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

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Developing an evidence-based reporting guideline for randomized controlled trial protocols: The SPIRIT Initiative

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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

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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 (*S*tandard *P*rotocol *I*tems for *R*andom*I*zed *T*rials) 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.

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List of Abbreviations

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

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[1], such as during recruitment, interim analyses or early stopping[2], and at completion, such as during analysis[3-5] and preparation for publication[6]. For example, the absence of concealed patient allocation[7-9], lack of blinding/masking[9] and inappropriate randomization methods[10] 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[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[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[12] and analysis methods including planned subgroup analyses[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[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%)[11], allocation concealment (59-83%, depending on stringency of definition)[19], power calculations (27%)[12] and sponsor and investigators roles in aspects of trial conduct[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[21-26]. Whereas some research suggests that inadequate

reporting does not necessarily indicate poor trial conduct [27-30], 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 (*CON*solidated *S*tandards *O*f *R*eporting *T*rials) Statement[31], 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[32], pragmatic trials[33] and equivalence and non-inferiority trials[34]; for specific intervention types, such as non-pharmacologic treatments[35] and herbal interventions[36]; and for other types of RCT reports, such as abstracts[37]. Additionally, following the motivation for CONSORT, other independent initiatives have been developed[38; 39]. Some of the initiatives, such as CONSORT and STARD (*ST*Andards for the *R*eporting of *D*iagnostic accuracy studies)[40]) have been empirically shown to improve report quality[41; 42]. As in the case of CONSORT, some have also become endorsed by major editorial groups such as the International Committee of Medical Journal Editors[43], the World Association of Medical Editors, the Council of Science Editors[44] and editorial boards of major healthcare journals.

As a consequence of some of these initiatives, the EQUATOR (*E*nhancing the *QUA*lity and *T*ransparency *O*f health *R*esearch) Network[45], 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[38] and a systematic review of reporting guidelines for healthcare research publications[39] 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[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[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.

[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[47-76].

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[47]; 25/27 (93%) included at least authors' names or contact information.

Three guidelines pertained only to RCT protocols[55; 59; 76], 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])[50] and three journal articles[48; 70; 76]. Of these four, one[76] was RCT-specific. Methods described for guideline development included consensus meetings[50; 76], informal consensus procedures[48; 76], field testing/pilot testing[76] and soliciting feedback from a broader group (e.g. public/stakeholders)[50; 76]. 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[76]. One additional guideline author reported soliciting comments from the general public and indicated future plans to pilot test their tool[48].

The total number of countries represented by members contributing to each guideline ranged from one (in 21/27 cases; 78%) to 11[76]. 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)[76].

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[64; 74] 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[76].

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[9] 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[77] 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[3, 5, 11] 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[6, 78, 79], 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[80]. Empirical evidence has highlighted the deficiencies and bias associated with non-systematic literature searches[81, 82]. 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[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[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[83] and clinical trial registration[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 (*S*tandard *P*rotocol *I*tems for *R*andom*I*zed *T*rials) 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"[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[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.[86] 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[85]. 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"[87] 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.

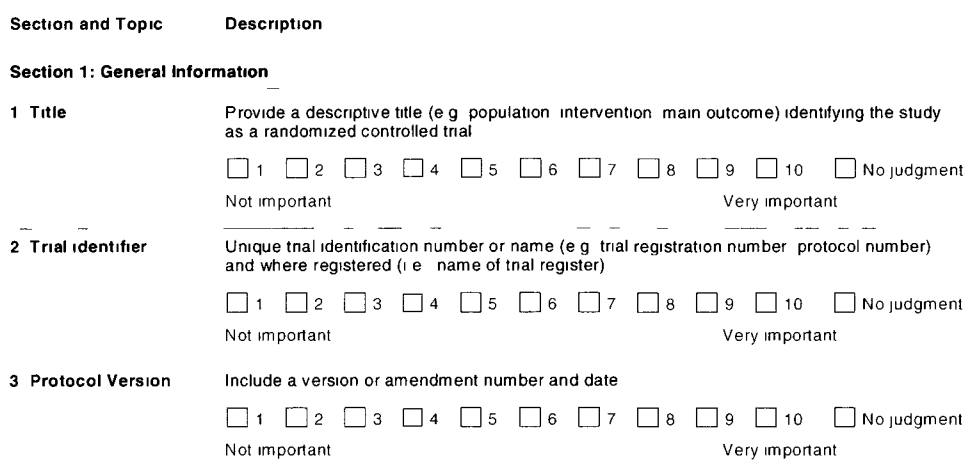
Once the lists of potential participants and initial candidate items were finalized, a three-round electronic Delphi survey was conducted to modify and refine the checklist. Prior to survey inception, potential participants were informed electronically about the upcoming survey and the background and 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.



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

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 $\geq$ 8; moderate importance - 6 $\leq$ median $\geq$ 7; low importance - median $\leq$ 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 $\geq$ 8 would be considered 'included' in the first draft of the SPIRIT Checklist and items with a median of $\leq$ 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.

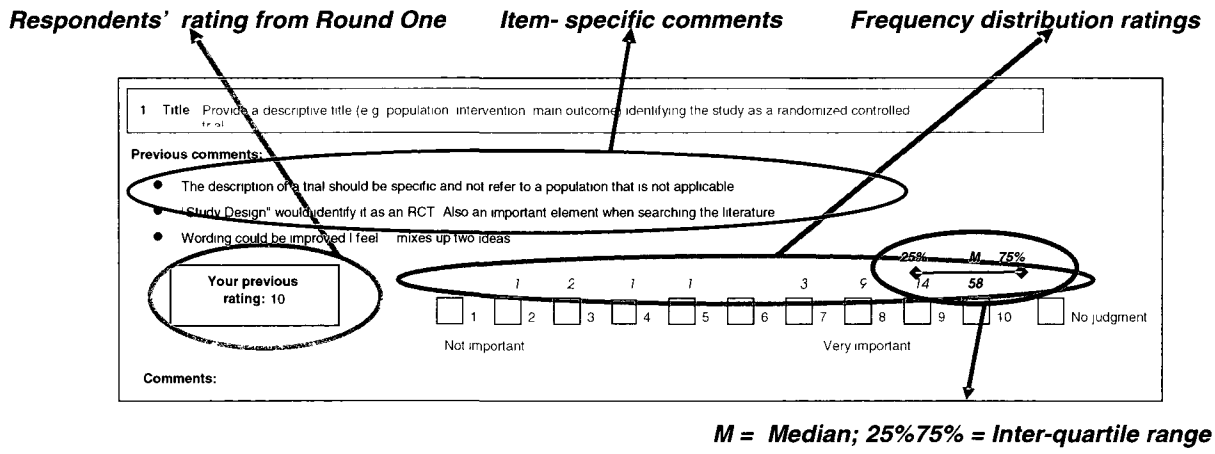


Figure 2: Example of questionnaire layout from Delphi Round 2

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).

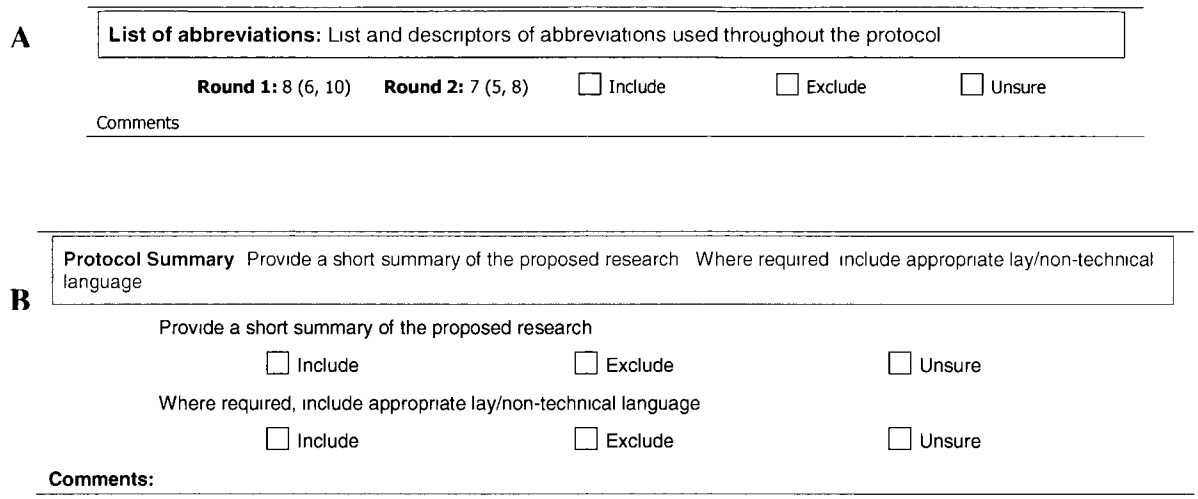


Figure 3: Example of questionnaire layout from Delphi Round 3: A) Items in Part 4, B) Items in Part 5.

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)

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

[a]Some 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.

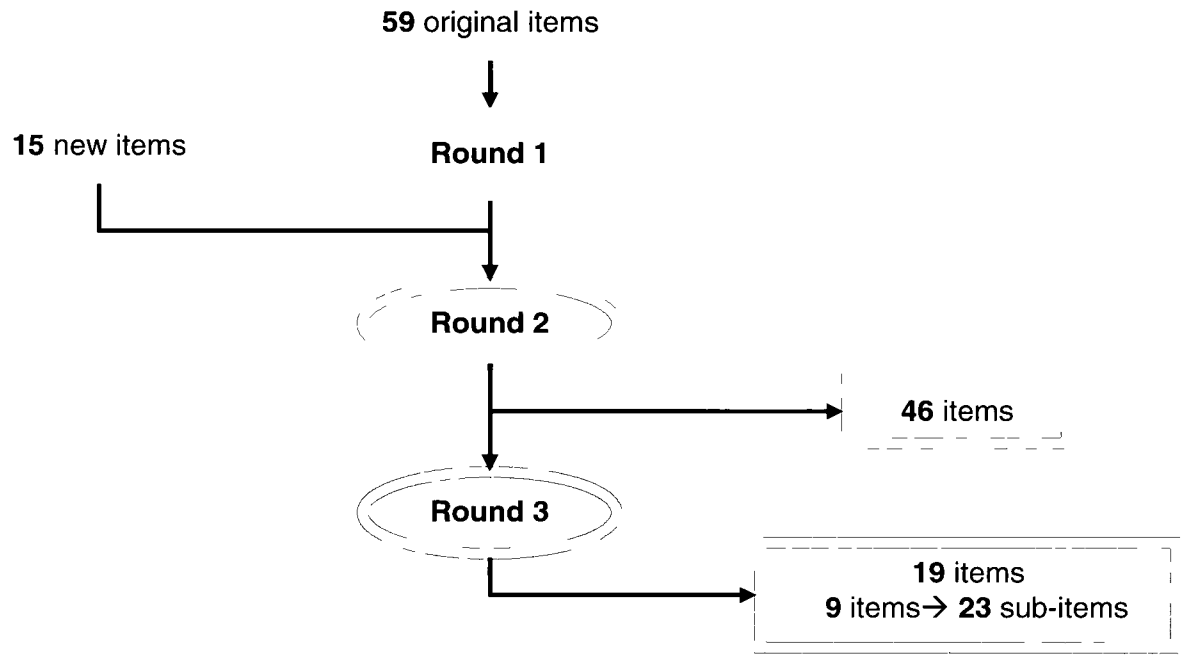


Figure 4: Flow of items through Delphi consensus survey

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 2: Initial set of checklist items results from Delphi survey Rounds 1 and 2

Section and Topic	Description	Round 1	Round 2
		Median (IQR)	
Section 1: General Information			
1. Title	Provide a descriptive title (e g population, intervention, main outcome) identifying the study as a randomized controlled trial	10 (9, 10)	10 (9, 10)
2. Trial identifier	Unique trial identification number or name (e g trial registration number, protocol number) and where registered (i e , name of trial register)	10 (9, 10)	10 (9, 10)
3. Protocol Version	Include a version or amendment number and date	10 (7, 10)	10 (8, 10)
4. Protocol Summary	Provide a short summary of the proposed research Where required, include appropriate lay/non-technical language	9 (7, 10)	9 (7, 10)[a]
5. Names and addresses	Provide names and addresses (i e , affiliated institution, company) of the primary investigators and sponsors	10 (9, 10)	10 (8, 10)
6. Table of contents	Provide a list of the contents of the protocol and associated page numbers	8 (6, 10)	8 (5, 9)
7. List of abbreviations	List and descriptors of abbreviations used throughout the protocol	8 (6, 10)	7 (5, 8)[a]
Section 2: Introduction			
8. Rationale	Outline the research topic and provide justification for undertaking the study	10 (9, 10)	10 (9 5, 10)
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 equipoise)	10 (9, 10)	10 (9, 10)
10. Preliminary data	Describe any results of preliminary studies already obtained in the area of the proposed study (e g by investigators)	9 (8, 10)	9 (8, 10)
11. Objectives	State the specific objectives and hypotheses of the study	10 (10, 10)	10 (10, 10)
12. General approach	Outline the general approach to address the research question	8 (6, 10)	7 (5, 9)[a]
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	9 (7, 10)	8 (7, 9)[a]
Section 3: Methods			
14. Population	Describe the target and study population and the source (e g catchment area) of the study population	10 (9, 10)	10 (9, 10)

Section and Topic	Description	Round 1	Round 2
		Median (IQR)	
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)[a]
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)[a]
20. Randomization: Sequence generation	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)
21. Randomization: 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	10 (9, 10)	10 (10, 10)
22. Randomization: Implementation	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)
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)[a]
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)

Section and Topic	Description	Round 1	Round 2
		Median (IQR)	
29. Data collection	Describe methods, including study instruments (e g questionnaires, laboratory measurements) and time point(s), of data collection, outcome measurement and recording	10 (9, 10)	10 (9, 10)
30. Follow-up	State follow-up plans including description and schedule of visits and logistics, if relevant	10 (8, 10)	10 (9, 10)
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	8 (7, 10)	8 (7, 9)
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	9 (8, 10)	9 (8, 10)
33. Compliance	Describe procedures and measures proposed to monitor participant compliance (e g tablet return), if relevant	9 (8, 10)	9 (8, 10)
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	10 (9, 10)	10 (9, 10)
35. Statistical methods	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)	10 (10, 10)	10 (10, 10)
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 state when a centre may be discontinued from the trial	10 (9, 10)	10 (9, 10)[a]
37. Missing data	Describe the methods to account for missing data or erroneous data	9 (8, 10)	9 (8, 10)
38. Data and Safety Monitoring Board	If relevant, describe the composition and role of the data and safety monitoring board	9 (8, 10)	9 (9, 10)
39. Interim trial monitoring	Describe the process and timing of any planned interim analyses	10 (8, 10)	10 (9, 10)
40. Stopping guidelines	State the criteria for the premature termination of the trial	10 (8, 10)	10 (9, 10)[a]
41. Adverse event reporting	Describe methods for recording and reporting both solicited and spontaneous adverse events, and provisions for dealing with them	10 (9, 10)	10 (9, 10)
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 by whom it can be broken in the event of an emergency	10 (8, 10)	10 (8, 10)
43. Limitations	Describe the limitations of the proposed study, including possible bias in data collection, measurement and analysis	9 (7, 10)	8 (6, 10)

Section and Topic	Description	Round 1	Round 2
		Median (IQR)	
Section 4: Trial organization and administration			
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	7 (5, 9)	6 (4, 7)[a]
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	7 (5, 8)	6 (4, 7)[a]
46. 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)	9 (7, 10)	9 (7, 10)[a]
47. Budget	Provide the budget for personnel, equipment, facilities and supplies	6 (3, 9)	5 (2, 6)
Section 5: Ethical considerations			
48. Potential benefits and risks	The potential benefits and risks of the research to study participants and to society	10 (9, 10)	10 (9, 10)
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	10 (9, 10)	10 (9, 10)
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	10 (9, 10)	10 (9, 10)
51. Confidentiality and Anonymity	The provisions for protecting the confidentiality and anonymity of personal data and respecting the privacy of participants	10 (8, 10)	10 (9, 10)
52. Ethics approval	State whether ethics approval has been obtained, if so, provide the name of the committee(s)	10 (9, 10)	10 (8, 10)
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	10 (8, 10)	10 (8, 10)
54. Conflict of Interest	Disclose financial or other real or perceived conflicts of interest	10 (9, 10)	10 (8, 10)
Section 6: Reporting and Dissemination			
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 of the protocol and/or the final report, as appropriate	9 (7 5, 10)	9 (7, 10)

Section and Topic	Description	Round 1	Round 2
		Median (IQR)	
56. Dissemination	Describe how the researcher(s) or sponsor(s) will disseminate the results to participants, health care professionals, the public, or other relevant groups.	8 (7, 10)	8 (7, 10)
57. Publication Policy	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.	9 (8, 10)	9 (7, 10)
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)[a]

[a]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). Fourty-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

Section and Topic	Description	Round 2	Round 3
		Median (IQR)	
60. Signatures	Provide appropriate signatures including principal investigator(s) or chief medical officer	6 (3, 9)	5 (2, 8)
61. Co-enrolment in studies	State regulations pertaining to co-enrolment of participants into other research studies	7 (5, 9)	7 (5, 8)
62. Investigational product(s)	If relevant, describe the formulation, packaging, labelling and supply of the investigational product and accountability procedures	8 (5, 9)	7 (5, 9)
63. Biological specimens	If relevant, describe plans for laboratory evaluation, specimen collection, storage and shipping to central laboratories	8 (6, 10)	8 (6, 9)
64. Data collection forms	Provide a summary table (e g matrix) of all forms to be collected at each time point	8 (5, 9)	8 (6, 9)
65. Validation of instrumentation	Describe reliability and validity of instruments to be used, including questionnaires, laboratory instruments, and analytic tests, if known, or plans to establish such validation	8 (6, 9)	8 (6, 9)
66. Trial Monitoring	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	8 (7, 9)	8 (6, 9)
67. Reporting of early stopping	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)	8 (5, 10)	8 (5, 10)
68. Ancillary and sub-studies	Describe any foreseen further uses of personal data or biological materials for related sub-studies or ancillary studies **and whether consent was obtained for these studies**	7 (4, 9)	7 (5, 9)
69. Pregnancy	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	8 (6, 10)	7 (4, 10)
70. Post-trial care	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	8 (6, 9)	8 (6, 9)
71. Post-trial data/materials storage	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	7 (5, 9)	7 (4, 8)
72. Feasibility	Justify the feasibility of the trial including the acceptability of the protocol for both participants and physicians and the capacity of recruitment	7 (4, 9)	6 (3, 8)
73. Insurance	Details of plans including insurance coverage, to provide treatment (including the funding of treatment) and compensation for research-related disability or death	6 (3, 8)	5 (2, 7)
74. Data ownership	State who has ownership of data and disclose any agreement or contract with sponsor that limits principal investigators ownership of data	8 (7, 10)	8 (7, 10)

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

Section and Topic	Description	Round 3 I = Include E = Exclude U = Unsure n (%)
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)

[a]Text 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 5: Items requiring additional delineation/clarification Results from Delphi survey Round 3

Section and Topic	Initial description	Sub-items	Round 3 I = Include E = Exclude U = Unsure n (%)
4. Protocol Summary	Provide a short summary of the proposed research Where required, include appropriate lay/non-technical language	**A.** Provide a short summary of the proposed research	I 78 (94) E 4 (5) U 1 (1)
		B. Where required, include appropriate lay/non-technical language	I 50 (63) E 21 (27) U 8 (10)
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	**A.** Briefly describe the sites(s) where the research is to be conducted	I 71 (87) E 9 (11) U 2 (2)
		B. Briefly justify the sites(s) where the research is to be conducted	I 38 (46) E 38 (46) U 6 (8)
		C. Briefly describe relevant demographic and epidemiological information about the country or region where the research is to be conducted	I 38 (46) E 29 (47) U 6 (8)
15. Eligibility criteria	Describe the criteria for inclusion and exclusion of potential participants, and justification for the exclusion of any subgroup	**A.** Describe the criteria for inclusion and exclusion of potential participants	I 81 (99) E 1 (1) U 0 (0)
		B. Justify the exclusion of any subgroup	I 55 (66) E 23 (28) U 5 (6)
19. Study timeline	Schematic diagram of study timetable and organizational chart including design, procedures and stages of trial	**A.** Schematic diagram of schedule of procedures and visits for participants through each stage of the trial	I 69 (84) E 8 (10) U 5 (6)
		B. Schematic diagram of the study timeline, specifying dates at which stages of the study are expected to be completed	I 48 (58) E 25 (30) U 10 (12)
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)	**A.** Provide precise details of the interventions intended for each group how they will be administered (e g dosage and dosage form, device), where applicable	I 82 (99) E 1 (1) U 0 (0)
		B. Justify the control interventions used (e g no treatment, placebo or active control)	I 72 (87) E 7 (8) U 4 (5)
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 state when a centre may be discontinued from the trial	**A.** State criteria that will be used to withdraw or exclude participants from the intervention (e g compliance requirements, safety concerns)	I 78 (95) E 2 (2) U 2 (2)
		B. Specify the data to be collected from withdrawn participants and how enrolled participants will be followed-up	I 70 (85) E 4 (5) U 8 (10)

		C. In a multi-centre study state when a centre may be discontinued from the trial	I· 45 (55) E 24 (30) U 13 (16)
40. Stopping guidelines	State the criteria for the premature termination of the trial	**A.** If relevant, state the predefined statistical stopping boundaries for the early termination of the trial	I 76 (92) E 5 (6) U 2 (2)
		B. If relevant, state any non-statistical predefined criteria for the early termination of the trial	I 63 (76) E· 10 (12) U 10 (12)
46. 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)	**A.** Name the source(s) of financial and material support	I. 78 (94) E 4 (5) U 1 (1)
		B. List the type(s) of support provided	I· 57 (70) E 17 (21) U 8 (10)
		C. State the amount of support provided	I 25 (30) E. 47 (57) U· 11 (13)
		D. State how source(s) of support are provided (e g to a research account or as an honorarium)	I 29 (35) E 44 (53) U· 10 (12)
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	**A.** Provide relevant materials including samples of the standardized case-report forms	I 53 (65) E 19 (23) U 10 (12)
		B. other data collection forms (e g questionnaires)	I 57 (70) E 17 (21) U 8 (10)
		C. consent/assent forms	I· 60 (72) E 19 (23) U 4 (5)

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)
- CMR (The Cochrane Library 2008, Issue 3, Wiley 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[88].

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[89] 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[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

Strength of evidence	Studies identified from systematic review		
	Study design	**Study objective for relevant item**	**Scope of study topic**
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	- broad - narrow if examples are across various ranges of specialties
	Cohort/cross-section of RCTs (protocols or reports)	- association between trial characteristic and outcome	- 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	- narrow if only one or two examples in narrow fields (i e possibly confounded by topic)
		- prevalence of trial characteristic or reporting in protocols	- 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

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[88] and Reference Manager 11[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.

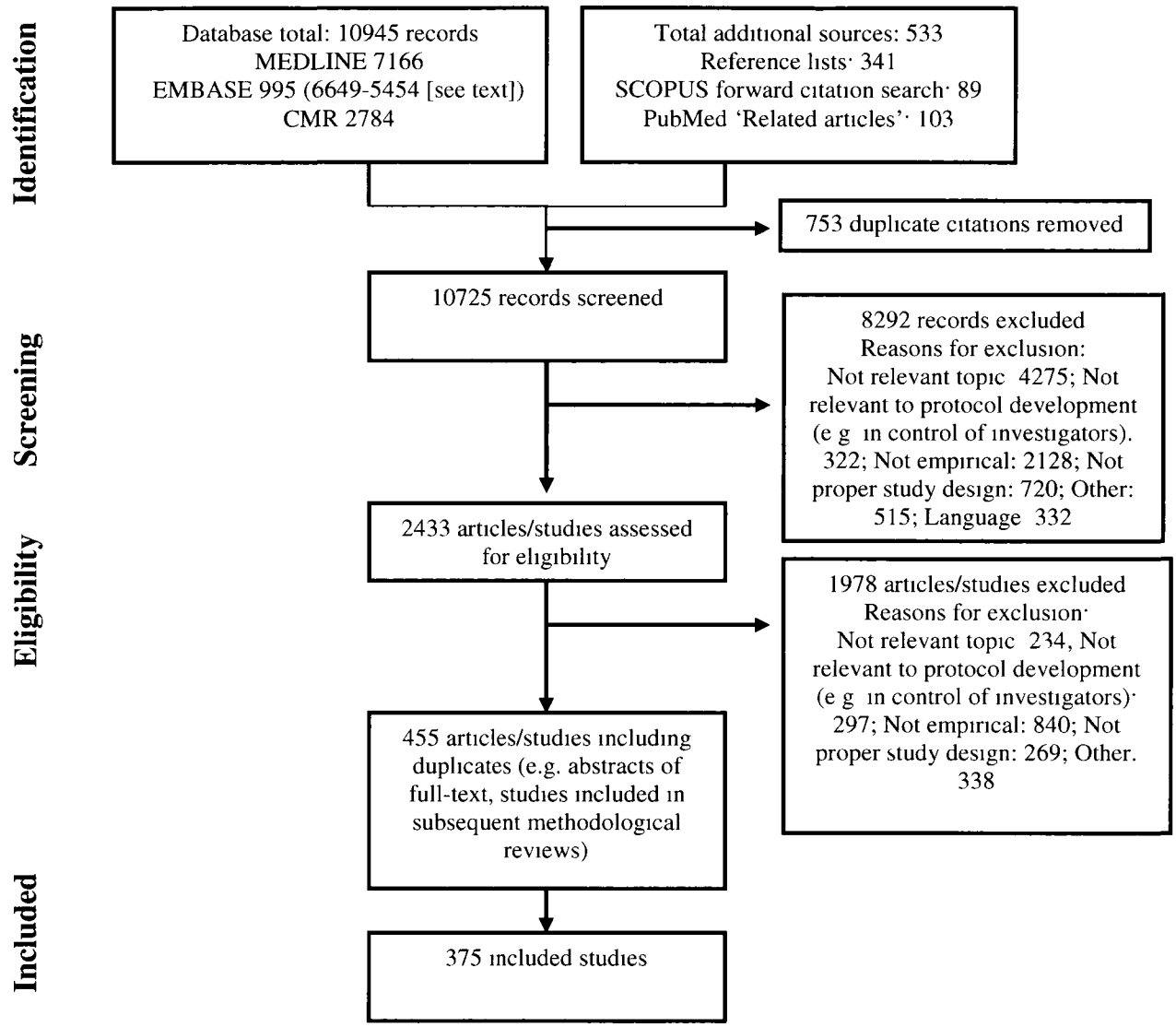


Figure 5: Systematic review flow-diagram

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

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

RCT randomized controlled trial, SR systematic Review, UK United Kingdom, USA Unites 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 8: Systematic review results

Section/ Topic[a]	SR	References[b]
Section 1: General Information		
1. Title	Weak/None	N/A
2. Trial identifier	Moderate	SR methods[97] Sample RCTs – prev [98]
3. Protocol Version	Weak/None	N/A
4. Protocol Summary A.	Weak/None	N/A
4. Protocol Summary B. Lay summary	Weak/None	N/A
5. Names and addresses	Weak/None	Sample RCT – prev[99,100]
6. Table of contents	Weak/None	N/A
7. List of abbreviations	Weak/None	N/A
Section 2: Introduction		
8. Rationale	Moderate	SR methods[97/101,102-104] Sample RCTs – other[81, 82] Sample RCTs – prev[96, 105]
9. Background of the study	Moderate	Sample RCTs – other[81, 82] Sample RCTs – prev[96, 105-110] *Incl: [111, 112]*
10. Preliminary data	Weak/None	SR methods[97/101] Sample RCTs – outcome[113] Sample RCTs – prev[114, 115] Other[116]
11. Objectives	Weak/None	SR methods[97/101, 102-104] Sample RCTs - prev [117-119]
12. General approach	Weak/None	SR methods[104]
13. Study location(s): A. Description of sites(s)	Strong	SR methods[97/101, 95, 104, 120-123] Sample RCTs – outcome[91, 94, 99, 124-132] Sample RCTs – prev[21, 133] Other[134/135] *Incl: [136, 137]*
13. Study location(s): B. Justification of sites(s)	Moderate	
13. Study locations C. Relevant demographic and epidemiological information	Moderate	
Section 3: Methods		
14. Population	Moderate	Sample RCTs – outcome[94, 138] Sample RCTs – prev[92, 139] (and others in Eligibility criteria)
15. Eligibility criteria A. Describe criteria	Strong	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]*
15. Eligibility criteria B. Justify exclusions	Strong	

Section/ Topic[a]	SR	References[b]
61. Co-enrolment in studies	Weak/None	N/A
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, 257 258
18. Type of study	Strong	SR methods[234] Sample RCTs - outcome[113, 259-262] Sample RCTs - prev[210, 215]
19. Study timeline: A. Schematic diagram of procedures and visits	Weak/None	SR methods[101] Sample RCTs - outcome[94 127, 130, 263 264] [c]See note
19. Study timeline B: Schematic diagram of trial calendar dates	Weak/None	N/A
20. Randomization: Sequence generation	Strong	SR methods[93, 97] 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.* [9 288]
21. Randomization: Allocation concealment	Strong	SR methods[93, 97, 289] 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 91 175 265 282 288 310 314]
22. Randomization: Implementation	Weak/None	SR methods[97] 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, 306-309, 320-329] Other (sample / survey)[330, 331]

Section/ Topic[a]	SR	References[b]
		Incl.[8, 9, 91, 175, 265, 288, 291, 310-312, 314, 314, 332-335]
24. Interventions A. Details of the interventions	Strong	SR methods[93, 97, 104, 123] Sample RCTs - outcome[91, 94, 107, 111-113, 127, 129, 130, 132, 263, 264, 268, 291, 336-341]
24. Interventions B. Justify the control interventions	Strong	Sample RCTs – other[82] Sample RCTs - prev[92, 96, 105, 133, 138, 202, 221, 323, 327, 342-345] Experimental in ≥ 1 RCT[346-348]
62. Investigational product(s)	Moderate	SR methods[349] Sample RCTs - outcome[337]
25. Schedule(s) of Intervention(s)	Moderate	SR methods[97] Sample RCTs - outcome[127, 350] [c]See note
26. Concomitant interventions	Weak/None	SR methods[93] Sample RCTs – prev[92, 222]
27. Risks/Harms	Weak/None	Sample RCTs - prev[221]
28. Outcomes	Strong	SR methods[5, 93, 97, 290] Sample RCTs - outcome[4, 98, 129, 183, 214, 293, 344, 351-354] Sample RCTs – prev[91, 92, 182, 185, 192, 209, 220, 222, 232, 271, 279 343, 355, 356] *Incl.*[3, 9, 11, 99, 202, 265, 314, 357, 358]
29. Data collection	Strong	SR methods[97]/[101, 123, 290, 359-363] Sample RCT - outcome[352, 364] Sample RCT - prev[92, 117, 185, 202, 222, 288, 322, 356] Experimental in ≥ 1 RCT[365-370]
65. Validation of instrumentation	Strong	SR methods[290, 361, 363] Sample RCTs - outcome[364] Sample RCTs - prev[92, 117, 296, 322, 356] Experimental in ≥ 1 RCT[365]
64. Data collection forms	Weak/None	N/A
63. Biological specimens	Weak/None	N/A
30. Follow-up	Strong	SR methods[93, 95, 97] Sample RCTs - outcome[94, 128, 260, 265, 270, 315, 339, 352] Sample RCTs – prev[d133, 222] Experimental in ≥ 1 RCT[e 371, 370, 372, 373]
31. Data management	Moderate	SR methods[359, 361] Experimental in ≥ 1 RCT[366, 368, 374]
32. Quality control	Moderate	SR methods[95, 97, 359] Sample RCTs - prev[117, 198, 221] Experimental in ≥ 1 RCT[375] *Incl.*[374]
33. Compliance	Moderate	SR methods[97]; [361] Sample RCTs - prev[221] Experimental in ≥ 1 RCT[346]
34. Safety Evaluations	Weak/None	Experimental in ≥ 1 RCT[365]
35. Statistical methods	Strong	SR methods[97]; [93]

Section/ Topic[a]	SR	References[b]
		Other MA of method. SR[10] Sample RCTs - outcome[91, 138, 175, 266-269, 271, 273, 293, 294, 322, 376-387] Sample RCTs - prev[12, 13, 21, 92, 114, 118, 119, 133, 149, 178, 181, 182, 185-188, 191, 193, 195-198, 201; 203, 205-210, 212, 213, 216, 219, 222-224, 226, 232, 270, 274, 275, 279, 280, 283, 284, 286, 298-300, 302-304, 307-309, 320, 321, 323, 327, 328, 344, 355, 388-398] Other[399-410] *Incl.* *[282, 288, 310, 311, 333]*
36. Withdrawals A. Criteria for withdrawal	Weak/None	Sample RCTs - outcome[266]
36. Withdrawals B. Data from withdrawals	Weak/None	Sample RCTs - prev[92]
36. Withdrawals C. Centre withdrawal	Weak/None	N/A
37. Missing data	Moderate	Sample RCTs - outcome[382, 387] Sample RCTs - prev[12, 198, 207, 232, 391, 395] Other[177, 399, 401, 403, 404, 411, 412]
38. Data and Safety Monitoring Board (DSMB)	Weak/None	SR methods[97] Sample RCTs - outcome[413] Sample RCTs - prev[96] Experimental in ≥ 1 RCT[375] Additional studies (not included)[414, 415]
39. Interim trial monitoring	Moderate	SR methods[97] Sample RCTs – prev [12, 96, 229, 413]
40. Stopping guidelines A. Statistical stopping guidelines	Moderate	SR methods[97] Sample RCTs - prev[96 413, 416]
40. Stopping guidelines B. Non-statistical stopping guidelines	Moderate	
41. Adverse event reporting	Weak/None	Experimental in ≥ 1 RCT[365]
42. Emergency code-breaking procedure	Weak/None	N/A
43. Limitations	Weak/None	N/A
Section 4: Trial organization and administration		
44. Personnel	Strong	SR methods[97/101; 95, 102, 120] Sample RCTs - outcome[91, 113, 126, 188, 310, 417, 418] Other[116, 368]
45. Logistics	Weak/None	SR methods[95]
46. Monetary and material support A. Source(s) of financial and material support.	Strong	SR methods[6, 78, 120, 419, 420] Sample RCTs - outcome[99, 107, 131, 132, 135, 136, 138, 268, 271 282, 291, 294, 421-436,437 (add-on data to 3)] Sample RCTs – prev[110, 118, 285, 297, 310, 320, 438, 439] *Incl.*[79, 105, 106, 319, 343, 440-443]

Section/ Topic[a]	SR	References[b]
46. Monetary and material support B. Type(s) of support	Moderate	Sample RCTs - outcome[294, 439, 442] Other[116]
46. Monetary and material support C. Amount of support	Weak/None	Sample RCTs - outcome[113]
46. Monetary and material support D. How support is provided	Weak/None	N/A
47. Budget	Weak/None	N/A
60. Signatures	Weak/None	N/A
66. Trial monitoring	Weak/None	SR methods[97]
70. Post-trial care	Weak/None	SR methods[95] Experimental in ≥ 1 RCT[370]
71. Post-trial data/materials storage	Weak/None	N/A
72. Feasibility	Moderate	SR methods[97, 103, 104, 122, 123, 238, 360] [c]See note
73. Insurance	Weak/None	N/A
74. Data ownership	Moderate	SR methods[78] Sample RCTs - outcome[106] Sample RCTs – prev[444] [c]See note
Section 5: Ethical considerations		
48. Potential benefits and risks	Moderate	SR methods[95, 101, 123] [c]See note
49. Agreement and consent	Strong	SR methods[97/101, 104/445, 95, 122, 234, 238, 446-452] Sample RCTs - outcome[453] Sample RCTs - prev[96, 221, 454, 455] Experimental in ≥ 1 RCT[456-462] *Incl.* [116, 251, 257, 463-469]
50. Surrogate consent or assent	Weak/None	N/A
51. Confidentiality and Anonymity	Weak/None	N/A
52. Ethics approval	Weak/None	Sample RCTs - prev[96, 100, 454]
53. Role of sponsor	Moderate	SR methods[78] Sample RCTs – outcome[106, 138, 294, 421, 422, 440] Sample RCTs – prev[444, 470]
54. Conflict of Interest	Strong	SR methods[78] Sample RCTs - outcome[79, 138, 268, 294, 297, 422, 429, 431-434, 439, 440]
68. Ancillary and sub-studies	Weak/None	N/A
69. Pregnancy	Weak/None	N/A
Section 6: Reporting and Dissemination		
55. Protocol Amendments	Strong	SR methods[5] Sample RCTs – outcome[4, 353] Sample RCTs – prev[12, 13, 19, 98, 148, 159, 325, 344, 354, 470]

Section/ Topic[a]	SR	References[b]
56. Dissemination	Strong	SR methods[5 97 120 121 438] Sample RCTs – outcome[99 129 353 386 471 473] *Incl* [136 137, 428 474 476]
67. Reporting of early stopping	Weak/None	Sample RCTs - prev[476]
57. Publication Policy	Moderate	SR of methods[78 438] Sample RCTs - outcome[386] Sample RCTs - prev[444 470] *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[363] Sample RCTs – outcome[364] Sample RCTs – prev[296] Experiment in ≥ 1 RCT[365]
59. Appendix materials C. Consent/assent forms	Strong	SR methods[104 / 445, 95 123 238 360 449-452, 446 / 448] Sample RCTs - prev[100 455] *Incl* [463 467-469]
Section 6: Reporting and Dissemination		
Protocol Authors	Weak/None	Sample RCT -prev[470]
Methods of increasing Adherence and retention	Moderate	SR methods[95 373] Experiment in ≥ 1 RCT [346]

[a]Item numbers are based on Delphi survey, see Chapter 3
[b]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)
[c] Studies may be indirectly relevant to item and additional indirect evidence may be included in other items
[d]Other potentially relevant studies not included if adequacy of follow-up was not clearly in control of the investigator
[e]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

Section/ Topic[a]	Delphi	SR	Recomm-endation	Additional considerations based on Delphi comments
1. Title	Strong	Weak/ None	Include	▪ Consider revising based on Delphi comments
2. Trial identifier	Strong	Moderate	Include	▪ Not relevant at all protocol stages (e.g. before funding). Suggest to add, "if applicable"
3. Protocol Version	Strong	Weak/ None	Include	-
4. Protocol Summary A.	Strong	Weak/ None	Include	-
4. Protocol Summary B. Lay summary	Moderate	Weak/ None	Exclude	▪ 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
5. Names and addresses	Strong	Weak/ None	Include	▪ Addresses should be changed to "affiliations" or clarified as institutional addresses.
6. Table of contents	Moderate	Weak/ None	Exclude	-
7. List of abbreviations	Moderate	Weak/ None	Exclude, further discussion	▪ 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%).

I = Include
[a]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

Section/ Topic[a]	Delphi	SR	Recommendation	Additional considerations based on Delphi comments
8. Rationale	Strong	Moderate	Include concept, consider overlap	▪ Consider merging with "Background of the study"
9. Background of the study	Strong	Moderate	Include concept , consider overlap	▪ Consider merging with "Rationale" ▪ *Re-examine rationale for* "equipoise/uncertainty" and "systematic review" (conflicting comments); ▪ Re-consider wording of "ideally" (RE: systematic review) (conflicting comments)
10. Preliminary data	Strong	Weak/ None	Include concept, consider overlap	▪ Consider merging with "Background of the study" (and also, possibly "Rationale" as per previous comments)
11. Objectives	Strong	Weak/ None	Include	-
12. General approach	Moderate	Weak/ None	Exclude	▪ Wording/concept too vague. ▪ Concept already captured/should be combined with other items: e.g. "Type of Study" or "Background of the study"/"Rationale"
13. Study location(s): A. Description of sites(s)	Strong	Strong	Include	▪ 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 "justification" of sites, although others find it important in certain situations. ▪ Emphasize "briefly describe" (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&E
13. Study location(s): B. Justification of sites(s)	Weak/ None	Moderate	Exclude	
13. Study locations C. Relevant demographic and epidemiological information	Weak/ None	Moderate	Exclude	

E&E = Explanation and elaboration document; I = Include
[a]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[81; 105; 105-107; 107-110] 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.

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Table 11: Synthesis of Delphi survey and systematic review results recommendations for the SPIRIT checklist - Section 3 Methods

Section/ Topic[a]	Delphi	SR	Recommendation	Additional considerations based on Delphi comments
14. Population	Strong	Moderate	Include item, consider overlap	▪ Consider overlap with "Eligibility criteria" and of last concept (describe "catchment area") with "Study location(s)" ▪ Consider if this is less relevant/too burdensome for multi-centre studies ▪ Despite considerations above, recommended for inclusion
15. Eligibility criteria A. Describe criteria	Strong	Strong	Include	▪ Consider revising sub-item ("justification") so as not to suggest all (e g obvious) exclusions need to be justified ▪ Consider concern with term 'obvious' (subjective), reiteration may be needed ▪ 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%)
15. Eligibility criteria B. Justify exclusions	Moderate	Strong	Include	
61. Co-enrolment in studies	Moderate	Weak/ None	Exclude	▪ Consider capturing concept in "Eligibility criteria"
16. Sample size	Strong	Strong	Include	▪ 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)
17. Recruitment	Strong	Strong	Include	▪ Comments suggest that recruitment methods may be site-specific, and thus difficult to describe in the protocol ▪ Many panellists 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
18. Type of study	Strong	Strong	Include	▪ Consider revising based on Delphi comments
19. Study timeline: A. Schematic diagram of procedures and visits	Strong	Weak/ None	Include concept, consider overlap	▪ Many Delphi panellists 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 ▪ 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)"), ▪ Consider including a suggestion, not a requirement, for a 'Schematic diagram' ▪ Sub-group analysis showed funding agency *representatives less supportive for inclusion* (I = 40%) than other groups (85%)
19. Study timeline B: Schematic diagram of trial calendar dates	Moderate	Weak/ None	Exclude	-

Section/ Topic[a]	Delphi	SR	Recommendation	Additional considerations based on Delphi comments
20. Randomization: Sequence generation	Strong	Strong	Include	▪ Consider excluding request for block size and possibly specifically requesting such information be omitted from protocol
21. Randomization: Allocation concealment	Strong	Strong	Include	-
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 panellists
62. Investigational product(s)	Moderate	Moderate	Exclude	▪ Consider addressing some concepts included in this item at a higher level within "Interventions"
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
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], "Data collection" or

Section/ Topic[a]	Delphi	SR	Recommendation	Additional considerations based on Delphi comments
			overlap	"Quality control" ▪ Consider explicitly asking for citations for instruments, if relevant ▪ Consider requesting forms as an appendix ▪ 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])
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 panellists 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 "Summarize " 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 panellists 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
33. Compliance	Strong	Moderate	Further discussion	▪ Some panellists felt this was less important in trials with intention to treat analyses

Section/ Topic[a]	Delphi	SR	Recommendation	Additional considerations based on Delphi comments
				▪ Consider refocusing to capture planned methods to *increase* compliance (and possibly retention) – concepts not explicitly addressed in checklist – rather than plans to *measure* it
34. Safety Evaluations	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 in concepts (and possible merging) with "Risks/Harms", "Adverse event reporting", "Outcomes" and/or "Data collection"
35. Statistical methods	Strong	Strong	Include	▪ Consider revising to state that if details are elsewhere (e g , Statistical analysis plan) an overview of methods and reference for details is appropriate ▪ Consider creating sub-items to delineate some of the (most) important concepts (based on empirical evidence)
36. Withdrawals A. Criteria for withdrawal	Strong	Weak/ None	Include	▪ Description needs to be revised to address concerns of terminology and phrasing ▪ Consider keeping concepts A and B as one item ▪ Sub-group analysis suggest that journal editors are more in favour of including sub-item C (I = 78%) than other groups (55%)
36. Withdrawals B. Data from withdrawals	Strong	Weak/ None	Include concept	
36. Withdrawals C. Centre withdrawal	Moderate	Weak/ None	Exclude	
37. Missing data	Strong	Moderate	Include item, further discussion	▪ Some panellists preferred including this in a separate document (e g analysis plan) ▪ Some panellists thought this item was important but felt it needed to be edited (e g change 'account for missing data') ▪ Evidence conflicted as to whether methods of dealing with missing data should be determined at the outset of a trial Pre-specification may avoid biased alteration of statistical analysis plan but it may be difficult (and possibly inappropriate) to pre-specify prior to knowing the pattern of (and reasons for) missing data ▪ Further discussion regarding level and type of information requested
38. Data and Safety Monitoring Board (DSMB)	Strong	Weak/ None	Further discussion	▪ Consider requesting only presence/absence of DSMB, details (e g composition) are suggested to be more appropriate for DSMB charter
39. Interim trial monitoring	Strong	Moderate	Include	▪ Consider revising to address most important concepts and request where further details may be found (e g , DSMB charter or analysis plan)
40. Stopping guidelines A. Statistical stopping guidelines	Strong	Moderate	Include	▪ Consider emphasizing that these are guidelines, not boundaries/rules ▪ Consider modifying description to state "early termination of trial" rather than "premature termination of trial" ▪ Consider clarifying intent of item (e g
40. Stopping guidelines B. Non-	Strong	Moderate	Include	

Section/ Topic[a]	Delphi	SR	Recomm-endation	Additional considerations based on Delphi comments
statistical stopping guidelines				DSMB-, Sponsor-, REC/IRB- or Steering committee- governed stopping guidelines) ▪ Consider guiding expected level of detail ▪ 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%)
41. Adverse event reporting	Strong	Weak/ None	Include concept, consider overlap	▪ Supporting evidence is likely topic-specific thus not included in review ▪ Consider overlap with "Risks/Harms" and "Safety evaluations" and consider merging into one or two items ▪ 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" ▪ 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).
42. Emergency code-breaking procedure	Strong	Weak/ None	Include concept, consider overlap	▪ Consider requesting only a higher-level description or within an existing item (e.g. Blinding, Safety evaluations/Adverse event reporting). ▪ Consider requesting where details of these procedures may be found (e.g. Standard operating procedures, Operations manual)
43. Limitations	Moderate	Weak/ None	Exclude	-

I = Include; IQR = Inter-quartile range
[a]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[96, 145, 146, 149] and that excluding certain subgroups may inadvertently exclude other seemingly independent subgroups[142, 161, 163]. Finally, eligibility criteria may be changed or selectively reported in different publications[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 *Randomization: Sequence generation*, *Allocation concealment*, *Blinding (masking)* and *Statistical methods*. Although individual study results conflict, methodological studies across a range of disciplines and methodological reviews[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[7, 12, 19, 325, 344] and inconsistent descriptions of trial methods between protocols and subsequent publications, often without justification or mention of protocol amendments[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[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 *Sequence Generation* should arguably not include block-sizes, where relevant, as this may jeopardize allocation concealment integrity[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 *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[95, 113, 116, 233-239, 241, 243-250] but also the type of participants recruited, and subsequently the generalizability of the trial results[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[78, 106, 107, 268, 419, 424]. 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[6, 29, 78, 135, 291, 310, 420, 421]. *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[102; 113], retention[95] and data collection[368]. 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[126, 310, 417, 418], although not all results were statistically significant[91; 188]. 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 12: Synthesis of Delphi survey and systematic review results recommendations for the SPIRIT checklist - Section 4: Trial organization and administration

Section/Topic[a]	Delphi	SR	Recommendation	Additional considerations based on Delphi comments
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
46. Monetary and	Weak/	Weak/	Exclude	▪ Subgroup analysis by profession shows

Section/Topic[a]	Delphi	SR	Recomm-endation	Additional considerations based on Delphi comments
material support D. How support is provided	None	None		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 ▪ Trend for increased support with lower self-perceived expertise
47. Budget	Weak/ None	Weak/ None	Exclude	▪ Funding may be unknown at outset; budgets may differ from site-to-site; budgets may change requiring many amendments to protocol; issues of privacy.
60. Signatures	Weak/ None	Weak/ None	Exclude	-
66. Trial monitoring	Moderate	Weak/ None	Further discussion	▪ Consider addressing concept in "Quality control" (or possibly "Data and Safety Monitoring Board", depending on intended scope)
70. Post-trial care	Moderate	Weak/ None	Further discussion	▪ Important for ethical reasons, if relevant; most obviously in trials without widespread access to standard treatments ▪ Concerns included feasibility of knowing this at outset of trial (before demonstrating intervention efficacy) ▪ If included, request only high level description, where relevant
71. Post-trial data/materials storage	Moderate	Weak/ None	Exclude, further discussion	▪ 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") ▪ Often governed locally by the sponsor or by regulatory bodies, making it difficult to specify in protocol ▪ Consider requesting disclosure of where this information can be found
72. Feasibility	Moderate	Moderate	Exclude	▪ Important but covered elsewhere in protocol (e.g. "Preliminary data", "Study locations(s)", "Recruitment", "Sample Size", "Agreement and Consent" and "Ethics approval") ▪ 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 ((Median (IQR) = 3 (1, 6)) vs. 6 (3, 8)). ▪ Subgroup analysis showed more support by trial coordinators (Median [IQR] = 9 [7, 10]) than other groups (5 [3, 8]).
73. Insurance	Weak/ None	Weak/ None	Exclude	-
74. Data ownership	Moderate	Moderate	Include concept, further discussion	▪ Unclear where this item belongs (e.g. Trial organization and administration, Ethical considerations or Reporting and Dissemination).

Section/Topic[a]	Delphi	SR	Recomm-endation	Additional considerations based on Delphi comments
				▪ Empirical evidence provided at most 'moderate' support but it may be considered stronger due to its association with "Monetary and Material support" and the bias found in industry-sponsored trials. ▪ Consider overlap with items "Dissemination" or "Publication policy". ▪ Consider revising based on Delphi comments.

E = Exclude, I = Include; IQR = Inter-quartile range; U = Unsure
[a]Item numbers are based on Delphi survey; see Chapter 3

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[234, 448, 457-460], many methodological studies suggest that the content, quantity and mode of delivery of consent information may affect trial recruitment[104, 116, 122, 238, 447, 477], participant comprehension[447, 449, 451, 452, 456, 461, 462, 477], anxiety[461, 477], retention[95, 453] and recruitment costs[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[79; 294; 421; 431-433; 439]. Furthermore, there is evidence that the processes and progress of a substantial number of industry-funded trials are in the sponsor's control[444; 470]. 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

Section/ Topic[a]	Delphi	SR	Recommendation	Additional considerations based on Delphi comments
48. Potential benefits and risks	Strong	Moderate	Include	▪ 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
49. Agreement and consent	Strong	Strong	Include	▪ Overlaps with "Appendix materials C Consent forms", 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 "name" 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
50. Surrogate consent or assent	Strong	Weak/ None	Include concept, consider overlap	▪ May be site-specific and therefore only general information may be relevant for the protocol ▪ Consider merging with "Agreement and consent"
51. Confidentiality and Anonymity	Strong	Weak/ None	Include	-
52. Ethics approval	Strong	Weak/ None	Include	▪ 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 , "all sites will obtain local REC/IRB approval", 2) remove specific request for names of committees as this may require many amendments for some trials
53. Role of sponsor	Strong	Moderate	Include	▪ Moderate support by evidence may be stronger due to association with "Monetary and Material support" ▪ Consider either revising terminology or defining the term "sponsor" ▪ 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 "Monetary and material support B types of support"
54. Conflict of Interest	Strong	Strong	Include	▪ Consider specifying whose conflict of interest is being requested (suggested examples included principal investigators and sponsor/funder) ▪ Many panellists 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
68. Ancillary and sub-studies	Moderate	Weak/ None	Exclude	▪ Some panellists 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,

Section/ Topic[a]	Delphi	SR	Recomm-endation	Additional considerations based on Delphi comments
				each ancillary study should have its own protocol and REC/IRB approval. ▪ Many respondents felt this should be a component of "Agreement and consent" (whether consent is given for future use of specimens and data).
69. Pregnancy	Moderate	Weak/ None	Exclude	▪ 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")

[a]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

Section/Topic[a]	Delphi	SR	Recommendation	Additional considerations based on Delphi comments
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.

[a]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[5, 97, 120, 129, 353, 386, 471, 473, 478]. Eventual publication also appears to be due to investigators or sponsors failing to submit, rather than journal failing to accept, negative or null results[5]. Similarly, evidence of ghost authorship and constraints on publication, particularly in industry-sponsored trials[444, 470], 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[470]. 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[95; 346; 373]. 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

Section/Topic[a]	Delphi	SR	Recommendation	Additional considerations based on Delphi comments
58. References	Strong	Weak/ None	Further discussion	-
59. Appendix materials A. Case-report forms	Moderate	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 B. Other data collection forms (e g questionnaires)	Moderate	Moderate	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 C. Consent/assent forms	Moderate	Strong	Include item, 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

I = Include
[a]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 concealment[7, 289, 290], vague or modified descriptions of primary and secondary outcomes[5] and in trials supported by commercial sources or including investigators/authors with conflicts of interest [6, 78, 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[95, 97, 101, 104, 122, 140, 233-239, 446, 449-452]; 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[84]. While the need for trial registration has been clearly demonstrated[5], 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[84], 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[479] and publication bias[480, 481]. 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[31; 482; 483], 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[83]. Where appropriate, the structure and wording of some items may follow the CONSORT statement[31], facilitating these comparisons.

Conceivably, all RCT trials will have a protocol. A study by Chan and Altman [484] 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[485]) and the minimum of 40% of trials not reaching full publication[478]. 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" [45; 486]. The Network has begun compiling guidance on reporting guideline development methods[487], 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 [85]. 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[488-494]: 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[e g ,495] 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[31, 482, 483]. 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[97, 496, 497], 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[97, 498]. For example, Prescott and colleagues conducted a systematic review of factors limiting the quality, number and progress of RCTs[97]. 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[499]. 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[38; 39]. 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[500; 501]. 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[500] and have been recommended for other broad or complex reviews[496; 502]. 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[496]. 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[497]. 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[50], those produced by the United States Centers for Disease Control and Prevention[47] and the National Institutes of Health[73], and the only RCT-specific guideline citing methods for development (PRACTIHC)[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[503] and that produced for the United Kingdom's National Health Service's University College of London[504]. The final guideline was selected as it is currently used by the Canadian Institutes of Health Research[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

- Appendix of case-report forms
- Appendix of data collection form

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[76]. 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[505]. 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[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[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[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[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[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[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[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[43, 44, 508] and have significantly improved reporting in trials[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

(1) Gluud LL Bias in clinical intervention research Am J Epidemiol 2006, 163 (6) 493-501

(2) Bassler D, Ferreira G, I, Briel M, Cook DJ, Devereaux PJ, Heels AD, et al. Systematic reviewers neglect bias that results from trials stopped early for benefit J Clin Epidemiol 2007; 60 (9)· 869-73

(3) Chan AW, Krleza-Jeri 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

(4) Chan AW, Altman DG Identifying outcome reporting bias in randomised trials on PubMed review of publications and survey of authors BMJ 2005; 330 (7494): 753

(5) Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias PloS ONE 2008, 3 (8). 3081

(6) Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review BMJ 2003, 326 (7400): 1167-70.

(7) Pildal J, Hróbjartsson A, Jørgensen KJ, Hilden J, Altman DG, Gøtzsche PC. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials Int J Epidemiol 2007, 36 847-57.

(8) Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998; 352 (9128) 609-13

(9) Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273 (5): 408-12

(10) Als-Nielsen B, Gluud LL, Gluud C. Methodological quality and treatment effects in randomised trials a review of six empirical studies [abstract]. 12th Cochrane Colloquium: Bridging the Gaps 2004 Oct 2-6; Ottawa, Ontario, Canada , 88-89. 2004.

(11) Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. JAMA 2004, 291 (20): 2457-65.

(12) Chan AW, Hróbjartsson A, Jørgensen KJ, Gøtzsche PC, Altman DG. Discrepancies in sample size calculations and data analyses reported in randomised trials: comparison of publications with protocols. BMJ 2008; 337: a2299.

(13) Hernández AV, Steyerberg EW, Taylor GS, Marmarou A, Habbema JD, Maas AI Subgroup analysis and covariate adjustment in randomized clinical trials of traumatic brain injury. a systematic review. Neurosurgery 2005; 57 (6) 1244-53

(14) Annals of Internal Medicine: Information for Authors. [Online] 2009 [cited 2010 Jan 2]; Available from· URL:http //www annals org/site/misc/ifora xhtml 2007 by the American College of Physicians.

(15) Lancet Information for authors [Online] 2009 [cited 2010 Jan 2], Available from URL http //download thelancet com/flatcontentassets/authors/lancet information for authors pdf ENGLAND

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

(17) *PLoS Medicine* Guidelines for Authors [Online] 2010 [cited 2010 Jan 2], Available from URL http //journals plos org/plosmedicine/guidelines php

(18) Open Medicine Author Guidelines [Online] 2010 [cited 2010 Jan 2], Available from URL http //www openmedicine ca/about/submissions#authorGuidelines

(19) Pildal J, Chan AW, Hróbjartsson A, Forfang E, Altman DG, Gøtzsche PC Comparison of descriptions of allocation concealment in trial protocols and the published reports cohort study BMJ 2005, 330 (7499) 1049

(20) Gøtzsche P, Hrøbjartsson A, Johansen H, Haahr M, Altman D, Chan A Ghost Authorship in Industry-Initiated Randomised Trials PLoS Med 2007, 4 (1) e19 doi 10 1371/journal pmed 0040019

(21) Eldridge SM, Ashby D, Feder GS, Rudnicka AR, Ukoumunne OC Lessons for cluster randomized trials in the twenty first century a systematic review of trials in primary care Clin 2004, 1 (1) 80-90

(22) Scales CD, Jr , Norris RD, Keitz SA, Peterson BL, Preminger GM, Vieweg J, et al A critical assessment of the quality of reporting of randomized, controlled trials in the urology literature J Urol 2007, 177 (3) 1090-4

(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

(25) Boutron I, Guittet L, Estellat C, Moher D, Hróbjartsson A, Ravaud P Reporting methods of blinding in randomized trials assessing nonpharmacological treatments Plos Medicine 2007, 4 (2) 0370-80

(26) Zhang XL, Li J, Zhang MM, Yuan WM [Assessing the reporting quality of randomized controlled trials on acupuncture for acute ischemic stroke using the CONSORT statement and STRICTA] Chinese Journal of Evidence Based Medicine 2006, 6 586-90

(27) Soares HP, Daniels S, Kumar A, Clarke M, Scott C, Swann S, et al Bad reporting does not mean bad methods for randomised trials observational study of randomised controlled trials performed by the Radiation Therapy Oncology Group BMJ 2004, 328 (7430) 22-4

(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

(29) Hill CL, LaValley MP, Felson DT Discrepancy between published report and actual conduct of randomized clinical trials J Clin Epidemiol 2002, 55 (8) 783-6

(30) Devereaux PJ, Choi PT, El-Dika S, Bhandari 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

(31) Moher D, Schulz KF, Altman DG The CONSORT statement revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001; 357 (9263) 1191-4

(32) Campbell MK, Elbourne DR, Altman DG, CONSORT group CONSORT statement: extension to cluster randomised trials. BMJ 2004; 328 (7441): 702-8.

(33) Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement BMJ 2008; 337. 1223-6 [abridged version]

(34) Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJW Reporting of noninferiority and equivalence randomized trials: An extension of the CONSORT statement. JAMA 2006; 295: 1152-60.

(35) Boutron I, Moher D, Altman DG, Schulz K, Ravaud P, for the CONSORT group Methods and Processes of the CONSORT Group: Example of an Extension for Trials Assessing Nonpharmacologic Treatments. Ann Intern Med 2008; -W60

(36) Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement Ann Intern Med 2006, 144 (5) 364-7

(37) Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. Lancet 2008; 371: 281-3.

(38) Simera I, Altman DG, Moher D, Schulz KF, Hoey J. Guidelines for Reporting Health Research: The EQUATOR Network's Survey of Guideline Authors. PLoS Med 2008; 5 (6): e139.

(39) Moher D, Weeks L, Ocampo M, Seely D, Sampson M, Altman DG, et al. Describing reporting guidelines for health research: a systematic review 2009. 30-12-2009.

(40) Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration The Standards for Reporting of Diagnostic Accuracy Group Croat Med J 2003, 44 (5): 639-50.

(41) Plint AC, Moher D, Morrison A, Schulz K, Altman DG, Hill C, et al. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. Med J Aust 2006; 185 (5): 263-7.

(42) Smidt N, Rutjes AW, van der Windt DA, Ostelo RW, Bossuyt PM, Reitsma JB, et al. The quality of diagnostic accuracy studies since the STARD statement: has it improved? Neurology 2006; 67 (5): 792-7

(43) International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Manuscript Preparation and Submission: Preparing a Manuscript for Submission to a Biomedical Journal. [Online] 2009 [cited 2010 Jan 2]; Available from: URL:http //www icmje org/manuscript_1prepare html.

(44) Council of Science Editors. Improving the Quality of Communication in the Sciences. [Online] 2009 [cited 2010 Jan 2]; Available from URL:http //www councilofscienceeditors org/pdf/mbi_brochure pdf.

(45) Equator Network· Enhancing the QUAlity and Transparency Of health Research. [Online] 2009 October 6 [cited 2010 Jan 2]; Available from URL http //www equator-network org/. Minervation.

(46) O'Toole LB. Consort statement on the reporting standards of clinical trials. MRC uses checklist similar to CONSORT's BMJ 1997, 314 (7087)· 1127.

(47) Centers for Disease Control and Prevention. Developing a protocol a guide for CDC investigators [Online] 2006 [cited 2010 Jan 2], Available from·
URL·http //www cdc gov/niosh/nas/mining/pdfs/Protocol%20Checklist pdf

(48) Chaput de Saintonge D. Aide-memoire for preparing clinical trial protocols Br Med J 1977; 1 (6072): 1323-4.

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

(50) ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6. [Online] 1998 [cited 2007 Feb 10]; Available from: URL:http //www ich org/cache/compo/276-254-1 html.

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

(52) Enarson DA, Kennedy SM, Miller DL. Getting started in research: the research protocol. Int J Tuberc Lung Dis 2004; 8 (8)· 1036-40

(53) Friedman LM, Furberg C, DeMets D Fundamentals of clinical trials New York Springer-Verlag; 1999.

(54) Gallin J.I Principles and practice of clinical research. San Diego, CA, USA: Academic Press; 2002

(55) Girling DJ. Important issues in planning and conducting multi-centre randomised trials in cancer and publishing their results. Crit Rev Oncol Hematol 2000; 36 (1) 13-25

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

(57) Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing clinical research : an epidemiologic approach. Philadelphia, PA, USA· Lippincott Williams and Wilkins; 2007.

(58) Indrayan A. Elements of medical research. Indian J Med Res 2004; 119 (3): 93-100.

(59) Ivanov A, Van GM. [Design, management and handling of a randomized trial]. [French]. Bull Cancer 1995; 82 Suppl 5. 553s-7s.

(60) Mann H. ASSERT statement. [Online] 2007 Available from· URL:http //www assert-statement org/statement html; http //www assert-statement org/explandoc pdf.

(61) Moorhead JE, Rao PV, Anusavice KJ Guidelines for experimental studies Dent Mater 1994; 10 (1)· 45-51.

(62) O'Brien K, Wright J. How to write a protocol J Orthod 2002; 29 (1): 58-61.

(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.

(65) Portney LG, Watkins MP Foundations of clinical research applications to practice Upper Saddle River, NJ, USA Prentice-Hall, Inc, 2000

(66) Smith F G Key topics in clinical research a user guide to researching, analyzing and publishing clinical data London, UK Taylor and Francis, 2003

(67) Spilker B Guide to clinical studies and developing protocols New York, NY Raven Press, 1984

(68) Spilker B Guide to clinical trials New York, NY Raven Press, 1991

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

(70) Warren MD Aide-memoire for preparing a protocol Br Med J 1978, 1 (6121) 1195-6

(71) Working group of the Commission on Dental Materials IEaT [Recommendation plan for research protocol FDI Commission on Dental Products, Instruments, Equipment and Therapeutic Agents (COMIET), G T Clinical trials The French version INCOGUDET] [French] Int Dent J 1977, 27 (3) 299 300

(72) Working group of the Commission on Dental Materials IEaT Recommended outline for a research protocol Prepared by a working group of the Commission on Dental Materials, Instruments, Equipment and Therapeutics Int Dent J 1977, 27 (1) 44-5

(73) U S Department of Health and Human Services Public Health Service Grant Application (PHS 398) Part I and Part II OMB No 0925-0001 [Online] 2006 [cited 2007 Mar 23], Available from URL http //grants nih gov/grants/funding/phs398/phs398 html

(74) Dalkara T How to construct a research project Acta Neurochir Suppl 2002, 83 7-9

(75) Draxler W, Mittlbock M Basic principles in the planning of clinical trials in surgical oncology European Surgery - Acta Chirurgica Austriaca Supplement 2006, 38 (1) 27-32

(76) Treweek S, McCormack K, Abalos E, Campbell M, Ramsay C, Zwarenstein M, et al The Trial Protocol Tool The PRACTIHC software tool that supported the writing of protocols for pragmatic randomized controlled trials J Clin Epidemiol 2006, 59 (11) 1127-33

(77) Freiman JA, Chalmers TC, Smith H, Jr , Kuebler RR The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial Survey of 71 "negative' trials N Engl J Med 1978, 299 (13) 690-4

(78) Bekelman JE, Li Y, Gross CP Scope and impact of financial conflicts of interest in biomedical research a systematic review JAMA 2003, 289 (4) 454-65

(79) Kjaergard LL, Is-Nielsen B Association between competing interests and authors' conclusions epidemiological study of randomised clinical trials published in the BMJ BMJ 2002, 325 (7358) 249

(80) ResearchNet Funding opportunities, Canadian Institutes of Health Research, Randomized Controlled Trials 2008 2009 [Online] 2009 January 15 [cited 2010 Jan 2], Available from URL http //www researchnet recherchenet ca/rnl16/viewOpportunityDetails do ?prog=478&view=secdlist&org=CIHR&type=AND&resultCount=25&sort=program&all=1&masterList=true&language=E

(81) Fergusson D, Glass KC, Hutton B, Shapiro S. Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding? Clin 2005, 2 (3). 218-29

(82) Puhan MA, Vollenweider D, Steurer J, Bossuyt PM, ter Riet G Where is the supporting evidence for treating mild to moderate chronic obstructive pulmonary disease exacerbations with antibiotics? A systematic review. BMC Medicine 2008; 6: 28.

(83) Chan A-W Bias, spin, and misreporting: Time for full access to trial protocols and results. PLoS Med 20085(11):e230.

(84) De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al Clinical trial registration: a statement from the International Committee of Medical Journal Editors Croat Med J 2004; 45 (5). 531-2

(85) Adler M, Ziglio 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

(87) Thomson ISI. ISI Web of Knowledge [v 3 0]: ISI Highlycited.com [Online] 2008 [cited 2007 Jul 14]; Available from: URL:http //isiwebofknowledge com/.

(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

(89) Reference Manager [computer program]. Version 11. New York, USA: Thomson Reuters Corporation; 2005.

(90) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al Grading quality of evidence and strength of recommendations BMJ 2004; 328 (7454): 1490.

(91) Balk EM, Bonis PA, Moskowitz H, Schmid CH, Ioannidis JP, Wang C, et al. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. JAMA 2002; 287 (22): 2973-82

(92) Smith PJ, Moffatt ME, Gelskey SC, et al Are community health interventions evaluated appropriately? A review of six journals. J Clin Epidemiol 1997; 50: 137-46

(93) Falagas ME, Grigori T, Ioannidou E A systematic review of trends in the methodological quality of randomized controlled trials in various research fields. J Clin Epidemiol 2009; 62 (3): 227-31.

(94) Lemieux J, Goodwin PJ, Pritchard KI, Gelmon KA, Bordeleau LJ, Duchesne T, et al Identification of cancer care and protocol characteristics associated with recruitment in breast cancer clinical trials. J Clin Oncol 2008; 26: 4458-65.

(95) Robinson KA, Dennison CR, Wayman DM, Pronovost PJ, Needham DM. Systematic review identifies number of strategies important for retaining study participants. J Clin Epidemiol 2007, 60: 757-65.

(96) Tuech JJ, Pessaux P, Moutel G, Thoma V, Schraub S, Herve C Methodological quality and reporting of ethical requirements in phase III cancer trials. J Med Ethics 2005; 31 (5): 251-5.

(97) Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, et al. Factors that limit the quality, number and progress of randomised controlled trials. Health Technol Assess 1999; 3 (20): 1-143.

(98) Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P, Mathieu S, et al. Comparison of registered and published primary outcomes in randomized controlled trials. JAMA 2009; 302 (9): 977-84.

(99) von Elm E, Rollin A, Blumle A, Wischi M, Egger E. Publication and non-publication of clinical trials: longitudinal study of applications submitted to a research ethics committee. Swiss Med Wkly 2008; 138 (13-14): 197-203.

(100) Fernandez CV, Kodish E, Taweel S, Shurin S, Weijer C, Children's Oncology Group Disclosure of the right of research participants to receive research results: an analysis of consent forms in the Children's Oncology Group Cancer 2003; 97 (11). 2904-9.

(101) Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials· a systematic review. J Clin Epidemiol 1999; 52 (12): 1143-56

(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).

(103) Tournoux C, Katsahian S, Chevret S, Levy V Factors influencing inclusion of patients with malignancies in clinical trials Cancer 2006; 106 (2)· 258-70.

(104) Fayter D, McDaid C, Ritchie G, Stirk L, Eastwood A. Systematic review of barriers, modifiers and benefits involved in participation in cancer trials. York, University of York Centre for Reviews and Dissemination; 2006. Report No.: 31.

(105) Djulbegovic B, Lacevic M, Cantor A, Fields KK, Bennett CL, Adams JR, et al. The uncertainty principle and industry-sponsored research. Lancet 2000; 356 (9230): 635-8.

(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.

(107) Min YI, Unalp-Arida A, Scherer R, Dickersin K. Assessment of equipoise using a cohort of randomized controlled trials [abstract]. International Congress on Peer Review and Biomedical Publication; 2005 Sept 16 18, Chicago, Illinois, USA 2005; 47.

(108) Djulbegovic B, Kumar A, Soares HP, Hozo I, Bepler G, Clarke M, et al. Treatment Success in Cancer. Arch Int Med 2008; 168 (6): 632-42.

(109) Joffe S, Harrington DP, George SL, Emanuel EJ, Budzinski LA, Weeks JC Satisfaction of the uncertainty principle in cancer clinical trials: retrospective cohort analysis. BMJ 2004; 328 (7454)· 1463.

(110) Fries JF, Krishnan E Equipoise, design bias, and randomized controlled trials: the elusive ethics of new drug development. Arthritis Res Ther 2004; 6 (3): R250-R255

(111) Kumar A, Soares H, Wells R, Clarke M, Hozo I, Bleyer A, et al. Are experimental treatments for cancer in children superior to established treatments? Observational study of randomised controlled trials by the Children's Oncology Group BMJ 2005; 331: 1295.

(112) Soares HP, Kumar A, Daniels S, Swann S, Cantor A, Hozo I, et al. Evaluation of new treatments in radiation oncology· are they better than standard treatments? JAMA 2005, 293· 970-8.

(113) Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knights R, et al Recruitment to randomised trials: Strategies for trial enrolment and participation study. The STEPS study. Health Technology Assessment 2007; 11 (48): iii-72.

(114) Ah-See KW, Molony NC A qualitative assessment of randomized controlled trials in otolaryngology. J Laryngol Otol 1998; 112 (5): 460-3.

(115) Vickers AJ. Underpowering in randomized trials reporting a sample size calculation J Clin Epidemiol 2003; 56 (8): 717-20

(116) Foy R, Parry J, Duggan A, Delaney B, Wilson S, Lewin-Van Den Broek NT, et al How evidence based are recruitment strategies to randomized controlled trials in primary care? Experience from seven studies. Fam Prac 2003; 20 (1): 83-92

(117) Bottomley A, Efficace F, Thomas R, Vanvoorden V, Ahmedzai S. Health-related quality of life in non small-cell lung cancer methodologic issues in randomized controlled trials J Clin Oncol 2003; 21 (15)· 2982-92

(118) Scholler K, Licht S, Tonn JC, Uhl E, Scholler K, Licht S, et al. Randomized controlled trials in neurosurgery--how good are we? Acta Neurochirurgica 2009; 151 (5)· 519-27

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

(120) Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K Publication bias in clinical trials due to statistical significance or direction of trial results. Cochrane Database Syst Rev 2009; 1 MR000006

(121) Scherer RW, Langenberg P, von EE Full publication of results initially presented in abstracts. Cochrane Database of Systematic Reviews: Reviews Cochrane Database Syst Rev 2007; (2).

(122) Ford JG, Howerton MW, Lai GY, Gary TL, Bolen S, Gibbons MC, et al Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer 2008; 112 (2) 228-42

(123) Mills EJ, Seely D, Rachlis B, Griffith L, Wu P, Wilson K, et al. Barriers to participation in clinical trials of cancer a meta-analysis and systematic review of patient-reported factors Lancet Oncol 2006; 7: 141-8.

(124) Elkins JS, Khatabi T, Fung L, Rootenberg J, Johnston SC. Recruiting subjects for acute stroke trials: a meta-analysis. Stroke 2006, 37 (1). 123-8.

(125) Sood A, Knudsen K, Sood R, Wahner-Roedler DL, Barnes SA, Bardia A, et al. Publication bias for CAM trials in the highest impact factor medicine journals is partly due to geographical bias. J Clin Epidemiol 2007; 60 (11): 1123-6.

(126) Liberati A, Himel HN, Chalmers TC A quality assessment of randomized control trials of primary treatment of breast cancer. J Clin Oncol 1986; 4 (6)· 942-51

(127) Fabricatore AN, Wadden TA, Moore RH, Butryn ML, Gravallese EA, Erondu NE, et al. Attrition from randomized controlled trials of pharmacological weight loss agents: a systematic review and analysis. Obesity Reviews 2009; 10 (3): 333-41

(128) Heo M, Papademetriou E, Meyers BS. Design characteristics that influence attrition in geriatric antidepressant trials: meta-analysis. Int J Geriatr Psychiatry 2009; 24 (9): 990-1001

(129) Rising K, Bacchetti P, Bero L Reporting bias in drug trials submitted to the Food and Drug Administration Review of publication and presentation Plos Medicine 2008, 5 (11) 1561-70

(130) Khan A, Kolts RL, Thase ME, Krishnan KR, Brown W Research design features and patient characteristics associated with the outcome of antidepressant clinical trials Am J Psychiatry 2004, 161 (11) 2045-9

(131) Jones R, Jones RO, McCowan C, Montgomery AA, Fahey T, Jones R, et al The external validity of published randomized controlled trials in primary care BMC Family Practice 2009, 10 5

(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

(135) Wu T, Li Y, Liu G, Bian Z, Li J, Zhang J, et al Investigation of authenticity of 'claimed randomized controlled trials (RCTs) and quality assessment of RCT reports published in China [abstract] XIV Cochrane Colloquium, 2006 October 23 26, Dublin, Ireland 2006, 52

(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

(138) Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine an exploratory analysis of head to head comparison studies of second-generation antipsychotics Am J Psychiatry 2006, 163 (2) 185 94

(139) Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, et al The causes and effects of socio-demographic exclusions from clinical trials Health Technol Assess 2005, 9 (38) iii-iiv

(140) Townsley CA, Selby R, Siu LL Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials J Clin Oncol 2005, 23 (13) 3112 24

(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, Billheimer 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

(145) Mitchell SL, Sullivan EA, Lipsitz LA Exclusion of elderly subjects from clinical trials for Parkinson disease Arch Neurol 1997, 54 (11) 1393-8

(146) 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

(147) Fowler RA. Eligibility criteria of randomized controlled trials. JAMA 2007, 298 (1)· 39.

(148) Shapiro SH, Weijer C, Freedman B. Reporting the study populations of clinical trials Clear transmission or static on the line? J Clin Epidemiol 2000; 53 (10): 973-9.

(149) Montori VM, Wang YG, onso-Coello P, Bhagra S. Systematic evaluation of the quality of randomized controlled trials in diabetes Diabetes Care 2006; 29 (8): 1833-8.

(150) Wei M, Zhang M. An investigation on the quality of randomized controlled trials in 11 non-key medical journals of traditional Chinese medicine from 1995-2000 [abstract]. 12th Cochrane Colloquium: Bridging the Gaps; 2004 Oct 2 6; Ottawa, Ontario, Canada 2004; 201-2.

(151) Lee P, Alexander K, Hammill B, Pasquali S, Peterson E. Representation of elderly persons and women in published randomised trials of acute coronary syndromes. JAMA 2001; 286· 708-13

(152) Uijen AA, Bakx JC, Mokkink HG, van Weel C Hypertension patients participating in trials differ in many aspects from patients treated in general practices. J Clin Epi 2007; 60 (4)· 330-5.

(153) Yuen SY, Pope JE Learning from past mistakes· Assessing trial quality, power and eligibility in non-renal systemic lupus erythematosus randomized controlled trials. Rheumatology 2008, 47 (9)· 1367-72

(154) Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van-der-Laar MA, de-Rooij DJ, et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis 2007, 66 (11) 1473-8

(155) Zetin M, Hoepner CT. Relevance of exclusion criteria in antidepressant clinical trials· a replication study. J Clin Psychopharmacol 2007; 27 (3) 295-301.

(156) Blanco C, Olfson M, Goodwin RD, Ogburn E, Liebowitz MR, Nunes EV, et al. Generalizability of clinical trial results for major depression to community samples· Results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2008, 68 (9): 1276-80

(157) Fortin M, Dionne J, Pinho G, Gignac J, Almirall J, Lapointe L. Randomized controlled trials: do they have external validity for patients with multiple comorbidities? Ann Fam Med 2006; 4 (2): 104-8

(158) Travers J, Marsh S, Williams M, Weatherall M, Caldwell B, Shirtcliffe P, et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? Thorax 2007; 62 (3): 219-23.

(159) Gandhi M, Ameli N, Bacchetti P, Sharp GB, French AL, Young M, et al. Eligibility criteria for HIV clinical trials and generalizability of results: the gap between published reports and study protocols AIDS 2005; 19: 1885-96.

(160) Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. Arch Intern Med 2002; 162 (15)· 1682-8.

(161) Storosum JG, Fouwels A, Gispen-de Wied CC, et al How real are patients in placebo-controlled studies of acute manic episode? Eur Neuropsychopharmacol 2004; 14: 319-23.

(162) Stirman SW, DeRubeis RJ, Crits 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

(163) Masoudi FA, Havranek EP, Wolfe P, Gross CP, Rathore SS, Steiner JF, et al Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure Am Heart J 2003, 146 (2) 250-7

(164) Travers J, Marsh S, Caldwell B, Williams M, Aldington S, Weatherall M, et al External validity of randomized controlled trials in COPD Respir Med 2007, 101 (6) 1313-20

(165) Herland K, Akselsen JP, Skjonsberg OH, Bjermer 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

(166) 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

(167) 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

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

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

(170) Hordijk-Trion M, Lenzen M, Wijns W, de JP, Simoons ML, Scholte op Reimer WJ, et al Patients enrolled in coronary intervention trials are not representative of patients in clinical practice results from the Euro Heart Survey on Coronary Revascularization Eur Heart J 2006, 27 (6) 671-8

(171) 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

(172) Zarin 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

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

(174) Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, et al Participation of patients 65 years of age or older in cancer clinical trials J Clin Oncol 2003, 21 (7) 1383-9

(175) Als-Nielsen B, Chen W, Gluud LL, Siersma V, Hilden J, Gluud C Are trial size and reported methodological quality associated with treatment effects? Observational study of 523 randomised trials [abstract] 12th Cochrane Colloquium Bridging the Gaps, 2004 Oct 2 6, Ottawa, Ontario, Canada 2004, 102-3

(176) Vranos G, Tatsioni A, Polyzoidis K, Ioannidis JP Randomized trials of neurosurgical interventions a systematic appraisal Neurosurgery 2004, 55 (1) 18-25

(177) Auleley GR, Giraudeau B, Baron G, Maillefert JF, Dougados M, Ravaud P The methods for handling missing data in clinical trials influence sample size requirements. J Clin Epidemiol 2004, 57 (5): 447-53.

(178) Varnell SP, Murray DM, Janega JB, Blitstein JL. Design and analysis of group-randomized trials a review of recent practices. Am J Public Health 2004, 94 (3): 393-9.

(179) Welk B, Afshar K, MacNeily AE Randomized controlled trials in pediatric urology room for improvement. J Urol 2006, 176 (1): 306-9.

(180) Breau RH, Carnat TA, Gaboury I. Inadequate statistical power of negative clinical trials in urological literature J Urol 2006; 176 (1): 263-6

(181) Hernández AV, Boersma E, Murray GD, Habbema JD, Steyerberg EW Subgroup analyses in therapeutic cardiovascular clinical trials· are most of them misleading? Am Heart J 2006; 151 (2)· 257-64

(182) Thabut G, Estellat C, Boutron I, Samama CM, Ravaud P Methodological issues in trials assessing primary prophylaxis of venous thrombo-embolism Eur Heart J 2006; 27 (2)· 227-36

(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.

(184) Bailey CS, Fisher CG, Dvorak MF Type II error in the spine surgical literature Spine 2004, 29 (10). 1146-9.

(185) Quinones D, Llorca J, Dierssen T, gado-Rodriguez M Quality of published clinical trials on asthma. J Asthma 2003; 40 (6): 709-19.

(186) Bhandari M, Richards RR, Sprague S, Schemitsch EH. The quality of reporting of randomized trials in the Journal of Bone and Joint Surgery from 1988 through 2000. J Bone Joint Surg Am 2002; 84-A (3): 388-96

(187) Djulbegovic B, Adams JR, Lyman GH, Lacevic M, Hozo I, Greenwich M, et al Evaluation and appraisal of randomized controlled trials in myeloma. Ann Oncol 2001; 12 (11): 1611-7

(188) Esposito M, Coulthard P, Worthington HV, Jokstad A. Quality assessment of randomized controlled trials of oral implants. Int J Oral Maxillofac Implants 2001; 16 (6): 783-92

(189) Lochner HV, Bhandari M, Tornetta P, III. Type-II error rates (beta errors) of randomized trials in orthopaedic trauma. J Bone Joint Surg Am 2001; 83-A (11): 1650-5.

(190) Kjaergard LL, Nikolova D, Gluud C. Randomized clinical trials in HEPATOLOGY· predictors of quality Hepatology 1999; 30 (5): 1134-8.

(191) Moss RL, Henry MC, Dimmitt RA, Rangel S, Geraghty N, Skarsgard ED. The role of prospective randomized clinical trials in pediatric surgery· state of the art? J Pediatr Surg 2001; 36 (8): 1182-6

(192) Kidwell CS, Liebeskind DS, Starkman S, Saver JL. Trends in acute ischemic stroke trials through the 20th century Stroke 2001; 32 (6): 1349-59.

(193) Peduzzi P, Donta S, Iwane M A review of the design of vaccine efficacy trials and a proposal for the design of the VA Cooperative Study of Active Immunotherapy of HIV Infection. Control Clin Trials 1997; 18 (5)· 397-419

(194) Costa L, Xavier A, del Giglio A. Negative results in cancer clinical trials-equivalence or poor accrual? Con Clin Tr 2004, 25 (5): 525-33.

(195) Isaakidis P, Ioannidis JP Evaluation of cluster randomized controlled trials in sub-Saharan Africa Am J Epidemiol 2003, 158 (9): 921-6.

(196) Enwere G. A review of the quality of randomized clinical trials of adjunctive therapy for the treatment of cerebral malaria. Trop Med Int Health 2005; 10 (11). 1171-5

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

(198) Wood AM, White IR, Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. Clin 2004; 1 (4)· 368-76

(199) Freedman KB, Back S, Bernstein J Sample size and statistical power of randomised, controlled trials in orthopaedics Journal of Bone & Joint Surgery British Volume 2001; 83 (3)· 397-402.

(200) Maggard MA, O'Connell JB, Liu JH, Etzioni DA, Ko CY Sample size calculations in surgery· are they done correctly? Surgery 2003; 134 (2)· 275-9.

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

(202) Hall JC, Mills B, Nguyen H, Hall JL. Methodologic standards in surgical trials Surgery 1996, 119 (4): 466-72.

(203) Kondili LA, Taliani G, Tosti ME, De BC, Pasquazzi C, Mele A Methodological issues in papers on IFN therapy time for reappraisal. J Viral Hepat 2000, 7 (3). 184-95

(204) Dickinson K, Bunn F, Wentz R, Edwards P, Roberts I. Size and quality of randomised controlled trials in head injury· review of published studies. BMJ 2000; 320 (7245): 1308-11.

(205) Simpson JM, Klar N, Donnor A. Accounting for cluster randomization: a review of primary prevention trials, 1990 through 1993. Am J Public Health 1995; 85 (10): 1378-83.

(206) Spring B, Pagoto S, Knatterud G, Kozak A, Hedeker D Examination of the analytic quality of behavioral health randomized clinical trials. J Clin Psychol 2007, 63 (1) 53-71

(207) Baron G, Boutron I, Giraudeau B, Ravaud P. Violation of the intent-to-treat principle and rate of missing data in superiority trials assessing structural outcomes in rheumatic diseases. Arthritis Rheum 2005, 52 (6)· 1858-65.

(208) Dimick JB, Diener-West M, Lipsett PA Negative results of randomized clinical trials published in the surgical literature: equivalency or error? Arch Surg 2001; 136 796-800.

(209) Tannock IF. False-positive results in clinical trials: multiple significance tests and the problem of unreported comparisons J Natl Cancer Inst 1996; 88: 206-7.

(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.

(211) Siegfried N, Clarke M, Volmink J, Van der Merwe L. African HIV/AIDS trials are more likely to report adequate allocation concealment and random generation than North American trials PloS ONE 2008; 3 (10): e3491.

(212) Pals SL, Murray DM, Alfano CM, Shadish WR, Hannan PJ, Baker WL. Individually randomized group treatment trials a critical appraisal of frequently used design and analytic approaches. Am J Pub Health 2008; 98 (8). 1418-24.

(213) Pua HL, Lerman J, Crawford MW, Wright JG An evaluation of the quality of clinical trials in anesthesia. Anesthesiology 2001; 95 (5): 1068-73.

(214) Villari P, Manzoli L, Boccia A. Methodological quality of studies and patient age as major sources of variation in efficacy estimates of influenza vaccination in healthy adults: a meta-analysis. Vaccine 2004; 22 (25-26): 3475-86.

(215) Krysan DJ, Kemper AR Claims of equivalence in randomized controlled trials of the treatment of bacterial meningitis in children. Pediatr Infect Dis J 2002; 21 (8)· 753-8

(216) Adamson J, Cockayne S, Puffer S, Torgerson DJ. Review of randomised trials using the post-randomised consent (Zelen's) design. Contemp Clin Trials 2006; 27 (4): 305-19.

(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

(218) Bedard PL, Krzyzanowska MK, Pintilie M, Tannock IF. Statistical power of negative randomized controlled trials presented at American Society for Clinical Oncology annual meetings J Clin Oncol 2007; 25 (23)· 3482-7.

(219) Lamont RF, Khan KS, Beattie B, Cabero RL, Di-Renzo GC, Dudenhausen JW, et al The quality of nifedipine studies used to assess tocolytic efficacy· a systematic review J Perinat Med 2005; 33: 287-95.

(220) Yazici Y, Adler NM, Yazici H Most tumour necrosis factor inhibitor trials in rheumatology are undeservedly called 'efficacy and safety' trials· a survey of power considerations Rheumatology (Oxford) 2008; 47 (7). 1054-7.

(221) Hammerschlag R, Morris MM. Clinical trials comparing acupuncture with biomedical standard care· A criteria-based evaluation of research design and reporting. Complement Ther Med 1997; 5 (3): 133-40.

(222) Gagnier J, Clarke J, Bombardier C. Methodological quality of randomized controlled intervention trials of spinal disorders [abstract]. 12th Cochrane Colloquium· Bridging the Gaps; 2004 Oct 2 6; Ottawa, Ontario, Canada 2004; 92-3.

(223) Murray DM, Pals SL, Blitstein JL, Alfano CM, Lehman J. Design and analysis of group-randomized trials in cancer: A review of current practices Journal of the National Cancer Institute 2008; 100 (7)· 483-91.

(224) Eldridge S, Ashby D, Bennett C, Wakelin M, Feder G. Internal and external validity of cluster randomised trials: Systematic review of recent trials. Br Med J 2008; 336 (7649): 876-80.

(225) Falagas ME, Pitsouni EI, Bliziotis IA. Trends in the methodological quality of published randomized controlled trials on antibacterial agents. Br J Clin Pharmacol 2008; 65 (6): 942-54.

(226) Lesaffre E, Garcia Zattera M-J, Redmond C, Huber H, Needleman I. Reported methodological quality of split-mouth studies. Journal of Clinical Periodontology 2007; 34 (9): 756-61.

(227) Magazın A, Kumar A, Soares H, Hozo I, Schell M, Djulbegovıc B Empırıcal ınvestıgatıon of optımısm bıas Oral presentatıon at the 16th Cochrane Colloquıum Evıdence ın the era of globalısatıon, 2008 Oct 3-7, Freıburg, Germany [abstract] Zeıtschrıft fur Evıdenz , Fortbıldung und Qualıtat ım Gesundheıtswesen 2008, 102 9

(228) Rıdgeway D, Khan A, Rıdgeway G, Cıerpıal MA, Lıneberry CG Subject numbers and placebo outcome varıabılıty ın clınıcal trıals of new CNS medıcatıons Drug Inf J 2007, 41 701-8

(229) Greenfield ML, Mhyre JM, Mashour GA, Blum JM, Yen EC, Rosenberg AL, et al Improvement ın the qualıty of randomızed controlled trıals among general anesthesıology journals 2000 to 2006 a 6-year follow-up Anesth Analg 2009, 108 (6) 1916-21

(230) Martıns RG, Fınkelstein DM, Selden MV The ımportance of beta, type II error, ın negatıve trıals ın oncology Proc Am Soc Clın Oncol 1997, 15 415a (abstr 1482)

(231) Oh K, Kım K-S, Park J-W, Kang J Qualıty evaluatıon of randomızed controlled trıals on complementary and alternatıve medıcıne Asıan Nursıng Research 2007, 1 (3) 153-64

(232) Pagoto SL, Kozak AT, John P, Bodenlos JS, Hedeker D, Sprıng B, et al Intentıon to Treat Analyses ın Behavıoral Medıcıne Randomızed Clınıcal Trıals Int J Behav Med 2009, Epub ahead of prınt

(233) Watson JM, Torgerson DJ Increasıng recruıtment to randomısed trıals a revıew of randomısed controlled trıals BMC Med Res Methodol 2006, 6 (1) 34

(234) Mapstone J, Elbourne D, Roberts I Strategıes to ımprove recruıtment to research studıes Cochrane Database of Systematıc Revıews Revıews Cochrane Database Syst Rev 2007, (2)

(235) Raftery J, Bryant J, Powell J, Kerr C, Hawker S Payment to healthcare professıonals for patıent recruıtment to trıals Systematıc revıew and qualıtatıve study Health Technology Assessment 2008, 12 (10) iii-87

(236) Laı GY, Gary TL, Tılburt J, Bolen S, Baffı C, Wılson RF, et al Effectıveness of strategıes to recruıt underrepresented populatıons ınto cancer clınıcal trıals Clın 2006, 3 (2) 133-41

(237) Yancey AK, Ortega AN, Kumanyıka SK Effectıve recruıtment and retentıon of mınorıty research partıcıpants Annu Rev Publıc Health 2006, 27 1-28

(238) Abraham NS, Young JM, Solomon MJ A systematıc revıew of reasons for nonentry of eligıble patıents ınto surgıcal randomızed controlled trıals Surgery 2006, 139 (4) 469-83

(239) UyBıco SJ, Pavel S, Gross CP Recruıtıng vulnerable populatıons ınto research a systematıc revıew of recruıtment ınterventıons J Gen Intern Med 2007, 22 (6) 852-63

(240) van Nieuwenhoven CA, Buskens E, van Tıel FH, Bonten MJ Relatıonshıp between methodologıcal trıal qualıty and the effects of selectıve dıgestıve decontamınatıon on pneumonıa and mortalıty ın crıtıcally ıll patıents JAMA 2001, 286 (3) 335-40

(241) Bjorn M, Brendstrup C, Karlsen S, Carlsen JE Consecutıve screenıng and enrollment ın clınıcal trıals the way to representatıve patıent samples? J Card Fail 1998, 4 (3) 225-30

(242) Haıdıch AB, Ioannıdıs JP Effect of early patıent enrollment on the tıme to completıon and publıcatıon of randomızed controlled trıals Am J Epıdemıol 2001, 154 873-80

(243) Monaghan H, Richens A, Colman S, Currie R, Girgis S, Jayne K, et al A randomised trial of the effects of an additional communication strategy on recruitment into a large scale, multi centre trial Contemp Clin Trials 2007, 28 1-5

(244) Tworoger SS Yasui YUCN Mailing strategies and recruitment into an intervention trial of the exercise effect on breast cancer biomarkers Cancer Epidemiol Biomarkers Prev 2002, 11 (1) 73-7

(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

(246) Miller NL, Markowitz JC, Kocsis JH, Leon AC, Brisco ST, Garno JL Cost effectiveness of screening for clinical trials by research assistants versus senior investigators J Psychiatr Res 1999, 33 (2) 81 5

(247) Fleissig A, Jenkins V, Fallowfield L Results of an intervention study to improve communication about randomised clinical trials of cancer therapy Eur J Cancer 2001, 37 (3) 322-31

(248) Kimmick GG, Peterson BL, Kornblith AB, Mandelblatt J, Johnson JL, Wheeler J, et al Improving accrual of older persons to cancer treatment trials a randomized trial comparing an educational intervention with standard information CALGB 360001 J Clin Oncol 2005, 23 (10) 2201-7

(249) Du W, Mood D, Gadgeel S, Simon MS An educational video to increase clinical trials enrollment among lung cancer patients Journal of Thoracic Oncology 2008, 3 (1) 23 9

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

(251) Donovan JL, Peters TJ, Noble S, Powell P, Gillatt D, Oliver SE, et al Who can best recruit to randomized trials? Randomized trial comparing surgeons and nurses recruiting patients to a trial of treatments for localized prostate cancer (the ProtecT study) J Clin Epidemiol 2003, 56 (7) 605-9

(252) Larkey LK, Staten LK, Ritenbaugh C, et al Recruitment of spanish women to the Women's Health Initiative the case of Embajadoras in Arizona Con Clin Tr 2002, 23 289-98

(253) Ford ME, Havstad SL, Davis SD A randomized trial of recruitment methods for older African American men in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Clin 2004, 1 343-51

(254) Kiernan M, Phillips K, Fair JM, King AC Using direct mail to recruit Hispanic adults into a dietary intervention an experimental study Ann Behav Med 2000, 22 (1) 89-93

(255) Kendrick D, Watson M, Dewey M, Woods AJ Does sending a home safety questionnaire increase recruitment to an injury prevention trial? A randomised controlled trial J Epidemiol Community Health 2001, 55 (11) 845 6

(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

(257) Aaronson NK, Visser Pol E, Leenhouts GH, Muller MJ, van der Schot AC, van Dam FS, et al Telephone-based nursing intervention improves the effectiveness of the informed consent process in cancer clinical trials J Clin Oncol 1996, 14 (3) 984-96

(258) Valanis B, Blank J, Glass A Mailing strategies and costs of recruiting heavy smokers in CARET, a large chemoprevention trial Control Clin Trials 1998, 19 (1) 25-38

(259) Gilbody S, Bower P, Torgerson D, Richards D. Cluster randomized trials produced similar results to individually randomized trials in a meta-analysis of enhanced care for depression J Clin Epidemiol 2008; 61: 160-8.

(260) Khan KS, Daya S, Collins JA, Walter SD Empirical evidence of bias in infertility research overestimation of treatment effect in crossover trials using pregnancy as the outcome measure. Fertility and Sterility 1996; 65 (5): 939-45.

(261) Katz J, Finnerup NB, Dworkin RH. Clinical trial outcome in neuropathic pain: relationship to study characteristics. Neurology 2008; 70 (4): 263-72.

(262) Lathyris D, Trikalinos TA, Ioannidis JPA. Evidence from crossover trials: Empirical evaluation and comparison against parallel arm trials. Int J Epidemiol 2007; 36 (2): 422-30

(263) Rabinowitz J, Levine SZ, Barkai O, Davidov O, Rabinowitz J, Levine SZ, et al Dropout rates in randomized clinical trials of antipsychotics: a meta-analysis comparing first- and second-generation drugs and an examination of the role of trial design features. Schizophrenia Bulletin 2009; 35 (4): 775-88.

(264) Papakostas GI, Fava M, Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD European Neuropsychopharmacology 2009; 19 (1): 34-40.

(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

(266) Verhagen AP, de Vet HC, Vermeer F, Widdershoven JW, de Bie RA, Kessels AG, et al. The influence of methodologic quality on the conclusion of a landmark meta-analysis on thrombolytic therapy Int J Technol Assess Health Care 2002; 18 (1). 11-23.

(267) Verhagen AP, de Bie RA, Lenssen AF, de Vet HC, Kessels AG, Boers M, et al. Impact of quality items on study outcome Treatments in acute lateral ankle sprains. Int J Technol Assess Health Care 2000; 16 (4). 1136-46

(268) Djulbegovic B, Cantor A, Clarke M The importance of preservation of the ethical principle of equipoise in the design of clinical trials: relative impact of the methodological quality domains on the treatment effect in randomized controlled trials. Account Res 2003; 10 (4): 301-15.

(269) Wahlbeck K, Tuunainen A, Gilbody S, Adams CE. Influence of methodology on outcomes of randomised clozapine trials Pharmacopsychiatry 2000; 33 (2): 54-9.

(270) Linde K, Scholz M, Ramirez G, Clausius N, Melchart D, Jonas WB. Impact of study quality on outcome in placebo-controlled trials of homeopathy. J Clin Epidemiol 1999; 52 (7): 631-6.

(271) Abrahamyan L, Johnson SR, Beyene J, Shah PS, Feldman BM. Quality of randomized clinical trials in juvenile idiopathic arthritis. Rheumatology (Oxford) 2008; 47 (5): 640-5

(272) Morrison B, Lilford RJ, Ernst E. Methodological rigour and results of clinical trials of homoeopathic remedies. Perfusion 2000; 13: 132-8.

(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

(274) Fahey T, Hyde C, Milne R, Thorogood M. The type and quality of randomized controlled trials (RCTs) published in UK public health journals. J Public Health Med 1995; 17 (4) 469-74.

(275) Liu J, Kjaergard LL, Gluud C Misuse of randomization: a review of Chinese randomized trials of herbal medicines for chronic hepatitis B Am J Chin Med 2002, 30 (1): 173-6

(276) Shakespeare TP, Thiagarajan A, Gebski V Evaluation of the quality of radiotherapy randomized trials for painful bone metastases Cancer 2005; 103 (9): 1976-81.

(277) Wahlbeck K, Adams C, Thornley B. Much to improve: A survey of controlled Nordic schizophrenia trials. Nordic Journal of Psychiatry 2000; 54 (2): 105-8

(278) Khan KS, Daya S, Jadad A. The importance of quality of primary studies in producing unbiased systematic reviews. Arch Intern Med 1996; 156 (6): 661-6

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

(280) Zhang J, Wu T. Quality analysis of literatures on clinical randomized controlled trial of pre-eclampsia treated with TCM [abstract]. XIII Cochrane Colloquium; 2005 Oct 22 26, Melbourne, Australia 2005; 88

(281) Anyanwu AC, Treasure T Surgical research revisited: clinical trials in the cardiothoracic surgical literature Eur J Cardiothorac Surg 2004, 25 299-303

(282) Hill CL, LaValley MP, Felson DT. Secular changes in the quality of published randomized clinical trials in rheumatology Arthritis Rheum 2002; 46 (3): 779-84

(283) Campbell H, Surry SA, Royle EM A review of randomised controlled trials published in Archives of Disease in Childhood from 1982-96. Arch Dis Child 1998; 79 (2) 192-7.

(284) Montenegro R, Needleman I, Moles D, Tonetti M. Quality of RCTs in periodontology - a systematic review J Dent Res 2002; 81 (12): 866-70.

(285) Kjaergard LL, Gluud C Funding, disease area, and internal validity of hepatobiliary randomized clinical trials. Am J Gastroenterol 2002; 97 (11). 2708-13.

(286) Zhang J, Wu T, Xie L, Yan Q. Authenticity investigation and quality assessment of claimed randomized controlled trials on upper respiratory infection [abstract]. 2006 p. 177.

(287) Verberk WJ, Kroon AA, Kessels AG, Nelemans PJ, Van Ree JW, Lenders JW, et al. Comparison of randomization techniques for clinical trials with data from the HOMERUS-trial. Blood Press 2005; 14 (5): 306-14.

(288) Koes BW, Malmivaara A, van Tulder MW. Trend in methodological quality of randomised clinical trials in low back pain Baillieres Best Pract Res Clin Rheumatol 2005; 19 (4): 529-39.

(289) Kunz R, Vist G, Oxman AD Randomisation to protect against selection bias in healthcare trials. Cochrane Database Syst Rev 2007; (2): MR000012.

(290) Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study BMJ 2008, 336 (7644) 601-5

(291) Kyriakidi M, Ioannidis JP. Design and quality considerations for randomized controlled trials in systemic sclerosis. Arthritis Rheum 2002; 47 (1): 73-81.

(292) Fenwick J, Needleman IG, Moles DR. The effect of bias on the magnitude of clinical outcomes in periodontology. A pilot study Journal of Clinical Periodontology 2008; 35 (9) 775-82

(293) Verhagen AP, de Vet HCW, Willemsen S, Stijnen T A meta-regression analysis shows no impact of design characteristics on outcome in trials on tension-type headaches. J Clin Epidemiol 2008; 61 (8): 813-8.

(294) Vlad SC, LaValley MP, McAlindon TE, Felson DT. Glucosamine for pain in osteoarthritis: why do trial results differ? Arthritis and Rheumatism 2007; 56 2267-77.

(295) Hewitt C, Hahn S, Torgerson DJ, Watson J, Bland JM. Adequacy and reporting of allocation concealment: review of recent trials published in four general medical journals. BMJ 2005; 330 (7499): 1057-8.

(296) Poolman RW, Struijs PAA, Krips R, Sierevelt IN, Marti RK, Farrokhyar F, et al. Reporting of outcomes in orthopaedic randomized trials: Does blinding of outcome assessors matter? J Bone Joint Surg Am 2007, 89 (3) 550-8

(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

(298) Akl EA, Muti P, Cook DJ, Puhan MA, Schunemann HJ, Montori VM, et al. Systematic evaluation of the quality of randomized controlled trials of anticoagulation in patients with cancer [abstract]. XV Cochrane Colloquium; 2007 Oct 23 27; Sao Paulo, Brazil 2007; 165-6

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

(300) Doig GS, Simpson F, Delaney A. A review of the true methodological quality of nutritional support trials conducted in the critically ill: time for improvement. Anesth Analg 2005; 100 (2). 527-33

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

(302) Wang Q, Wu T, Gao X, Chen X Quality analysis of randomized controlled trials on Chinese medicinal herbs for unstable angina pectoris [abstract]. XIII Cochrane Colloquium; 2005 Oct 22 26, Melbourne, Australia 2005, 99.

(303) Karanicolas PJ, Bhandari M, Taromi B, Akl EA, Bassler D, Alonso-Coello P, et al. Blinding of outcomes in trials of orthopaedic trauma: an opportunity to enhance the validity of clinical trials. J Bone Joint Surg Am 2008; 90 (5). 1026-33.

(304) Pienaar ED, Volmink J, Zwarenstein M, Swingler GH Randomised trials in the South African Medical Journal, 1948-1997. SAMJ , S 2002; Suid-Afrikaanse Tydskrif Vir Geneeskunde. 92 (11): 901-3

(305) Puffer S, Torgerson D, Watson J. Evidence for risk of bias in cluster randomised trials: review of recent trials published in three general medical journals. [4 refs]. BMJ 2003; 327 (7418): 785-9

(306) Bian ZX, Li YP, Moher D, Dagenais S, Liu L, Wu TX, et al. Improving the quality of randomized controlled trials in Chinese herbal medicine, part I: clinical trial design and methodology Zhong Xi Yi Jie He Xue Bao 2006; 4 (2). 120-9.

(307) Boots I, Van DE, Kuin L, Offringa M, Caron H, Kremer L. Methodological quality of randomised controlled trials in paediatric oncology published in 2001 and 2002 [abstract]. 12th Cochrane Colloquium: Bridging the Gaps; 2004 Oct 2 6; Ottawa, Ontario, Canada 2004; 92.

(308) Manriquez J, Valdivia G, Rada G, Letelier LM. Critical assessment of randomized controlled trials published in biomedical Chilean journals [abstract]. XIV Cochrane Colloquium; 2006 October 23 26; Dublin, Ireland 2006; 81.

(309) 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

(310) Llorca J, Martinez-Sanz F, Prieto-Salceda D, Farinas-Alvarez C, Chinchon MV, Quinones D, et al. Quality of controlled clinical trials on glaucoma and intraocular high pressure. J Glaucoma 2005; 14 (3): 190-5

(311) Strippoli GF, Craig JC, Schena FP The number, quality, and coverage of randomized controlled trials in nephrology J Am Soc Nephrol 2004; 15 (2): 411-9

(312) Kjaergard LL, Frederiksen SL, Gluud C Validity of randomized clinical trials in gastroenterology from 1964-2000 Gastroenterology 2002, 122 (4) 1157-60

(313) Chalmers TC, Celano P, Sacks HS, Smith H, Jr. Bias in treatment assignment in controlled clinical trials. N Engl J Med 1983; 309 (22): 1358-61.

(314) Egger M, Juni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study Health Technol Assess 2003; 7 (1): 1-76.

(315) Ioannidis JP, Cappelleri JC, Sacks HS, Lau J The relationship between study design, results, and reporting of randomized clinical trials of HIV infection. Control Clin Trials 1997; 18 (5): 431-44

(316) Crawford CC, Huynh MT, Kepple A, Jonas WB, Crawford CC, Huynh MT, et al. Systematic assessment of the quality of research studies of conventional and alternative treatment(s) of primary headache. Pain Physician 2009; 12 (2): 461-70.

(317) Miller JN, Colditz GA, Mosteller F. How study design affects outcomes in comparisons of therapy. II· Surgical. Stat Med 1989; 8 (4). 455-66.

(318) Colditz GA, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy I: Medical. Stat Med 1989; 8 (4): 441-54.

(319) Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials· a reflection of treatment effect or adverse events? JAMA 2003; 290 (7)· 921-8.

(320) Garcia-Alamino JM, Perrotta C, Clope´s A, Parera A, Pe´rez-de-la-Ossa N, Bonfill X. Description of controlled trials published in methods and findings,1979-2002. Methods and Findings in Experimental and Clinical Pharmacology 2006, 28 (8): 527-31.

(321) Duan X, Zhou L, Wu T Analyzing the quality of clinical randomized control trial of traditional Chinese medicine for coronary heart disease (CHD) [abstract]. XIII Cochrane Colloquium; 2005 Oct 22 26; Melbourne, Australia 2005; 101.

(322) Roberts L, Counsell C. Assessment of clinical outcomes in acute stroke trials. Stroke 1998, 29 (5) 986-91.

(323) Cowan J, Lozano CS, Ring D. Quality of prospective controlled randomized trials. Analysis of trials of treatment for lateral epicondylitis as an example. Journal of Bone and Joint Surgery 2007; 89· 1693-9

(324) Park J, White AR, Stevinson C, Ernst E Who are we blinding? A systematic review of blinded clinical trials Perfusion 2001; 14 (8): 296

(325) Hróbjartsson A, Pildal J, Chan A-W, Haahr MT, Altman DG, Gøtzsche PC. Reporting on blinding in trial protocols and corresponding publications was often inadequate but rarely contradictory. J Clin Epidemiol 2009; 62 (9): 967-73.

(326) Dumbrigue HB, Jones JS, Esquivel JF Control of bias in randomized controlled trials published in prosthodontic journals J Prosthet Dent 2001; 86 (6): 592-6

(327) Tang J-L, Zhan S-Y, Ernst E Review of randomised controlled trials of traditional Chinese medicine. Br Med J 1999; 318 (7203)· 160-1.

(328) D'Amico FJ Assessing statistical analyses of clinical trials· primer in statistical methods for thoracic surgeons. Semin Thorac Cardiovasc Surg 2003; 15 (4): 386-96.

(329) EU-PSI-Consortium PsiTri - a survey of the state of the mental health trials. 10th Cochrane Colloquium Abstracts, 31 July 3 August 2002 in Stavanger 2002; 48.

(330) Haahr MT, Hróbjartsson A. Who is blinded in randomized clinical trials? A study of 200 trials and a survey of authors Clin 2006, 3 (4): 360-5.

(331) Devereaux PJ, Manns BJ, Ghali WA, Quan H, Lacchetti C, Montori VM, et al. Physician interpretations and textbook definitions of blinding terminology in randomized controlled trials. JAMA 2001; 285 (15): 2000-3.

(332) Noseworthy JH, Ebers GC, Vandervoort MK, Farquhar RE, Yetisir E, Roberts R. The impact of blinding on the results of a randomized, placebo-controlled multiple sclerosis clinical trial Neurology 1994; 44 (1) 16-20.

(333) Karassa FB, Tatsioni A, Ioannidis JP. Design, quality, and bias in randomized controlled trials of systemic lupus erythematosus. J Rheumatol 2003; 30 (5): 979-84

(334) Avenell A, Grant AM, McGee M, McPherson G, Campbell MK, McGee MA, et al The effects of an open design on trial participant recruitment, compliance and retention--a randomized controlled trial comparison with a blinded, placebo-controlled design. Clin 2004; 1 (6)· 490-8

(335) Hemminki E, Hovi SL, Veerus P, Sevon T, Tuimala R, Rahu M, et al Blinding decreased recruitment in a prevention trial of postmenopausal hormone therapy. J Clin Epidemiol 2004; 57 (12): 1237-43.

(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

nonsteroidal antiinflammatory drug trials for arthritis treatment J Clin Epidemiol 1999; 52 (2): 113-22.

(337) Kamper SJ, Machado LA, Herbert RD, Maher CG, McAuley JH Trial methodology and patient characteristics did not influence the size of placebo effects on pain. J Clin Epidemiol 2008; 61 256-60.

(338) Sneed JR, Rutherford BR, Rindskopf D, Lane DT, Sackeim HA, Roose SP. Design makes a difference: a meta-analysis of antidepressant response rates in placebo-controlled versus comparator trials in late-life depression. Am J Geriatr Psychiatry 2008, 16 (1)· 65-73.

(339) Rutherford BR, Sneed JR, Roose SP Does study design influence outcome?. The effects of placebo control and treatment duration in antidepressant trials. Psychother Psychosom 2009; 78 (3): 172-81

(340) Soares HP, Djulbegovic B, Kumar A, Tanvetyanon T, Bepler G. Evaluation of publicly-sponsored lung cancer trials in US: are experimental treatments better than the control ones? [abstract] Journal of Clinical Oncology Supplement 2006; 24 (18S): 403s.

(341) Khan A, Khan SR, Walens G, Kolts R, Giller EL. Frequency of positive studies among fixed and flexible dose antidepressant clinical trials: an analysis of the food and drug administration summary basis of approval reports. Neuropsychopharmacology 2003; 28 (3)· 552-6

(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.

(343) Nieto A, Mazon A, Pamies R, Linana JJ, Lanuza A, Jime´nez FO, et al. Adverse effects of inhaled corticosteroids in funded and nonfunded studies. Arch Intern Med 2007; 167 (19)· 2047-53.

(344) Chappell L, Alfirevich Z, Chien 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.

(345) Van Luijn JCF, Van Loenen AC, Gribnau FWJ, Leufkens HGM. Choice of comparator in active control trials of new drugs. Annals of Pharmacotherapy 2008, 42 (11). 1605-12.

(346) Huang HY, Maguire MG, Miller ER, III, Appel LJ. Impact of pill organizers and blister packs on adherence to pill taking in two vitamin supplementation trials. Am J Epidemiol 2000; 152 (8): 780-7.

(347) Welton AJ, Vickers MR, Cooper JA, Meade TW, Marteau TM. Is recruitment more difficult with a placebo arm in randomised controlled trials? A quasirandomised, interview based study. Br Med J 1999; 318 (7191): 1114-7.

(348) Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome BMJ 2008; 336 (7651): 999-1003.

(349) de Craen AJ, Roos PJ, de Vries AL, Kleijnen J. Effect of colour of drugs: systematic review of perceived effect of drugs and of their effectiveness. BMJ 1996; 313 (7072)· 1624-6.

(350) Lee S, Walker JR, Jakul L, Sexton K. Does elimination of placebo responders in a placebo run-in increase the treatment effect in randomized clinical trials? A meta-analytic evaluation Depression and Anxiety 2004; 19 (1). 10-9

(351) Gilbody S, Bower P, Sutton AJ. Randomized trials with concurrent economic evaluations reported unrepresentatively large clinical effect sizes. J Clin Epidemiol 2007; 60 (8): 781-6

(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

(353) Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008; 358 (3): 252-60.

(354) Al-Marzouki S, Roberts I, Evans S, Marshall T. Selective reporting in clinical trials: analysis of trial protocols accepted by the Lancet Lancet 2008; 372 (9634): 201.

(355) Bhandari M, Whang W, Kuo JC, Devereaux PJ, Sprague S, Tornetta P, III The risk of false-positive results in orthopaedic surgical trials Clin Orthop 2003; 63-9

(356) Efficace F, Horneber M, Lejeune S, Van DF, Leering S, Rottmann M, et al. Methodological quality of patient-reported outcome research was low in complementary and alternative medicine in oncology. J Clin Epidemiol 2006; 59 (12) 1257-65

(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.

(358) Hahn S, Williamson PR, Hutton JL Investigation of within-study selective reporting in clinical research: follow-up of applications submitted to a local research ethics committee J Eval Clin Pract 2002, 8 (3). 353-9

(359) Lane SJ, Heddle NM, Arnold E, Walker I A review of randomized controlled trials comparing the effectiveness of hand held computers with paper methods for data collection. BMC Med Inform Decis Mak 2006; 6: 23

(360) Howerton MW, Gibbons MC, Baffi CR, Gary TL, Lai GY, Bolen S, et al. Provider roles in the recruitment of underrepresented populations to cancer clinical trials Cancer 2007, 109 (3). 465-76.

(361) Dale O, Hagen KB. Despite technical problems personal digital assistants outperform pen and paper when collecting patient diary data J Clin Epidemiol 2007; 60 (1): 8-17.

(362) Gwaltney CJ, Shields AL, Shiffman S. Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. Value Health 2008; 11 (3): 322-33.

(363) Kryworuchko J, Stacey D, Bennett C, Graham ID, Kryworuchko J, Stacey D, et al. Appraisal of primary outcome measures used in trials of patient decision support. Patient Educ Couns 2008; 73 (3): 497-503

(364) Marshall M, Lockwood A, Bradley C, Adams C, Joy C, Fenton M. Unpublished rating scales: a major source of bias in randomised controlled trials of treatments for schizophrenia. Br J Psychiatry 2000; 176: 249-52

(365) Bent S, Padula A, Avins AL. Brief communication: Better ways to question patients about adverse medical events: a randomized, controlled trial.[erratum appears in Ann Intern Med. 2006 Jul 18,145(2):156]. Ann Intern Med 2006; 144 (4): 257-61.

(366) Litchfield J, Freeman J, Schou H, Elsley M, Fuller R, Chubb B. Is the future for clinical trials internet-based? A cluster randomised clinical trial. Clin Tr 2005; 2 (1) 72-9.

(367) Bedard M, Molloy DW, Standish T, Guyatt GH, D'Souza J, Mondadori C, et al. Clinical trials in cognitively impaired older adults home versus clinic assessments. J Am Geriatr Soc 1995; 43 (10): 1127-30.

(368) Jasperse DM, Ahmed SW The Mid-Atlantic Oncology Program's comparison of two data collection methods. Control Clin Trials 1989; 10 (3): 282-9.

(369) Guyatt GH, Townsend M, Keller JL, Singer J. Should study subjects see their previous responses data from a randomized control trial. J Clin Epidemiol 1989; 42 (9): 913-20.

(370) Renfroe EG, Heywood G, Foreman L, Schron E, Powell J, Baessler C, et al. The end-of-study patient survey methods influencing response rate in the AVID Trial.[erratum appears in Control Clin Trials 2002 Dec,23(6).774]. Control Clin Trials 2002; 23: 521-33

(371) Couper MP, Peytchev A, Strecher VJ, Rothert K, Anderson J Following up nonrespondents to an online weight management intervention: Randomized trial comparing mail versus telephone Journal of Medical Internet Research 2007; 9 (2): e16

(372) Bowen D, Thornquist M, Goodman G, Omenn GS, Anderson K, Barnett M, et al Effects of incentive items on participation in a randomized chemoprevention trial Journal of Health Psychology 2000; 5 (1): 109-15

(373) Ford ME, Havstad S, Vernon SW, Davis SD, Kroll D, Lamerato L, et al Enhancing adherence among older African American men enrolled in a longitudinal cancer screening trial Gerontologist 2006, 46 (4) 545-50.

(374) Reynolds-Haertle RA, McBride R Single vs double data entry in CAST. Con Clin Tr 1992, 13. 487-94.

(375) Lienard J-L, Quinaux E, Fabre-Guillevin E, Piedbois P, Jouhaud A, Decoster G, et al. Impact of on-site initiation visits on patient recruitment and data quality in a randomized trial of adjuvant chemotherapy for breast cancer Clin 2006; 3 (5) 486-92

(376) Bloom BS, de PN, Libert S Classic or Bayesian research design and analysis Does it make a difference? Int J Technol Assess Health Care 2002; 18 (1): 120-6

(377) Porta N, Bonet C, Cobo E. Discordance between reported intention-to-treat and per protocol analyses. J Clin Epidemiol 2007; 60 (7): 663-9

(378) Bath PM, Gray LJ, Collier T, Pocock S, Carpenter J Can we improve the statistical analysis of stroke trials? Statistical reanalysis of functional outcomes in stroke trials. Stroke 2007; 38: 1911-5

(379) Tierney JF, Stewart LA. Investigating patient exclusion bias in meta-analysis. Int J Epidemiol 2005; 34 (1): 79-87

(380) Bhaskar R, Reitman D, Sacks HS, Smith H, Jr., Chalmers TC. Loss of patients in clinical trials that measure long-term survival following myocardial infarction. Control Clin Trials 1986, 7 (2): 134-48.

(381) Blumberg N, Zhao H, Wang H, Messing S, Heal JM, Lyman GH. The intention-to-treat principle in clinical trials and meta-analyses of leukoreduced blood transfusions in surgical patients Transfusion 2007; 47 (4): 573-81

(382) Rabinowitz J, Davidov O, Rabinowitz J, Davidov O. A composite approach that includes dropout rates when analyzing efficacy data in clinical trials of antipsychotic medications. Schizophrenia Bulletin 2008; 34 (6): 1145-50.

(383) Brittain E, Lin D. A comparison of intent-to-treat and per-protocol results in antibiotic non-inferiority trials. Stat Med 2005; 24 (1): 1-10.

(384) Abraha I, Duca PG, Montedori A. Empirical evidence of bias: modified intention to treat analysis of randomised trials affects estimates of intervention efficacy. Oral presentation at the 16th Cochrane Colloquium: Evidence in the era of globalisation; 2008 Oct 3-7; Freiburg, Germany [abstract]. Zeitschrift fur Evidenz , Fortbildung und Qualitat im Gesundheitswesen 2008; 102: 9.

(385) Verret WJ, Dorsey G, Nosten F, Price RN, Verret WJ, Dorsey G, et al The effect of varying analytical methods on estimates of anti-malarial clinical efficacy Malaria Journal 2009; 8: 77

(386) Melander H, hlqvist-Rastad J, Meijer G, Beermann B Evidence b(i)ased medicine--selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. BMJ 2003; 326 (7400). 1171-3.

(387) Lancaster T, Stead L. Dealing with drop-outs in clinical trials and meta-analyses 7th Annual Cochrane Colloquium Abstracts, October 1999 in Rome 1999.

(388) 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.

(389) Otwombe KN, Ogutu B. Intention-to-treat analysis in the chronic suppurative otitis media trials. East Afr Med J 2003; 80 (6): 308-11.

(390) Kruse RL, Alper BS, Reust C, Stevermer JJ, Shannon S, Williams RH. Intention-to-treat analysis: who is in? Who is out?[erratum appears in J Fam Pract. 2002 Dec;51(12):1079]. J Fam Pract 2002; 51 (11): 969-71.

(391) Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ 1999, 319 (7211): 670-4

(392) Bhandari M, Devereaux PJ, Li P, Mah D, Lim K, Schunemann HJ, et al. Misuse of baseline comparison tests and subgroup analyses in surgical trials. Clinical Orthopaedics and Related Research 2006; 447: 247-51.

(393) Assmann SF, Pocock SJ, Enos LE, et al Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 2000; 355: 1064-9

(394) Abraha I, Montedori 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.

(395) Gravel J, Opatrny L, Shapiro S The intention-to-treat approach in randomized controlled trials: are authors saying what they do and doing what they say? Clin 2007; 4 (4): 350-6.

(396) Jansen ML, Schwartz F. Analysis by intention to treat in randomized clinical trials: a survey of the literature [abstract] Control Clin Trials 1996; 17 (2 Suppl): 51S.

(397) Burnside G, Pine CM, Williamson PR. Statistical aspects of design and analysis of clinical trials for the prevention of caries Caries Res 2006; 40 (5). 360-5.

(398) Parienti JJ, Verdon R, Massari V Methodological standards in non-inferiority AIDS trials: moving from adherence to compliance. BMC Med Res Methodol 2006; 6 46.

(399) Houck PR, Mazumdar S, Koru-Sengul T, Tang G, Mulsant BH, Pollock BG, et al Estimating treatment effects from longitudinal clinical trial data with missing values comparative analyses using different methods. Psychiatry Res 2004; 129 (2): 209-15.

(400) Peduzzi P, Wittes J, Detre K, Holford T Analysis as-randomized and the problem of non-adherence: an example from the Veterans Affairs Randomized Trial of Coronary Artery Bypass Surgery. Stat Med 1993, 12 (13): 1185-95

(401) Raboud JM, Montaner JS, Thorne A, Singer J, Schechter MT Impact of missing data due to dropouts on estimates of the treatment effect in a randomized trial of antiretroviral therapy for HIV-infected individuals Canadian HIV Trials Network A002 Study Group Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 1996, 12 (1): 46-55

(402) Wu AW, Gray SM, Brookmeyer R Application of random effects models and other methods to the analysis of multidimensional quality of life data in an AIDS clinical trial. Med Care 1999, 37 (3) 249-58

(403) Fairclough DL, Peterson HF, Cella D, Bonomi P. Comparison of several model-based methods for analysing incomplete quality of life data in cancer clinical trials. Stat Med 1998; 17 (5-7): 781-96.

(404) Nich C, Carroll K Now you see it, now you don't a comparison of traditional versus random-effects regression models in the analysis of longitudinal follow-up data from a clinical trial J Consult Clin Psychol 1997; 65 (2): 252-61

(405) Heitjan DF. Causal inference in a clinical trial a comparative example. Control Clin Trials 1999; 20 (4): 309-18.

(406) MacLennan G, Cook J, Ramsay C, Campbell M. Excess zeros in randomised controlled trials [abstract]. Clin 2006; 3: 208

(407) Peters TJ, Richards SH, Bankhead CR, Ades AE, Sterne JA. Comparison of methods for analysing cluster randomized trials: an example involving a factorial design Int J Epidemiol 2003; 32 (5): 840-6.

(408) Greene PJ. Independent re-analysis of identical data sets implications for peer review [abstract]. International Congress on Peer Review and Biomedical Publication, 2005 Sept 16 18; Chicago, Illinois, USA 2005; 55-6.

(409) Peduzzi P, Detre K, Wittes J, Holford T. Intent-to-treat analysis and the problem of crossovers. An example from the Veterans Administration coronary bypass surgery study J Thorac Cardiovasc Surg 1991; 101 (3): 481-7.

(410) Wood AM, White IR, Hillsdon M, Carpenter J. Comparison of imputation and modelling methods in the analysis of a physical activity trial with missing outcomes. Int J Epidemiol 2005; 34 (1): 89-99.

(411) Oostenbrink JB, Al MJ, Rutten-van Molken MP. Methods to analyse cost data of patients who withdraw in a clinical trial setting. Pharmacoeconomics 2003; 21 (15): 1103-12.

(412) Niimi M, Yamamoto S, Fukuda H, Ishizuka N, Akaza H. The Influence of handling censored data on estimating progression-free survival in cancer clinical trials (JCOG9913-A). Jpn J Clin Oncol 2002; 32 (1) 19-26

(413) Floriani I, Rotmensz N, Albertazzi E, Torri V, De Rosa M, Tomino C, et al. Approaches to interim analysis of cancer randomised clinical trials with time to event endpoints: A survey from the Italian National Monitoring Centre for Clinical Trials. Trials 2008; 9: 46.

(414) Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, et al Issues in data monitoring and interim analysis of trials. Health Technol Assess 2005; 9 (7): 1-238.

(415) Li L, Hutton E, Jong P, Ross S, Hannah M. The role of data and safety monitoring board in clinical trials· a systematic review [abstract] Control Clin Trials 2002; 23S: 62S.

(416) Lee JJ, Feng L. Randomized phase II designs in cancer clinical trials: current status and future directions. J Clin Oncol 2005; 23 (19) 4450-7.

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

(418) Delgado-Rodriguez M, Ruiz-Canela M, De Irala-Estevez J, Llorca J, Martinez-Gonzalez MA. Participation of epidemiologists and/or biostatisticians and methodological quality of published controlled clinical trials. J Epidemiol Community Health 2001; 55 (8) 569-72.

(419) Golder S, Loke YK. Is there evidence for biased reporting of published adverse effects data in pharmaceutical industry-funded studies? Br J Clin Pharmacol 2008; 66: 767-73

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

(421) Montgomery JH, Byerly M, Carmody T, Li B, Miller DR, Varghese F, et al An analysis of the effect of funding source in randomized clinical trials of second generation antipsychotics for the treatment of schizophrenia Control Clin Trials 2004; 25 (6): 598-612

(422) 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

(423) Tulikangas 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.

(424) Etter JF, Burri M, Stapleton J The impact of pharmaceutical company funding on results of randomized trials of nicotine replacement therapy for smoking cessation: a meta-analysis Addiction 2007; 102· 815-22

(425) Huss A, Egger M, Hug K, Huwiler MK, Roosli M Source of funding and results of studies of health effects of mobile phone use: systematic review of experimental studies. Environ Health Perspect 2007; 115. 1-4.

(426) Higgins A, Lord S, Wortley S, Belcher J. Endometrial ablation for heavy menstrual bleeding: the relationship between funding sources and trial outcome [abstract]. XIII Cochrane Colloquium, 2005 Oct 22 26, Melbourne, Australia 2005; 129.

(427) Davis JM, Chen N, Glick ID. Issues that may determine the outcome of antipsychotic trials: Industry sponsorship and extrapyramidal side effect. Neuropsychopharmacology 2008, 33 (5): pp. 971-5

(428) Dickersin K, Min YI Publication bias· the problem that won't go away Ann N Y Acad Sci 1993; 703 135-46.

(429) Bhandari M, Busse JW, Jackowski D, Montori VM, Schunemann H, Sprague S, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. CMAJ 2004; 170 (4): 477-80.

(430) Finucane T E., Boult C E. Association of funding and findings of pharmaceutical research at a meeting of a medical professional society. Am J Med 2004; 117: 842-5.

(431) Jagsi R, Sheets N, Jankovic A, Motomura AR, Amarnath S, Ubel PA, et al. Frequency, nature, effects, and correlates of conflicts of interest in published clinical cancer research. Cancer 2009; 115 (12): 2783-91.

(432) Liss H. Publication bias in the pulmonary/allergy literature: effect of pharmaceutical company sponsorship Israel Medical Association Journal 2006; 8 (7): 451-4

(433) Perlis RH, Perlis CS, Wu Y, Hwang C, Joseph M, Nierenberg AA. Industry sponsorship and financial conflict of interest in the reporting of clinical trials in psychiatry Am J Psychiatry 2005; 162 (10): 1957-60.

(434) Perlis CS, Harwood M, Perlis RH Extent and impact of industry sponsorship conflicts of interest in dermatology research J Am Acad Dermatol 2005; 52 (6): 967-71

(435) Ridker PM, Torres J Reported outcomes in major cardiovascular clinical trials funded by for-profit and not-for-profit organizations 2000-2005 JAMA 2006, 295 (19): 2270-4

(436) Khan SN, Mermer MJ, Myers E, Sandhu HS The roles of funding source, clinical trial outcome, and quality of reporting in orthopedic surgery literature. Am J Orthop 2008; 37 (12) E205-E212.

(437) Moja PL, Moschetti I, D'Amico R Outcome reporting bias in government-funded RCTs CMAJ 2005; 172: 857.

(438) Ahmer S, Haider II, Anderson D, Arya P Do pharmaceutical companies selectively report clinical trial data? Pakistan Journal of Medical Sciences 2006; 22 (3): 338-46.

(439) Ahmer S, Arya P, Anderson D, Faruqui R Conflict of interest in psychiatry. Psychiatric Bulletin 2005; 29· 302-4.

(440) Rochon PA, Gurwitz JH, Simms RW A study of manufacturer supported trials of non-steroidal anti-inflammatory drugs in the treatment of arthritis. Archives of Int Med 1994; 9 (3): 157-63.

(441) Davidson RA Source of funding and outcome in clinical trials. J Gen Int Med 1986; 1 (3): 155-8.

(442) Yaphe J, Edman R, Knishkowy B, Herman J The association between funding by commercial interests and study outcome in randomized controlled drug trials. Fam Pract 2001; 18 (6)· 565-8.

(443) Clifford TJ, Barrowman NJ, Moher D. Funding source, trial outcome and reporting quality: are they related? Results of a pilot study BMC Health Serv Res 2002; 2 (1): 18

(444) Gøtzsche PC, Hróbjartsson A, Johansen HK, Haahr MT, Altman DG, Chan AW. Constraints on publication rights in industry-initiated clinical trials. JAMA 2006; 295 (14): 1645-6.

(445) McDaid C, Hodges Z, Fayter D, Stirk L, Eastwood A Increasing participation of cancer patients in randomised controlled trials: a systematic review. Trials 2006; 7: 16

(446) Edwards SJ, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J Ethical issues in the design and conduct of randomised controlled trials. Health Technol Assess 1998; 2 (15): i-vi.

(447) Ryan RE, Prictor MJ, McLaughlin KJ, Hill SJ. Audio-visual presentation of information for informed consent for participation in clinical trials. Cochrane Database Syst Rev 2008; (1): CD003717.

(448) Robinson EJ, Kerr CE, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, et al. Lay public's understanding of equipoise and randomisation in randomised controlled trials. Health Technol Assess 2005; 9 (8): 1-192

(449) Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review JAMA 2004, 292 (13): 1593-601.

(450) Verheggen FW, van Wijmen FC. Informed consent in clinical trials. Health Policy 1996; 36 (2): 131-53

(451) Cohn E, Larson E. Improving participant comprehension in the informed consent process Journal of Nursing Scholarship 2007; 39 (3): 273-80

(452) Sugarman J, McCrory DC, Hubal RC. Getting meaningful informed consent from older adults: a structured literature review of empirical research J Am Ger Soc 1998; 45: 517-24

(453) Schellings R, Kessels AG, Ter RG, Knottnerus JA, Sturmans F. Randomized consent designs in randomized controlled trials: systematic literature search Contemp Clin Trials 2006; 27 (4): 320-32.

(454) Lingler JH, Parker LS, DeKosky ST, Schulz R Caregivers as subjects of clinical drug trials: a review of human subjects protection practices in published studies of Alzheimer's disease pharmacotherapies IRB 2006, 28 (3): 11-8

(455) Paris A, Cracowski JL, Ravanel N, Cornu C, Gueyffier F, Deygas B, et al. [Readability of informed consent forms for subjects participating in biomedical research: updating is required]. [French]. Presse Med 2005; 34 (1): 13-8.

(456) Wirshing DA, Sergi MJ, Mintz J A videotape intervention to enhance the informed consent process for medical and psychiatric treatment research [erratum appears in Am J Psychiatry. 2005 Apr;162(4):832]. Am J Psychiatry 2005; 162 (1). 186-8.

(457) Stoy D, Greenwald B. Obtaining informed consent: comparison of conventional and nonconventional methods [abstract] Control Clin Trials 1984, 5: 293.

(458) Wray RJ, Stryker JE, Winer E, Demetri G, Emmons KM. Do cancer patients fully understand clinical trial participation? A pilot study to assess informed consent and patient expectations. Journal of Cancer Education 2007; 22 (1): 21-4.

(459) Lavori PW, Wilt TJ, Sugarman J Quality assurance questionnaire for professionals fails to improve the quality of informed consent. Clin Trials 2007, 4 (6): 638-49

(460) Hack TF, Whelan T, Olivotto IA, Weir L, Bultz BD, Magwood B, et al Standardized audiotape versus recorded consultation to enhance informed consent to a clinical trial in breast oncology. Psychooncology 2007; 16 (4): 371-6.

(461) Hutchison C, Cowan C, McMahon T, Paul J A randomised controlled study of an audiovisual patient information intervention on informed consent and recruitment to cancer clinical trials Br J Cancer 2007; 97 (6): 705-11.

(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

(464) Simes RJ, Tattersall MH, Coates AS, Raghavan D, Solomon HJ, Smartt H Randomised comparison of procedures for obtaining informed consent in clinical trials of treatment for cancer British Medical Journal Clinical Research Ed 1986, 293 (6554) 1065-8

(465) Davis S, Seay J, Stone J Does knowing about clinical trials increase participation? 1990 p A232

(466) Tindall B, Forde S, Ross MW, Goldstein D, Barker S, Cooper DA Effects of two formats of informed consent on knowledge amongst persons with advanced HIV disease in a clinical trial of didanosine Patient Educ Couns 1994, 24 (3) 261-6

(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

(468) Coyne CA, Xu R, Raich P, Plomer K, Dignan M, Wenzel LB, et al Randomized, controlled trial of an easy-to-read informed consent statement for clinical trial participation a study of the Eastern Cooperative Oncology Group J Clin Oncol 2003, 21 (5) 836 42

(469) Guarino P, Elbourne D, Carpenter J, Peduzzi P Consumer involvement in consent document development a multicenter cluster randomized trial to assess study participants' understanding Clin 2006, 3 (1) 19-30

(470) Gøtzsche PC, Hrobjartsson A, Johansen HK, Haahr MT, Altman DG, Chan A-W Ghost authorship in industry-initiated randomised trials Plos Medicine 2007, 4 (1) 0047 52

(471) Liebeskind DS, Kidwell CS, Sayre JW, Saver JL Evidence of publication bias in reporting acute stroke clinical trials Neurology 2006, 67 (6) 973-9

(472) Takeda A, Loveman E, Harris P, Hartwell D, Welch K Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias a short systematic review Health Technol Assess 2008, 12 (32) 1-46

(473) Lee K, Bacchetti P, Sim I Publication of clinical trials supporting successful new drug applications A literature analysis PLoS Med 2008, 5 (9) e191

(474) Cheng K, Preston C, Ashby D, O'Hea U, Smyth RL Time to publication as full reports of abstracts of randomized controlled trials in cystic fibrosis Pediatr Pulmonol 1998, 26 (2) 101-5

(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 6

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

(477) Edwards SJ, Lilford RJ, Thornton J, Hewison J Informed consent for clinical trials in search of the "best" method Social Science and Medicine 1998, 47 (11) 1825-40

(478) Scherer RW, Langenberg P, von EE. Full publication of results initially presented in abstracts. Cochrane Database Syst Rev 2007, (2): MR000005.

(479) Vedula SS, Bero L, Scherer RW, Dickersin K Outcome reporting in industry-sponsored trials of gabapentin for off-label use N Engl J Med 2009, 361 (20). 1963-71.

(480) Koletsi D, Karagiannı A, Pandis N, Makouc M, Polychronopoulou A, Eliades T. Are studies reporting significant results more likely to be published? American Journal of Orthodontics and Dentofacial Orthopedics 2009, 136 (5): e1-e5.

(481) Song F, Parekh-Bhurke S, Hooper L, Loke YK, Ryder JJ, Sutton AJ, et al Extent of publication bias in different categories of research cohorts· a meta-analysis of empirical studies. BMC Med Res Methodol 2009; 9 (1)· 79

(482) von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement· guidelines for reporting observational studies. Lancet 2007; 370 (9596): 1453-7.

(483) Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses The PRISMA Statement PLoS Med 2009; 6 (6). e1000097 doi 10 1371/journal pmed1000097

(484) Chan AW, Altman DG Epidemiology and reporting of randomised trials published in PubMed journals Lancet 2005; 365 (9465): 1159-62.

(485) Dickersin K, Scherer R, Lefebvre C Identifying relevant studies for systematic reviews. BMJ 1994, 309 (6964) 1286-91

(486) Altman DG, Simera I, Hoey J, Moher D, Schulz K EQUATOR· reporting guidelines for health research. Lancet 2008; 371 (9619)· 1149-50.

(487) Moher D, Schulz KF, Simera I, Altman DG. Guidance for Developers of Health Research Reporting Guidelines. PLoS Med 2009; In press.

(488) Edwards PJ, Roberts I, Clarke MJ, DiGuiseppi C, Wentz R, Kwan I, et al. Methods to increase response to postal and electronic questionnaires. Cochrane Database Syst Rev 2009(2) MR000008.

(489) Dillman DA. Mail and Internet Surveys. The Tailored Design Method. 2 ed. Wiley; 1999

(490) Linstone H, Turoff M. The Delphi Method: techniques and applications [book on the internet]. 2nd ed. Murray Turoff and Harold A. Linstone; 2002.

(491) Keeney S, Hasson F, McKenna H. Consulting the oracle: ten lessons from using the Delphi technique in nursing research. J Adv Nurs 2006; 53 (2): 205-12.

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

(493) Rattray J, Jones MC. Essential elements of questionnaire design and development. Journal of Clinical Nursing 2005; 16: 234-43.

(494) Skulmoski GJ, Hartman FT, Krahn J. The Delphi Method for Graduate Research. Journal of Information Technology Education 2007, 6

(495) SurveyMonkey [homepage on the Internet] 2009 [cited 2009 Dec 26]; Available from: URL.http //www surveymonkey com/. SurveyMonkey.com

(496) Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. BMJ 2005 2005, 331 1064-5

(497) Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C. An evidence-based practice guideline for the peer review of electronic search strategies. J Clin Epidemiol 2009, 62 (9): 944-52.

(498) Sampson M, McGowan J, Lefebvre C, Moher D, Grimshaw J. *PRESS: Peer Review of Electronic Search Strategies*. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008.

(499) NIHR Health Technology Assessment programme. Details of HTA journal title: Factors that limit the quality, number and progress of randomised controlled trials: a review (Prescott) 143 pages, Volume 3, number 20. [Online] 2009 December 22 [cited 2010 Jan 8]; Available from: URL:http //www hta ac uk/project/928 asp.

(500) Grant MJ, Booth A. A typology of reviews. an analysis of 14 review types and associated methodologies. Health Information and Libraries Journal 2009; 26 (2) 91-108

(501) Arksey H, O'Malley L Scoping Studies: Towards a Methodological Framework International Journal of Social Research Methodology 20058(1):19-32

(502) Whitlock EP, Lin JS, Chou R, Shekelle P, Robinson KA Using Existing Systematic Reviews in Complex Systematic Reviews Ann Intern Med 2008; 148: 776-82

(503) Council for International Organizations of Medical Sciences. International ethical guidelines for biomedical research involving human subjects. Bull Med Ethics 2002; (182): 17-23

(504) Medical Statistics Unit UCLHNR&Dd. Guide to clinical trial protocol content and format [Online] 2006 January [cited 2009 Dec 20]; Available from: URL:http //www uclh nhs uk/NR/rdonlyres/8CC66584-38AF-4FEA-B3BD-2761456020E3/0/CT_protocol_guidelines_2006 pdf.

(505) Evans D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions Journal of Clinical Nursing 2003; 12: 77-84

(506) Higgins JPT, Green S, editors Cochrane Handbook for Systematic Reviews of Interventions. Chichester, UK: John Wiley & Sons, Ltd.; 2008

(507) Hopewell S, Eisinga A. The *Cochrane Methodology Register* Issue 2 2009. [Online] 2009 Available from: URL:http //cmr cochrane org/help htm.

(508) Hopewell S, Altman DG, Moher D, Schulz KF Endorsement of the CONSORT Statement by high impact factor medical journals: a survey of journal editors and journal 'Instructions to Authors'. Trials 2008, 9: 20.

9.0 Appendices

9.1 Appendix A: Items Included in Previous Protocol Guidelines

Table 16: Items included in previous protocol guidelines

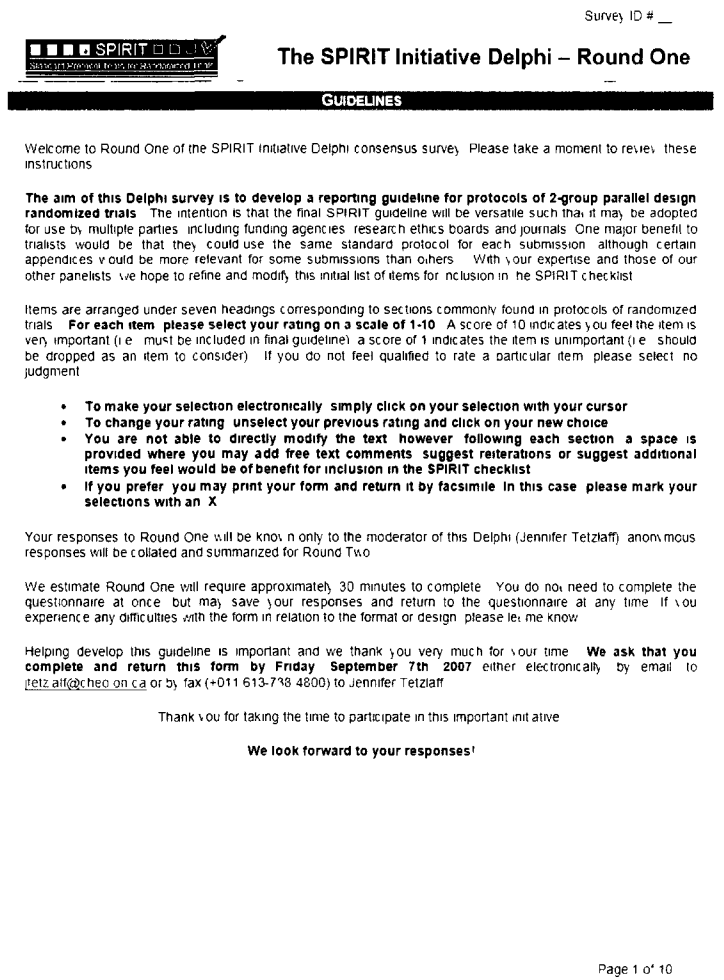
Item	Frequency (%)[a] N = 27
Title/Fact sheet/Title Page	13 (48)
Summary/Abstract	11 (41)
Table of contents	6 (22)
Introduction	
General aims/Problem/Questions	14 (52)
Background information	24 (89)
Preliminary data/previous work by investigator	5 (19)
Additional details	6 (22)
Specific Objectives/Hypotheses	20 (74)
Study Design	
Overview of design	18 (67)
Time frame/period of study	11 (41)
Additional details	5 (19)
Subjects	
Clearly identify target population	7 (26)
Subject selection	19 (70)
Eligibility criteria	19 (70)
Sampling design	6 (22)
Allocation/Allocation concealment	5 (19)
Randomization/Stratification procedures	5 (19)
Patient consent procedures	6 (22)
Procedures	
Measurements and Methods	
Eligibility/Baseline	9 (33)
Variables/Outcomes	
Statement of outcomes (two ask for primary and secondary outcomes, some specify predictor vs. confounder vs. outcome)	25 (93)
Definitions and measurements of variables	17 (63)
Treatment/Intervention	18 (67)
Details (e.g. description and schedule, dosage regimen packaging)	9 (33)
Allowable concomitant therapies/treatments	5 (19)
Timing	6 (22)
Blinding	5 (19)
Pre-testing/training plans	5 (19)
Methods of data collection/handling	14 (52)
Data management, monitoring and quality control	14 (52)
Statistical Issues (general)	20 (74)
Sample size	18 (67)
Compliance and missing data (strategies)	6 (22)
Statistical tests to be performed	6 (22)

Item	Frequency (%)[a] N = 27
Monitoring trial progress	
Interim analyses	6 (22)
Early stopping rules/termination policy	7 (26)
Procedures for handling/reporting adverse events	10 (37)
Protocol amendments	5 (19)
Project management	
Personnel and committees	6 (22)
Administrative responsibilities (and how they will be shared)	6 (22)
Roles of collaborators/investigators	7 (26)
Biosketches/CV's of investigators	5 (19)
Resources required (staff, facilities, equipment and supplies)	9 (33)
Cost/Budget	13 (48)
Ethical and legal issues	17 (63)
Patient consent	7 (26)
Reporting (methods of dissemination of findings, politics of publication)	10 (37)
References	14 (52)
Appendices/Supplements	9 (33)
Sample patient consent form	7 (26)
Flowcharts/Diagrams (e.g. patient flow, organizational schema, etc.)`	5 (19)

[a]These 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 # __

SPIRIT

The SPIRIT Initiative Delphi – Round One

GUIDELINES

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 those of our other panelists we hope to refine and modify this 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**
- **You are not able to directly modify the text however following each section a space is provided where you may add free text comments suggest reiterations or suggest additional items you feel would be of benefit for inclusion in the SPIRIT checklist**
- **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 collated 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 in relation to the format or design please let me 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 jtetzlaff@ohri.ca or by fax (+011 613-798 4800) to Jennifer Tetzlaff.

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

We look forward to your responses!

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Survey ID # __

ITEMS

Section and Topic	Description
Section 1 General Information	
1 Title	Provide a descriptive title (e.g. population intervention main outcome) identifying the study as a randomized controlled trial. ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐No judgment. Not important … Very important
2 Trial identifier	Unique trial identification number or name (e.g. trial registration number protocol number) and where registered (i.e. name of trial register). ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐No judgment. Not important … Very important
3 Protocol Version	Include a version or amendment number and date. ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐No judgment. Not important … Very important
4 Protocol Summary	Provide a short summary of the proposed research. Where required include appropriate lay/non-technical language. ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐No judgment. Not important … Very important
5 Names and addresses	Provide names and addresses of the primary investigators and sponsors. ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐No judgment. Not important … Very important
6 Table of contents	Provide a list of the contents of the protocol and associated page numbers. ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐No judgment. Not important … Very important
7 List of abbreviations	List and descriptors of abbreviations used throughout the protocol. ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐No judgment. Not important … Very important
Comments or additional items (Section 1)	

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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

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

Not important Very important

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 equipoise)

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

Comments or additional items (Section 2):

Section 3: Methods

Participants

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

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

Study design

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)

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

Not important Very important

19 Study timeline Schematic diagram of study time-table and organizational chart including design procedures and stages of trial

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

Not important Very important

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)

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

Not important Very important

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

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

Not important Very important

22. Implementation Describe who will generate the allocation sequence who will enroll participants and who will assign participants to their group

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

Not important Very important

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

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

Not important Very important

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)

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

28 Outcomes Describe and define primary and secondary outcome measures

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

35. Statistical methods 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)

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

Not important Very important

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 state when a centre may be discontinued from the trial

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

Not important Very important

37 Missing data Describe the methods to account for missing data or erroneous data

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

Not important Very important

38 Data and Safety Monitoring Board If relevant describe the composition and role of the data and safety monitoring board

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

Not important Very important

39 Interim trial monitoring Describe the process and timing of any planned interim analyses

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

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 by whom it can be broken in the event of an emergency

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

Not important Very important

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

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

Not important Very important

Comments or additional items (Section 3)

Section 4 Trial organization and administration

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

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

Not important Very important

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

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

Not important Very important

46 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)

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

Not important Very important

47 Budget Provide the budget for personnel equipment facilities and supplies

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

Not important Very important

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

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

Not important Very important

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

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

Not important Very important

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

Comments or additional items (Section 5):

Section 6: Reporting and Dissemination

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 of the protocol and/or the final report as appropriate

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

Not important Very important

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

☐ 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 (i e principle investigator(s) co-investigator(s), sponsor), including publication restrictions and authorship guidelines

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

Not important Very important

Comments or additional items (Section 6):

Section 7: Other

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 or 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

Comments or additional items (Section 7):

60. Please rate your perceived level of expertise on the topics covered in this Delphi survey:

☐ High level ☐ Mid-high level ☐ Mid-level ☐ Low-mid level ☐ Low level /no expertise

Demographic Details:

61. Please indicate your principal profession:

☐ Health care professional (e g clinician)
☐ Clinical trialist
☐ Statistician
☐ Methodologist
☐ Ethics review board head/member
☐ Funding agency representative
☐ Regulatory board member
☐ Trial coordinator
☐ Journal editor
Other (please describe)

62. Please indicate which of the following best describes your place of employment:

☐ Government
☐ Hospital
☐ University
☐ For profit private organization (e g pharmaceutical company)
☐ Non-profit private organization (e g non-governmental organization charity)
☐ Self-employed
Other (please describe)

Additional Comments:

9.2.2 Round 2

Survey ID # __

SPIRIT
Standard Protocol Items for Randomized Trials

The SPIRIT Initiative Delphi – Round Two

GUIDELINES

Welcome to Round Two! Thank you once again for completing Round One of this 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 view the ratings and comments of the other panelists and with consideration of this information to provide you with the opportunity to re rate each item We have not made changes to the checklist based on comments received to date All comments have been anonymized and summarized all major content has been retained Unless otherwise indicated by a number in brackets comments were made by one panelist

This round contains five parts: Part 1 General comments on the scope of the SPIRIT Checklist Part 2 Items of high importance (median ≥8) organized under headings corresponding to those presented in Round One Part 3 Items of moderate importance (6 ≤ median ≥ 7) Part 4 Items of low importance (median ≤ 5) and Part 5 Additional checklist items that were not included in the original checklist but which were generated as a result of comments 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 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 2-4 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' from the Checklist. You will not be asked to rate these items in the third and final round of the Delphi***
Section 5 All items newly-introduced in Round One will be re-circulated 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 reiterations
Alternatively you may print your form and return it by facsimile In this case please mark your selections with an 'X'

We thank you very much for your time and **ask that you please complete and return this form by Wednesday, September 26th**, either electronically by email to jtetzlaff@cheo on ca or by fax (+011 613-738-4800) to Jennifer Tetzlaff

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 and 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 they felt a 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 deserve[s] a detailed reporting at any stage (1)
- 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 standardised items could be made available through other sources (e g websites) (2)
- One respondent stated that while all are potentially important elements it depends on the length of the protocol (1)
- Some panelists found it difficult to respond to specific items which contained multiple concepts (e g if the panelist felt that one concept within an item was of importance 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 this 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 reporting guideline for protocols to 2-group parallel design randomized controlled trials (RCTs) We received some insightful comments and have had some preliminary discussions as a result This guideline was intended to focus on the 2-group parallel design trial to model to development 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 cluster 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 be addressed if the study 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 efforts to agree a unique form for protocol presentation/dissemination/publication are welcome 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 contraints) 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 developing a protocol regardless of its ultimate user (granting agency REB journal) As such many of the proposed items may be primarily relevant to those developing a complete clinical trial protocol

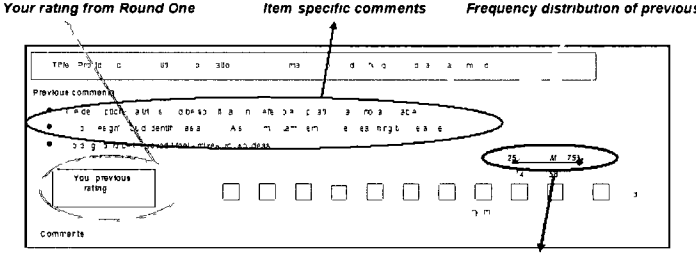
Protocol – Definition

- 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 things like the Statistical Charter and the contract deal with issues related to data management/analysis and remuneration and publication Another stated that currently the research application we receive as a funder and the final 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 objective(s) design methodology statistical considerations and organizational or administrative aspects of a clinical trial

LEGEND

The following provides a description of the components presented for each item presented below

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



M = Median 25% 75% = Inter quartile range

PANELISTS

Eight[illegible] nine panelists located in 17 countries participated in Round One of this Delphi consensus survey. Below is a summary of the demographic information gathered from Round One

Question	N (%)
Profession*	
Clinical Trialist	27 (30)
Healthcare Professional	24 (27)
Ethics review board head member	10 (11)
Funding agency representative	5 (6)
Journal Editor	10 (11)
Methodologist	2 (28)
Regulator/regulatory board member	3 (3)
Statistician	16 (18)
Trial coordinator	11 (13)
Other (e.g. project manager)	5 (6)
Place of employment*	
For profit organization	4 (5)
Government	13 (15)
Hospital	27 (30)
Non-profit organization	6 (7)
Self-employed	0 (0)
University	(62)
Other (e.g. World Health Organization)	(6)
Please rate your perceived level of expertise on the topics covered in this Delphi survey	
High level	47 (54)
Mid high level	31 (36)
Mid level	8 (9)
Low-mid level	1 (1)
Low/no expertise	0 (0)

*Some respondents made multiple selections

PART 2: 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 (e.g. population intervention main outcome) identifying the study as a randomized controlled trial

Previous comments

- The description of a trial 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 I feel mixes up two ideas

Your previous rating ?

25% 4 M 75% 58

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

Not important — Very important

Comments

2 Trial identifier Unique trial identification number or name (e.g. trial registration number protocol number) and where registered (i.e. name of trial register)

Previous comments

- 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 work of registering the trial prior to getting funding (3). This should be made clearer to reflect this point
- Trial identification-having an acronym is not an quality issue but more a marketing and profiling issue
- There may be some sorts of trials which don't get registraton numbers but in general it should be 10
- Trial registration data are very important and need to be located in an easy to access location

Your previous rating

25% 8 M 75% 59

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

Not important — Very important

Comments

3 Protocol Version Include a version or amendment number and date

Previous comments

- We can talk about protocol versions of different type a) refining the protocol following ethics or another review process or even after having another co investigator join in PRIOR TO to starting the recruitment. In this case I reckon that it is a work in progress and we do not need to know all details of it. Also it might be quite difficult to state and trace them all. B) versions of protocol during trial. Those need to be described and dated also indication should be made how many trial participants were recruited prior to that change
- Version dates are extremely important in ensuring that sites and REBs are up to date

Your previous rating 6

25% 6 M 75% 46

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

Not important — Very important

Comments

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 understandability should 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 sites duration of treatment duration and frequency of follow up and the sample size
- The lay summary is effectively in the written information provided to the patient

Your previous rating ~

25% M 75%

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

Not important Very important

Comments

5 Names and addresses Provide names and addresses of the primary investigators and sponsors

Previous comments

- I'm not sure what you mean by names and addresses I do think having names and addresses available SOMEWHERE is important but am not sure I'd want them in the protocol itself especially not in a version of the protocol that might be posted publicly
- Could be split into 2 seperate aspects
- Names included addresses not

Your previous rating 10

25% M 75%

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

Not important Very important

Comments

6 Table of contents Provide a list of the contents of the protocol and associated page numbers

Previous comments

- A bit too prescriptive
- Add if deemed necessary (e g 40 pages or more)

Your previous rating

25% M 75%

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

Not important Very important

Comments

7 List of abbreviations List 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

Your previous rating 8

25% M 75%

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

Not important Very important

Comments

Section 2 Introduction

General

- From a research funders perspective these items are very important in terms of the application submitted This is not currently exactly the same thing as the final protocol

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

Previous comments

- Could be clearer what is meant by outline
- Included in this section should be rationale for the trial in the context of existing evidence namely systematic reviews could be merged with item Background of the Study
- Often not sufficiently described in detail

Your previous rating 8

25% M 75%

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

Not important Very important

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 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)

Previous comments

- Delete ideally as it weakens the requirement for a systematic review
- Also point out systematic review/meta anlaysis whichever is appropriate
- Equipoise really relates 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 within the protocol appropriate literature citations will usually be sufficient
- Often concerned about using unpublished data
- Often not sufficiently described in detail

Your previous rating 8

25% M 75%

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

Not important Very important

Comments

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

Previous comments

- Already part of Background of the study they could be merged (2)
- Add or 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
- Edit the question to clarify whether this PIs preliminary studies or someone elses
- I dislike the idea of preliminary data (usually open uncontrolled underpowered study) (1) may not be applicable (1)
- Preliminary data can be minimized and/or referenced in an investigators brochure Most important to highlight the key theoretical foundations for the proposal at hand

Your previous rating ~

25% M 75%

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

Not important Very important

Comments

11 Objectives State the specific objectives and hypotheses of the study

Your previous rating: 9

25% M 75%
1 0 78

☐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

Previous comments.

- Too vague (3) Unclear what this means (7) Not necessary as is articulated in other sections (2)
- Often not sufficiently described in detail

Your previous rating: 4

25% M 75%
1 2 1 8 10 8 13 9 27 0

☐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

Previous comments:

- The importance of describing this information seems to differ from trial to trial Not convinced it applies to all trials (it looks like you should not preform a trial in a single contry) (2)
- As part of the motivation for the study the one aspect of the study location(s) that is important to be described is the potential of the site to produce the number of patients required given the inclusion criteria and resources at the site(s)
- Also include information about type of healthcare system
- Why justify the study location and not the outcome chosen on the eligibility criteria?
- There are two questions mixed together one asking whether the sites (region) where the study is to be conducted should be identified with some justification (*which those who commented here felt should be included*) and another asking for relevant demographic and epidemiologic information (*which they felt less sure needs to be in the protocol*)(3) The exception was if the study is dealing with a very specific epidemiological situation (1) otherwise this should be stated briefly
- The complication of having study sites listed (if there are many) is that it requires a formal amendment if the sites change which is prone to happening in any large multicenter study
- Identification is important but I am not sure about the issue of justification - doubt that this will be helpful I should score 9 for description but only 4 for justification
- Item 'Study location(s) and Question 14 Participants seem to overlap

Your previous rating 8

25% M 75%
2 1 1 3 4 14 24 12 23 4

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

Not important Very important

Comments

Section 3: Methods

General:

- *A few panelists felt that although some items may be mentioned in the protocol, they could be included in detail elsewhere (e g Trial Master File, Study Procedure Manual, Manual of Operations, Statistical Analysis Plan or appendices to the trial protocol) so that the protocol is an 'accessible and usable document (3)*
- I found this section difficult to fill out because it is too general
- I scored certain items at 6-9 rather than 9-10 because their importance depends on the study
- I think there are too few items about the data collection *(New items added based on associated comments)*
- Quality control is missing *(New items added based on associated comments)*

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

Previous comments:

- Unclear distinction between target and study population (2)
- Clarify whether individuals or centres – preferably both
- Items Study location(s) and Population seem to overlap

Your previous rating: 9

25% M 75%
1 3 8 10 37 1

☐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

Previous comments:

- Less sure about the *justification* of exclusions

Your previous rating. 9

25% M 75%
3 13 72

☐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

Previous comments:

- I think that there are three approaches- where sample size is under control of investigator do a formal sample size calculation where size is not under control of investigator –e g limited number of patients do a power analysis and if power is not impressively high explain why study is worth doing anyway
- One of the key assumptions is effect size The effect size used should be substantiated against meaningful clinical effects and motivated in terms of the expected non-compliance in the two arms of the study or stratification The sample size should also be outlined against the statistical method that is going to be used for analysing the primary outcome Expected loss to follow up and planned interim analysis should also be part of the final sample size motivation
- The basis for sample size calculation ought to be data from adequately conducted trials included in a meta-analysis to estimate the potential size of the intervention effect The proportion of participants in the control group with the primary outcome in question ought to also come from the meta-analysis of adequately conducted trials maybe verified / supported with data from the centres going to participate in the new trial of the intervention effect
- The importance of the sample size 'is in the eyes of the beholder' For anyone who should approve the protocol (e g regulatory agency funding organisation or ethics review board) the sample size calculation and assumptions are very important but for the evaluation of the results of a trial (e g regulatory agency or journal editor) it is of less value

Continued on next page

Sample size (continued)

- The minimum clinically important difference must be stated with an explanation of how this determination was made For a non inferiority trial the value for delta (the non inferiority margin should be specified and a justification for this particular determination provided In reference to existent knowledge with citations
- I dislike the word estimate referring to sample size these are calculations not estimates

Your previous rating 9

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

Not important — Very important

Comments

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

Previous comments

- A short sentence is OK but not worth going into a lot of detail given it is a randomized trial
- Recruitment can be (should be some would argue) described separately Here you are getting at basic methods but recruitment could rapidly get into discussions of compliance conflict of interest (who gets paid how much to encourage enrollment?) etc

Your previous rating 9

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

Not important — Very important

Comments

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

Previous comments

- The type of study drug trial or not with Clinical Trial Authorization application or not is important because several items may take different weight
- Second part not necessary should be combined in description of design

Your previous rating 9

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

Not important — Very important

Comments

19 Study timeline Schematic diagram of study time table and organizational chart including design procedures and stages of trial

Previous comments

- Having a study flow chart with all actions and procedures listed is useful
- Recruitment and timeline are tied through the expected rate of recruitment so the recruitment rate expected should be an element of the timeline
- Could be made more specific I answered as though you are asking about time points during follow up at which particular procedures or visits should take place as opposed to calendar dates at which certain portions of the study are expected to be completed
- This has been interpreted as a flow chart for an individual patient If it concerns time plan for the entire study i.e. calendar time it is less important
- Schematic should be a grid of visits by procedures

Your previous rating 8

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 random sequence list 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 will not know it (4)
- It is very important NOT to describe sequence generation in the protocol in order to minimize physician selection bias Respondents suggested alternate documents for this information including the Statistical Analysis Plan a separate addendum or in a randomization procedure so that it has limited distribution (3)

Your previous rating 9

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

Not important — Very important

Comments

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

Your previous rating

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

Not important — Very important

Comments

22 Implementation Describe who 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 who will obtain it
- The last part of the question is ambiguous implies an element of choice in the randomisation process

Your previous rating 9

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

Not important — Very important

Comments

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

Previous comments

- No single double blinding statement is useful but the indication who is is not blinded and about which aspects type of intervention other outcomes (2)
- Others in addition to those mentioned may may need to be blinded more than just those three (2)
- Assessing the success of blinding during the study seems not relevant
- Should be recorded to match the upcoming revision of CONSORT Statement

Your previous rating 9

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

Not important — Very important

Comments

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 (eg no treatment placebo or active control)

Previous comments

- Please match the wording with the WHO International standards for trial registration
- Two questions the first more important

Your previous rating 10

25% M 75%
8 79

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

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

Your previous rating 9

25% M 75%
12 63

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

Not important — Very important

Comments

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

Previous comments

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

Your previous rating 9

25% M 75%
12 58

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

No 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
- Use the term adverse event (in place of adverse reactions)
- Would also be helpful if the risks were well articulated (i.e. enumerated) This would assist with REB submission review and consent form development

Your previous rating 9

25% M 75%
11 63

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

Not important — Very important

Comments

28 Outcomes Describe and define primary and secondary outcome measures

Previous comments

- The sequence (and necessary link) between Outcomes Outcome definitions and Outcome assessment could be strengthened The concept of end point should be introduced

Your previous rating 10

25% M 75%
9 79

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

No important — Very important

Comments

29 Data collection Describe methods including study instruments (e.g. questionnaires laboratory measurements) and time point(s) 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 9

25% M 75%
5 59

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

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

Your previous rating 9

25% M 75%
20 47

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

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) I would leave in records retention requirements (3) More details should be provided in a data management handbook/procedures manual
- This should only be a very high level view

Your previous rating 9

25% M 75%
11 17 20

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

No important — Very important

Comments

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

Previous comments

- This is important but could be in study procedures

Your previous rating: 9

25% M 75%

1	2	3	4	5	6	7	8	9	10	No judgment
	2			2	1	16	18	17	33	

Not important — Very important

Comments

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

Previous comments

- Add compliance with treatment as well as compliance with followup requirements
- The importance of compliance is dependent on the objective of the trial It is more important in non-inferiority studies and less important in superiority studies

Your previous rating: 9

25% M 75%

1	2	3	4	5	6	7	8	9	10	No judgment
2	1			2	5	4	22	13	40	

Not important — Very important

Comments

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

Previous comments.

- This should also mention who receives safety reports and when
- This item ovelaps with item #41 [Adverse Event Reporting]
- Not clear here if you are talking about follow up WITHIN the trial or after it's completed
- Data management plans should be fully described in a separate document

Your previous rating: 9

25% M 75%

1	2	3	4	5	6	7	8	9	10	No judgment
1	1					3	13	14	58	1

Not important — Very important

Comments

35 Statistical methods 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)

Previous comments

- While the statistical analysis methods are very important I would expect them to be covered in detail in a separate statistical analysis plan thus an overview (enough to explain what is being done but not in excruciating detail) would only be required in the protocol The detail goes in a separate document usually called a statistical analysis plan or something similar (3)
- Add sensitivity analyses
- For multicenter studies describe how adjustment for differences across sites will be handled in analysis
- Regarding statistics it would be useful to know the qualification of the statistician
- I have found of variability in how people define the intention to treat population I recommend that the protocol clearly state how missing data and loss to follow-up will be handled in the "intent-to-treat population definition

Your previous rating. 9

25% M 75%

1	2	3	4	5	6	7	8	9	10	No judgment
					2	1	8	0	68	

Not important — Very important

Comments

36 Withdrawals State criteria that will be used to withdraw or exclude participants from the trial (eg 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

Previous comments.

- Withdrawals in a 2 group parallel design shouldn't happen All those that are randomized should be included in the analysis or be listed as lost to follow up So having people have to say what they will do with withdrawals is probably a good thing so the reviewers can judge if they are doing the right thing Discontinuing centres is common thing and should be included
- No participants randomized should be excluded from the trial' for compliance or any other reason If the word "trial' is replaced with "intervention" I would have no objection to this wording At the end of this question I would add "and how enrolled patients will continue to be followed ' after all they signed a consent and volunterred themselves
- I would score criteria to withdraw or exclude participants as a 9 data to be collected on withdrawn participants as a 10 and the discontinuation of a centre as a 6
- Mixing two questions one about withdrawal of patients and one about withdrawal of centers I feel much less strongly about specifying the conditions for dropping centers as that is a more complicated decision often made by a steering committee after lots of discussion and site visits
- Not clear but important area

Your previous rating: 8

25% M 75%

1	2	3	4	5	6	7	8	9	10	No judgment
		2				4	11	14	58	

Not important — Very important

Comments

37 Missing data Describe the methods to account for missing data or erroneous data

Previous comments.

- Details in the analysis plan not protocol (2)
- How missing data will be handled should be in a grant submission I am not so sure I would feel it essential in a publication of a protocol
- Missing data and erroneous data should not be tolerated I don't think this section should say how it will be 'accounted for The process should be how missing data will be avoided and if you know data is erroneous it should be corrected! It is also important to describe the steps that will be taken to avoid erroneous data
- Can be worded better

Your previous rating. 9

25% M 75%

1	2	3	4	5	6	7	8	9	10	No judgment
	1			3	4	10	16	19	35	1

Not important — Very important

Comments.

38 Data and 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 procedure (3)
- A DSMB should be the default and any omission of such an entity should be justified
- Add justification for having one if relevant

Your previous rating: 8

25% M 75%

1	2	3	4	5	6	7	8	9	10	No judgment
1	1			2	4	7	17	14	42	1

Not important — Very important

Comments

39 Interim trial monitoring Describe the process and timing of any planned interim analyses

Your previous rating: 9

25% M 75%

3 5 13 15 49

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

Not important Very important

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 re defined each time by a trialist
- It may occur that we need to stop the trial for reasons unsuspected at time of design
- Can be worded better
- Ambiguous for me I don't know whether you were asking about 'stopping" boundaries or about the process regarding communication of a DSMB Recommendation to the trial's Steering Committee Sponsor and or Principal Ethics Committee
- 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 earlier than planned
- Stopping rules - from funder perspective - in the research application (which is not the same as the protocol) stopping rules will not be set out - but agreed once a final version of protocol is approved by trial oversight and monitoring bodies Hence this is not an essential element as currently handled

Your previous rating 9

25% M 75%

1 4 6 10 10 54 1

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

Not important Very important

Comments

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

Previous comments:

- *Some respondents felt that this item overlapped 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 I'm not sure
- The CONSORT extension concerning harms the reporting of harms should be incorporated into this initiative
- I think this item could be renamed harms

Your previous rating. 9

25% M 75%

1 1 4 4 10 12 57

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

Not important Very important

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 by whom it can be broken in the event of an emergency

Previous comments:

- Should be in the grant submission and trial protocol but not necessarily in a protocol publication (if space limitations)
- It is important that this item is indicated in teams enrolling patients but it might not be necessary for reporting the protocol in a public RCT registration database

Your previous rating 9

25% M 75%

1 4 1 2 4 8 14 7 46 1

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

Not important Very important

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 but not necessarily in a protocol publication (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 (1) Bias in data collection measurement and analysis should not be tolerated (1) This section should be the steps taken to eliminate bias
- Interesting Still I am uncertain whether it should be a standard requirement

Your previous rating 8 or no judgment

25% M 75%

3 1 1 3 5 4 6 13 9 41 2

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

Not important Very important

Comments

Section 4: Trial organization and administration

General.

- Much of this section would do better in a document separate from the protocol (8)
- Protocols that are changed need to be amended so items that may change frequently should not be part of a protocol otherwise for example every time a staff changes one would have to amend the protocol and resubmit to all IRBs A roster can be kept and if 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 and lower scores for a journal (1)
- More part of agreements between the sponsor, centre(s) and trial sites
- While there may be a nod of perfunctionary description of these things I do not think they should be a primary focus
- From a funder perspective these are all essentials on any application
- Important to demonstrate that adequate trial resources are provided, but should not be attributed too much space in the trial protocol in order to keep it still readable

Note Items 44 45 and 47 have been rated with a median ≤ 7 and have been moved to a separate part of this questionnaire

46 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)

Previous comments

- It is important to list who is funding/supporting the trial but full 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
- While I think this item is important I m not that happy with the wording
- 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 other items that might be candidate ones
- 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 At our place this could not be quantified I don t think Everything but the very basic office space and furniture has to be covered by the research grants
- Not sure about all elements here

Your previous rating: 9

25% M 75%

3 5 5 4 7 16 14 30 2

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

Not important Very important

Comments

Section 5 Ethical considerations

General

- If there is IRB approval many of these items can be summarized very briefly do not need to be in detail in the protocol (3)
- These items are crucial to REBs and have varying degrees of importance to journals
- These items are important but some should not be included in the protocol
- This information could be placed in a separate document attached to the application to the ethics review board
- 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 # of sties 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 (ie at the time of research application) Currently the final protocol is approved by trial steering committee and sent for ethical approval anticipated there will be iteration between these committees until final ethically approved protocol confirmed

48 Potential benefits and risks The potential benefits and risks of the research to study participants and to society

Your previous rating 4

25% M 75%
1 3 5 7 15 56
☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐No judgment
Not important Very important

Comments

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

Previous comments

- Consent details should always 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 consenting process ie 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 (4) Local IRB/REB take care of the actual details at each site (1)
- Need to specify that it is nearly always written consent that must be obtained and if not why not In addition should specify if samples will be stored for future use and if so whether consent was obtained for this
- My response to the methods component would be 10 and to the name of the individual resoponsible 3 since in a mult centre trial there will be many such individuals and even at a particular centre there could be many such individuals if there is staff turnover during the course of the study
- Include acceptable modalities of consent (e g in-person telephone)
- Process for solicitation of consent post intervention from patient if consent initially obtained from a substitute decision maker (i e ICU or emergency consent) Ongoing assessment of patient capacity for consent an issue that is becoming prominent in critical care It is unclear at present for how long this process is to occur
- Descr be mode of consent (prospective versus deferred/delayed versus waived)
- I think the consent form is an appendix to the protocol

Your previous rating 4

25% M 75%
3 1 2 4 7 10 60
☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐No judgment
Not important Very important

Comments

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 consent ng age provide information on how assent and permission from a legal guard an or other authorized individual will be obtained

Previous comments

- Each site may have their own way of dealing with this issue For example there is no legal age of consent the age of assent is locally determined The information will vary so much that I m not sure how this can be relayed in a protocol (3)
- Consent details should always be in the protocol submitted or registered but I am not sure need to be included in a published protocol

Your previous rating 4

25% M 75%
2 1 3 4 6 12 59 1
☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐No judgment
Not important Very important

Comments

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

Previous comments

- Need to have a plan to store data for required period after study complete Who will be responsible for data?

Your previous rating 4

25% M 75%
2 1 3 5 12 10 51
☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐No judgment
Not important Very important

Comments

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

Previous comments

- Please edit the initial approval and the number of that REB approval Preferably for the main site one per country If we want it for all sites please indicate in a separate question
- This level of detail is not necessary in a protocol (2) only that it is obtained locally (1)
- Cannot be known when preparing the protocol (2)
- Clearly the approval needs to be obtained and documented but I m not sure it s always practical to specify all that in the protocol Ethics approval may not be obtained until the protocol is funded or approved so depends a little on whether protocol is prepared in order to go to ethics committee or after I m just not sure of the timing in item (e g may not be relevant for grant submissions or some ethics submissions) (4) Would probably have different answers if I was looking at the instrument for use in a grants review panel REB/IRB or a journal editor (1)
- The tense of this statement should be in the future since this is a protocol that would be submitted to an IRB Providing the actual names of each committee seems overkill Just state the regulatory requirements for an institution In the US if it is a government sponsored protocol each site needs an FWA as well These types of requirements would be useful as a list of site requirements in the protocol
- A protocol should have a statement that ethics approval by a local REB is required prior to a site initiating a trial etc but listing who has approval by what committee?
- Of equal importance is to include scientific review Many institutions require that the proposal is now approved by Scientific Review Committee before it is sent to IRB

Your previous rating 8

25% M 75%
4 1 2 1 3 8 5 63 1
☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐No judgment
No important Very important

Comments

53 Role of Sponsor Describe the role of the sponsor in the trial design data collection access to trial data (includ ng interim data audits and regulatory inspections) data analys s and interpretation and manuscript preparation

Previous comments

- Should be disclosed but not in the protocol (3)
- Name all sponsors there are sometimes several Also ask for funders CIHR is not a sponsor but 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 is 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

Your previous rating ○

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

25% 12 M 11 75% 51 4

Not important — Very important

Comments

54 Conflict of Interest Disclose 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
- I find it difficult to define what a conflict of interest is in the context
- Not clear whose conflict of interest is being referred to
- It is 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

Your previous rating ○

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

25% 10 M 55 75%

Not important — Very important

Comments

Section 6· Reporting and Dissemination

General

- Clarification of these outcomes is crucial in conducting multi-centre trials The information is of priority to REBs and potentially regulators The details are less important to funding agencies and journals
- As a funder we have requirements under our terms and conditions of award - these are not essential elements described in the research application itself I can see however from different perspectives these may be important in a published protocol
- All need to be documented but not necessarily in the protocol

55 Protocol Amendments Descr be 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

Previous comments

- Why would 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 outlined as well and thus 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 shell tables and more details including specific details regarding the randomization
- Forgot 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

Your previous rating ○

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

25% 18 M 12 75% 37

Not important — Very important

Comments

56 Dissemination Describe how the researcher(s) or sponsor(s) will d sseminate the results to participants health care 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 somehow 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/interested in 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 center studies there can be legislative differences concerning how information is shared

Your previous rating ~

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

25% 7 M 17 13 75% 23

Not important — Very important

Comments

57 Publication Policy Details on who has the right to publish the study results or modify the manuscript f e principal investigator(s) co investigator(s) sponsor) including publicat on 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 don t think this necessarily belongs in the protocol itself (2) Most pharmaceutical companies have policies around these issues but I don t know that they need to be stated in the protocols
- Publication policy is usually discussed and approved by the TSC

Your previous rating /

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

25% 4 M 13 75% 41

Not important — Very important t

Comments

Section 7: Other

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

Your previous rating 8

1 1 1 1 4 2 8 25% 9 M 75% 61

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

Not important Very important

Comments

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

Previous comments

- CVs 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
- Timelines are helpful in the appendices (i.e. schedule of events)

Your previous rating 7

4 1 2 5 8 25% 4 10 M 8 75% 36

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

Not important Very important

Comments

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

Previous comments

- This may change quite often over the course of a trial (2) Would need a process to be kept current (1)
- Should not be in a protocol (2)
- I'd split this question into several one for each role for example of the pi of statistician of recruiting md of nurse etc
- I find it very difficult to pin down the time I devote to that or other part of my work Besides some of these people devote less time if everything goes on well and a lot if there is some trouble
- Important but I don't think needs to be included in a published protocol but rather in the grant submission
- Should not be in the protocol but the study project manager will collect the delegation of authority signature list CVs staff contact information etc
- If this protocol is used to obtain funding it is very difficult to provide names of people who will be recruited specifically for the study

Your previous rating 8

7 2 5 3 25% 5 9 M 15 16 75% 7 14 2

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

Not important Very important

Comments

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

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

Your previous rating 9

6 4 7 3 25% 8 11 M 14 17 75% 9 7

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

Not important Very important

Comments

47 Budget 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

Your previous rating 6

14 5 25% 7 4 11 M 6 5 10 75% 6 1 2

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

Not important Very important

Comments

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

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

Not important Very important

Comments

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

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

Not important Very important

Comments

Co enrolment in studies

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

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

Not important — Very important

Comments

Investigational product(s)

If relevant describe the formulation packaging labeling and supply of the investigational product and accountability procedures

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

Not important — Very important

Comments

Biological specimens

If relevant describe plans for laboratory evaluation specimen collection storage and shipping to central laboratories

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

Not important — Very important

Comments

Data collection forms

Provide a summary table (e g matrix) of all forms to be collected at each time point

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

Not important — Very important

Comments

Validation of instrumentation

Describe reliability and validity of instruments to be used including questionnaires laboratory instruments and analytic tests if known or plans to establish such validation

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

Not important — Very important

Comments

Trial Monitoring

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

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

Not important — Very important

Comments

Reporting of early stopping

Describe how the researcher(s) or sponsor(s) of trials will disseminate the results of trials that were stopped early (for benefits harms or utility)

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

Not important — Very important

Comments

Ancillary and sub studies

Describe any foreseen further uses of personal data or biological materials for related sub studies or ancillary studies *and whether consent was obtained for these studies*

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

Not important — Very important

Comments

Although this point was suggested within this item it is uncertain whether it would belong within this item or as a component of the item Agreement and Consent

Pregnancy

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

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

Not important — Very important

Comments

Post trial care

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

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

Not important — Very important

Comments

Please Note Aspects of this item were covered in previous item Follow up This point has been elaborated here to distinguish it from follow up within the trial

Post trial data/materials storage

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

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

Not important — Very important

Comments

Feasibility

Justify the feasibility of the trial including the acceptability of the protocol for both participants and physicians and the capacity of recruitment

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

Not important — Very important

Comments

Insurance

Details of plans including insurance coverage to provide treatment (including the funding of treatment) and compensation for research related disability or death

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

Not important — Very important

Comments

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

Comment	Notes from Moderator
Often good to provide trial acronym if available	Is included in existing item "Trial identifier (i e trial name)
Clinical question Provide a clear presentation of the clinical questions to be answered	Covered in "Objectives
Describe if this is an efficacy trial or a pragmatic trial	Can be covered in "General Approach" or "Type of Study'
If possible give tel nos/contact details for randomisation service	Could be included in existing item (e g one of the items detailing randomization methods)
Need guidance on termination of patient from study i e for safety concerns- not just direction for stoppage of the trial itself	This topic could be covered by adding "(e g compliance requirements **safety concerns**)' to Withdrawals
Need information about the data collector or assessor (number training)	Is included in existing item Quality Control"
Describe how the protocol is kept under review and kept up-to-date I would score this 8	Covered in "Protocol Amendments
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 enroll 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	This topic could be more clearly covered in item Recruitment"
Risk assessment	Risk assessment may be covered off in a number of items including Risks' "Potential Benefits and Risks
Separate question to ask whether we wish to see the REB following amendments	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

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!

9.2.3 Round 3

Survey ID # ___

SPIRIT Standard Protocol Items for Interventional Trials

The SPIRIT Initiative Delphi – Round Three

GUIDELINES

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 86 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 ≥ 8
Part 2 Items rated of low importance (excluded) median ≤
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 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 30th 2007** either electronically by email to jetzlaff@cheo.on.ca or by fax (+001 613 738-4800) to Jennifer Tetzlaff

Thank you again for your contribution to this initiative

We look forward to your responses to this final round!

Survey ID # ___

PART 1: DRAFT ONE OF PROPOSED CHECKLIST AND RATINGS

- **This section includes items that have been rated with a median ≥ 8 in Round Two**
- **This section is only for your information** You do not need to comment in the importance of these items again
- **Please note this is a draft of the checklist based on summary scores Most iterative suggestions have not yet been included** but will be considered in upcoming stages of this process through discussions with a core working group and will consider comments received by our panelists
- **Some items may be merged** as suggested by comments received by our panelists
- **'Denotes items where further feedback is deemed necessary based on comments** Specific questions are included in Part

Section and Topic	Description	Round 1 Median (IQR)	Round 2 Median (IQR)
Section 1 General Information			
Title	Provide a descriptive title (e g population intervention main outcome) identifying the study as a randomized controlled trial	10 (9 10)	10 (9 10)
Trial identifier	Unique trial identification number or name (e g trial registration number protocol number) and where registered (i e name of trial register)	10 (9 10)	10 (9 10)
Protocol Version	Include a version or amendment number and date	10 (7 10)	10 (8 10)
Protocol Summary*	Provide a short summary of the proposed research Where required include appropriate lay/non technical language	9 (7 10)	9 (7 10)
Names and addresses	Provide names and addresses (i e affiliated institution company) of the primary investigators and sponsors	10 (9 10)	10 (8 10)
Table of contents	Provide a list of the contents of the protocol and associated page numbers	8 (6 10)	8 (5 9)
Section 2 Introduction			
Rationale	Outline the research topic and provide justification for undertaking the study	10 (9 10)	10 (9 10)
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 equipoise)	10 (9 10)	10 (9 10)
Preliminary data	Describe any results of preliminary studies already obtained in the area of the proposed study (e g by investigators)	9 (8 10	9 (8 10)
Objectives	State the specific objectives and hypotheses of the study	10 (10 10)	10 (10 10)
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	9 (7 10)	8 (7 9

Survey ID # ___

Section and Topic	Description	Round 1 Median (IQR)	Round 2 Median (IQR)
Section 3 Methods			
Population	Describe the target and study population and the source (e g catchment area) of the study population	10 (9 10)	10 (9 10)
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)
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)
Recruitment	Describe the process of recruitment (e g advertisements physician contacts) and enrolment	9 (8 10)	9 (8 10)
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)
Study timeline*	Schematic diagram of study time-table and organizational chart including design procedures and stages of trial	9 (8 10)	9 (9 10)
Randomization Sequence generation	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)
Randomization 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	10 (9 10)	10 (10 10
Randomization Implementation	Describe who will generate the allocation sequence who will enroll participants and who will assign participants to their group	10 (8 10)	10 (8 10)
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)
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)
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)
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)
Risks *To become Harms*	State the known or potential risks and adverse reactions for each study intervention	10 (9 10)	10 (10 10)
Outcomes	Describe and define primary and secondary outcome measures	10 (10 10)	10 (10 10)

Survey ID # ___

Section and Topic	Description	Round 1 Median (IQR)	Round 2 Median (IQR)
Data collection	Describe methods including study instruments (e g questionnaires laboratory measurements) and time point(s) of data collection outcome measurement and recording	10 (9 10)	10 (9 10)
Follow-up	State follow-up plans including description and schedule of visits and logistics if relevant	10 (8 10)	10 (9 10)
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	8 (7 10)	8 (7 9)
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	9 (8 10)	9 (8 10)
Compliance	Describe procedures and measures proposed to monitor participant compliance (e g tablet return) if relevant	9 (8 10)	9 (8 10)
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	10 (9 10)	10 (9 10)
Statistical methods	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)	10 (10 10)	10 (10 10)
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 state when a centre may be discontinued from the trial	10 (9 10)	10 (9 10)
Missing data	Describe the methods to account for missing data or erroneous data	9 (8 10)	9 (8 10)
Data and Safety Monitoring Board	If relevant describe the composition and role of the data and safety monitoring board	9 (8 10)	9 (9 10)
Interim trial monitoring	Describe the process and timing of any planned interim analyses	10 (8 10)	10 (9 10)
Stopping guidelines*	State the criteria for the premature termination of the trial	10 (8 10)	10 (9 10)
Adverse event reporting	Describe methods for recording and reporting both solicited and spontaneous adverse events and provisions for dealing with them	10 (9 10)	10 (9 10)
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 by whom it can be broken in the event of an emergency	10 (8 10)	10 (8 10)
Limitations	Describe the limitations of the proposed study including possible bias in data collection measurement and analysis	9 (7 10)	8 (6 10)

Section and Topic	Description	Round 1 Median (IQR)	Round 2 Median (IQR)
Section 4: Trial organization and administration			
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)	9 (7, 10)	9 (7, 10)
Section 5: Ethical considerations			
Potential benefits and risks	The potential benefits and risks of the research to study participants and to society	10 (9, 10)	10 (9, 10)
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	10 (9, 10)	10 (9, 10)
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	10 (9, 10)	10 (9, 10)
Confidentiality and Anonymity	The provisions for protecting the confidentiality and anonymity of personal data and respecting the privacy of participants	10 (8, 10)	10 (9, 10)
Ethics approval	State whether ethics approval has been obtained. If so, provide the name of the committee(s)	10 (9, 10)	10 (8, 10)
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	10 (8, 10)	10 (8, 10)
Conflict of Interest	Disclose financial or other real or perceived conflicts of interest	10 (9, 10)	10 (8, 10)
Section 6: Reporting and Dissemination			
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 of the protocol and/or the final report, as appropriate	9 (7.5, 10)	9 (7, 10)
Dissemination	Describe how the researcher(s) or sponsor(s) will disseminate the results to participants, health care professionals, the public, or other relevant groups	8 (7, 10)	8 (7, 10)
Publication Policy	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	9 (8, 10)	9 (7, 10)
Section 7. Other			
References	Provide a list of the references cited in the protocol	10 (9, 10)	10 (9, 10)
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)

PART 2: ITEMS EXCLUDED AFTER ROUND 2

Budget	Provide the budget for personnel, equipment, facilities and supplies	6 (3, 9)	5 (2, 6)

Subgroup (Round 2)

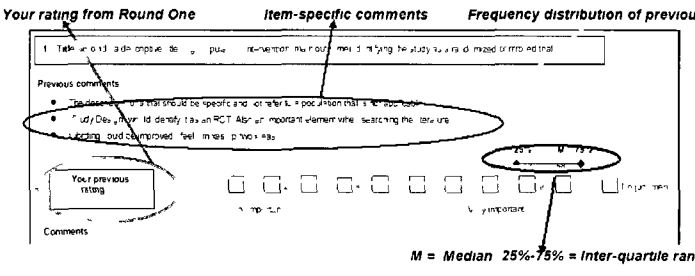
Healthcare worker/clinical trialists/trial coordinator (39)	5 (3, 6)
Statistician/Methodologist (37)	5 (1.5, 8)
Ethics board head member (10)	6 (1, 8.5)
Funding agency representative (5)	6 (3, 9)
Regulator (3)	4 (1, 5)
Journal editor (8)	6 (2, 7.5)

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 brackets, 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 (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). 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 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 from the Checklist.

LEGEND



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

Previous comments

- This may be the only opportunity to specify this info
- Belongs outside the protocol (4). Clinical trial contract issue (2). Ethical issue - needed for reb - less certain for protocol (1)
- Could be a part of Section 6: Reporting and Dissemination (1); part of Publication Policy (former Item 57) (2); part of Dissemination (former Item 56) (1)
- Could be part of Role of Sponsor (former Item 53) (2)
- See constraints paper in JAMA 2004
- This is a G & C office matter

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- i e the banking of study specimens/data for future research
- This should be in individual contracts not protocol
- Vital

Your previous rating 6

25% M 75%

6 3 4 2 1 3 7 15 8 33 2

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

Not important Very important

Comments:

Biological specimens If relevant describe plans for laboratory evaluation specimen collection storage and shipping to central laboratories

Previous comments:

- Briefly/High level (3) I don't think anyone needs to know if its FedEx or US mail (1)
- Could be in trial operations manual (2)/lab manual (3) instead
- Specimen collection plan should be in the protocol all other items should be in the laboratory manual
- Important if relevant but does not have to be in the protocol (2)
- Important in a protocol but not in a publication – especially
- This belongs in an appendix
- This is all part of QC and can be very imporatnt to ensure lack of cross contamination for example in PCR studies

Your previous rating: 6

25% M 75%

6 3 3 1 5 4 10 16 7 22 7

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

Not important Very important

Comments:

Reporting of early stopping: Describe how the researcher(s) or sponsor(s) of trials will disseminate the results of trials that were stopped early (for benefit harms or futility)

Previous comments.

- I think this is already covered elsewhere (2) Not sure how this adds to what is already there (1)
- Very hard to pre-specify this in advance (3) Would be better to outline the process for deciding what this should be (1)
- Crucially important I am especially concerned about trials of a licensed product stopped with primary outcome going in wrong direction but results reported as "futile"
- Hard to say at protocol stage However important issue
- Trial registration is the current approach to dealing with trials which 'dissapear' due to unwanted results I don t think we need belt and braces for this
- Important but do not have be stated in the protocol
- Merge with item "Dissemination (2)
- Might be spelled out just as well in another document
- Can be very short
- The problem with this is that there could be various forms of dissemination depending on the reason for stoppage Does this pertain to informing patients investigators funding agencies general public etc vague
- This is as per publication and is not a separate topic
- This will likely depend on reason trial is stopped early

Your previous rating: 0

25% M 75%

7 3 3 2 6 4 6 17 12 21 2

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

Not important Very important

Comments:

Pregnancy 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

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 two people and require plans for both (1)
- Depends entirely on specific trial We don't in general commit triallists 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)
- Should be included in the risks section if the monitoring is considered additional to the core sutdy monitoring (i e it is being conducted for safety concerns)
- Part of overall monitoring

Your previous rating: 6

25% M 75%

4 3 4 2 3 4 6 12 10 27 10

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

Not important Very important

Comments:

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

Previous comments

- Part of background
- Already covered Data Collection (former Item 29)
- An investigator meeting/site initiation issue not in the protocol
- Brief description is fine details not necessarily in protocol (2)
- With appropriate references/citations to confirm validity (2)
- Covered in Outcomes (former Item 28) (2)
- Depends on the type of study
- Important for publication not protocol
- See earlier item dealing with this
- Should be in Appendix Materials
- This is a tall order - 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 it is required in the grant application
- This should only be necessary for non-standard instruments/questionnaires

Your previous rating: 0

25% M 75%

4 1 1 3 6 7 11 17 14 18 1

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

Not important Very important

Comments:

Trial Monitoring 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

Previous comments:

- Covered by Quality control (former Item 32) (2)
- Again 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
- Already covered
- 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 What about Monitoring for Management Only the generic elements of this monitoring should be in the protocol (1)
- I think that this point is useful
- Important but belongs elsewhere (4) – e g Manual of operations (2)
- Is that refering to monitoring by DSMB? (1) Short overview only - Similar to DSMB (1)
- Not applicable to all trials
- This will have an impact on the budget and personnel resources

Your previous rating: 9

25% M 75%

4 1 3 5 4 3 7 28 12 17 2

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

Not important Very important

Comments:

Post-trial care: 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

Previous comments:

- Agree that this could be a separate item from "Follow-up" within the trial
- Better to have a single item on follow-up and access to treatment (3)
- If available 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
- Important if relevant
- Important but do not have be stated in the protocol (2)
- Important but very controversial See heated discussions about Declaration of Helsinki's statement (29) about this I m not sure it should be in the Protocol
- Long term follow-up (if necessary) should be incorporated in the specifics of the study (i e interventions or data collection or outcomes) if it is considered an intergral part of the protocol If you are referring to follow-up determined necessary post hoc this would be very difficult to firmly articulate pre-study (i e during the protocol development phase?)
- This is mainly for the REB submission (2) in the scientific protocol I think a general remark on the duration of ethical obligation- to end of trial or beyond and extent- side effects or all care- is enough (1)
- Not always pertinent (2) should not be mandatory (1)
- The protocol requires concise statements
- This is very important - under what conditions will the participants roll over into active treatment? How will they be followed? When will they be unblinded?

Your previous rating. 6

25% M 75%

4 5 3 1 2 10 6 18 6 10 5

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

Not important Very important

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)

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
- General details
- Gives snapshot and speaks to patient acceptance
- Perhaps I misunderstand this item but including Case Report Form is quite critical (this is where the "rubber hits the road" when 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

Your previous rating. 6

25% M 75%

12 3 1 1 5 6 10 1 6 20 4

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

Not important Very important

Comments:

Post-trial data/materials storage 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

Previous comments:

- Brief nod possibly but more details should be in the contract as this will depend on regulatory requirements (i e 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 30)
- Does not have be stated in the protocol (3)
- Important for manual of operations not protocol (2)
- Funder /sponsor may have specified requirements
- I would put this as part of the early question about samples of biological materials
- It is ethical issue
- 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
- Since trial reports are generally not reliable it is important to know where the raw data are
- This does not necessarily belong in protocol but is needed in sponsor SOP with awareness by investigator sites
- Vital to a protocol not in a publication

Your previous rating: 6

25% M 75%

8 4 4 2 10 6 8 12 8 10 2

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

Not important Very important

Comments:

Investigational product(s) If relevant describe the formulation packaging labeling and supply of the investigational product and accountability procedures

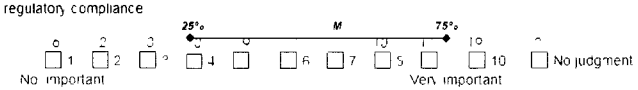
Previous comments

- 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 cues 'no
- Two separate issues here Important but belongs elsewhere
- Should be included with item Interventions (3)
- For regulatory inspection
- High level briefly (2)
- If important for success of blinding (2)

Investigational product(s) continued

- Important if relevant but could also be specified somewhere other than the protocol (2)
- Important in a protocol but not in a publication – especially
- This is needed for GCP / regulatory compliance

Your previous rating ○



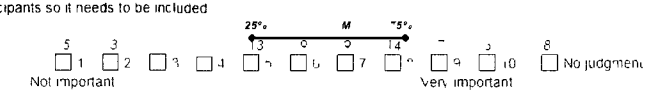
Comments

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
- Not sure of the meaning of this term
- Parameters for non co enrolment could be mentioned But co enrolment should be outlined in detail at the investigators meeting/site initiation since the availability of other studies will vary during the life of the trial This would require too many protocol amendments
- Regulatory issue hard to handle in summary
- State the potential impact of co enrolment on outcomes adverse effects effectiveness compliance
- Could have a general statement about whether or not this is an absolute contraindication (i e whether it would be scientifically permissable) but would steer clear of specific statements as the ethics of this will likely be locally determined this could also be addressed very simply in the study inclusion/exclusion criteria
- There is ongoing research into this area Not clear if it can be fully described in the protocol itself
- These are sponsor policy issues The process for implementing the policy should be available but is not required in protocol
- This is becoming an increasing issue so specifying this up front would be helpful
- This may exclude participants so it needs to be included

Your previous rating ○



Comments

Ancillary and sub-studies Describe any foreseen further uses of personal data or biological materials for related sub studies or ancillary studies *"and whether consent was obtained for these studies"*

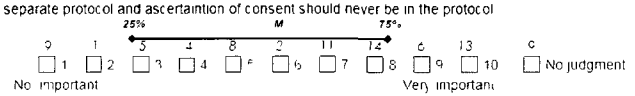
Previous comments

- "Should be a component of the item Agreement and Consent (4)
- Important but belongs elsewhere (4) informed consent document (3) and manual of operations (1)
- What about unforeseen? Does it belong to protocol?
- Important for ethical committee but presence might be discussed in a general template
- Important issue of good practice but useless unless carefully framed no one is likely to report a deliberate intention to break the law
- This item needs clarification Embedded prospective correlative studies should be described The process of banking specimens for potential correlative studies should be described The process for determining potential uses of banked specimens does not need to be in protocol but should be available through sponsor policy documents
- This is important especially with the increased frequency of genetics substudies and specimen banking
- This is only relevant if the objectives of the trial requires this long term follow up All hypothesis free storage could be dealt with as an ethics issue in the REB submission which I see as separate
- Not possible

Ancillary and sub studies (continued)

- Substudies should have a separate protocol and ascertaintion of consent should never be in the protocol

Your previous rating ○



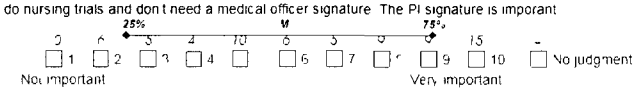
Comments

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

Previous comments

- Not sure why it needs to be part of protocol should be collected separately from the protocol – 3
- Required for funding not protocol
- Not really relavant nowadays
- Accountability and responsibility
- Depends on the format (hard copies electronic submission) and recipient (funding agency publication) Should be in a separate document
- Keep this requirement minimal only the overall PI (please note that this individual is referred to as a qualified investigator as per Health Canada)
- Protocol as published (for example) does not require signatures I think this is more REB application and various contracts
- There should be a signature page after the title page
- Why medical officer we do nursing trials and don't need a medical officer signature The PI signature is imporant

Your previous rating ○



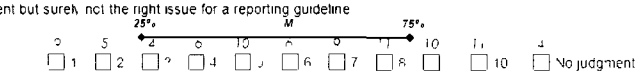
Comments

Feasibility Justify the feasibility of the trial including the acceptability of the protocol for both participants and physicians and the capacity of recruitment

Previous comments

- Important but not sure this needs a separate section (4) can be covered within sample (1)/ sample size (2) setting (1) / agreement and consent (1) / Ethics approval (1)
- Capacity for recruitment is a changing phenomenon It is common for actual recruitment to lag beind projections Certainly any pilot work done to demonstrate feasibility should be included
- The acceptability of the protocol may be subjective (1)/ not sure how one may judge claims about these issues (1)
- Capacity for recruitment is a good item
- Does not belong to the protocol (2)
- Important for the funding body (5) but may not belong in the protocol (3)
- I persist to think that this point is very important
- If feasibility in doubt should not be funded (1) run or registered (1)
- Important but other issue
- Important but claims of acceptability and recruitment are always vastly overstated
- This is a site selection issue and should not be in the protocol
- This is equivalent to reporting on the results of the pilot study Not every trial will have a pilot but feasibility is part of the justification for the trial (1) This seems to come under preliminary studies so not a separate item (1) already covered in many of the background sections (1)
- Vital before commencement but surely not the right issue for a reporting guideline

Your previous rating ○



Comments

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 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 regulaton and governance frameworks
- Not applicable to all trials I don't think
- Not relevant in every country
- Role of ethical committee
- Vital to a protocol not in a publication
- Statements are required in protocol and or 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 that 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

Your previous rating 0

25% M 75%

3 0 5 5 11 7 6 10 5 12 4

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

Not important — Very important

Comments

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 from Round One and Two are available on request Please feel free to contact jtetzlaff@cheo on ca*
- Summary scores listed are medians and inter quartile ranges

List of abbreviations List and descriptors of abbreviations used throughout the protocol

Round 1 8 (6 10) **Round 2** 7 (5 8) ☐ Include ☐ Exclude ☐ Unsure

Comments

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

Note from Moderator This item was intended to briefly outline the approach taken to address the question (e g pragmatic explanatory) which may overlap conceptually with "Type of study If you believe it should be included but combined with an existing item please state this in the comments

Round 1 8 (6 10) **Round 2** 7 (5 8) ☐ Include ☐ Exclude ☐ Unsure

Comments

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

Note from Moderator This item has been reiterated below based on some comments received in Round One and Round Two

Provide names affiliations and contact details of key trial personnel including investigators statisticians and other relevant staff (e g consultants)

Round 1 7 (5 8 5) **Round 2** 6 (4 7 5) ☐ Include ☐ Exclude ☐ Unsure

Comments

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

Round 1 7 (5 8) **Round 2** 6 (4 7) ☐ Include ☐ Exclude ☐ Unsure

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

Provide a short summary of the proposed research

☐ Include ☐ Exclude ☐ Unsure

Where required include appropriate lay/non technical language

☐ Include ☐ Exclude ☐ Unsure

Comments lay summary could be considered an ADDITIONAL document so actually don't think it is part of the protocol

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

Briefly describe the sites(s) where the research is to be conducted

☐ Include ☐ Exclude ☐ Unsure

Briefly justify the sites(s) where the research is to be conducted

☐ Include ☐ Exclude ☐ Unsure

Briefly describe relevant demographic and epidemiological information about the country or region where the research is to be conducted

☐ Include ☐ Exclude ☐ Unsure

Comments

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

Describe the criteria for inclusion and exclusion of potential participants

☐ Include ☐ Exclude ☐ Unsure

Justify the exclusion of any subgroup

☐ Include ☐ Exclude ☐ Unsure

Comments

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

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

☐ Include ☐ Exclude ☐ Unsure

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

☐ Include ☐ Exclude ☐ Unsure

Comments

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)

Provide precise details of the interventions intended for each group how they will be administered (e g dosage and dosage form device) where applicable

☐ Include ☐ Exclude ☐ Unsure

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

☐ Include ☐ Exclude ☐ Unsure

Comments

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 state when a centre may be discontinued from the trial

State criteria that will be used to withdraw or exclude participants from the intervention (e g compliance requirements safety concerns)

☐ Include ☐ Exclude ☐ Unsure

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

☐ Include ☐ Exclude ☐ Unsure

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

☐ Include ☐ Exclude ☐ Unsure

Comments

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

☐ Include ☐ Exclude ☐ Unsure

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

☐ Include ☐ Exclude ☐ Unsure

Comments

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)

Name the source(s) of financial and material support

☐ Include ☐ Exclude ☐ Unsure

List the type(s) of support provided

☐ Include ☐ Exclude ☐ Unsure

State the amount of support provided

☐ Include ☐ Exclude ☐ Unsure

State how source(s) of support are provided (e g to a research account or as an honorarium)

☐ Include ☐ Exclude ☐ Unsure

Comments

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 *Please note CVs have been removed from this item*

Samples of case report forms

☐ Include ☐ Exclude ☐ Unsure

Other data collection forms (e g questionnaires)

☐ Include ☐ Exclude ☐ Unsure

Consent/assent forms

☐ Include ☐ Exclude ☐ Unsure

Comments

You have completed the SPIRIT Delphi Consensus Survey!

We would like to recognize the substantial contribution you have made to the preliminary stages of this initiative Your feedback will continue to be an important component for further development of this tool

We are extremely grateful Thank you again

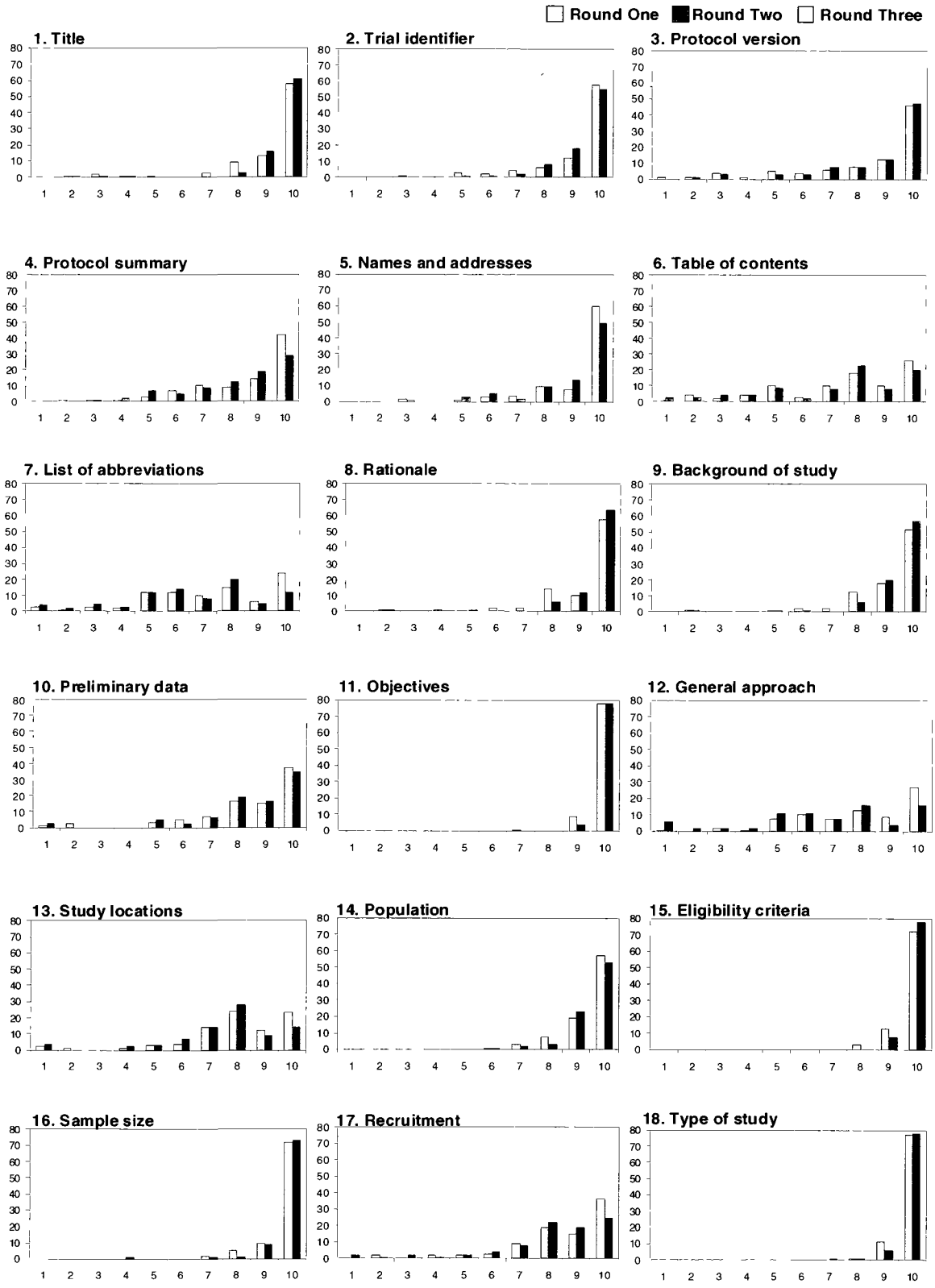
Additional comments

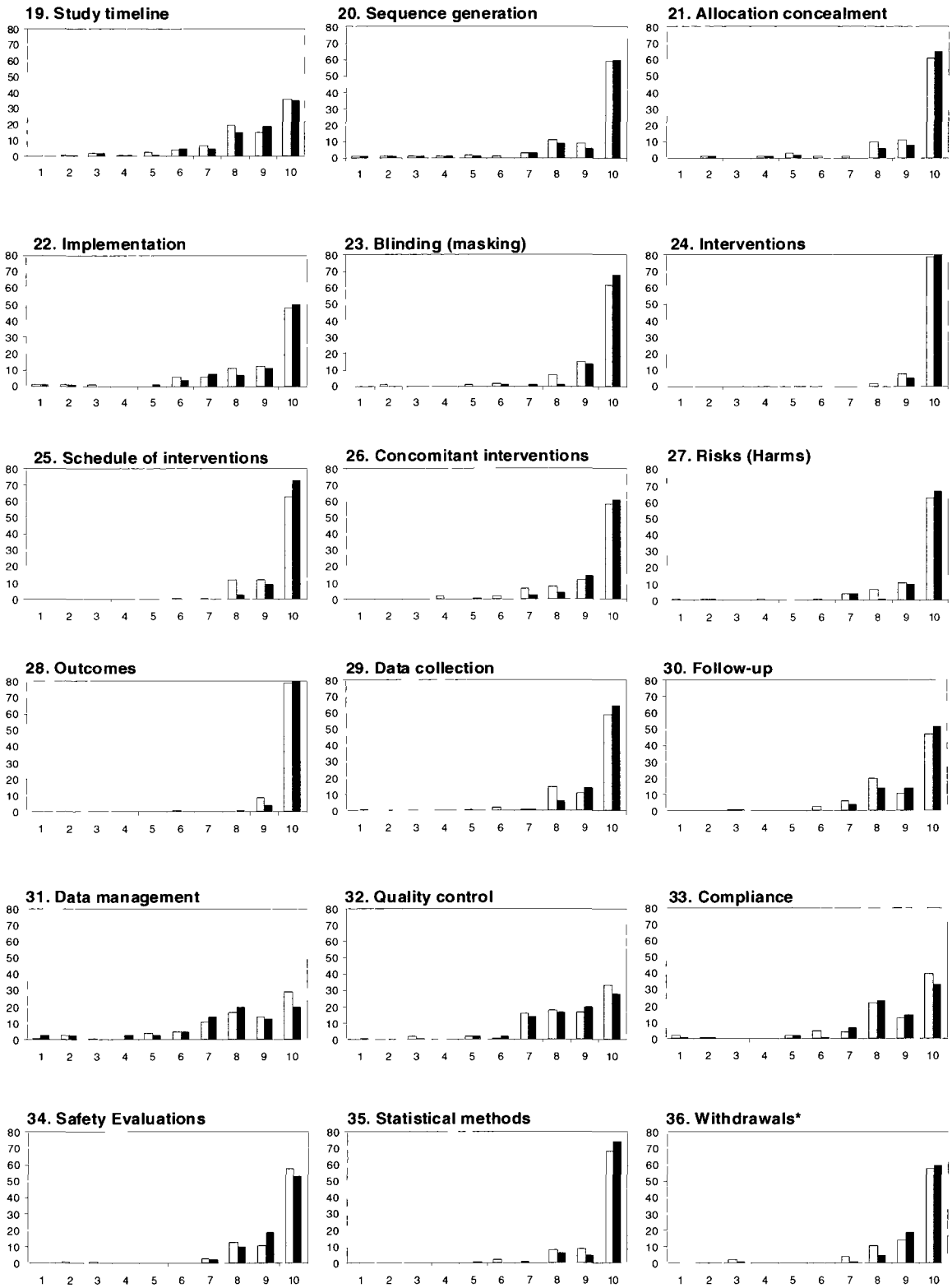
9.3 Appendix C: SPIRIT Delphi Panellists

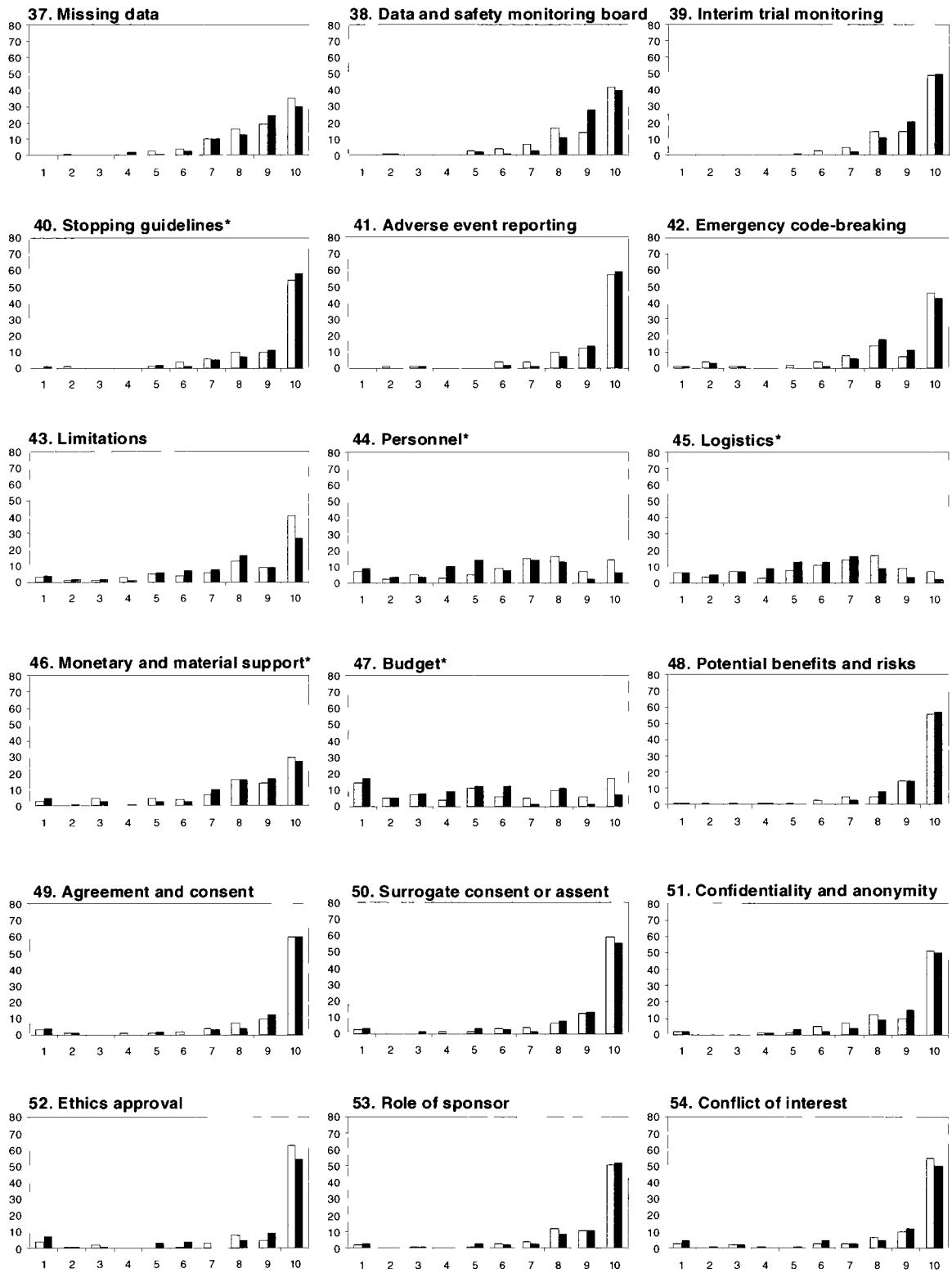
Peter Aaby, Guinea-Bissau
Edgardo Abalos, Argentina
Douglas Altman, UK
Pierre Amarenco, France
Richard E Ashcroft, UK
Virginia Barbour, UK
Elinor Ben-Menachem, Sweden
Jesse Berlin, USA
Bernard Burnand, Switzerland
Ian Cameron, Australia
Marion K Campbell, UK
An-Wen Chan, Canada
Erin Cherban, Canada
Stephen 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 Dickersin, USA
Dennis Dixon, USA
Ben Djulbegovic, USA
Caroline Dore, UK (MRC)
Lelia Duley, UK
Don Easton, USA
Diana Elbourne, UK
Dean Fergusson, Canada
Curt Furberg
Carole Gentile, Canada
Davina Ghersi, Switzerland
Kathleen Glass, Canada (University)
Christian Gluud, Denmark
Michael Goodyear, Canada
Peter Gøtzsche, Denmark
Trish Groves, UK
Metin Gulmezoglu, Switzerland
Robert Hart, USA
Paul Hébert, Canada
Lynda Hoey, Canada
Sally Hopewell, UK
Asbjørn Hróbjartsson, Denmark
Mirjana Huic, Croatia
Clay Johnston, USA
Susan Kahn, Canada
Michael Kramer, Canada
Deborah Kraus, Canada
Karmela Krleža-Jerić, 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
Julie Weston, Canada
Janet Wittes, USA
TaixiangWu, China
Merrick Zwarenstein, Canada

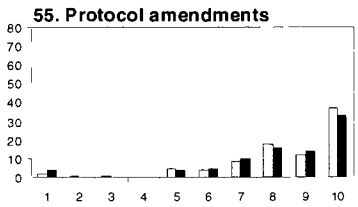
Notes 1 Responses were based on panellists' personal views and do not necessarily represent the views of their employers or other organizations to which they are affiliated
2 Two panellists preferred not to be acknowledged

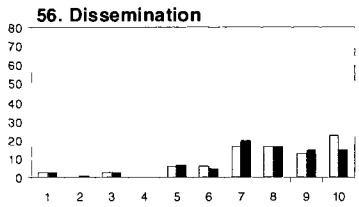
9.4 Appendix D: Delphi Survey Frequency Distributions

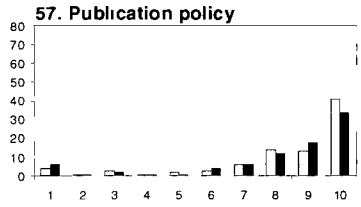


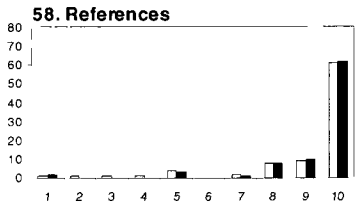

19. Study timeline
20. Sequence generation
21. Allocation concealment
22. Implementation
23. Blinding (masking)
24. Interventions
25. Schedule of interventions
26. Concomitant interventions
27. Risks (Harms)
28. Outcomes
29. Data collection
30. Follow-up
31. Data management
32. Quality control
33. Compliance
34. Safety Evaluations
35. Statistical methods
36. Withdrawals*

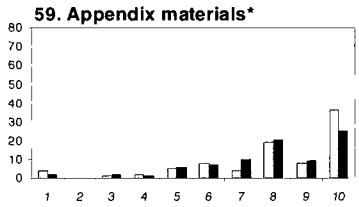

37. Missing data
38. Data and safety monitoring board
39. Interim trial monitoring
40. Stopping guidelines*
41. Adverse event reporting
42. Emergency code-breaking
43. Limitations
44. Personnel*
45. Logistics*
46. Monetary and material support*
47. Budget*
48. Potential benefits and risks
49. Agreement and consent
50. Surrogate consent or assent
51. Confidentiality and anonymity
52. Ethics approval
53. Role of sponsor
54. Conflict of interest

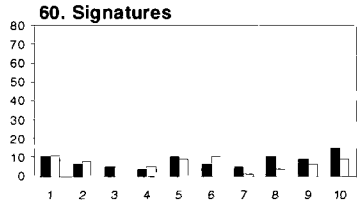

55. Protocol amendments

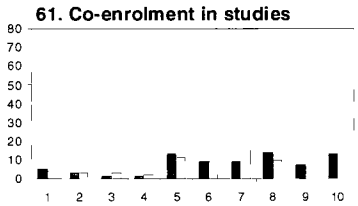

56. Dissemination

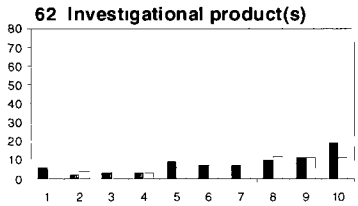

57. Publication policy

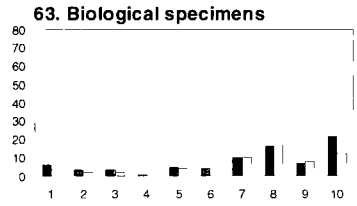

58. References

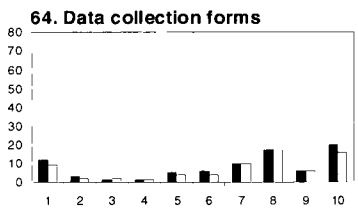

59. Appendix materials*

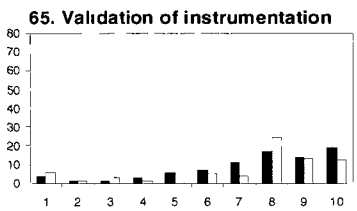

60. Signatures

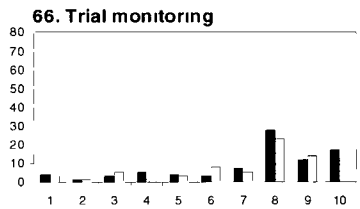

61. Co-enrolment in studies

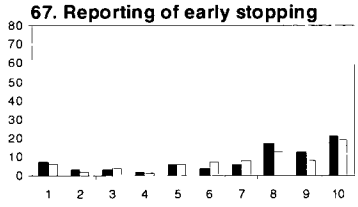

62 Investigational product(s)

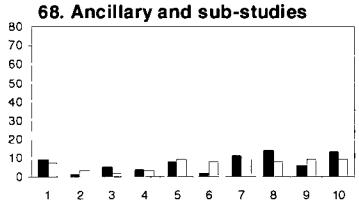

63. Biological specimens

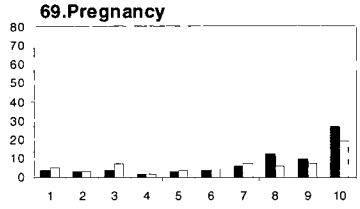

64. Data collection forms

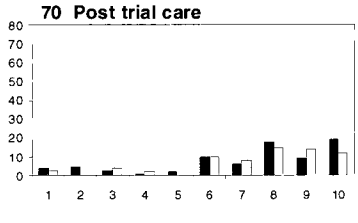

65. Validation of instrumentation

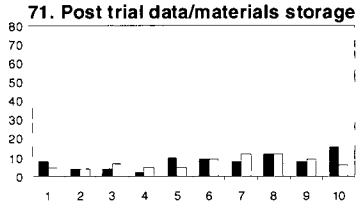

66. Trial monitoring

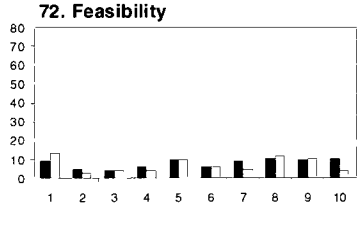

67. Reporting of early stopping

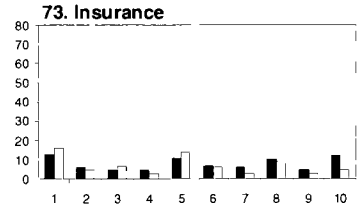

68. Ancillary and sub-studies

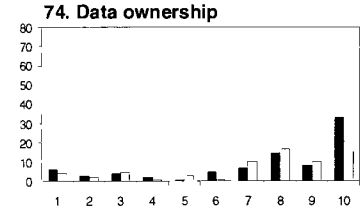

69.Pregnancy


70 Post trial care


71. Post trial data/materials storage


72. Feasibility


73. Insurance


74. Data ownership

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/
		36	Authorship/
7	or/1-6	37	Writing/
8	research design/	38	Adverse Drug Reaction Reporting Systems/
9	Randomized Controlled Trials/es, st [Ethics, Standards]	39	exp Patient rights/
		40	exp informed consent/
10	Clinical Trials/st, es [Standards, Ethics]	41	exp Ethics/
11	Controlled Clinical Trials/st, es [Standards, Ethics]	42	Health Resources/
		43	Budgets/
12	Clinical Protocols/st, mt [Standards, Methods]	44	Epidemiologic Factors/
		45	Research Support/
13	or/8 12	46	Registries/
14	patient selection/	47	drug labelling/
15	exp bias epidemiology/	48	dosage forms/
16	Research Subjects/	49	drug packaging/
17	Research Personnel/	50	drug storage/
18	statistics/	51	Records/
19	risk/	52	Medical Records/
20	risk assessment/	53	Disclosure/
21	Data Interpretation, Statistical/	54	Truth Disclosure/
22	models, statistical/	55	Confidentiality/
23	"Probability"/	56	Scientific misconduct/
24	treatment outcome/	57	Fraud/
25	(protocol adj2 amendment$) tw	58	or/14-57
26	guidelines/	59	(protocol$ or proposal$ or trial$ or medical research or biomedical research) ti,ab
27	"codes of ethics"/		
28	exp Epidemiologic Research Design/	60	(editorial or news or comment) pt
29	Product Labeling/	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).

[ ] No (exclude)
[ ] Yes/Don't know – please answer question 2

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)?

[ ] No (exclude)
[ ] Yes/Don't know – please answer question 3

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.

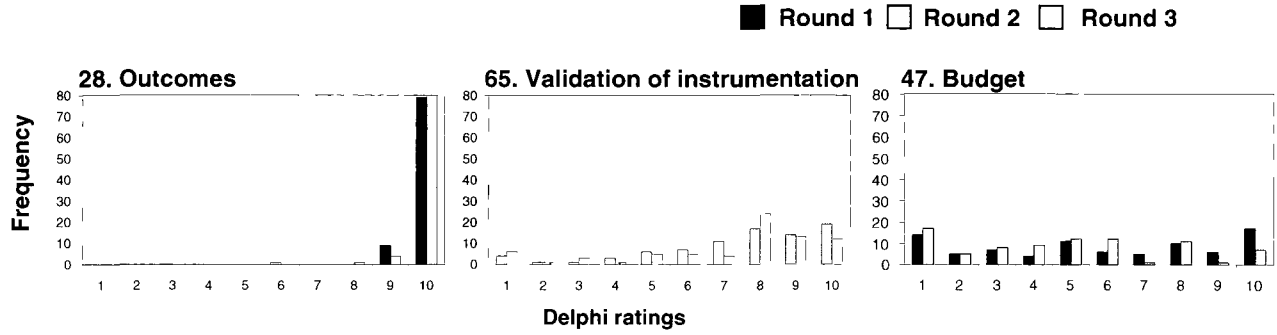


Figure 6: Examples of Delphi frequency distributions

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).

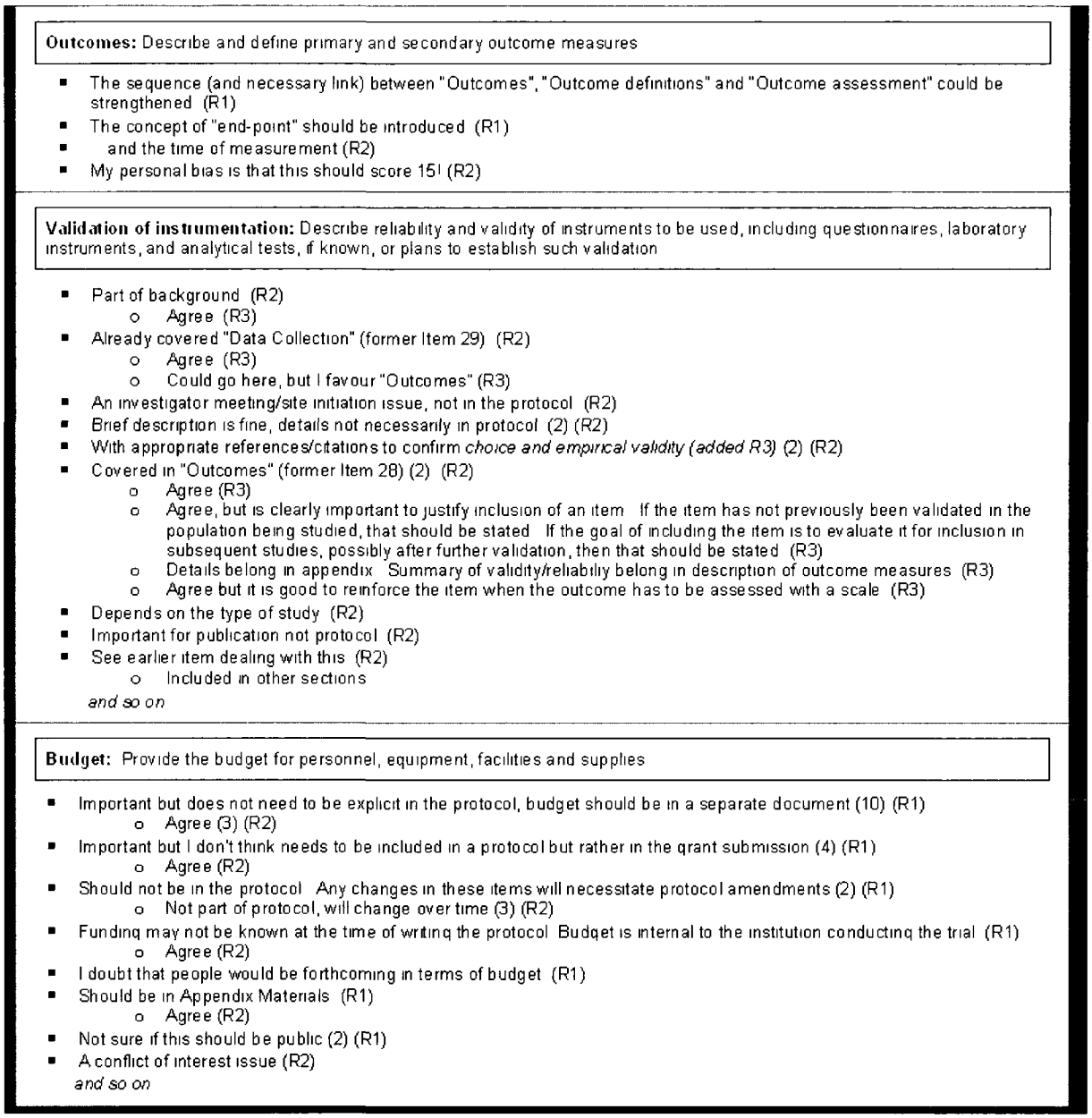


Figure 7: Examples of item-specific Delphi comments
Note: R1 = comment from Round 1; R2 = comment from Round 2; R3 = comment from Round 3.

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. One study may have contained 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.		
1. 874 Thabut et al. (2006)[182]	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.	1. A primary endpoint was defined in 62 reports (80.5%)
2. 8380 Bhandari et al. (2002)[183]	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)	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.
3. 1614 (included in SR) Chan et al. (2004)[3]	3. Cohort of RCTs funded by CIHR/MRC between 1990 and 1998 and subsequent publications: comparison of outcomes reported.	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)*
4. 2043 Quinones et al. (2003)[185]	4. Cross-sectional (1984-1997) study of clinical trials (92% RCTs) of interventions to treat asthma	4. Criteria for measuring outcomes was not considered to be objective in 17 (5%) and partially objective in 107 (33%) of trials.
5. 2807 Balk et al. (2002)[91]	5. SR of 26 MAs (276 RCTs) in one of 4 major medical fields (up to 2000)	5. Appropriate outcome studied (based on topic, study design, intervention) in 99% RCTs.
6. 3166 Kidwell et al. (2001)[192]	6. SR of RCTs of acute ischemic stroke (166 RCTs in 178 CCTs) published in English	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.
7. 1362 Chan and Altman (2005)[4]	7. Cross-section of RCTs (519) published in Dec. 2000 and indexed in PubMed.	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....
.....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

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

SPIRIT Recommendation / Topic	CIOMS	CIHR	NHS	CDC	PRACTIHC	ICHE6	NIH
Monetary and material support A. Source(s) of financial and material support.	√		√	√		√	√
Potential benefits and risks	√		√			√	√
Agreement and consent	√		√		√	~√	√
Confidentiality and Anonymity	√			√		~√	√
Ethics approval	√		√			~√	√
Role of sponsor				~√		~√	√
Conflict of Interest				√		~√	~√
Protocol Amendments						√	
Dissemination	√		√	√	√		~√
Publication Policy	√		√	√	√	√	√
Appendix materials C. Consent/assent forms		√	√			~√	√
Include concept/further discussion							
Risks/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	√					~√	√

SPIRIT Recommendation / Topic	CIOMS	CIHR	NHS	CDC	PRACTIHC	ICHE6	NIH
Appendix materials B. Other data collection forms (e.g. questionnaires)			√	√		~√	
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