items in Section 1, both ethical and practical rationale governed the importance of many items in this section (e.g. Confidentiality and anonymity and Ethics approval).

Strong empirical evidence, however, supported the item Agreement and Consent. Although some results conflict\textsuperscript{234, 448, 457-460}, many methodological studies suggest that the content, quantity and mode of delivery of consent information may affect trial recruitment\textsuperscript{104, 116, 122, 238, 447, 477}, participant comprehension\textsuperscript{447, 449, 451, 452, 456, 461, 462, 477}, anxiety\textsuperscript{461, 477}, retention\textsuperscript{95, 453} and recruitment costs\textsuperscript{251}, providing strong support for disclosure of consent methods. As asserted by some Delphi panellists, the evidence does not support a separate item for Surrogate consent or assent; these concepts could be addressed together.

The items Role of sponsor and Conflict of interest also received strong support from the Delphi with moderate and strong support, respectfully, from the review. Additionally, their conceptual association with the item Monetary and material support (sub-items A and B) and corresponding overlapping empirical evidence supports these items. Studies suggested that the risk of bias may be higher in trials with participating trial sponsors (Role
of sponsor) or investigators standing to benefit from the trial outcome (Conflict of interest), in particular in industry-sponsored trials. Furthermore, there is evidence that the processes and progress of a substantial number of industry-funded trials are in the sponsor’s control. Thus, disclosing this involvement or these conflicts may be important at the outset of the trial and these items were recommended for inclusion.

Overall, seven concepts in this section were recommended for inclusion (one for merging) and two for exclusion from the SPIRIT checklist.
Table 13: Synthesis of Delphi survey and systematic review results recommendations for the SPIRIT checklist - Section 5 Ethical considerations

<table>
<thead>
<tr>
<th>Section/ Topic</th>
<th>Delphi</th>
<th>SR</th>
<th>Recommendation</th>
<th>Additional considerations based on Delphi comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>48. Potential benefits and risks</td>
<td>Strong</td>
<td>Moderate</td>
<td>Include</td>
<td>- Due to breadth of concept, assigning relevant research to this item was somewhat difficult. Additional relevant empirical support may be present in other items. Consider revising to describe information requested more clearly.</td>
</tr>
<tr>
<td>49. Agreement and consent</td>
<td>Strong</td>
<td>Strong</td>
<td>Include</td>
<td>- Overlaps with &quot;Appendix materials C Consent forms&quot;, request for forms may be omitted from this item with a reference to appendices. Note consent form may vary by institution, request for a template might be more appropriate than actual forms. Remove request for &quot;name&quot; of individual who will seek consent, as this will vary. Consider revising to request type of trial personnel (e.g., primary care physician, nurse, PI) who will obtain consent. Consider revising based on Delphi comments.</td>
</tr>
<tr>
<td>50. Surrogate consent or assent</td>
<td>Strong</td>
<td>Weak/ None</td>
<td>Include</td>
<td>May be site-specific and therefore only general information may be relevant for the protocol. Consider merging with &quot;Agreement and consent.&quot;</td>
</tr>
<tr>
<td>51. Confidentiality and Anonymity</td>
<td>Strong</td>
<td>Weak/ None</td>
<td>Include</td>
<td>-</td>
</tr>
<tr>
<td>52. Ethics approval</td>
<td>Strong</td>
<td>Weak/ None</td>
<td>Include</td>
<td>- Consider modifying description to address Delphi comments 1) capture situations where REC/IRB approval has not yet been obtained to request if it will be (e.g., &quot;all sites will obtain local REC/IRB approval&quot;), 2) remove specific request for names of committees as this may require many amendments for some trials.</td>
</tr>
<tr>
<td>53. Role of sponsor</td>
<td>Strong</td>
<td>Moderate</td>
<td>Include</td>
<td>- Moderate support by evidence may be stronger due to association with &quot;Monetary and Material support&quot;. Consider either revising terminology or defining the term &quot;sponsor.&quot; Consider moving this item to Section 4 Trial organization and administration (recommended) or Section 3 Methods, whether this information is purely ethical is subjective. Consider overlap with &quot;Monetary and material support B types of support.&quot;</td>
</tr>
<tr>
<td>54. Conflict of Interest</td>
<td>Strong</td>
<td>Strong</td>
<td>Include</td>
<td>- Consider specifying whose conflict of interest is being requested (suggested examples included principal investigators and sponsor/funder). Many panelists felt, while important, this should not be in the protocol. Consider adding clause requesting where details of conflict of interest may be found if not detailed in protocol.</td>
</tr>
<tr>
<td>68. Ancillary and sub-studies</td>
<td>Moderate</td>
<td>Weak/ None</td>
<td>Exclude</td>
<td>- Some panelists felt concepts in this item did not belong in the protocol due to varying issues of complexity and lack of knowledge of these studies at the time of protocol development. Additionally,</td>
</tr>
<tr>
<td>Section/ Topic</td>
<td>Delphi</td>
<td>SR</td>
<td>Recommendation</td>
<td>Additional considerations based on Delphi comments</td>
</tr>
<tr>
<td>---------------</td>
<td>--------</td>
<td>----</td>
<td>----------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>3 Delphi SR</td>
<td></td>
<td></td>
<td></td>
<td>each ancillary study should have its own protocol and REC/IRB approval.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Many respondents felt this should be a component of “Agreement and consent” (whether consent is given for future use of specimens and data).</td>
</tr>
<tr>
<td>69. Pregnancy</td>
<td>Moderate</td>
<td>Weak/None</td>
<td>Exclude</td>
<td>• Comments suggest this is important but too specific for this checklist; underlying concepts are already addressed in existing items, (e.g., “Follow-up”, “Post-trial care”, “Risks/Harms” and “Safety evaluations”)</td>
</tr>
</tbody>
</table>

Item numbers are based on Delphi survey; see Chapter 3

Section 6: Reporting and Dissemination. No items in this section received strong support from the Delphi and only two were supported by strong empirical evidence (Table 14). Firstly, recent studies show changes between pre-specified methods (e.g. as stated in trial protocols, registration or regulatory data) and those disclosed in trial reports, such as primary outcomes\(^4, 5, 98, 353, 354\), sample size calculations\(^{12}\), eligibility criteria\(^{148, 159}\), allocation concealment\(^{19}\) and blinding\(^{325}\) methods, descriptions of intervention\(^{344}\) and analysis methods\(^{12, 13, 353, 354}\). In some cases, these changes appear to favour statistically significant results\(^4, 5, 353\) and in very few are modifications or reasons for modifications disclosed in available protocol amendments or final trial reports\(^3, 11, 12, 354\). Therefore highlighting how potential changes will be communicated to appropriate stakeholders is important and the item Protocol amendments was recommended for inclusion.
Table 14: Synthesis of Delphi survey and systematic review results: recommendations for the SPIRIT checklist - Section 6: Reporting and Dissemination

<table>
<thead>
<tr>
<th>Section/Topic*</th>
<th>Delphi</th>
<th>SR</th>
<th>Recommendation</th>
<th>Additional considerations based on Delphi comments</th>
</tr>
</thead>
</table>
| 55. Protocol Amendments | Moderate | Strong | Include | ▪ Many panellists felt this should be covered in a separate document such as the Statistical analysis plan or Standard Operating Procedure, or in the final publication  
▪ If covered, the importance depends on type of protocol change; a general statement would suffice  
▪ Consider revising based on Delphi comments |
| 56. Dissemination | Moderate | Strong | Include | ▪ Comments suggest this will often not be known at the outset and risks becoming a ritualistic/mechanical statement with little useful information. Others state that indicating whether a publication plan exists is sufficient (and if so, by whom). |
| 67. Reporting of early stopping | Moderate | Weak/None | Exclude | ▪ Consider merging concept with “Dissemination” |
| 57. Publication Policy | Moderate | Moderate | Include | ▪ Some panellists felt this was more appropriate for the contract than the protocol; consider requesting only higher level information and a reference to where details may be found. |

*Item numbers are based on Delphi survey; see Chapter 3

With respect to the item Dissemination, no evidence currently supports disclosure of all dissemination plans (e.g., direct contact with study participants, investigators, consumer associations, policy makers). However, there is a clear increased tendency for studies with significant results to be published, published sooner and published more often than studies with negative or non-significant results. Eventual publication also appears to be due to investigators or sponsors failing to submit, rather than journal failing to accept, negative or null results. Similarly, evidence of ghost authorship and constraints on publication, particularly in industry-sponsored trials, support the need for the item Publication policy. In concert with the evidence for bias in industry-sponsored research (see Monetary and material support), disclosing these details may help relevant parties assess the eventual accessibility and potential impact of trial results and make sponsors/investigators accountable for disseminating trial results.
Section 7: Other. All items in this final checklist section showed conflicting support. While one item was recommended for inclusion (Appendix materials [C]: consent/assent forms), further discussion was recommended for all four (Table 15). For example, similar to items such as Title and Trial identifier (recommended for inclusion), the practical importance of the item References may supersede the lack of empirical evidence. However, as with items such as Table of contents and Abbreviations (recommended for exclusion), specifically requesting this heading may be overly prescriptive in a guideline such as SPIRIT. Further discussion is recommended.

Additional concepts. Finally, as mentioned in Chapter 4, two new concepts not captured in the Delphi were identified in the course of the systematic review. The first, an item requesting the names of protocol authors, may be important for accountability and issues of ghost authorship. In one study of industry-sponsored trial protocols, no protocols explicitly stated who had contributed to the trial design and only five (of 44) stated the author of the protocol. None of these individuals, who were all employed by industry, were listed as authors or acknowledged in subsequent publications. This evidence alone contributed weak support for this item.

The systematic review results also supported an item on methods for increasing adherence or retention. Two existing items, Follow-up and Compliance, are somewhat related, however neither explicitly requests a description of methods planned to increase compliance/adherence or retention, the latter focusing currently on methods planned to measure compliance/adherence. Therefore, consideration of this concept for the checklist, possibly as a modification to the current item “Compliance”, is recommended.
Table 15 Synthesis of Delphi survey and systematic review results recommendations for the SPIRIT checklist - Section 7. Other

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Delphi</th>
<th>SR</th>
<th>Recommendation</th>
<th>Additional considerations based on Delphi comments</th>
</tr>
</thead>
</table>
| 58. References | Strong | Weak/None| Further discussion | • Some panellists noted that case report forms are subject to change (requiring amendments) and thus should not be in the protocol but rather in an Operations manual  
• If excluded, consider requesting where this information can be found  
• Subgroup analysis by profession suggested greater support by journal editors and trial coordinators (I = 78 and 80%, respectfully) than other groups (I = 63%) |
| 59. Appendix materials A. Case-report forms | Moderate | Weak/None | Further discussion | • May be a matter of preference rather than need as results/comments seem divided yet overall in favour of including this concept  
• Subgroup analysis by profession suggested greater support by journal editors and trial coordinators (I = 78 and 80%, respectfully) than other groups (I = 67%) |
| 59. Appendix materials B. Other data collection forms (e.g. questionnaires) | Moderate | Moderate | Further discussion | • Consent forms may be site-specific and require site-specific amendments; thus this may be difficult to fulfill in practice  
• Currently covered in “Agreement and consent”, need to address overlap.  
• Subgroup analysis by profession suggested less support by funding agency and regulatory board representatives (I = 43%) than other groups (I = 72%)  
• Consider reverting Appendix materials to one item, modifying wording to ‘request’ relevant materials, ‘including...’, if relevant', rather than mandating each one |
| 59. Appendix materials C. Consent/assent forms | Moderate | Strong | Include item, further discussion | |

I = Include  
*Item numbers are based on Delphi survey, see Chapter 3

5.3.3 Summary of recommendations

Cumulatively, the results of the synthesis of the Delphi survey and systematic review identified 41 concepts/items that were recommended for inclusion in the SPIRIT checklist. An additional 23 concepts, some of which overlapped with existing items, received conflicting support and were recommended for further discussion. Two new concepts were identified that were not previously addressed, one of which is recommended for further consideration. Finally, 24 items were not strongly supported from either study and were recommended for exclusion from the SPIRIT checklist.
6.0 Discussion

6.1 Summary of main findings

This thesis has produced a large and rich volume of information for further development of the SPIRIT Initiative. In isolation, the Delphi and systematic review each provide complementary yet different perspectives. Together they provide substantive evidence for concepts that every RCT protocol should address. They also highlight congruencies and discrepancies between current expert advice and the available evidence and emphasize areas for further research.

Ninety-six panellists from 17 countries and varying areas of expertise participated in the Delphi consensus. The process began with 59 candidate items derived mostly from existing checklists, subsequently adding 15 items and 14 sub-items while deleting items in succeeding rounds. Overall, the Delphi yielded strong support for 50 items, moderate support for 29 items and weak/no support for 9 items.

The systematic review, on the other hand, provided empirical support for substantially fewer items: 23 items received strong support, 23 items moderate support and 44 items weak/no support and included two potential new concepts. Empirical evidence included both primary and secondary methodological research, some associating various trial characteristics with outcomes, such as recruitment and effect estimates, and others estimating the prevalence of adequate trial methodology and protocol reporting.

Cumulatively, perfect agreement between the Delphi and systematic review was attained for 30 items (17 Strong, 7 moderate, 6 weak/none) using the categories developed for this synthesis. As empirical evidence was not anticipated for some items relevant to trial logistics or ethics, many discrepancies were predictable; the Delphi was important for
capturing these items. Correspondingly, the sections ‘General information’ and ‘Ethical considerations’ contained many discrepancies while the section ‘Methods’ included many congruent ratings.

The final recommendations were based on the quantitative Delphi results and the systematic review, and guided partly by Delphi panellists’ item-specific comments. Ultimately, 41 concepts/items were recommended for inclusion, 24 for further discussion (e.g. overlapping items) and 25 for exclusion from the SPIRIT checklist.

6.2 Relevance to key groups

These findings have implications for various stakeholder groups. Most immediately, they provide a solid foundation for development of the SPIRIT Statement. The main expected products for the SPIRIT group include the Statement, describing the final checklist and its development, and an explanatory document, describing each item including the rationale and supporting evidence for the item and an exemplar of good reporting. The data and synthesis described herein provide substantial information for the SPIRIT group to develop and support recommendations.

The results also highlight the volume of existing empirical research, emphasizing areas of abundant and deficient evidence, of relevance for clinical research methodologists. For example, substantial research indicates a risk of bias in trials with inadequate allocation concealment7, 289, 290, vague or modified descriptions of primary and secondary outcomes5 and in trials supported by commercial sources or including investigators/authors with conflicts of interest6, 78, 79, 419, 429. This supports the need to disclose these details in protocols (and possibly trial registries) and, hence, indicates important concepts for the SPIRIT checklist. In other cases, such as the items Recruitment and Agreement and consent,
many overlapping secondary methodological studies (i.e., methodological systematic reviews) were located; the results often identified the need, and prioritized topics, for future primary research studies.

Still other concepts are supported by strong pragmatic, regulatory, scientific or ethical rationale but not currently by direct empirical evidence. For example, trial registration (and associated numbers: see item Trial identifier) has been adopted for a number of reasons including increasing recruitment and decreasing unnecessary duplication of effort, publication bias and selective reporting of trial results. While the need for trial registration has been clearly demonstrated, evidence suggesting it meets its intended goals (e.g., by helping researchers locate unpublished registered trials and hence decreasing the effect of publication bias on systematic reviews, or by decreasing selective outcome reporting by making investigators/sponsors accountable for their choices), is still needed. As broadly mandated trial registration is still in its infancy, studying its effects is only recently possible and additional research may assess its impact. By requesting this information and hence ensuring trials are registered in accessible registries at the outset, the SPIRIT Statement may play an important role in promoting general adherence to such initiatives; only then can their true value be realized.

Interestingly, the results suggest an exponentially expanding volume of relevant methodological literature. Indeed, since the search for this review was completed (August 2009), more relevant research has been published; for example, examining selective outcome reporting and publication bias. Updating the literature search for future SPIRIT checklist revisions would be prudent.

By informing the SPIRIT checklist’s further development, these results also have a broader significance for other groups. Firstly, the SPIRIT checklist should be of practical
benefit for trial investigators and personnel. Conceivably, developing one protocol meeting the needs of different ethics and funding submissions saves time and energy and provides consistency versus drafting multiple versions. Such a guideline also ideally encourages important discussions before trial initiation, such as plans for outcome assessment, analysis, authorship and publication. Additionally, it will ideally increase the accessibility of many methodological trial details, ensuring they are easily retrievable from protocols when needed. We hope it may also serve as a valuable educational tool for less experienced trialists.

By improving RCT protocol reporting quality, the SPIRIT initiative may facilitate ethics, grant application and manuscript review processes. Submission of completed checklists with protocols may decrease the need for revisions to address incomplete content, thus facilitating initial trial phases. Also, if trialists indicate where information may be found (i.e., page number) as recommended by other guidelines, it will facilitate information retrieval.

SPIRIT may also benefit consumers and trial participants. By clearly delineating information associated with bias in trials, protocols adhering to SPIRIT may help them to better assess whether and how their involvement will contribute to advancing healthcare. Although, conceivably, the average potential participant will not access the full protocol when deciding to participate, having this information accessible is important. For example, some consumers may wish to have a full list of expected benefits and risks, while others may wish to know how and where to access individual and final trial results. The transparency of protocols following the SPIRIT guideline may help potential participants make informed decisions.

Finally, the SPIRIT Statement may also significantly impact peer reviewers, journal editors, systematic reviewers, and policymakers. By increasing the transparency in
protocols, it may facilitate comparisons with reports of trial results, affecting publication and post-publication activities, and decision-making. However, barriers to trial protocol access will also need to be overcome. Where appropriate, the structure and wording of some items may follow the CONSORT statement, facilitating these comparisons.

Conceivably, all RCT trials will have a protocol. A study by Chan and Altman suggested that PubMed indexes over 6,000 RCTs annually. This finding does not account for trials indexed in other databases (e.g. between 20% and 70% of trials depending on the discipline) and the minimum of 40% of trials not reaching full publication. SPIRIT may improve the transparency and accessibility of information known to be associated with bias, and ultimately decrease bias in trials. Thus, the broad applicability of the results of this thesis and the SPIRIT Initiative is clear.

6.2.1 Feedback for reporting guideline development

The results of this research may also have relevance for those considering or embarking on development of a reporting guideline. The recently established EQUATOR Network aims primarily to “improve reliability and value of medical research literature by promoting transparent and accurate reporting of research studies.” The Network has begun compiling guidance on reporting guideline development methods, although, within the Network, this is a new and evolving process. This thesis may provide useful feedback for the Network by highlighting some lessons learned, particularly related to process efficiency relative to return. Other lessons are discussed below.

Firstly, from the author’s perspective, the Delphi process was an efficient method yielding a very rich volume of information. Most importantly, our panellists, selected to represent multifarious potential users of SPIRIT, were experienced, interested and committed
to completing the process; we obtained approximately 90% response rates for each round and 77% of panellists completed all three rounds. The Delphi could not have been successful without their continued dedication. Selecting potential panellists requires sufficient time and thought to ensure they meet the criteria suggested by previous guidance -- namely that they have extensive knowledge and experience in the topic under investigation, capacity, willingness and sufficient time to participate, and effective communication skills. This step is pivotal to both Delphi success and validity.

The current study used personalized surveys sent individually by email. Although time-consuming, this method may have helped yield our high response rates. Our response rates were also likely increased by other development and delivery methods, some of which are supported by empirical evidence: survey pre-notification/invitation to participate, notification of (and adherence to) expected arrival times of rounds, clear outline of expectations including time-commitments, written commitment by panellists to participate (reply by email), follow-up contacts with questionnaires (two in this case) to non-respondents, previous rounds’ responses and assurance of confidentiality. Future endeavours should consider these methods.

Distributing the survey and collating the data using an Internet-based tool may substantially increase Delphi efficiency. Such options existed but were cost-prohibitive for the current work. Some inexpensive Internet-based survey tools were investigated; however, at the time they did not provide the ability to feedback individual subject responses which was deemed important for ease of panellist participation and the validity of our process. These will likely become more accessible and should be explored for future work.

Secondly, the systematic review was also an important component for this thesis. However, it may have possibly been conducted more efficiently for its purposes herein. It
was initially planned and executed as a traditional systematic review, aiming for an exhaustive, comprehensive search for relevant evidence, representing a potential improvement over previous guidelines which appear to have relied mostly on expert knowledge of the empirical literature. As such, we employed broad search strategies and extensive data extraction. This search retrieved a substantial amount of non-relevant literature and relied on methods other than database searches for locating relevant methodological research, the limitations of which are discussed below. The diversity of the literature also made screening difficult. Consequently, screening criteria were revised numerous times, requiring re-screening of records and substantially increasing time and effort.

Other groups conducting similarly broad reviews have noted analogous problems, concluding that topics of this scope do not amend themselves well to the standard systematic review format due to the immense breadth of literature and the difficulty retrieving, screening, extracting and synthesizing data in a systematic (and reproducible) way. For example, Prescott and colleagues conducted a systematic review of factors limiting the quality, number and progress of RCTs. Like the present review, they included studies of varied designs and topics and noted a level of subjectivity in the screening and data extraction processes.

Unlike the current review, however, they opted for a systematic rather than comprehensive approach, limiting their search to electronically indexed literature and to research published over a 10-year period. Even given these publication limits and recognition that not all relevant studies were located, they advised: "Given the breadth of this review, it should probably not be revisited in its entirety. The authors found that the
workload was excessive, and even though an update would not repeat all that has been done here it would still be a large undertaking.”

Although only one example, this review had significant supporting resources; it was commissioned and funded by the United Kingdom’s National Health Service, National Institutes of Health Research and was completed by a team of ten researchers. Our current review, on the other hand, was not funded and was conducted by a much smaller review team. Indeed, evidence (including the background systematic review of existing protocol guidelines) suggests that few reporting guidelines receive funding for their development. Furthermore, funding for personnel/research assistant support has been nearly non-existent for such initiatives. Therefore, unless significant resources are available, logistical constraints for future initiatives may warrant consideration of alternative review methods.

To aid future work, an initial scoping exercise is recommended to gauge the quantity and characteristics of available research. This process may more clearly delineate the types of studies and data present to help prioritize search and extraction methods accounting for logistical constraints. Although increasing time up-front, a scoping exercise may reduce overall time for the review.

Alternative approaches to literature retrieval and review conduct may also be appropriate and have been recommended for other broad or complex reviews. For example, one complex systematic review located most studies (70%) by personal files and expert knowledge (24%) or supplementary search methods (46%), with few located by ‘protocol’ driven database searches. We identified most included studies (74%) by electronic search strategies; however, we did not contact experts specifically to identify literature.
Alternatively, step-wise literature retrieval, such as targeted searches and retrieval by study hierarchy, or prioritized data extraction, such as preliminarily categorizing the evidence by study type and objectives, may have increased the efficiency of this process. In these instances, the intent is to find sufficient evidence to formulate and support recommendations rather than be exhaustive. For example, Sampson and colleagues conducted a systematic review to identify evidence to develop a checklist for peer review of electronic search strategies. Their initial electronic literature search was supplemented by additional methods (e.g., reference lists) only for checklist concepts where less than five supporting studies had been identified.

However, using comprehensive search strategies to locate and collate evidence has greater face-validity for reporting guideline development. In the current circumstance, assuring that important studies would have been located by using such alternate approaches is not possible and comparisons of different search strategies would be useful for future research. Nevertheless, unless financial and logistical resources significantly increase for such processes, the development of other guidelines or future updates of SPIRIT may benefit from more restrictive and tailored approaches to literature retrieval and synthesis.

Overall, the Delphi and systematic review ultimately yielded complementary information. Although both components are recommended for future endeavours, consideration of some alternative approaches to those described for the current studies may be warranted.

6.3 Comparison with other existing guidelines

No existing RCT-specific protocol guidelines have employed development approaches as comprehensive as in the current research. Nevertheless, the prominence of
some existing guidelines may call into question the need for the SPIRIT initiative. To examine how the current recommendations align with existing guidelines, a rudimentary mapping of such concepts to seven prominent guidelines is provided in Appendix H. Four of these guidelines were included in this thesis’ background review: the ICH E6\textsuperscript{50}, those produced by the United States Centers for Disease Control and Prevention\textsuperscript{47} and the National Institutes of Health\textsuperscript{73}, and the only RCT-specific guideline citing methods for development (PRACTIHC)\textsuperscript{76}. This analysis also included two additional high-status guidelines not identified for that review: the Council for International Organizations of Medical Sciences’ International Ethical Guidelines for Biomedical Research Involving Human Subjects\textsuperscript{503} and that produced for the United Kingdom’s National Health Service’s University College of London\textsuperscript{504}. The final guideline was selected as it is currently used by the Canadian Institutes of Health Research\textsuperscript{80}, one of the agencies funding SPIRIT’s consensus meetings. Although a selected sample, this exemplifies the current recommendations compared to existing recognized guidelines.

The majority of concepts recommended for inclusion or further discussion for the SPIRIT checklist are included in most of these guidelines. However, less than half of the guidelines included the following items, which have been recommended for further consideration for SPIRIT:

- Trial identifier
- Protocol version
- Preliminary data
- Allocation concealment
- Implementation of randomization
- Schematic of study timeline/Schedule of interventions
- Justification of control interventions
- A specific item on follow-up (although all requested this information within other items)
- Data from withdrawals
- Presence of DSMB
- Specific request for both statistical and non-statistical stopping rules
- Monetary and material support – types of support
- Post-trial care
- Data ownership
- Ethics approval
- Role of sponsor
- Conflict of interest
- Protocol amendments
As defined, most of these items received strong support from either or both the Delphi and systematic review, thus corroborating their potential importance in protocols and suggesting missing components from some previous guidelines. The four items above receiving only moderate support from this thesis (Monetary and material support – types of support, Post-trial care, Data ownership and Appendix of data collection forms) were all recommended for further discussion.

No items recommended for exclusion from the SPIRIT checklist were present in greater than half of the exemplar guidelines.

Re-examining the introductory systematic review shows one item present in many (13/27) previous guidelines, which is currently recommended for exclusion: ‘costs’ or ‘budget’. The evidence/methods cited in previous guidelines for recommending this item was based on guidance from books and informal expert consensus. In our formal consensus, this item received the lowest support of any item. It was also not supported by empirical evidence, and thus was recommended for exclusion from the SPIRIT checklist. This does not suggest that budgetary considerations are unimportant for all stakeholders. Rather, it indicates that this concept is not supported for inclusion in a minimal set of items for all RCT protocols. Relevant groups requiring this information, such as funding agencies, may request this in addition to the protocol.

The current project did not directly address at least 50 additional concepts in the seven guidelines, some of which were specific sub-components of broader concepts already addressed in the draft checklist (e.g. specific request for dissemination procedures in the case of a negative outcome - the current draft requests disclosure of all dissemination plans
regardless of outcome). Most were recommended in only one guideline, suggesting little support from other experts groups.

As previously mentioned, the preliminary SPIRIT Delphi list was generated from items included in at least three guidelines in the reporting guideline systematic review (Chapter 1: Introduction). Two concepts included in three of current exemplar guidelines were not circulated in this preliminary list. The first, an appendix of patient leaflets/information for patients, was not circulated as it was present in only one guideline identified for the background review. The second, Planned/dummy tables and figures, was included in three previous guidelines but was the only item suggested for exclusion by the Steering Group executive from the preliminary Delphi list. Further discussion may be warranted for these concepts.

An additional nine items were present in two of the exemplar guidelines:

- Justification of route of administration, dosage etc.
- Support for feasibility of recruitment (estimated numbers of eligible/recruited participants and time needed to meet sample size requirements)
- Whether withdrawn patients are to be replaced
- Type and duration of follow-up for participants after adverse events
- Statements pertaining to adherence to research governance good clinical practice and/or the specific guidelines themselves
- Economic evaluations
- Consumer involvement
- Intended use of study findings
- ‘Other’ measures taken to avoid/minimize biases

Again, some of these concepts are included within existing items. Few are supported by empirical evidence from the systematic review, with the exception of justification of route of administration and dosage (addressed indirectly in Interventions [A] and [B]) and possibly feasibility of recruitment (addressed indirectly in Sample size). The items above may warrant further consideration for SPIRIT, such as incorporation into existing items or for discussion in the explanation and elaboration document.
Overall, the current recommendations are highly congruent with those enforced by existing prominent guidelines. However, the evidence derived in this thesis supports including additional empirically supported items not previously addressed in most of these guidelines, suggesting areas of deficiency in previous guidance.

6.4 Limitations of approaches

Although Delphi surveys enable collaboration of respondents from various geographical locations in a confidential, non-threatening environment, their results are only as valid as the opinions of the experts constituting the panel. Even if consensus is attained, validating whether this consensus is ‘truth’ is difficult, and expert opinion remains considered among the lowest levels of empirical evidence. To safeguard the validity of our results we carefully selected a panel representing key stakeholders. Furthermore, structured, pre-defined methods were employed to minimize biased response collation. The Delphi results indicated support for similar components as other major guidelines with no major evident omissions, suggesting some congruency with other expert groups.

Despite this, our Delphi was limited by the ultimate participation of relatively few panellists representing specific groups. Firstly, few respondents self-identified as funding agency or regulatory board representatives (n = 5 and 3, respectively) or for-profit organization employees (n = 4). Thus, these groups’ views could not significantly influence overall ratings. This was addressed by reviewing subgroup results and noting differences where relevant.

We also did not directly capture consumers/trial participants’ views. One consumer representative was initially nominated for the Delphi by a SPIRIT Steering group member with the intent to request additional nominations from this individual. Despite pursuing
different approaches, current contact information was not found for this individual for the Delphi nor were alternate representatives located/nominated. Very few existing guidelines have captured the views of this important group\textsuperscript{38,39} and it is unclear how their participation may have affected the results. Considering this unique perspective for future SPIRIT activities such as pilot testing the checklist will be important.

Delphi validity is also dependent on question phrasing and respondents having appropriate opportunities to communicate their perspectives effectively. In our study, each round was pilot tested to increase survey comprehensibility, and ideally, results validity. The survey design was also flexible to capture the panellists’ needs as they arose. For example, at their request, we increased the number of text boxes for additional comments and addressed major general comments and ambiguities in each survey round. Finally, we delineated items requiring further clarification.

The validity of our systematic review depended on study selection, risk of bias in included studies and synthesis methods. To minimize selection bias, a thorough literature search was conducted, eligibility was not limited by publication status and pre-defined selection criteria were employed. Many included studies were located by supplementary search methods (e.g. screening reference lists (7%), PubMed related articles searches (10%) and citation snowballing (9%)), potentially subjecting the results to reporting biases including citation and location bias\textsuperscript{506}. Not all relevant studies will likely have been identified despite comprehensive searching, as developing precise search strategies for methodological literature and complex reviews is difficult\textsuperscript{496,507}. Due to logistical constraints, search strategies relied mostly on subject headings (e.g. Medical Subject Headings in MEDLINE) except in instances where no relevant subject headings existed, rather than a mixture of MeSH and free text as is often suggested\textsuperscript{497,506}. 
The resulting volume of literature also made duplicate screening of records and data extraction (as initially planned) logistically impossible; duplicate screening and extraction of a smaller sample of records/studies instead validated the processes. Many studies required discussion between reviewers, suggesting some eligibility criteria were subjective. As screening and extraction were conducted mostly by one reviewer, study selection and allocation of evidence may have been subject to bias. Whenever obvious ambiguity arose, a second (or third) reviewer was consulted.

Although based on objective criteria wherever possible, grading the empirical evidence was qualitative and somewhat subjective. However, good agreement was attained between reviewers, giving strength to the validity of this process.

Finally, the cumulative recommendations were based on one researcher’s interpretation of the Delphi’s quantitative and qualitative results and the systematic review’s data. Where possible, these recommendations were derived from objective criteria (Delphi scores, strength of empirical evidence), however, this synthesis was not validated and recommendations are intended as a guide. The component information is provided to enable independent assessment of the evidence, and the SPIRIT steering committee will have access to all extracted data.

6.5 Next steps for the SPIRIT Initiative

The SPIRIT Steering group and select stakeholders have participated in two consensus meetings. The first built on the Delphi results. Since then, the second consensus meeting was held and the checklist and explanatory document have been drafted independently from the current work, providing a unique opportunity to compare current drafts to cumulative evidence from this thesis.
The next steps for the SPIRIT initiative include finalizing the guideline by developing the associated Statement and explanatory documents for publication, and determining final publication strategies (i.e. multiple simultaneous publication as has been done for other guidelines\textsuperscript{31; 40; 482; 483}); processes currently underway. The SPIRIT checklist will also need to be pilot tested to assess its usability and comprehensibility and to determine if it facilitates protocol development (i.e. for trialists), protocol review or submission processes (i.e., for REC/IRB, funding and regulatory agencies, journals) or protocol use (i.e. for trialists, trial coordinators/personnel, consumers) as intended.

Moher and colleagues have recently developed guidance for developing reporting guidelines\textsuperscript{487}. They recommend a number of post-publication activities of relevance for SPIRIT, some of which are currently underway, including seeking endorsement by some major stakeholders. In alignment with their recommendations, evaluating SPIRIT’s impact will also be important, as will encouraging adherence to the checklist and seeking and collating stakeholders’ feedback for possible future updates.

6.6 Barriers to the uptake of SPIRIT

One barrier to the SPIRIT Initiative’s success is the existence of previous guidelines. The methodological shortcomings of most previous guidelines, and the absence of several important concepts (some clearly associated with bias in trials), however, demonstrates a clear need for this evidence-based guidance. No other guidelines identified for reporting RCT protocols have used such comprehensive development methods, including the collaboration of such a broad group of stakeholders and a comprehensive systematic review for relevant empirical evidence to inform recommendations.
An additional barrier is the concern that adhering to the SPIRIT checklist may increase the time burden for trialists. Using the background systematic review of existing protocol guidelines as a guide, prominent institutional/governmental guidelines included a median (IQR) of 54 (53, 56) items. As an illustration, if the current recommendations were adopted exactly, the SPIRIT statement would include between 41 and 65 items (in the unlikely event that no items were merged), suggesting minimal, if any, increased demand on trialists. However, assessing SPIRIT’s impact on perceived burden and protocol length will be important components of pilot testing and impact assessment.

Identifying funding for SPIRIT and similar initiatives remains a challenge. While the SPIRIT Initiative has benefited from financial support to host two consensus meetings, all research and planning for this initiative, as with many others\textsuperscript{38, 39} have remained largely voluntary. This poses a challenge for maintaining the currency of such guidelines and it is hoped that initiatives such as the EQUATOR Network will help call attention to this need.

Finally, SPIRIT’s success depends ultimately on the uptake and endorsement of the guideline by relevant groups. We invited various stakeholders to participate in the guideline development process in an attempt to ensure we adequately addressed their views. Additional initiatives are also currently underway to seek endorsement by other groups.

The need for this initiative and the methodological strength supporting the final checklist will ideally overcome the challenges described above. Other guidelines such as CONSORT have faced similar barriers, but have received endorsement by major groups and journals\textsuperscript{43, 44, 508} and have significantly improved reporting in trials\textsuperscript{41}. These results are encouraging and suggest reason for optimism. Having been built upon and potentially ameliorating the evidence-based approach of previous guidelines, it is hoped that the SPIRIT Initiative will similarly influence the transparency of RCT protocols.
7.0 Conclusions

This thesis provides a large volume of rich information to guide the development of the SPIRIT checklist, an evidence-based guideline for reporting RCT protocols. The divergent methods - one reliant on formal consensus of experts from diverse areas and the other on empirical evidence from the methodological literature - have yielded sometimes conflicting, but ultimately complementary, guidance on important concepts for reporting in RCT protocols. This work will be of value for development of the SPIRIT checklist and associated documents. By increasing the transparency and accessibility of information known to be associated with bias in trials, these findings are ultimately aspired to effect a much larger group of stakeholders by helping to improve the reliability and validity of the medical literature guiding healthcare decisions.
8.0 References


(3) Chan AW, Krleza-Jerkić K, Schmid I, Altman DG. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. CMAJ 2004; 171 (7): 735-40


(16) British Medical Journal Article Requirements 2010 [cited 2010 Jan 2], Available from URL http://resources.bmj.com/bmj/authors/article-submission/article_requirements


(23) Kane RL, Wang J, Garrard J Reporting in randomized clinical trials improved after adoption of the CONSORT statement J Clin Epidemiol 2007, 60 (3) 241-9

(24) Geller SE, Adams MG, Carnes M Adherence to federal guidelines for reporting of sex and race/ethnicity in clinical trials J Womens Health (Larchmt) 2006, 15 (10) 1123-31


(28) Manheimer E, Ezzo J, Hadhazy V, Berman B Published reports of acupuncture trials showed important limitations J Clin Epidemiol 2006, 59 (2) 107-13


(30) Devereaux PJ, Choi PT, El-Dika S, Bhandan M, Montori VM, Schunemann HJ, et al An observational study found that authors of randomized controlled trials frequently use concealment of
randomization and blinding, despite the failure to report these methods. J Clin Epidemiol 2004; 57 (12): 1232-6


(49) Coggon D Planning research Occup Med (Oxf) 1997; 47 (4) 247-8.


(51) DeRenzo EG, Moss J Writing clinical research protocols · ethical considerations Burlington, MA, USA· Elsevier Academic Press; 2006.


(56) Good PI. The design and conduct of clinical trials. Hoboken, New Jersey, USA: John Wiley and Sons, Inc; 2006.


(63) Piantadosi S. Clinical trials : a methodologic perspective Hoboken, NJ, USA: John Wiley and Sons, Inc; 2002

(64) Pocock SJ Clinical trials · a practical approach. John Wiley and Sons, Ltd, 1983.


(69) Streiner DL. 'While you're up, get me a grant': a guide to grant writing. Can J Psychiatry 1996, 41 (3): 137-43.


(85) Adler M, Zigho E. Gazing into the oracle Bristol, PA Jessica Kingsley Publishers; 1996

(86) Delbecq AL, Van de Ven AH, Gustafson DH Group techniques for program planning: A guide to nominal group and Delphi processes Glenview, Ill. Scott, Foresman, and Company; 1975


(88) Sampson M, McGowan J, Cogo E, Horsley T Managing database overlap in systematic reviews using Batch Citation Matcher: case studies using Scopus Journal of the Medical Library Association 2006; 94 (4) 461-3, e219


(102) Rendell JM, Merritt RK, Geddes JR. Incentives and disincentives to participation by clinicians in randomised controlled trials. Cochrane Database of Systematic Reviews: Reviews Cochrane Database Syst Rev 2007; (2).


(106) Djulbegovic B, Bennett C, Lyman G. Violation of the Uncertainty Principle in Conduct of Randomized Controlled Trials (RCTs) of Erythropoietin (EPO). Blood 1999; 94: 399a.


(119) Aulakh AK, Anand SS. Sex and gender subgroup analyses of randomized trials. Women's Health Issues 2007; 17: 342-50


(132) Herbison P  Full publication of abstracts of randomized controlled trials published at International Continence Society Meetings Neurourol Urodyn 2004, 23 101-3

(133) Hotopf M, Lewis G, Normand C  Putting trials on trial—the costs and consequences of small trials in depression a systematic review of methodology Journal of Epidemiology and Community Health 1997, 51 354-8

(134) Wu T, Li Y, Bian Z, Liu G, Moher D  Randomized trials published in some Chinese journals how many are randomized? Trials 2009, 10 46


(136) Krzyzanowska MK, Pintilie M, Tannock IF  Factors associated with failure to publish large randomized trials presented at an oncology meeting JAMA 2003, 290 (4) 495-501

(137) Scherer RW, Dickersin K, Langenberg P  Full publication of results initially presented in abstracts A meta-analysis JAMA 1994, 272 (2) 158-62


(141) Weijer C  Characterizing the population in clinical trials barriers, comparability, and implications for review Division of Experimental Medicine, Faculty of Medicine, McGill University, 1995

(142) Gurwitz JH, Col NF, Avorn J  The exclusion of the elderly and women from clinical trials in acute myocardial infarction JAMA 1992, 268 (11) 1417-22

(143) Uchino K, Bilheimer D, Cramer SC  Entry criteria and baseline characteristics predict outcome in acute stroke trials Stroke 2001, 32 (4) 909-16

(144) Posternak MA, Zimmerman M, Keitner GI, Miller IW  A reevaluation of the exclusion criteria used in antidepressant efficacy trials Am J Psychiatry 2002, 159 (2) 191-200

Van Spall HGC, Toren A, Kiss A, Fowler RA. Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals: A Systematic Sampling Review. JAMA 2007; 297: 1233-40


Stirman SW, DeRubeis RJ, Cnnts CP, Brody PE Are samples in randomized controlled trials of psychotherapy representative of community outpatients? A new methodology and initial findings J Consult Clin Psychol 2003, 71 963-72


Herland K, Akselsen JP, Skjonsberg OH, Bjørner L How representative are clinical study patients with asthma or COPD for a larger ‘real life’ population of patients with obstructive lung disease? Respir Med 2005, 99 (1) 11-9

Sokka T, Pincus T Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission J Rheumatol 2003, 30 (6) 1138-46

Sokka T, Pincus T Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis Arthritis Rheum 2003, 48 313-8

Dowd R, Recker RR, Heaney RP Study subjects and ordinary patients Osteoporos Int 2000, 11 (6) 533-6

Lloyd-Jones DM, O'Donnell CJ, D'Agostino RB, Massaro J, Silbershatz H, Wilson PW Applicability of cholesterol lowering primary prevention trials to a general population the Framingham heart study Arch Int Med 2001, 161 949-54


Rabinowitz J, Bromet EJ, Davidson M Are patients enrolled in first episode psychosis drug trials representative of patients treated in routine clinical practice? Schizophr Res 2003, 61 (2-3) 149-55

Zann DA, Young JL, West JC Challenges to evidence-based medicine a comparison of patients and treatments in randomized controlled trials with patients and treatments in a practice research network Social Psychiatry and Psychiatric Epidemiology 2005, 40 27-35

Levy BR, Ding L, Lakra D, Kostea J, Niccolai L Older persons' exclusion from sexually transmitted disease risk-reduction clinical trials Sexually Transmitted Diseases 2007, 34 (8) 541-4


(183) Bhandari M, Lochner H, Tornetta P, III. Effect of continuous versus dichotomous outcome variables on study power when sample sizes of orthopaedic randomized trials are small. Archives of Orthopaedic & Trauma Surgery 2002; 122 (2): 96-8.


(197) Keen HI, Pile K, Hill CL. The prevalence of underpowered randomized clinical trials in rheumatology J Rheumatol 2005; 32 (11) 2083-8


(201) Vail A, Gardener E. Common statistical errors in the design and analysis of subfertility trials Hum Reprod 2003, 18 (5) 1000-4


(210) Tinmouth JM, Steele LS, Tomlinson G, Glazier GH. Are claims of equivalency in digestive diseases trials supported by the evidence. Gastroenterology 2004; 126: 1700-10.


(217) Kumar A, Soares H, Djulbegovic B. High proportion of high quality randomized clinical trials conducted by the NCI are negative or inconclusive [abstract] XIII Cochrane Colloquium; 2005 Oct 22 26, Melbourne, Australia 2005; 52


(228) Ridgeway D, Khan A, Ridgeway G, Cierpial MA, Lineberry CG. Subject numbers and placebo outcome variability in clinical trials of new CNS medications. Drug Inf J 2007, 41:701-8


(245) Gerace TA, George VA, Arango IG. Response rates to six recruitment mailing formats and two messages about a nutrition program for women 50-79 years old. Con Clin Tr 1995, 16:422-31


(250) Fortmann SP, Killen JD. Who shall quit? Comparison of volunteer and population-based recruitment in two minimal contact smoking cessation studies. Am J Epidemiol 1994, 140:39-51


(256) Nystuen P, Hagen KB. Telephone reminders are effective in recruiting nonresponding patients to randomized controlled trials. J Clin Epidemiol 2004, 57(8):773-6


(265) Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses Ann Intern Med 2001, 135 (11) 982-9


(273) Bausell RB, Lee WL, Soeken KL, Li YF, Berman BM Larger effect sizes were associated with higher quality ratings in complementary and alternative medicine randomized controlled trials. J Clin Epidemiol 2004, 57 (5) 438-46


(279) Forsetlund L, Reinand LM. Quality of reporting and methodology of studies on interventions for trophic ulcers in leprosy: a systematic review. Indian J Dermatol Venereol Leprol 2008; 74 (4): 331-7


(297) Bero L, Oostvogel F, Bacchetti P, Lee K. Factors associated with findings of published trials of drug-drug comparisons: why some statins appear more efficacious than others. Plos Medicine 2007, 4: e184


(299) Bhogal SK, Teasell RW, Foley NC, Speechley MR. Quality of the stroke rehabilitation research. TOP 2003, 10 (1): 8-28


(301) Lincoln NB, Bowen A. The need for randomised treatment studies in neglect research. Restor Neurol Neurosci 2006, 24 (4-6): 401-8


Stelfox HT, Goverman J, Stelfox HT, Goverman J. The number, content, and quality of randomized controlled trials in the prevention and care of injuries Journal of Trauma-Injury Infection & Critical Care 2008; 65 (6): 1488-93


(336) Rochon PA, Binns MA, Litner JA, Litner GM, Fischbach MS, Eisenberg D, et al. Are randomized control trial outcomes influenced by the inclusion of a placebo group?: a systematic review of


(342) Hugenholtz GW, Heerdink ER, Stolker JJ, Meijer WE, Egberts AC, Nolen WA Haloperidol dose when used as active comparator in randomized controlled trials with atypical antipsychotics in schizophrenia: comparison with officially recommended doses J Clin Psychiatry 2006; 67 897-903.


(344) Chappell L, Alfirevich Z, Chen P, Jarvis S, Thornton JG. A comparison of the published version of randomized controlled trials in a specialist clinical journal with the original trial protocols [abstract] International Congress on Peer Review and Biomedical Publication; 2005 Sept 16 18; Chicago, Illinois, USA 2005; 27.


(352) Beyer WE. Heterogeneity of case definitions used in vaccine effectiveness studies—and its impact on meta-analysis Vaccine 2006, 24 (44-46). 6602-4


(357) Ghersi D. Issues in the design, conduct and reporting of clinical trials that impact on the quality of decision making. School of Public Health, Faculty of Medicine, University of Sydney; 2006.


Whittaker K, Sutton C, Burton C Pragmatic randomised controlled trials in parenting research: the issue of intention to treat. Journal of Epidemiology and Community Health 2006; 60: 858-64.


Abraha I, Montedon A. What is meant by modified intention to treat? Investigating randomised controlled trials [abstract] In Fifth Annual Meeting HTAi; 2008 July 6-9; Montreal, Canada 2008, T1.


Haines SJ. Randomized clinical trials in neurosurgery Neurosurgery 1983; 12 (3) 259-64.


Lexchin J. Interactions between physicians and the pharmaceutical industry: what does the literature say? CMAJ 1993; 149 (10) 1401-7


Barden J, Derry S, McQuay HJ, Moore RA. Bias from industry trial funding? A framework, a suggested approach, and a negative result. Pain 2006; 121 (3): 207-18

Tulkangas PK, Ayers A, O’Sullivan DM. A meta-analysis comparing trials of antimuscarinic medications funded by industry or not. BJU Int 2006; 98 (2) 377-80.


(462) Hietanen PS, Aro AR, Holli KA, Schreck M, Peura A, Joensuu HT A short communication course for physicians improves the quality of patient information in a clinical trial Acta Oncol 2007, 46 42-8

(463) Rogers CG, Tyson JE, Kennedy KA, Broyles RS, Hickman JF Conventional consent with opting in versus simplified consent with opting out: an exploratory trial for studies that do not increase patient risk J Pediatr 1998, 132 (4) 606-11


(467) Williams CJ, Zwitter M Informed consent in European multicentre randomised clinical trials - Are patients really informed? Eur J Cancer 1994, 30 (7) 907-10


(475) Ioannidis JP Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials JAMA 1998, 279 (4) 281-5

(476) Pich J, Carne X, Arnaz JA, Gomez B, Trulla A, Rodes J Role of a research ethics committee in follow-up and publication of results Lancet 2003, 361 (9362) 1015-6


(492) Okoli C, Pawlowski SD. The Delphi method as a research tool: an example, design considerations and applications. Information & Management 2004; 42: 15-29.


9.0 Appendices

9.1 Appendix A: Items Included in Previous Protocol Guidelines

Table 16: Items included in previous protocol guidelines

<table>
<thead>
<tr>
<th>Item</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title/Fact sheet/Title Page</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Summary/Abstract</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Table of contents</td>
<td>6 (22)</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
</tr>
<tr>
<td>General aims/Problem/Questions</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Background information</td>
<td>24 (69)</td>
</tr>
<tr>
<td>Preliminary data/previous work by investigator</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Additional details</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Specific Objectives/Hypotheses</td>
<td>20 (74)</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td></td>
</tr>
<tr>
<td>Overview of design</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Time frame/period of study</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Additional details</td>
<td>5 (19)</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td></td>
</tr>
<tr>
<td>Clearly identify target population</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Subject selection</td>
<td>19 (70)</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>19 (70)</td>
</tr>
<tr>
<td>Sampling design</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Allocation/Allocation concealment</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Randomization/Stratification procedures</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Patient consent procedures</td>
<td>6 (22)</td>
</tr>
<tr>
<td><strong>Procedures</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Measurements and Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Eligibility/Baseline</td>
<td>9 (33)</td>
</tr>
<tr>
<td><strong>Variables/Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Statement of outcomes (two ask for primary and secondary outcomes, some specify predictor vs. confounder vs. outcome)</td>
<td>25 (93)</td>
</tr>
<tr>
<td>Definitions and measurements of variables</td>
<td>17 (63)</td>
</tr>
<tr>
<td>Treatment/Intervention</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Details (e.g. description and schedule, dosage regimen packaging)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Allowable concomitant therapies/treatments</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Timing</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Blinding</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Pre-testing/training plans</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Methods of data collection/handling</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Data management, monitoring and quality control</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Statistical Issues (general)</td>
<td>20 (74)</td>
</tr>
<tr>
<td>Sample size</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Compliance and missing data (strategies)</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Statistical tests to be performed</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Item</td>
<td>Frequency (%)</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Monitoring trial progress</td>
<td></td>
</tr>
<tr>
<td>Interim analyses</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Early stopping rules/termination policy</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Procedures for handling/reporting adverse events</td>
<td>10 (37)</td>
</tr>
<tr>
<td>Protocol amendments</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Project management</td>
<td></td>
</tr>
<tr>
<td>Personnel and committees</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Administrative responsibilities (and how they will be shared)</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Roles of collaborators/investigators</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Biosketches/CV’s of investigators</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Resources required (staff, facilities, equipment and supplies)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Cost/Budget</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Ethical and legal issues</td>
<td>17 (63)</td>
</tr>
<tr>
<td>Patient consent</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Reporting (methods of dissemination of findings, politics of publication)</td>
<td>10 (37)</td>
</tr>
<tr>
<td>References</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Appendices/Supplements</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Sample patient consent form</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Flowcharts/Diagrams (e.g. patient flow, organizational schema, etc.)</td>
<td>5 (19)</td>
</tr>
</tbody>
</table>

*aThese values should be considered approximate due to incomplete overlap between items across checklists and differences in terminology; this process will be validated in subsequent review updates.

Note: Concepts included at least five guidelines
9.2 Appendix B: Delphi Surveys

9.2.1 Round 1

Survey ID # __

The SPIRIT Initiative Delphi – Round One

Welcome to Round One of the SPIRIT Initiative Delphi consensus survey. Please take a moment to review these instructions.

The aim of this Delphi survey is to develop a reporting guideline for protocols of 2-group parallel design randomized trials. The intention is that the final SPIRIT guideline will be versatile such that it may be adopted for use by multiple parties including funding agencies, research ethics boards and journals. One major benefit to trialists would be that they could use the same standard protocol for each submission, although certain appendices would be more relevant for some submissions than others. With your expertise and that of our other panelists, we hope to refine and modify, the initial list of items for inclusion in the SPIRIT checklist.

Items are arranged under seven headings corresponding to sections commonly found in protocols of randomized trials. For each item please select your rating on a scale of 1-10. A score of 10 indicates you feel the item is very important (i.e., must be included in final guideline), a score of 1 indicates the item is unimportant (i.e., should be dropped as an item to consider). If you do not feel qualified to rate a particular item please select no judgment.

To make your selection electronically, simply click on your selection with your cursor.

To change your rating, unselect your previous rating and click on your new choice.

If you prefer you may print your form and return it by facsimile. In this case please mark your selections with an X.

Your responses to Round One will be known only to the moderator of this Delphi (Jennifer Tetzlaff). Anonymous responses will be tallied and summarized for Round Two.

We estimate Round One will require approximately 30 minutes to complete. You do not need to complete the questionnaire at once but may save your responses and return to the questionnaire at any time. If you experience any difficulties with the form or format, please let us know.

Helping develop this guideline is important and we thank you very much for your time. We ask that you complete and return this form by Friday, September 7th, 2007. Either electronically by email to jtetzaif@dcheo.on.ca or by fax (+1 613-738-4300) to Jennifer Tetzlaff.

Thank you for taking the time to participate in this important initiative.

We look forward to your responses!

Please note: Delphi surveys have been compressed. For full size surveys, please contact the author.
Section 2: Introduction

8. Rationale
Outline the research topic and provide justification for undertaking the study.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

9. Background of the study
Summarize previous studies on the topic, including unpublished studies known to the investigators and sponsors, and animal studies or other preclinical data where relevant. Ideally, a relevant up-to-date systematic review should be referenced or reported supporting the need for the current trial (e.g., clinical evidence).

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

10. Preliminary data
Describe any results of preliminary studies already obtained in the area of the proposed study (e.g., by investigators).

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

11. Objectives
State the specific objectives and hypotheses of the study.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

12. General approach
Outline the general approach to address the research question.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

13. Study location(s)
Briefly describe and justify the site(s) where the research is to be conducted, including relevant demographic and epidemiological information about the country or region concerned.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

Comments or additional items (Section 2):

Section 2: Methods

14. Population
Describe the target and study population and the source (e.g., catchment area) of the study population.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

Survey ID = __

15. Eligibility criteria
Describe the criteria for inclusion and exclusion of potential participants and justification for the exclusion of any subgroup.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

16. Sample size
The estimated number of research participants needed to achieve the study objective, and how this was determined including any assumptions and calculations used.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

17. Recruitment
Describe the process of recruitment (e.g., advertisements, physician contacts) and enrollment.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

Study design

18. Type of study
A description of the type of design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and trial framework (e.g., exploratory, superiority, equivalence, non-inferiority).

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

19. Study timeline
Schematic diagram of study timetable and organizational chart including design procedures and stages of trial.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

Randomization

20. Sequence generation
Describe the method to be used to generate the random sequence list, including details of any restriction (e.g., blocking, stratification).

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

21. Allocation concealment
Describe the method used to implement the random allocation sequence (e.g., numbered containers or central telephone) clarifying whether the sequence will be concealed until interventions are assigned.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

Page 3 of 10
22. Implementation
Describe who will generate the allocation sequence; who will enroll participants; and who will assign participants to their group.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

23. Blinding (masking)
State whether or not participants, those administering the interventions, and those assessing the outcomes will be aware of group assignment; if relevant, how the success of blinding will be assessed.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

24. Interventions
Provide precise details of the interventions intended for each group, how they will be administered (e.g., dosage and dosage form/device), where applicable. Justify the control interventions used (e.g., no treatment, placebo, or active control).

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

25. Schedule(s) of Intervention(s)
State the number and duration of treatment periods including run-in and washouts, where applicable.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

26. Concomitant interventions
List treatment(s)/intervention(s) that are permitted or not prior to and/or during the study.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

27. Risks
State the known or potential risks and adverse reactions for each study intervention.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

28. Outcomes
Describe and define primary and secondary outcome measures.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

29. Data collection
Describe methods, including study instruments (e.g., questionnaires, laboratory measurements), and time point(s) of data collection, outcome measurement, and recording.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

30. Follow-up
State follow-up plans including description and schedule of visits and logistics (e.g., post trial drug-supply) if relevant.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

31. Data management
Describe plans for data entry, editing, and management, including handling data collection forms and different versions of data, coding, and data storage.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

32. Quality control
State any methods used to enhance the quality of outcome assessment (e.g., duplicate observations, training of assessors, pilot testing, validation etc.) and data records to ensure the completeness and accuracy of information.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

33. Compliance
Describe procedures and measures proposed to monitor participant compliance (e.g., tablet return if relevant).

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

34. Safety Evaluations
State plans for monitoring the continuing safety of interventions administered for purposes of the trial, including specification of methods and timing of measuring safety parameters.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

35. Statistical methods
Describe statistical methods to be employed to compare groups for primary outcomes and secondary outcome(s) as well as methods for additional analyses such as subgroup analyses and adjusted analyses. State whether intention-to-treat or other analysis will be used for the primary comparison(s).

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
</tbody>
</table>

36. Withdrawals
State criteria that will be used to withdraw or exclude participants from the trial (e.g., compliance requirements), and specify the data to be collected from withdrawn participants and follow-up in a multi-centre study when a centre may be discontinued from the trial.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very important</td>
</tr>
<tr>
<td>Section 4: Trial organization and administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44 Personnel</td>
<td>Provide names, affiliations, contact details, qualifications, time commitment and job descriptions of trial personnel including investigators, statisticians, and other relevant staff including consultants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 Logistics</td>
<td>Describe the availability of resources and logistics of the trial including administrative responsibilities (e.g., how they will be shared), equipment, and physical facilities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46 Monetary and material support</td>
<td>Name the source(s) of financial and material support, type of support provided, amount, and how (e.g., to a research account or as an honorarium)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47 Budget</td>
<td>Provide the budget for personnel, equipment, facilities, and supplies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comments or additional items (Section 4)**

**Section 5: Ethical considerations**

| 48 Potential benefits and risks | The potential benefits and risks of the research to study participants and to society |
| 49 Agreement and consent | Describe the method to obtain individual informed consent information provided to the patient and the name and position of the person responsible for obtaining consent. Provide a copy of the consent form and patient information leaflet |

**Comments or additional items (Section 5)**
50. Surrogate Consent or Assent
If a prospective participant is not capable of informed consent, provide information on how permission will be obtained from an authorized individual. In the case of individuals below legal consenting age, provide information on how assent and permission from a legal guardian or other authorized individual will be obtained.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ No judgment
Not important Very important

51. Confidentiality and Anonymity
The provisions for protecting the confidentiality and anonymity of personal data and respecting the privacy of participants.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ No judgment
Not important Very important

52. Ethics approval
State whether ethics approval has been obtained, if so provide the name of the committee(s).

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ No judgment
Not important Very important

53. Role of Sponsor
Describe the role of the sponsor in the trial design, data collection, access to trial data (including interim data audits and regulatory inspections), data analysis and interpretation, and manuscript preparation.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ No judgment
Not important Very important

54. Conflict of Interest
Disclose financial or other real or perceived conflicts of interest.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ No judgment
Not important Very important

57. Publication Policy
Details on who has the right to publish the study results or modify the manuscript: principle investigator(s), co-investigator(s), sponsor, editor-in-chief, or any other authorship guidelines.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ No judgment
Not important Very important

58. References
Provide a list of the references cited in the protocol.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ No judgment
Not important Very important

59. Appendix Materials
Provide relevant materials including samples of the standardized case-report forms, other data collection forms (e.g., questionnaires), consent/assent forms, and curriculum vitae of each investigator.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ No judgment
Not important Very important
Welcome to Round Two! Thank you once again for completing Round One of the Delphi survey aimed at developing a new checklist of essential items to be included in protocols of parallel-group randomized trials.

Please take a few moments to read through this introduction to Round Two.

The second round of this Delphi survey contains all of the items from Round One; however, they have been grouped in order of importance as a result of the collated median scores for each checklist item from Round One. This round allows you to review the ratings and comments of the other panelists and with consideration of this information, to provide you with the opportunity to rate each item. We have not made changes to the checklist based on comments received to date. All comments have been anonymized and summarized; major content has been retained unless otherwise indicated by a number in brackets comments were made by one panelists.

This round contains five parts: Part 1. General comments on the scope of the SPIRIT Checklist. Part 2. Items of high importance (median ≥ 5) organized under headings corresponding to those presented in Round One. Part 3. Items of moderate importance (median 3 to 5.9) Part 4. Items of low importance (median ≤ 2) and Part 5. Additional checklist items that were not included in the original checklist but which were generated as a result of comments on Round One.

Instructions for Round Two

To respond to this survey, please read the comments provided by panelists and select your new rating for each item on a scale of 1-10. A score of 10 indicates you feel the item is very important; i.e., must be included in the final guideline. A score of 1 indicates the item is unimportant; i.e., should be dropped as an item. Each item is accompanied by 1) panelists comments 2) your previous rating 3) the frequency distribution of responses and 4) the median and interquartile range (IQR) summarized from responses to Round One. If you do not feel qualified to rate a particular item please select no judgment. Please feel free to state if you agree or disagree with any comment presented.

Section 2.2 Please note that following this round, items with a median of ≥ 8 will be considered included in the first draft of the SPIRIT Checklist and items with a median of ≤ 5 will be considered excluded. The checklist will not be rated to rate these items in the third and final round of the Delphi.

Section 3 All items newly-introduced in Round One will be re-considered in Round Three.

To make your selection electronically, simply click on your selection with your cursor. Change your rating by unselecting your previous rating and clicking on your new choice. You are not able to modify the text; however, following each item, a space is provided where you may add free text comments or suggest modifications.

In this case, please make your selection and do not use an 'X'.

We thank you very much for your time and ask that you please complete and return this form by September 26, either electronically by email to delphi@ihe.on.ca or by fax (+011 613-738-4800) to Jennifer Tetzold.

Thank you for taking the time to participate in this important initiative.

Once again, we look forward to your responses.

Part 1: General Summary

Checklist
- Many respondents felt that while there were many items, most were important. As a result, they rated most quite high. Although there must be a balance between guiding researchers and being too prescriptive, some respondents stated that a page one comprehensive list would be more useful in light of the evidence for poor reporting in protocols (6) and due to the serious business of clinical trials which occurs (in a detailed reporting at any stage).
- One respondent felt that there were too many rules; people will do nothing than follow rules and papers will become unreadable (1).
- Two panelists stated that standardisation items should be made available through other sources (e.g. websites) (2).
- One respondent stated that while all are potentially important, it depends on the length of the protocol (1).
- Some respondents listed it difficult to respond to specific items which contained multiple concepts (i.e., if the panel felt that one concept within an item was important while another was not) (3). We have not modified the items for this round; however, we encourage you to provide us with comments for specific items if you feel that certain elements within items are of greater or lesser importance to you. As some panelists have already done. These comments will be considered in the process of the development of the guideline.
- One respondent was unsure if much of the operational information was needed in the protocol.
- Another respondent cautioned about ensuring guidelines such as the International Conference on Harmonisation are considered to ensure that we address issues relevant to some regulatory agencies. We have consulted the ICH and other guidelines to inform the development of the initial set of items presented in Round One.

Scope — Study Design
- In Round One, we stated that the SPIRIT initiative aims to develop a research guideline for protocols of 2-group parallel design randomized controlled trials (RCTs). We received some insightful comments and have had some preliminary discussions as a result. The guideline was intended to focus on the 2-group parallel design that is most to develop of the CONSORT statement and associated extensions. Some panelists questioned why we limited to 2 groups (2) and upon discussion we do not see immediate limitations to this checklist being relevant to trials with more than two arms.
- It was also questioned how broad the scope of the checklist was intended to be with regard to the use of randomization (2).

The guideline is intended for parallel group design trials with individuals as the unit of randomization. Additional reporting measures would be required for clustered randomized trials although the main concepts would be the same.

Scope — End User
- Many respondents stated that they would rate certain items differently depending on where the protocol was being submitted.
- For example, some details would be important to a submitted study that is funded but may be viewed as excessive for the applicant and grant reviewers if the protocol was prepared for grant review. Alternatively, although it was stated that all tips to a unique form for protocol presentation/dissemination/publication are welcome items such as logistics/management could be differently appreciated by a funding body (who would like as much detail as possible) than by others (publishers always have space constraints). As an alternative, one respondent stated that we may wish to consider suggestions about which items should be recommended as the minimal for an ethical committee a granting agency or for publication in a clinical trial register. In general, we are aiming the proposed checklist at all those who are discussing as a result. This guideline was intended to provide a common checklist for development of the 2-group parallel design randomized controlled trials. We received some insightful comments and have had some preliminary discussions as a result. The guideline was intended to focus on the 2-group parallel design that is most to develop of the CONSORT statement and associated extensions. Some panelists questioned why we limited to 2 groups (2) and upon discussion we do not see immediate limitations to this checklist being relevant to trials with more than two arms.
- It was also questioned how broad the scope of the checklist was intended to be with regard to the unit of randomization (2).

This guideline is intended for parallel group design trials with individuals as the unit of randomization. Additional reporting measures would be required for clustered randomized trials although the main concepts would be the same.

Protocol — Definition
- Three respondents raised the issue of differences in views of what constitutes a protocol. For example, one stated that they viewed the protocol as the clinical guidance document for the study, while others like the Statistical Charter and the contract deal with issues related to data management analysis and randomization and publication. Another stated that currently, the research application we receive as a funder and the trial protocol is not one and the same. There are several issues to consider when defining a clinical trial protocol. In general, we consider a protocol to be a document written prior to participant enrolment to describe the objectives, design methodology, statistical considerations and organizational or administrative aspects of a clinical trial.
The following provides a description of the components presented for each item presented below.

**LEGEND**

*Your rating from Round One*  
*Item specific comments*  
*Frequency distribution of previous ratings*

M = Median 25% 75% = Inter quartile range

---

**PART2: ITEMS OF HIGH IMPORTANCE**

### Section 1 General Information

**General comments**
- All items in section 1 should be included in the trial protocol. However this does not mean that they are important. Only trial identifier and protocol version are essential for the evaluation of the trial protocol and/or trial report.
- The important thing is that the trial and PI can be identified.
- All items in this section are very important allowing for quick orientation.

#### 1 Title
- Provide a descriptive title i.e. population, intervention, main outcome, identifying the study as a randomized controlled trial.
- The description should be specific and not refer to a population that is not applicable.
- Study Design would identify it as an RCT. Also an important element when searching the literature.
- Wording could be improved/feel mixed up two ideas.

#### 2 Trial identifier
- Unique trial identification number or name (e.g. trial registration number, protocol number) and where registered (i.e. name of trial registry).
- Trial identifier is critical but not sure if everyone will have one at the start of the protocol stage, generally only available after the trial is funded (i.e. after submission). Someone may not go to the trouble of registering the trial prior to getting funding. This information should be made clearer to reflect this.
- Having an acronym is not an issue but more a marketing and profiling issue.
- There may be some sorts of trials that do not get registration numbers but in general, it should be done.
- Trial registration data are very important and need to be located in an easy to access location.

#### 3 Protocol Version
- Include a version or amendment number and date.
- We can talk about versions of different types: a) refining the protocol following ethics or another review process or even after having another co investigator join in PRIOR TO starting the recruitment. In this case, we need to know all the details of it. Also it might be quite difficult to state and follow them all. b) versions of protocols during trial. These need to be described and dated and also data should be made from main trial participants once recruited prior to that change.

---

Survey ID #
4 Protocol Summary

Provide a short summary of the proposed research. Where required, include appropriate lay/non-technical language.

Previous comments

- I don’t think a lay summary is important here if done poorly, it is worse than useless. Understanding might be an important consideration in accepting the protocol for publication in any case.
- This summary should include the primary hypothesis, randomized interventions, the population to be studied, the number of sides, duration of treatment, duration and frequency of follow-up, and the sample size.
- The lay summary is effective in the written information provided to the patient.

Comments

§ Your previous rating

1 2 3 4 5 6 7 8 9 10

Not important Very important

Your previous rating

5

Comments

6 Table of contents

Provide a list of the contents of the protocol and associated page numbers.

Previous comments

- Add if deemed necessary. (e.g., 48 pages or more).

Comments

§ Your previous rating

1 2 3 4 5 6 7 8 9 10

Not important Very important

Your previous rating

6

Comments

7 List of abbreviations

Line and descriptors of abbreviations used throughout the protocol.

Previous comments

- I suggest that abbreviations should not be used unless they are standard, unambiguous, and widely accepted (2).
- A bit too prescriptive.
- Not always necessary.
- If the abbreviations are defined in the text, there is no need for a separate list of abbreviations.

Comments

§ Your previous rating

1 2 3 4 5 6 7 8 9 10

Not important Very important

Your previous rating

8

Comments

Survey ID # ___

Section 2 Introduction

General

- From a reader’s feeling perspective, these items are very important in terms of the application submitted. This is not currently exact, the same thing as the final protocol.

§ Your previous rating

1 2 3 4 5 6 7 8 9 10

Not important Very important

Your previous rating

8

Comments

8 Rationale

Outline the research topic and provide an outline of the main aspects.

Previous comments

- Should be clear.
- Outline included in this section should be outlined in the context of existing evidence.
- Could be merged with item Background of the Study.
- Often not sufficiently described in detail.

Comments

§ Your previous rating

1 2 3 4 5 6 7 8 9 10

Not important Very important

Your previous rating

6

Comments

9 Background of the study

Summarize previous studies on the topic, including unpublished studies known to the investigators and sponsors, and animal studies or other preclinical data. Do not repeat the entire relevant history. Ideally, a relevant, up-to-date systematic review should be referenced or reported supporting the need for the current trial (e.g., clinical equipoise).

Previous comments

- Delete, even if it weakens the requirement for a systematic review.
- Also point out systematic review/meta analysis, e.g., if relevant.
- Equivalence related to the justification of control intervention (you may link this item to Interventions in Methods). I did not quote higher score because of the mention of the need to have a systematic review.
- Please avoid clinical equipoise. I prefer uncertainty.
- Need not recapitulate the entire relevant history. You can provide critical literature citations. It usually is sufficient.
- Often concerned about using unpublished data.
- Often not sufficiently described in detail.

Comments

§ Your previous rating

1 2 3 4 5 6 7 8 9 10

Not important Very important

Your previous rating

7

Comments

10 Preliminary data

Describe any results of preliminary studies or a draft obtained in the area of the proposed study (e.g., D
d investigators).

Previous comments

- Already part of Background of the Study. They could be merged (2).
- I added others next to investigators. I see this section as providing all the evidence suggesting the assumptions made in the design of the trial are reasonable and justified.
- I think these data should be discussed from/with the PI’s perspective, not someone else.
- I agree that preliminary data should be used. Open controlled underpowered study (1) may not be applicable (1). Preliminary data can be minimized at some risk in an investigation. Bypass important highlight key theorems.

Comments

§ Your previous rating

1 2 3 4 5 6 7 8 9 10

Not important Very important

Your previous rating

10

Comments

Page 6 of 2
11 Objectives State the specific objectives and hypotheses of the study

- Your previous rating: 6
  - 1 2 3 4 5 6 7 8 9 10 No judgment
  - Not important Very important
  
  Comments:

12 General approach Outline the general approach to address the research question

- Your previous rating: 6
  - 1 2 3 4 5 6 7 8 9 10 No judgment
  - Not important Very important
  
  Comments:

13 Study location(s) Briefly describe and justify the site(s) where the research is to be conducted, including relevant demographic and epidemiological information about the country or region concerned

- Your previous rating: 6
  - 1 2 3 4 5 6 7 8 9 10 No judgment
  - Not important Very important
  
  Comments:

14 Population Describe the target and study population and the source (e.g., catchment area) of the study population

- Your previous rating: 6
  - 1 2 3 4 5 6 7 8 9 10 No judgment
  - Not important Very important
  
  Comments:

15 Eligibility criteria Describe the criteria for inclusion and exclusion of potential participants and justification for the exclusion of any subgroup

- Your previous rating: 6
  - 1 2 3 4 5 6 7 8 9 10 No judgment
  - Not important Very important
  
  Comments:

16. Sample size The estimated number of research participants needed to achieve the study objective and how this was determined including any assumptions and calculations used

- Your previous rating: 6
  - 1 2 3 4 5 6 7 8 9 10 No judgment
  - Not important Very important
  
  Comments:
**Randomization**

20 Sequence generation

- **Describe the method to be used to generate the randomization sequence**, including details of any restriction (e.g., blocking, stratification).

**Previous comments**
- It should be clear that the size of the block should not be in the protocol so that investigators do not know (4).
- It is very important NOT to describe sequence generation in the protocol or to minimize physician selection bias. Respondents suggested alternative documents for this information, including the Statistical Analysis Plan, a separate addendum or in a randomization procedure so that it has limited distribution (3).

**Comments**

21 Allocation concealment

- **Describe the method used to implement the random allocation sequence** (e.g., numbered envelopes, central telephone, computer system). None the sequence will be concealed until interventions are assigned.

**Previous comments**
- It is very important to record the allocation sequence, not on describing how will obtain it (1).

**Comments**

22 Implementation

- **Describe how will generate the allocation sequence** who will enroll participants and who will assign participants to their group.

**Previous comments**
- Should be focused on how to obtain the allocation not on describing how will obtain it (1).

**Comments**

23 Blinding (masking)

- **State whether or not participants, those administering interventions, and those assessing the outcomes will be aware of group assignment**. If relevant, how the success of blinding will be assessed.

**Previous comments**
- No single double-blind statement is useful, but the indication of who is not blinded and about which aspects of intervention other outcomes (2).
- Others in addition to those mentioned may need to be blinded more than those three (2).

**Comments**
**24 Interventions**

Provide precise details of the interventions intended for each group (i.e., dosage and dosage form device) where applicable. Justify the control intervention used (e.g., no treatment, placebo or active control).

**Previous comments**
- Please match the wording with the WHO international standards for trial registration
- To questions the first more important

**Your previous rating**

Your previous rating:
- Not important
- Very important

**Comments**

**25 Schedule(s) of intervention(s)**

State the number and duration of treatment periods including run in and washouts where applicable.

**Previous comments**
- Only relevant concomitant medications should be included
- List only those medications not permitted

**Your previous rating**

Your previous rating:
- Not important
- Very important

**Comments**

**26 Concomitant interventions**

List treatment/interventions that are permitted or not prior to and during the study.

**Previous comments**
- Only relevant concomitant medications should be included
- List only those medications not permitted

**Your previous rating**

Your previous rating:
- Not important
- Very important

**Comments**

**27 Risks**

State the known or potential risks and adverse reactions for each study intervention.

**Previous comments**
- This formulation should be harms

**Your previous rating**

Your previous rating:
- Not important
- Very important

**Comments**

**28 Outcomes**

Describe and define primary and secondary outcome measures.

**Previous comments**
- The sequence and necessary links between outcomes, outcome definitions, and outcome assessment could be strengthened. The concept of an end point should be introduced.

**Your previous rating**

Your previous rating:
- Not important
- Very important

**Comments**

**29 Data collection**

Describe methods including study instruments (e.g., questionnaires, laboratory measurements) and time points of data collection, outcome measurement and recording.

**Previous comments**
- A short description of the psychometric properties of each study form and questionnaire is useful.

**Your previous rating**

Your previous rating:
- Not important
- Very important

**Comments**

**30 Follow up**

State follow up plans including description and schedule of visits and logistics (e.g., post trial drug supply) if relevant.

**Previous comments**
- Add that start windows should be stated that define the acceptable interval in which each visit can be conducted before it is considered missed.
- Obviously important not sure if it is essential as part of a trial protocol though more operational manual

**Your previous rating**

Your previous rating:
- Not important
- Very important

**Comments**

**31 Data management**

Describe plans for data entry, editing and management, including handling data collection forms and different versions of data, data coding, and data storage.

**Previous comments**
- These do not need to be fully articulated in the protocol document (2.7) could leave in records retention requirements (3.2).
- More details should be provided in a data management handbook/procedures manual.

**Your previous rating**

Your previous rating:
- Not important
- Very important

**Comments**
32 Quantity control State any methods used to enhance the quality of outcome assessment (e.g., duplicate observations, training of assessors, pilot testing, validation, etc.) and data records to ensure the completeness and accuracy of information.

Previous comments:
- This is important but could be expanded on in study procedures.

33 Statistical methods Describe statistical methods to be employed to compare groups for primary outcomes and secondary outcomes, as well as methods for additional analyses, such as subgroup analyses and adjusted analyses.

Previous comments:
- This should also be expanded on in study procedures.

34 Safety Evaluation State plans for monitoring the continuing safety of interventions administered for purposes of the trial including specification of methods and timing for measuring safety parameters.

Previous comments:
- This should also be expanded on in study procedures.

35 Withdrawals State criteria that will be used to withdraw or exclude participants from the trial (e.g., compliance requirements), and specify the data to be collected from withdrawn participants and follow-up in a multi-centre study when a centre may be discontinued from the trial.

Previous comments:
- Withdrawals in a 2 group parallel design shouldn’t happen at all what is to be done with withdrawals probably is a good thing so the reviewers can judge if they are doing the right thing. Discontinuing centres is a common thing and should be included.

36 Missing data Describe the methods to account for missing data or erroneous data.

Previous comments:
- Missing data and erroneous data should not be tolerated. I don’t think this section should say how it will be accounted for in the results.

37 Data Safety Monitoring Board: If relevant, describe the composition and role of the data and safety monitoring board.

Previous comments:
- The existence of a DSMB should be specified in the protocol but the details of its composition and its specific charge are often provided in a separate document (e.g., DMC charter) or operating procedures.

Comments:
- Your previous rating: [Score]
39 Interim trial monitoring. Describe the process and timing of any planned interim analyses.

<table>
<thead>
<tr>
<th>Your previous rating:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

40 Stopping guidelines. State the criteria for the premature termination of the trial

Previous comments:
- There should be common, universal rules for early stopping and those should not be redefined each time by a committee.
- It may occur that we need to stop the trial for reasons unsuspected at the time of design.
- Stopping rules - from the funder perspective - in the research application (which is not the same as the protocol).
- I dislike the word "premature" to modify "termination" if a treatment is harmful, then the study should be terminated and therefore termination is not premature, it is either planned or unplanned.
- Ambiguous for me. I don't know whether you were asking about stopping boundaries or about the process regarding it.
- it may occur that we need to stop the trial for reasons unsuspected at the time of design.
- Previous comments:
  - I think this item could be renamed "harms".
  - The CONSORT extension concerning harms in the reporting of harms should be incorporated into this initiative.
  - I think this item could be renamed "harms".

<table>
<thead>
<tr>
<th>Your previous rating:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

41 Adverse event reporting. Describe methods for recording and reporting both solicited and spontaneous adverse events and procedures for dealing with them.

Previous comments:
- Some respondents felt that this item was overdone and/or could be combined with "risks" (2) or with "safety evaluations" (1) or that all three could possibly be merged into a single item (1).
- Many companies have standard operating procedures that deal with how events get reported. These are very detailed and need to comply with regulatory requirements. So I absolutely agree that this information needs to be specified, but whether it needs to be specified in detail in the body of the protocol is not clear.
- The CONSORT extension concerning harms in the reporting of harms should be incorporated into this initiative.
- I think this item could be renamed "harms".

<table>
<thead>
<tr>
<th>Your previous rating:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

42 Emergency code-breaking procedure. Information about how the code, if any, for the participants' identity is established where it will be kept and when how and whom can be broken in the event of an emergency.

Previous comments:
- It is important to list who is funding/supporting the trial. However, the details of the nature of the support (e.g., who is spending how much) is not necessary for the protocol itself. The details should be outlined in contracts with the supporting bodies (3).
- Although important should not be included in the protocol.
- I wonder whether there needs to be a single item getting at issues of funding. I'm not suggesting to get rid of items. There are either items that might be candidate items.
- Is this not going to be for the application for funding? Do you mean how much the sites will be given? or do you mean how much the institution where the research is being coordinated from will be giving? All of our sites could not be quantified. I don't think. Everything out the very basic office space and furniture has to be covered by the research grant.
- Not sure about all elements here.

<table>
<thead>
<tr>
<th>Your previous rating:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

43 Limitations. Describe the limitations of the proposed study, including possible bias in data collection/measurement and analysis.

Previous comments:
- Should be in the grant submission and trial protocol. Not necessarily in a protocol submission (if space limitations). Limitations is better discussed in a manuscript than in a protocol.
- I don't see why there should be this paragraph as the trial should be designed to minimize biases. It is in data collection/measurement and analysis should not be tolerated. This section should be the steps taken to eliminate bias.
- The CONSORT extension concerning harms the reporting of harms should be incorporated into this initiative.
- I think this item could be named "harms".

<table>
<thead>
<tr>
<th>Your previous rating:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

Section 6: Trial organization and administration

General.
- Much of this section would do better in a document separate from the protocol.
- Protocols that are changed need to be amended so items that may change frequently should not be part of a protocol. For example, every time a staff change one would have to amend the protocol and resubmit to all trials. A roster can be kept and under FDA 1572s are updated to track change in personnel. The staff qualification requirements however should be stated in the protocol.
- These depend on the target audience (2). e.g., higher scores for a funding agency. The trial qualifications requirements depend on the target audience (2).
- Previous comments:
  - There may be a need for functional description of the processes. I think these comments are for the primary focus.
  - From a funder perspective these are all essentials on any application.

46 Monetary and material support. Name the sources of financial and material support and type of support provided amount, and how (e.g., to a research account or as an honorarium).

Previous comments:
- It is important to list who is funding/supporting the trial. However, the details of the nature of the support (e.g., who is spending how much) is not necessary for the protocol itself. The details should be outlined in contracts with the supporting bodies (3).
- Although important should not be included in the protocol.
- I wonder whether there needs to be a single item getting at issues of funding. I'm not suggesting to get rid of items. There are either items that might be candidate items.
- Is this not going to be for the application for funding? Do you mean how much the sites will be given? or do you mean how much the institution where the research is being coordinated from will be giving? All of our sites could not be quantified. I don't think. Everything out the very basic office space and furniture has to be covered by the research grant.
- Not sure about all elements here.

<table>
<thead>
<tr>
<th>Your previous rating:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

Survey ID # __
Some funding bodies do not require ethics to be in place before an award is made (i.e., at the time of research application). Remembering that protocol amendments can be burdensome to both sponsors and sites, you want to keep information that is going to change on a frequent basis (i.e., if sites with ethics approval) to a minimum. This information should be shared in a different way.

Some funding bodies do not require ethics to be in place before an award is made (i.e., at the time of research application). Currently, the final protocol is approved by the trial steering committee and sent for ethical approval. Anticipated there will be variation between these committees until final ethics-approved protocol confirmed.

Consent details always should be in the protocol submitted or registered but I am not sure need to be included in a published protocol. Regarding the issue of consent, the consent form will vary by institution and country as well as who will be obtaining consent. Perhaps a description of the general consent process in the physician will approach the participant and ask if they would be willing to speak with a research assistant about participating in a research study. Certainly privacy legislation is an area of different between Canada and the US for example. Local IRB/REB take care of the actual details at each site.

Regarding the issue of consent, the consent form will vary by institution and country as well as who will be obtaining consent. Perhaps a description of the general consent process in the physician will approach the participant and ask if they would be willing to speak with a research assistant about participating in a research study. Certainly privacy legislation is an area of different between Canada and the US for example. Local IRB/REB take care of the actual details at each site.
53 Role of Sponsor
Describe the role of the sponsor in the trial design, data collection, access to trial data (including interim data, audits, and regulatory inspections), data analyses, and interpretation and manuscript preparation.

Previous comments
- Should be disclosed but not in the protocol (6)
- Name all sponsors - there are sometimes several. Also ask for funders. CIHR is not a sponsor but is a funder.
- Transparency in sponsors and declarations of interest will be important.
- Sponsors don't apply to trials where there are no devices, no drugs, etc.
- It's a matter of judgement whether this item is primarily ethical or primarily methodological or relating to trial organisation. If they are placed under trial organisation we could avoid some overlap.
- Sponsor role of sponsor under current regulatory/governance directives, we only seek confirmation of who is taking on this role.

Comments

54 Conflict of Interest
Describe financial or other real or perceived conflicts of interest.

Previous comments
- Important and should be disclosed. But not in the protocol (3)
- Transparency in sponsors and declarations of interest will be important.
- It's a matter of judgement whether this item is primarily ethical or primarily methodological or relating to trial organisation. If they are placed under trial organisation we could avoid some overlap.
- I worry about over-reporting of potential conflicts. If everyone reports every possible conflict then the actual conflicts can get blurred.
- Statements about potential conflict of interest belong in publications not necessarily in reporting standards.

Comments

55 Protocol Amendments
Describe how changes to the original protocol, including the statistical plan, will be communicated to investigators and ethics committees and how these will be reported and justified in subsequent amendments to the protocol and/or the final report as appropriate.

Previous comments
- Why should the statistical analysis plan be changed? It should be set at the beginning before any data are collected. The stopping rules for interim analyses should be defined as well as what changes would be acceptable part way through a study.
- The Statistical Analysis Plan (SAP) should be a document separate from the protocol with a smaller dissemination. The points would be appropriate in the statistical section of the protocol. The SAP would have tables and more details including specific details regarding the randomization.
- Forget the Health Protection and Food Branch (who to report SAEs to and who will inform HPFB about reportable SAEs).
- It may depend on the type of protocol amendment. Some protocol amendments are strictly administrative.
- Different groups more important to describe dissemination to patients

Comments

56 Dissemination
Describe how the researcher(s) or sponsor(s) will disseminate the results to participants, healthcare professionals, the public or other relevant groups.

Previous comments
- Some of it might be decided up front, but they might develop it on the road. Often not precisely known before the end (3)
- Basics of this should be somewhat covered by some universal guidelines.
- As long as I have a registration name and number and details of the investigators I am not personally worried about dissemination.
- I would include an expectation of publication.
- I agree with the principle here but don't think this necessarily belongs in the protocol itself. Most pharmaceutical companies have policies around these issues.
- Not sure if this item will give useful information.
- Especially for multi-centre studies there can be legislative differences concerning how information is shared.

Comments

57 Publication Policy
Describe who has the right to publish the study results or modify the manuscript(s), investigator(s), sponsor(s), including publication restrictions and authorship guidelines.

Previous comments
- Publication rights tend to be detailed in study contracts not necessarily in the study protocol. As such, there may be subtle differences between participating sites (4).
- I agree with the principle here. But I don't think this necessarily belongs in the protocol itself (2). Most pharmaceutical companies have policies for these issues, but I don't know that they need to be stated in the protocol.
- Publication policy is usually discussed and approved by the TSC.

Comments
Section 7: Other

58 References

Provide a list of the references cited in the protocol

<table>
<thead>
<tr>
<th>Your previous rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

Provide a list of the references cited in the protocol.

Previous comments
- CV's should not be part of the protocol (10)
- Some but not all of these should be in protocol (3), the rest should be documented in the Trial Master File (1)
- Should be handled separately from the protocol as part of a detailed manual of operations for example
- A copy of the consent template (English and French) should be included as an appendix
- Case Report Forms (CRFs) should not be included as they are subject to change. CRFs and detailed instructions and definitions for completion should be in a separate data management handbook or user's guide

59 Appendix Materials

Provide relevant materials including samples of the standardized case report forms or other data collection forms (e.g., questionnaires), consent/assent forms and curriculum vitae of each investigator

<table>
<thead>
<tr>
<th>Your previous rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

Provide relevant materials including samples of the standardized case report forms or other data collection forms (e.g., questionnaires), consent/assent forms and curriculum vitae of each investigator.

PART 3: ITEMS OF MODERATE IMPORTANCE

44 Personnel

Provide names, affiliations, contact details, qualifications, time commitment, and job descriptions of trial personnel including investigators, statisticians, and other relevant staff, including consultants

<table>
<thead>
<tr>
<th>Your previous rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

Provide names, affiliations, contact details, qualifications, time commitment, and job descriptions of trial personnel including investigators, statisticians, and other relevant staff, including consultants.

Previous comments
- This may change quite often over the course of the trial (2)
- Would need a process to be kept current (1)
- Should be handled separately from the protocol, as part of a detailed manual of operations, for example
- A copy of the consent template (English and French) should be included as an appendix
- Case Report Forms (CRFs) should not be included as they are subject to change. CRFs and detailed instructions and definitions for completion should be in a separate data management handbook or user's guide
- Timelines are helpful in the appendices (see schedule of events)

45 Logistics

Describe the availability of resources and logistics of the trial including administrative responsibilities (e.g., how they will be shared), equipment, and physical facilities

<table>
<thead>
<tr>
<th>Your previous rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

Describe the availability of resources and logistics of the trial including administrative responsibilities (e.g., how they will be shared), equipment, and physical facilities.

Previous comments
- Any central resource centers (central labs, reading centers, data and statistical center) should be named with their role summarized
- Detailed staff listings are not necessary in the protocol but should be available in a roster
- This may change quite often over the course of a trial; this item should not be in the protocol

47 Budget

Provide the budget for personnel, equipment, facilities, and supplies

<table>
<thead>
<tr>
<th>Your previous rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

Provide the budget for personnel, equipment, facilities, and supplies.

Previous comments
- Important but does not need to be explicit in the protocol; budget should be in a separate document (5)
- Important but I don't think needs to be included in a protocol but rather in the grant submission (2)
- Should not be in the protocol. Any changes in these items will necessitate protocol amendments
- Should be in Appendix Materials
- Funding may not be known at the time of writing the protocol. Budget is internal to the institution conducting the trial
- I doubt that people would be forthcoming in terms of budget
- Not sure if this should be public

PART 4: ITEMS OF LOW IMPORTANCE

No items were rated with a median ≤ 5 in Round One of this Delphi

PART 5: ADDITIONAL CHECKLIST ITEMS

Signatures

Provide appropriate signatures including principal investigator(s) or chief medical officer

<table>
<thead>
<tr>
<th>Your previous rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

Provide appropriate signatures including principal investigator(s) or chief medical officer.

CTA no objection letter

Provide date of CTA no objection letter on title/cover page

<table>
<thead>
<tr>
<th>Your previous rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

Provide date of CTA no objection letter on title/cover page.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Co enrollment in studies</td>
<td>State regulations pertaining to co-enrolment of participants into other research studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Investigational product(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biological specimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Data collection forms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Validation of instrumentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trial Monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reporting of early stopping</td>
</tr>
<tr>
<td>11</td>
<td>Ancillary and sub studies</td>
<td>Describe any, foreseen further uses of personal data or biological materials for related sub studies or ancillary studies and if neither consent was obtained for these studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post trial care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post trial data/materials storage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feasibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insurance</td>
</tr>
</tbody>
</table>

**Survey ID = ___**

**Survey ID = ___**
Survey ID: _

Data ownership

State who has ownership of data and disclose any agreement or contract with sponsor that limits principal investigators ownership of data

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ No judgment

Not important Very important

Comments

Additional Items

Some concepts were suggested which we have not included as new items as we see them as being covered in existing concepts. With changes in the initial iterations we anticipate that we can address some of these points. We encourage you to let us know if you agree or disagree with these comments.

<table>
<thead>
<tr>
<th>Comment</th>
<th>Notes from Moderator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often good to provide trial acronym if available</td>
<td>Is included in existing item “Trial identifier (i.e. trial name)“</td>
</tr>
<tr>
<td>Clinical question Provide a clear presentation of the clinical questions to be answered</td>
<td>Covered in “Objectives“</td>
</tr>
<tr>
<td>Describe if this is an efficacy trial or a pragmatic trial</td>
<td>Can be covered in “General Approach“ or “Type of Study“</td>
</tr>
<tr>
<td>If possible give tel nos/contact details for randomisation service</td>
<td>Could be included in existing item (e.g. one of the items detailing randomisation methods)</td>
</tr>
<tr>
<td>Need guidance on termination of patient from trial i.e. for safety concerns, not just direction for stoppage of the trial itself.</td>
<td>This topic could be covered by adding (e.g. compliance requirements, safety concerns) to “Withdrawals“</td>
</tr>
<tr>
<td>Need information about the data collector or assessor (number, training)</td>
<td>Is included in existing item “Quality Control“</td>
</tr>
<tr>
<td>Describe how the protocol is kept under review and kept up-to-date</td>
<td>Covered in “Protocol Amendments“</td>
</tr>
<tr>
<td>There should be an item about how patients will be considered for inclusion in trial to avoid “assembly“ bias. Although it is often scheduled to enrol consecutive patients it is not always done so in busy clinics and practice. There should be a description about how all eligible patients were proposed to participate or not</td>
<td>This topic could be more clearly covered in item “Recruitment“</td>
</tr>
<tr>
<td>Risk assessment</td>
<td>Risk assessment may be covered in a number of items including “Risks“ “Potential Benefits and Risks“</td>
</tr>
<tr>
<td>Separate question to ask whether we wish to see the REB following amendments</td>
<td>This would likely fall under general REB approval if amendments are made they are generally associated with the original REB approval and can be tracked</td>
</tr>
</tbody>
</table>

Thank you for taking the time to complete Round Two! Your expertise is very important to this initiative and we are grateful for your participation as a panelist!

Page 25 of 25
9.2.3 Round 3

Survey ID # __________

The SPIRIT Initiative Delphi – Round Three

Welcome to Round Three – This is the final round of the SPIRIT Initiative Delphi.

We would like to take this opportunity to thank you once again for your participation in this Delphi survey aimed at developing a new checklist of essential items to be included in protocols of parallel-group randomized trials.

We received 76 responses to Round Two and we thank you again for your thoughtful comments.

The third round of this Delphi survey contains five parts:

Part 1: Items rated of high importance (included) median ≥ 9
Part 2: Items rated of very importance (excluded) median < 9
Part 3: Items introduced in Round Two
Part 4: Items rated of moderate importance
Part 5: Included items requiring additional feedback

Parts 1 and 2 are for your information only; you do not need to comment on the importance of these items.

To make your selections electronically, click on your selection with your cursor.

Change your rating by unselecting your previous rating and clicking on your new choice.

You are not able to modify the text here, however, spaces are provided where you may add free text comments or suggest reiterations.

Alternatively, you may print your form and return it by facsimile. In this case, please mark your selections with an X.

We estimate Round Three will require approximately 25 minutes to complete. If you experience any difficulties with the form in relation to the format or design, please let me know. Your responses will be summarized with group responses and will be considered in forthcoming development stages of this checklist.

We thank you very much for your time and ask that you please complete and return the form by Friday, November 30, 2007, either electronically by email to jietzlaff@cheo.on.ca or by fax (+1 613 735-4800) to Jennifer Tetzlaff.

Thank you again for your contribution to this initiative.

We look forward to your responses to this final round.

---

PART 1: DRAFT ONE OF PROPOSED CHECKLIST AND RATINGS

<table>
<thead>
<tr>
<th>Section and Topic</th>
<th>Description</th>
<th>Round 1</th>
<th>Round 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>Provide a descriptive title (e.g., population, intervention, main outcome)</td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
</tr>
<tr>
<td><strong>Trial identifier</strong></td>
<td>Unique trial identification number or name (e.g., trial registration number, protocol number) and where registered (e.g., name of trial register)</td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
</tr>
<tr>
<td><strong>Protocol Version</strong></td>
<td>Include a version or amendment number and date</td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
</tr>
<tr>
<td><strong>Protocol Summary</strong></td>
<td>Provide a short summary of the proposed research. Where required include appropriate lay, non-technical language</td>
<td>9 (7-10)</td>
<td>9 (7-10)</td>
</tr>
<tr>
<td><strong>Names and addresses</strong></td>
<td>Provide names and addresses of the primary investigators and sponsors</td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
</tr>
<tr>
<td><strong>Table of contents</strong></td>
<td>Provide a list of the contents of the protocol and associated page numbers</td>
<td>8 (6-10)</td>
<td>8 (6-10)</td>
</tr>
</tbody>
</table>

**Section 2: Introduction**

**Rationale**
Outline the research topic and provide justification for undertaking the study.

**Background of the study**
Summarize previous studies on the topic including unpublished studies known to the investigators and sponsors and animal studies or other preclinical data where relevant. Identify a relevant up to date systematic review should be referenced or reported supporting the need for the current trial (e.g., clinical equipoise).

**Preliminary data**
Describe any results of preliminary studies already obtained in the area of the proposed study (e.g., 3 or 4 investigations).

**Objectives**
State the specific objectives and hypotheses of the study.

**Study location(s)**
Describe, describe, and justify, the sites where the research will be conducted, including relevant demographic and epidemiological information about the country or region concerned.
<table>
<thead>
<tr>
<th>Section and Topic</th>
<th>Description</th>
<th>Round 1 Median (IQR)</th>
<th>Round 2 Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Section 3 Methods</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Describe the target and study population and the source (e.g., catchment area) of the study population</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>Eligibility criteria*</td>
<td>Describe the criteria for inclusion and exclusion of potential participants and justification for the exclusion of any subgroup</td>
<td>10 (10, 10)</td>
<td>10 (10, 10)</td>
</tr>
<tr>
<td>Sample size</td>
<td>The estimated number of research participants needed to achieve the study objective and how this was determined including any assumptions and calculations used</td>
<td>10 (10, 10)</td>
<td>10 (10, 10)</td>
</tr>
<tr>
<td>Recruitment</td>
<td>Describe the process of recruitment (e.g., advertisements, physician contacts) and enrolment</td>
<td>9 (9, 10)</td>
<td>9 (9, 10)</td>
</tr>
<tr>
<td>Type of study</td>
<td>A description of the type/design of trial to be conducted (e.g., double blind, placebo-controlled, parallel design) and trial framework (e.g., exploratory, superiority, equivalence, non-inferiority)</td>
<td>10 (10, 10)</td>
<td>10 (10, 10)</td>
</tr>
<tr>
<td>Study timeline*</td>
<td>Schematic diagram of study time-table and organizational chart including design procedures and stages of trial</td>
<td>9 (9, 10)</td>
<td>9 (9, 10)</td>
</tr>
<tr>
<td>Randomization Sequence generation</td>
<td>Describe the method to be used to generate the random sequence list including details of any restriction (e.g., blocking, stratification)</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>Randomization Allocation concealment</td>
<td>Describe the method used to implement the random allocation sequence (e.g., numbered containers or central telephone) clarifying whether the sequence will be concealed until interventions are assigned</td>
<td>10 (9, 10)</td>
<td>10 (10, 10)</td>
</tr>
<tr>
<td>Randomization Implementation</td>
<td>Describe who will generate the allocation sequence who will enroll participants and who will assign participants to their group</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>State whether or not participants administering the interventions and those assessing the outcomes will be aware of group assignment. If relevant, how the success of blinding will be assessed</td>
<td>10 (9, 10)</td>
<td>10 (10, 10)</td>
</tr>
<tr>
<td>Interventions*</td>
<td>Provide precise details of the interventions intended for each group how they will be administered (e.g., dosage and dosage form device) where applicable. Justify the control interventions used (e.g., no treatment placebo or active control)</td>
<td>10 (10, 10)</td>
<td>10 (10, 10)</td>
</tr>
<tr>
<td>Schedule(s) of Intervention(s)</td>
<td>State the number and duration of treatment periods including run in and washouts where applicable</td>
<td>10 (9, 10)</td>
<td>10 (10, 10)</td>
</tr>
<tr>
<td>Concurrent interventions</td>
<td>List relevant treatments/intervention(s) that are permitted or not prior to and/or during the study</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
</tr>
<tr>
<td>Risks To become Harms</td>
<td>State the known or potential risks and adverse reactions for each study intervention</td>
<td>10 (10, 10)</td>
<td>10 (10, 10)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Describe and define primary and secondary outcome measures</td>
<td>10 (10, 10)</td>
<td>10 (10, 10)</td>
</tr>
</tbody>
</table>
### Section 4: Trial organization and administration

<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
<th>Round 1</th>
<th>Round 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monetary and material support*</td>
<td>Name the source(s) of financial and material support type of support provided: amount and how (e.g. to a research account or as an honorarium)</td>
<td>9 (7 10)</td>
<td>9 (7 10)</td>
</tr>
</tbody>
</table>

### Section 5: Ethical considerations

<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
<th>Round 1</th>
<th>Round 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential benefits and risks</td>
<td>The potential benefits and risks of the research to study participants and to society</td>
<td>10 (9 10)</td>
<td>10 (9 10)</td>
</tr>
<tr>
<td>Agreement and consent</td>
<td>Describe the method to obtain individual informed consent information provided to the patient and the name and position of the person responsible for obtaining consent. Provide a copy of the consent form and patient information sheet.</td>
<td>10 (9 10)</td>
<td>10 (9 10)</td>
</tr>
<tr>
<td>Surrogate Consent or Assent</td>
<td>If a prospective participant is not capable of informed consent, provide information on how permission will be obtained from an authorized individual. In the case of individuals below legal consenting age, provide information on how access and permission from a legal guardian or other authorized individual will be obtained.</td>
<td>10 (9 10)</td>
<td>10 (9 10)</td>
</tr>
<tr>
<td>Confidentiality and Anonymity</td>
<td>The provisions for protecting the confidentiality and anonymity of personal data and respecting the privacy of participants</td>
<td>10 (8 10)</td>
<td>10 (8 10)</td>
</tr>
<tr>
<td>Ethics approval</td>
<td>State whether ethics approval has been obtained or provide the name of the committee(s)</td>
<td>10 (9 10)</td>
<td>10 (8 10)</td>
</tr>
<tr>
<td>Role of Sponsor</td>
<td>Describe the role of the sponsor in the trial design data collection access to trial data (including interim data audits and regulatory inspections), data analysis, and manuscript preparation.</td>
<td>10 (8 10)</td>
<td>10 (8 10)</td>
</tr>
<tr>
<td>Conflict of Interest</td>
<td>Disclose financial or other real or perceived conflicts of interest.</td>
<td>10 (9 10)</td>
<td>10 (8 10)</td>
</tr>
</tbody>
</table>

### Section 6: Reporting and Dissemination

<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
<th>Round 1</th>
<th>Round 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Amendments</td>
<td>Describe how changes to the original protocol including the statistical plan will be communicated to investigators and ethics committees and how these will be reported and justified in subsequent amendments of the protocol and/or the final report as appropriate</td>
<td>9 (7 10)</td>
<td>9 (7 10)</td>
</tr>
<tr>
<td>Dissemination</td>
<td>Describe how the researcher(s) or sponsor(s) will disseminate the results to participants, health care professionals, the public, or other relevant groups</td>
<td>8 (7 10)</td>
<td>9 (7 10)</td>
</tr>
<tr>
<td>Publication Policy</td>
<td>Details on who has the right to publish the study results or modify the manuscript (i.e., principle investigator(s) co-investigator(s) sponsor) including publication restrictions and authorship guidelines</td>
<td>9 (8 10)</td>
<td>9 (7 10)</td>
</tr>
<tr>
<td>References</td>
<td>Provide a list of the references cited in the protocol</td>
<td>10 (9 10)</td>
<td>10 (9 10)</td>
</tr>
<tr>
<td>Appendix Materials</td>
<td>Provide relevant materials including samples of the standardized data collection forms (e.g., questionnaires) and consent/assent forms</td>
<td>9 (7 10)</td>
<td>5 (7 10)</td>
</tr>
</tbody>
</table>

---

**Legend**

- **M** = Median
- **25%-75% = Inter-quartile range
- **Max = Maximum**
- **Min = Minimum**
- **Median (IQR) = Median and Interquartile Range**

**Data ownership:** State who has ownership of data and disclose any agreement or contract with sponsor that limits principal investigators or ownership of data.

**Previous comments:**
- This may be the only opportunity to specify this info.
- BELONGS OUTSIDE THE PROTOCOL (A) Clinical trial contract issue (B) Ethical issue (C) Conflict of Interest (D) Other (specify item 56 or 57) (E) A score of 8 indicates the item is important and must be included in the final guidelines; 4 indicates the item is unimportant (i.e., should be dropped as an item). The legend is presented below.
- **Please note that if during this round items with a median of 5 will be considered included in the first draft of the SPIRIT Checklist and items with a median of 3 will be considered excluded from the Checklist.**

---

**PART 2: ITEMS EXCLUDED AFTER ROUND 2**

- **Budget:** Provide the budget for personnel, equipment, facilities and supplies.

**Subgroup (Round 2):**

- Health care worker local trial site coordinator (7)
- Statistician/Methodologist (27)
- Ethics board member (10)
- Funding agency representative (C)
- Regulator (3)
- Journal editor (3)

**PART 3: ITEMS INTRODUCED IN ROUND TWO**

- This section contains the 15 items that were newly introduced in Round Two. These items have been ordered by median ratings from Round Two.
- All comments have been anonymized and summarized all major content has been retained. Unless otherwise indicated by a number in parentheses, comments were made by one panelist.
- To respond, please read the comments provided by panelists and select your new rating for each item on a scale of 1-10. A score of 10 indicates you feel the item is very important and must be included in final guidelines; a score of 1 indicates the item is unimportant (i.e., should be dropped as an item). The legend is presented below.
- If you feel a concept should be included but as part of an existing item, please indicate this as a comment.

**Please note that if during this round items with a median of 8 will be considered included in the first draft of the SPIRIT Checklist and items with a median of 6 will be considered excluded from the Checklist.**

**Your rating from Round One**

**Item specific comments**

**Frequency distribution of previous ratings**
Data ownership (continued)
• This is a matter for the contract. However, perhaps there should be some discussion of what is done with the data at the end of the study. This is becoming an issue with genetics research – e.g., the banking of study specimens/data for future research.
• This should be in a separate document.

Survey ID: ___

Pregnancy

For research on pregnant women, specify plans for monitoring the health of the woman and the short- and long-term health of the child.

Previous comments:
• Not clear why pregnant women have been selected out in this way.
• All our research is on pregnant women. We are looking at non-pharmaceutical interventions. The trial is not responsible for monitoring the health of the mother or baby. This is the responsibility of the caregiver that the woman has.
• Could include under “Follow-up” if the study included pregnant women (3). Could highlight that this may involve more people and require plans for both (1).
• Depends entirely on specific trial. We don’t in general commit to monitoring long-term health of participants why specifically for pregnant women?
• I would expand this somewhat, for research not only on pregnant women, but research that by happenstance includes some pregnant women.
• Important. Another issue to address at another time, with different objectives.
• Included in regular methods section in my opinion. Separate section not needed (1). In studies in pregnant women this would be covered in the sections on efficacy and safety measurements (1).
• Item is too specific (3). Little research is done on pregnant women (1).
• Included in the safety section if the monitoring is considered additional to the care study monitoring (i.e., if being conducted for safety concerns).
• Important. Another issue to address at another time, with different objectives.
• Important. Another issue to address at another time, with different objectives.
• Important. Another issue to address at another time, with different objectives.

Survey ID: ___

Validation of instrumentation

Describe reliability and validity of instruments to be used, including questionnaires, laboratory instruments, and analytical tests. If known, plans to establish such validation.

Previous comments:
• Part of background.
• Already covered Data Collection (former Item 29).
• An investigative meeting/site visitation issue not in the protocol.
• Brief description is fine. Details not necessary in protocol (2).
• With appropriate references. Citations to confirm validity (2).
• Covered in Outcomes (former Item 28) (2).
• Depends on type of study.
• Important for publication not protocol.
• See earlier item dealing with this.
• Should be in Appendix Materials.
• This is a last resort – may not be in protocol. It should be somewhere but I would prefer it in a separate document.
• This is not necessary in the protocol if it is required in the grant application.
• This should only be necessary for non-standard instruments/questionnaires.

Survey ID: ___

Biological specimens

If relevant, describe plans for laboratory evaluation, specimen collection, storage, and shipping to central laboratories.
Survey ID = ___

**Trial Monitoring**
Describe the plans for trial monitoring (e.g., a Clinical Research Associate) including if the monitoring process was independent from the principal investigator and sponsor and how often trial sites will be monitored.

**Previous comments:**
- Covered by Quality control (former item 32) (2)
- Agreed this seems to mix a few different aspects of monitoring I am less interested in how often a site will be monitored but I am interested in the independence (2)
- Already covered (3)
- High level (3) indicate that a process exists (1) details elsewhere (2) not detailed plan as this is subject to change (1)
- Explain what is meant by monitoring (2) The terminology trial monitoring can be confused with other monitoring functions (3)
- What about Monitoring for Management? One the elements of this monitoring should be in the protocol (1)
- I think this point is useful (2)
- Important but belongs elsewhere (4) e.g., Manual of operations (2)
- Is that relating to monitoring by DBAHP? (1) Short overview only - similar to DSMB (1)
- Not applicable to all trials (2)
- This will have an impact on the budget and personnel resources

**Comments:**

**Post-trial care:**
State plans for post trial follow up and access to investigational treatment if relevant, specifying the means of implementing the duration of care and the individual or organization responsible for financing, supporting this care.

**Previous comments:**
- Agree that this could be a separate item from “Follow-up” within the trial (3)
- Better to have a single item on follow-up and access to treatment (3)
- If applicable you could mention it but not useful for pilot or proof-of-concept studies since you do not know if the trial will be followed by a larger study (7)
- Important if relevant (2)
- Important: do not have to be stated in the protocol (2)
- Important but controversial (2) See heated discussions about Declaration of Helsinki statement (2) about this (I am not sure it should be in the Protocol)
- Long-term follow-up (if necessary) should be incorporated into the specifics of the study (i.e., interventions or data collection or outcomes) if it is considered an integral part of the study (1) If you are referring to follow-up determined necessary post-trial, this would be very difficult to fully articulate in the pre-study (i.e., during the protocol development phase) (5)
- This is greatly for the REB submission (3) in the scientific protocol I think a general remark on the duration of ethical obligations to end of trial or beyond and extend side effects or all care is enough (1)
- Not always pertinent (2) should be mandatory (1)
- The protocol requires concise statements (3)
- This is very important - under what conditions will the participants rollover into active treatment? How will they be followed? When will they be unblinded?

**Comments:**

**Data collection forms**
Provide a summary table (e.g., matrix) of all forms to be collected at each time point.

**Previous comments:**
- Depends on study (2) not sure it needs to be mandatory (1)
- Can be very difficult to get an overview of the trial without this
- Could be helpful/useful but need not be in the protocol (3)

**Survey ID = ___**  

**Data collection forms (continued):**
- Covered earlier in Study timeline (3)
- For the scientific protocol I think it is reasonable that not all of these forms are fully prepared and that several of the forms could be simply given headings with explanation - instrument not yet selected (4)
- General details (2)
- Gives sample and sample to patient acceptance (3)
- Perhaps I misunderstand this item: but including Case Report Form is quite critical this is where the "rubber hits the road" where it comes operationalization of actual data collection - missing data etc. That is this is a source document for most trials
- Useful but perhaps subject to change (2) would require protocol amendments (1)
- Yes to make sure that certain data does not go missing (4)

**Previous comments:**
- Brief not possible but more details should be in the contract as this will depend on regulatory requirements e.g., Health Canada mandates 25 years but this is not universal and costs (sites must now budget for this in their contracts)
- Covered off in follow up (former item 50)
- Does not have to be stated in the protocol (3)
- Important for manual of operations and protocol (2)
- Funder/sponsor may have specified requirements (1)
- I would put this as part of the emergency questions about samples of biological materials (1)
- Is it ethical issues?
- It seems to me that there is no need to report in the scientific protocol on the storage requirements beyond those needed for the analyses and outcomes listed in the protocol itself. This seems to refer to long-term storage with no hypothesis in mind. While I think this is generally a good idea I don't think it belongs in the scientific protocol but perhaps could be included in the REB submission (4)
- Since trial reports are generally not reliable it is important to know where the raw data are kept and where the raw data are kept - an important part of the protocol (3)
- This does not necessarily belong in protocol but is needed in sponsor SOP with awareness of investigator sites
- Vital to a protocol not in a publication

**Comments:**

**Investigational products**
If relevant describe the formulation, packaging, labeling and supply of the investigational product and accountability procedures.

**Previous comments:**
- A detailed and thorough protocol eliminates the need for an Ops Manual - however if the info in this section is really detailed and long general information could go in the protocol (1) detailed info / procedures could be outlined in a pharmacy manual that accompanies the protocol (3)
- Accountability procedure "yes" All other "no"
- The separate issues here important but belongs elsewhere
- Should be included with item interventions (3)
- For regulatory inspection (3)
- High level brief (2)
- Important for success of blinding (2)

Page 9 of 16

154
In investigational product(s) continued

• Important if relevant but could also be specified elsewhere (other than the protocol)
• Important in a protocol but not in a publication – especially
• This is needed for GCP /regulatory compliance

Your previous rating

\[\begin{array}{cccccccc}
\text{No important} & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & \text{No judgment}
\end{array}\]

Comments

Co-enrolment in studies

• Co-enrolment in studies State regulations pertaining to co-enrolment of participants into other research studies

Previous comments

• May vary across sites (2)
• May change with time (1)
• May have implications for recruitment (1) may shed light on feasibility of recruitment e.g. oncology trials (1)
• It is important to note if participants are in more than one study and have good cross-referencing
• Change regulations to restrictions?
• I didn’t know there were any such regulations
• This may exclude participants so it needs to be included
• This is becoming an increasing issue so specify this up front would be helpful
• There is ongoing research into this area Not clear if it can be fully described in the protocol itself
• This is needed for GCP / regulatory compliance
• Important in a protocol but not in a publication – especially
• Important if relevant but claims of acceptability and recruitment are always vastly overstated
• Important but not sure this needs a separate section (4)
• Substudies should have a separate protocol and receipt of consent should never be in the protocol
• Important but this is a site selection issue and should not be in the protocol
• Important but not sure this needs a separate section
• Important but other issue

Your previous rating

\[\begin{array}{cccccccc}
\text{No important} & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & \text{No judgment}
\end{array}\]

Signatures

Provide appropriate signatures including principal investigator(s) and chief medical officer

Previous comments

• Important but not sure this needs a separate section (4) can be covered within sample size (2) setting (1) agreement and consent (1) ethics approval (1)
• This is a site selection issue and should not be in the protocol
• Important for the funding body (1) but must not belong in the protocol (3)
• Important to achieve feasibility (1) run or registered (1)
• Important but not sure this needs a separate section
• Important but claims of acceptability and recruitment are always vastly overstated
• Important but claims of acceptability and recruitment are always vastly overstated

Your previous rating

\[\begin{array}{cccccccc}
\text{No important} & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & \text{No judgment}
\end{array}\]
Insurance
Details of plans including insurance coverage to provide treatment (including the funding of treatment) and compensation for research-related disability or death.

Previous comments
- Essential to inform the ethics committee and participants of this but not the right issue for a reporting guideline
- You may want to add liability insurance for the investigators but that may be included in their contracts
- Belongs somewhere other than the protocol (4) Contract issue (1) included in a good consent form (3)
- High level
- In some countries trials in patients without medical coverages are forbidden
- May be covered by regulation and governance frameworks
- Not applicable to all trials (1) don't think
- Not relevant in every country
- Role of ethics committee
- Vital to a protocol not a publication
- Statements are required in protocol and consent
- This in a clinical trial contract issue should not be in the protocol only the consent form (e.g., then only in the appendices since the consent template should be included in the appendices)
- Where appropriate this is moving into ethics territory and I am not sure that this issue should be dealt with in such detail in the scientific protocol but should of course be dealt with in enormous detail in the REB submission.

PART 4: ITEMS RATED OF MODERATE IMPORTANCE

This section contains 4 items which were rated of moderate importance (6 > median < 7) in Round Two.

Please state whether you think these concepts should be included or excluded from this draft guideline.

Comments

PART 5: ITEMS REQUIRING FURTHER FEEDBACK

Comments suggested that the components of some items were of differing importance. We have tried to separate the major concepts for these items.

Please select whether you believe the following concepts should be included as items (or part of items) in a guideline for reporting protocols of parallel group design randomized controlled trials:

Protocol summary
Provide a short summary of the proposed research. Where required include appropriate lay/non-technical language:

- Include
- Exclude
- Unsure

Comments

Study location(s)
Briefly describe and justify the sites where the research is to be conducted, including relevant demographic and epidemiological information about the country or region concerned:

- Include
- Exclude
- Unsure

Comments
**Eligibility criteria**

Describe the criteria for inclusion and exclusion of potential participants and justify the exclusion of any subgroup.

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

Justify the exclusion of any subgroup.

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

**Study timeline**

Schematic diagram of study time table and organizational chart including design procedures and stages of trial.

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

Schematic diagram of schedule of procedures and visits for participants through each stage of the trial.

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

Schematic diagram of the study timeline specifying dates at which stages of the study are expected to be completed.

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

**Interventions**

Provide precise details of the interventions intended for each group for how they will be administered (e.g., dosage and dosage form device) where applicable and the control interventions used (e.g., no treatment, placebo or active control).

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

Justify the control interventions used (e.g., no treatment, placebo or active control).

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

**Withdrawals**

State criteria that will be used to withdraw or exclude participants from the trial (e.g., compliance requirements) and specify the data to be collected from withdrawn participants and how enrolled participants will be followed up in a multi-centre study when a centre may be discontinued from the trial.

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

Specific the data to be collected from withdrawn participants and how enrolled participants will be followed up.

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

In a multi-centre study, state when a centre may be discontinued from the trial.

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

**Monetary and material support**

Name the source(s) of financial and material support, type of support provided, amount and how (e.g., to a research account or as an honorarium).

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

List the type(s) of support provided.

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

State the amount of support provided.

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

State how sources of support are provided (e.g., to a research account or as an honorarium).

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

**Stopping guidelines**

State the criteria for the premature termination of the trial.

If relevant, state the predefined statistical stopping boundaries for the early termination of the trial.

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

If relevant, state any non-statistical predefined criteria for the early termination of the trial.

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
<th>Unsure</th>
</tr>
</thead>
</table>

**Comments**

Additional comments
9.3 Appendix C: SPIRIT Delphi Panellists

Peter Aaby, Guinea-Bissau
Edgardo Abalos, Argentina
Douglas Altman, UK
Pierre Amarenco, France
Richard E Ashcroft, UK
Virginia Barbour, UK
Elinor Ben-Menachem, Sweden
Jesse Berlin, USA
Bernard Burnand, Switzerland
Ian Cameron, Australia
Marion K Campbell, UK
An-Wen Chan, Canada
Erin Cherban, Canada
Stephen Choi, Canada
Mike J Clarke, UK
Jean-Paul Collet, Canada
Deborah Cook, Canada
Dominique Costagliola, France
Janet Darbyshire, UK
Anthony M Dart, Australia
Barry Davis, USA
Kay Dickersn, USA
Dennis Dixon, USA
Ben Djulbegovic, USA
Caroline Dore, UK (MRC)
Leila Duley, UK
Don Easton, USA
Diana Elbourne, UK
Dean Fergusson, Canada
Curt Furberg
Carole Gentile, Canada
Davina Gherzi, Switzerland
Kathleen Glass, Canada (University)
Christian Gluud, Denmark
Michael Goodyear, Canada
Peter Gotzsche, Denmark
Trish Groves, UK
Metin Gulmezoglu, Switzerland
Robert Hart, USA
Paul Hebert, Canada
Lynda Hoey, Canada
Sally Hopewell, UK
Asbjørn Hrøbjartsson, Denmark
Mirjana Huc, Croatia
Clay Johnston, USA
Susan Kahn, Canada
Michael Kramer, Canada

Deborah Kraus, Canada
Karmela Krleža-Jerčić, Canada (CIHR)
Andreas Laupacis, Canada
Robert J Levine, USA
Anne Lindblad, USA
Klaus Linde, Germany
Carl Lombard, South Africa
Pisake Lumbiganon, Thailand
Howard Mann, USA
Ellen McDonald, Canada
Alison McDonald, UK
Hans Melander, Sweden
Ralph Meyer, Canada
Luciano Mignini, Argentina
Franklin G Miller, USA
David Moher, Canada
Victor Montori, USA
Ian Needleman, UK
Kevin O’Brien, UK
Wendy Parulekar, Canada
Lesly Pearce, USA
Amy Plint, Canada
Philippe Ravaud, France
Drummond Rennie, USA
Morven Roberts, UK
Paula Rochon, Canada
Frank Rockhold, USA
Igna Rossion, Germany
Dave Sackett, Canada
Raphael Saginur, Canada
Christopher H Schmid, USA
Ken Schulz, USA
Christoph Seiler, Germany
Stan Shapiro, Canada
Joel Singer, Canada
Orla Smith, Canada
Hal Sox, USA
Shyam Sundar, India
Marc Taylor, UK
Robert Temple, USA
Norma Terrin, USA
Juan Carlos, Cuba
Juie Weston, Canada
Janet Wittes, USA
Taixiang Wu, China
Merrick Zwarenstein, Canada

Notes
1 Responses were based on panellists’ personal views and do not necessarily represent the views of
their employers or other organizations to which they are affiliated
2 Two panellists preferred not to be acknowledged
9.4 Appendix D: Delphi Survey Frequency Distributions

1. Title
2. Trial identifier
3. Protocol version
4. Protocol summary
5. Names and addresses
6. Table of contents
7. List of abbreviations
8. Rationale
9. Background of study
10. Preliminary data
11. Objectives
12. General approach
13. Study locations
14. Population
15. Eligibility criteria
16. Sample size
17. Recruitment
18. Type of study
19. Study timeline

20. Sequence generation

21. Allocation concealment

22. Implementation

23. Blinding (masking)

24. Interventions

25. Schedule of interventions

26. Concomitant interventions

27. Risks (Harms)

28. Outcomes

29. Data collection

30. Follow-up

31. Data management

32. Quality control

33. Compliance

34. Safety Evaluations

35. Statistical methods

36. Withdrawals*
9.5 Appendix E: Systematic Review MEDLINE Search Strategy

| 1 | exp epidemiologic studies/ | 30 | Quality Assurance, Health Care/ |
| 2 | clinical trials/ | 31 | Patient Compliance/ |
| 3 | controlled clinical trials/ | 32 | Patient Dropouts/ |
| 4 | randomized controlled trials/ | 33 | withdrawals tw |
| 5 | sampling studies/ | 34 | Quality Control/ |
| 6 | (comparative study or evaluation studies or meta analysis) pt | 35 | Publishing/ |
| 7 | or/1-6 | 36 | Authorship/ |
| 8 | research design/ | 37 | Writing/ |
| 9 | Randomized Controlled Trials/es, st [Ethics, Standards] | 38 | Adverse Drug Reaction Reporting Systems/ |
| 10 | Clinical Trials/st, es [Standards, Ethics] | 39 | exp Patient rights/ |
| 11 | Controlled Clinical Trials/st, es [Standards, Ethics] | 40 | exp informed consent/ |
| 12 | Clinical Protocols/st, mt [Standards, Methods] | 41 | exp Ethics/ |
| 13 | or/8 12 | 42 | Health Resources/ |
| 14 | patient selection/ | 43 | Budgets/ |
| 15 | exp bias epidemiology/ | 44 | Epidemiologic Factors/ |
| 16 | Research Subjects/ | 45 | Research Support/ |
| 17 | Research Personnel/ | 46 | Registries/ |
| 18 | statistics/ | 47 | drug labelling/ |
| 19 | risk/ | 48 | dosage forms/ |
| 20 | risk assessment/ | 49 | drug packaging/ |
| 21 | Data Interpretation, Statistical/ | 50 | drug storage/ |
| 22 | models, statistical/ | 51 | Records/ |
| 23 | "Probability"/ | 52 | Medical Records/ |
| 24 | treatment outcome/ | 53 | Disclosure/ |
| 25 | (protocol adj2 amendment$) tw | 54 | Truth Disclosure/ |
| 26 | guidelines/ | 55 | Confidentiality/ |
| 27 | "codes of ethics"/ | 56 | Scientific misconduct/ |
| 28 | exp Epidemiologic Research Design/ | 57 | Fraud/ |
| 29 | Product Labeling/ | 58 | or/14-57 |
| 30 | Quality Assurance, Health Care/ | 59 | (protocol$ or proposal$ or trial$ or medical research or biomedical research) ti,ab |
| 31 | Patient Compliance/ | 60 | (editorial or news or comment) pt |
| 32 | Patient Dropouts/ | 61 | (7 and 13 and 58 and 59) not 60 |

Notes: MEDLINE (Ovid interface) search run 09/08/07. MEDLINE indexing changed in 2008 substituting for new terms not included above. Based on new indexing, strategy would require modification for future updates. Updated strategy available from the author.
### 9.6 Appendix F: SPIRIT Systematic Review Screening Questions and Elaboration

Note: data were extracted in Microsoft Excel 2003

All included studies must have a response “Yes” to questions 1-4 and “No” to question 5. Please reply “Don’t know” if information is not sufficient in the report or if this should be discussed. If you answer “No” to questions 1, 2, 3 or 4, stop responding to questions: the reference is now excluded.

**Question 1: TOPIC**

Is one of the primary objectives of this study **at least one of the following**?
- □ to examine the reporting of RCT protocols (e.g. methodological, organizational, ethical aspects)
- □ to examine methodological, organizational or ethical aspect(s) of RCTs (e.g. as described in protocols or other reports)
- □ to examine the association between the above and the final trial outcome

Note: The report may also be relevant to protocols of other study designs (i.e. mixed RCT and non-RCT).

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ]</td>
<td>No (exclude)</td>
</tr>
<tr>
<td>[ ]</td>
<td>Yes/Don't know – please answer question 2</td>
</tr>
</tbody>
</table>

**Elaboration:**
- Studies limited solely to examining the REPORTING in trial publications will be excluded.
- Association between trial characteristics and trial outcome need not be limited to efficacy or harms data. Trial outcome could also include measures of trial acceptability and feasibility (e.g. recruitment or retention rates) or other aspects suggesting an association between a characteristic and risk of bias in the trial.
- Reports must describe, but need not be limited to, studies examining protocols or trials of any type of RCT (e.g. parallel-group, cross-over trials, non-inferiority trials, cluster-randomized trials), of healthcare interventions. Research on non-randomized studies alone will not be considered.

**Question 2: RELEVANCE TO REPORTING PROTOCOLS**

Could this be of relevance for reporting protocols of RCTs (and is in the control of the investigators)?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ]</td>
<td>No (exclude)</td>
</tr>
<tr>
<td>[ ]</td>
<td>Yes/Don't know – please answer question 3</td>
</tr>
</tbody>
</table>

**Elaboration:**
- This requires judgment and consideration of the realm of possible items for a clinical trial protocol reporting guideline. This could include existing and other possible items. The clause “and is in the control of the investigators” requires that the topic being considered is in the investigator’s control at the time of protocol development (e.g. evidence of bias due to methodological considerations would be included while evidence that potential trial participants’ views affect recruitment would not).
Question 3: EMPIRICAL?

In this a primary report of an empirical study (i.e. an experimental or observational study which uses the scientific method [e.g. has an objective, methods and results] and is based on verifiable facts [i.e. is reproducible])?

[ ] No (exclude)
[ ] Yes/Don't know – please answer question 4

Question 4: DESIGN

Is the design of this empirical study one of the following: systematic review, cohort, case-control or cross-section of RCTs or studies including RCTs OR experimental 'primary' study (e.g. RCT or quasi-RCT) within the context of a trial?

[ ] No (exclude) - please state 'No - reason for exclusion' (e.g. simulation study, hypothetical trial, case study, observational study in one trial, survey (expert views))
[ ] Yes/Don't know – please answer question 5 - please state 'Yes - study design' (e.g. SR, cohort, case-control, RCT)

Elaboration:
- Cohorts, case-controls or cross-sectional studies of trials must be either a complete series of trials (e.g. all registered during a specified time period) or an unbiased sample (e.g. random sample) of trials. Studies including a limited number of trials without clearly indicating how they were chosen will be excluded.
- Surveys of trial investigators are excluded, although there may be some exceptions. The original grant proposal indicated that such studies might be eligible but they do not appear appropriate. If you see such examples, please flag them for discussion.
- Case reports, case series, simulation studies and hypothetical trials are excluded.

Question 5: OTHER EXCLUSION(S)

Is there any other reason to exclude this report (e.g. non-generalizable, such as a specific medical procedure, condition or laboratory test, other)? If so, please describe and exclude.

[ ] No (include if all others 'Yes') (if others 'don't know', need to discuss with other reviewer)
[ ] Yes (exclude) - please state 'Yes - reason for exclusion' (e.g. Language other than English/French, too specific, qualitative)

Elaboration:
- Quantitative data required. If limited to qualitative data study is not eligible for inclusion.
- For practical reasons, only studies published in English or French were eligible.
- Post-hoc additions:
  - If study examines RCTs AND non-RCTs, results for RCTs must either be reported separately or, if not reported separately must comprise at least 80% of the total number of included studies.
  - Limited to cohorts/cross-sections/SRs that include trials published/conducted in 1992 or later (i.e., exclude cohorts/SRs/cross-sections prior to 1992)
9.7 Appendix G: Examples of synthesis of Delphi survey and systematic review results

The following includes three examples of the synthesis process used in this review. The exemplar items were chosen to represent items recommended for inclusion (28.Outcomes), further discussion (65.Validation of Instrumentation) or exclusion (47.Budget) from the SPIRIT checklist.

Delphi

The results from the Delphi showed strong and support and clear consensus for ‘Outcomes’ (Median [IQR] = 10 [10, 10], moderate support for ‘Validation of instrumentation’ (8 [6, 9]) and weak/no support for ‘Budget’ (5 [2, 6]). Figure 6 includes response frequency distributions.

Figure 6: Examples of Delphi frequency distributions

Item-specific Delphi comments for these items supported the numerical ratings for *Outcomes* (comments were few and supportive), and *Budget* (comments indicated that panellists did not support item inclusion) (Figure 7). Comments for *Validation of instrumentation*, however, suggested that some panellists felt this was important but could be covered elsewhere, such as other documents or existing items (Figure 7).
### Outcomes: Describe and define primary and secondary outcome measures

- The sequence (and necessary link) between "Outcomes", "Outcome definitions" and "Outcome assessment" could be strengthened (R1)
- The concept of "end-point" should be introduced (R1)
- and the time of measurement (R2)
- My personal bias is that this should score 151 (R2)

### Validation of instrumentation: Describe reliability and validity of instruments to be used, including questionnaires, laboratory instruments, and analytical tests, if known, or plans to establish such validation

- Part of background (R2)
  - Agree (R3)
  - Already covered "Data Collection" (former Item 29) (R2)
    - Agree (R3)
    - Could go here, but I favour "Outcomes" (R3)
- An investigator meeting/site initiation issue, not in the protocol (R2)
- Brief description is fine, details not necessarily in protocol (2) (R2)
- With appropriate references/citations to confirm choice and empirical validity (added R3) (2) (R2)
- Covered in "Outcomes" (former Item 28) (2) (R2)
  - Agree (R3)
  - Agree, but is clearly important to justify inclusion of an item. If the item has not previously been validated in the population being studied, that should be stated. If the goal of including the item is to evaluate it for inclusion in subsequent studies, possibly after further validation, then that should be stated (R3)
  - Details belong in appendix. Summary of validity/reliability belong in description of outcome measures (R3)
  - Agree but it is good to reinforce the item when the outcome has to be assessed with a scale (R3)
- Depends on the type of study (R2)
- Important for publication not protocol (R2)
- See earlier item dealing with this (R2)
  - Agree but it is good to reinforce the item when the outcome has to be assessed with a scale (R3)
- Called in other sections and so on

### Budget: Provide the budget for personnel, equipment, facilities and supplies

- Important but does not need to be explicit in the protocol, budget should be in a separate document (10) (R1)
  - Agree (R3)
  - Important but I don’t think needs to be included in a protocol but rather in the grant submission (4) (R1)
  - Agree (R2)
- Should not be in the protocol. Any changes in these items will necessitate protocol amendments (2) (R1)
  - Not part of protocol, will change over time (3) (R2)
- Funding may not be known at the time of writing the protocol. Budget is internal to the institution conducting the trial (R1)
  - Agree (R2)
- I doubt that people would be forthcoming in terms of budget (R1)
  - Should be in Appendix Materials (R1)
  - Agree (R2)
- Not sure if this should be public (2) (R1)
  - A conflict of interest issue (R2)
  - Agree (R2)
  - and so on

---

**Figure 7:** Examples of item-specific Delphi comments

Note: R1 = comment from Round 1; R2 = comment from Round 2; R3 = comment from Round 3.

---

**Systematic review**

Data were extracted by study in Microsoft Excel. Each study was allocated to relevant candidate items and relevant data were extracted for each item. Each study may have maintained relevant data for multiple candidate items. Data for each item were then organized in Microsoft Word with a brief description of each contributing study and results relevant to that item. An example is shown for Outcomes (Table 17).

Twenty-nine main empirical studies (and included studies) informed the item Outcomes; 10 informed Validation of instrumentation and none informed Budget. The evidence based on the results of these included studies was considered to provide Strong, Strong and Weak/No support for inclusion of these items in the SPIRIT checklist.
Table 17: Example of item-specific systematic review data extraction table

**28. Outcomes:** Describe and define primary and secondary outcome measures.

<table>
<thead>
<tr>
<th>1. 874</th>
<th>1. Cross-sectional study (1994-2003) of RCTs (77) of primary prophylactic treatment for venous thromboembolism published in one of 60 major general medical or specialists high impact factor journals.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thabut et al. (2006)</td>
<td>1. A primary endpoint was defined in 62 reports (80.5%)</td>
</tr>
<tr>
<td>2. 8380</td>
<td>2. SR of RCTs (76) in orthopaedic trauma with 50 or fewer participants: assessment of relationship between power and type of outcome (continuous or dichotomous)</td>
</tr>
<tr>
<td>Bhandari et al. (2002)</td>
<td>2. Those studies that reported continuous outcomes had a significantly greater study power and twice as many studies that reported conventionally accepted study power (80% or more) than those studies reporting dichotomous outcomes (p=0.042 and 37% vs. 18.6%, respectively, p=0.04). Conclusion: When small sample sizes are expected, statistical power can be increased by choosing a continuous outcome variable.</td>
</tr>
<tr>
<td>3. 1614 (included in SR) Chan et al. (2004)</td>
<td>3. 42/48 trials (88%) with efficacy outcomes and 16/26 (62%) trials with harms outcomes had at least 1 unreported outcome. Most common reasons: lack of clinical importance or statistical significance. Incompletely reported efficacy and harm outcomes were found in 96% (46/48) and 81% (21/26) of the trials respectively. Primary outcomes were incompletely reported in 7 (16%) of 45 trials that defined such outcomes in their publications. The pooled odds ratio for bias across all trials was 2.7 (95% confidence interval 1.5–5.0) and 7.7 (0.5–111) for efficacy and harm outcomes respectively. (and on)</td>
</tr>
<tr>
<td>4. 2043 Quinones et al. (2003)</td>
<td>4. Criteria for measuring outcomes was not considered to be objective in 17 (5%) and partially objective in 107 (33%) of trials.</td>
</tr>
<tr>
<td>5. 2807 Balk et al. (2002)</td>
<td>5. Appropriate outcome studied (based on topic, study design, intervention) in 99% RCTs.</td>
</tr>
<tr>
<td>6. 3166 Kidwell et al. (2001)</td>
<td>6. Forty-seven percent of trials reported using at least 1 validated outcome measure, and this number increased from 0% of trials in the 1950s to 95% in the 1990s.</td>
</tr>
<tr>
<td>7. 1362 Chan and Altman (2005)</td>
<td>7. 519 trials with 553 publications and 10,557 outcomes were identified. Survey responders (response rate 69%) provided information on unreported outcomes but were often unreliable—for 32% of those who denied the existence of such outcomes there was evidence to the contrary in their publications. On average, over 20% of the outcomes measured in a parallel group trial were incompletely reported.</td>
</tr>
</tbody>
</table>

......and so on...
Synthesis of Delphi and systematic review

An overall recommendation based on the results above was then derived for the SPIRIT checklist.

Outcomes received strong support by both the Delphi results and empirical evidence (e.g., selective outcome reporting, effect of outcome definitions on treatment effect estimates) and had no outstanding issues as indicated by the Delphi comments. Based on this information, this item was recommended for inclusion in the SPIRIT checklist.

Validation of instrumentation received moderate support and conflicting comments from the Delphi. Some panellists felt this concept was not important for inclusion in a protocol but should be detailed elsewhere, while others felt it was important, but did not necessitate its own item as it overlapped with other concepts. The item received strong support from the systematic review (e.g., evidence that non-validated instruments can lead to biased treatment effect estimates). Based on this information, this concept was recommended for inclusion in the SPIRIT checklist but it was suggested that consideration be given to including it in an existing item.

Budget received weak/no support from both the Delphi and systematic review and had few comments lending support for its inclusion (with the exception of one panellist who stated ‘The secrecy suggested in the comments are not in the best interests of the patients and the society’). Based on this information (lack of evidence), this item was recommended for exclusion from the SPIRIT checklist.
## 9.8 Appendix H: Comparison of Recommendations with Select Prominent Guidelines

Table 18: Comparison of recommendations with select prominent guidelines

<table>
<thead>
<tr>
<th>SPIRIT Recommendation / Topic</th>
<th>CIOMS</th>
<th>CIHR</th>
<th>NHS</th>
<th>CDC</th>
<th>PRACTIHC</th>
<th>ICHE6</th>
<th>NIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Include</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Trial identifier</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol Version</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Protocol Summary A.</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Names and addresses</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Objectives</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Study location(s): A.</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Description of sites(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Eligibility criteria A.</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Describe criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility criteria B.</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Justify exclusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Recruitment</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Type of study</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Randomization: Sequence</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization: Allocation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>concealment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization: Implementation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Interventions A. Details of</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>the interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventions B. Justify the</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>control interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant interventions</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Outcomes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Data collection</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Follow-up</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Withdrawals A. Criteria for</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>withdrawal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Interim trial monitoring</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Stopping guidelines A.</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Predefined statistical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stopping guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stopping guidelines B.</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Predefined non-statistical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stopping guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

170
<table>
<thead>
<tr>
<th>SPIRIT Recommendation / Topic</th>
<th>CIOMS</th>
<th>CIHR</th>
<th>NHS</th>
<th>CDC</th>
<th>PRACTIHC</th>
<th>ICHE6</th>
<th>NIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monetary and material support A. Source(s) of financial and material support.</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Potential benefits and risks</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Agreement and consent</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Confidentiality and Anonymity</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ethics approval</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Role of sponsor</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Conflict of Interest</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Protocol Amendments</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dissemination</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Publication Policy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Appendix materials C. Consent/assent forms</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Include concept/further discussion

<p>| Risk/Harms | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Rationale | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Background of the study | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Preliminary data | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Study timeline: A. Schematic diagram of procedures and visits | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Schedule(s) of Intervention(s) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Validation of instrumentation | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Quality control | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Safety Evaluations | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Withdrawals B. Data from withdrawals | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Adverse event reporting | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Emergency code-breaking procedure | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Data ownership | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Surrogate consent or assent | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Data management | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Compliance | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Data and Safety Monitoring Board | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Monetary and material support B. Type(s) of support | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Trial monitoring | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Post-trial care | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| References | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Appendix materials A. Case-report forms | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |</p>
<table>
<thead>
<tr>
<th>SPIRIT Recommendation / Topic</th>
<th>CIOMS</th>
<th>CIHR</th>
<th>NHS</th>
<th>CDC</th>
<th>PRACTHC</th>
<th>ICHE6</th>
<th>NIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix materials B. Other data collection forms (e.g. questionnaires)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Exclude

- Protocol Summary B. Lay summary
- Table of contents
- List of abbreviations
- General approach
- Study location(s): B. Justification of sites(s)
- Study locations C. Relevant demographic and epidemiological information

Co-enrolment in studies

- Study timeline B: Schematic diagram of trial calendar dates
- Investigational product(s)
- Data collection forms
- Biological specimens
- Withdrawals C. Centre withdrawal
- Limitations
- Logistics
- Monetary and material support C. Amount of support
- Monetary and material support D. How support is provided
- Budget
- Signatures
- Post-trial data/materials storage
- Feasibility
- Insurance
- Ancillary and sub-studies
- Pregnancy
- Reporting of early stopping

√ = INCLUDED IN GUIDELINE; ~√ = VARIATION OR CLOSELY RELATED CONCEPT INCLUDED IN GUIDELINE

CDC: US Centers for Disease Control and Prevention; CIHR: Canadian Institutes of Health Research; CIOMS: Council for International Organizations of Medical Sciences’ International Ethical Guidelines for Biomedical Research Involving Human Subjects; ICH E6: International Conference on Harmonization Tripartite Guideline for Good Clinical Practice; NHS: Guideline prepared for the UK National Health Service’s University College of London; NIH: Guideline prepared for US National Institutes of Health