Guidelines for Reporting Outcomes in Trial Protocols
The SPIRIT-Outcomes 2022 Extension

Nancy J. Butcher, PhD; Andrea Monsour, MPH; Emma J. Mew, MPH, MPhil; An-Wen Chan, MD, DPhil; David Moher, PhD; Evan Mayo-Wilson, DPhil; Caroline B. Terwee, PhD; Alyssandra Chee-A-Tow, MPH; Ami Baba, MRes; Frank Gavin, MA; Jeremy M. Grimshaw, MBCHB, PhD; Lauren E. Kelly, PhD; Leena Saeed, BSc, BEd; Lehana Thabane, PhD; Lisa Askie, PhD; Maureen Smith, MEd; Mufiza Farid-Kapadia, MD, PhD; Paula R. Williamson, PhD; Peter Szatmari, MD; Peter Tugwell, MD; Robert M. Golub, MD; Suneeta Monga, MD; Sunita Vohra, MD; Susan Marlin, MSc; Wendy J. Ungar, PhD; Martin Offringa, MD, PhD

IMPORTANCE Complete information in a trial protocol regarding study outcomes is crucial for obtaining regulatory approvals, ensuring standardized trial conduct, reducing research waste, and providing transparency of methods to facilitate trial replication, critical appraisal, accurate reporting and interpretation of trial results, and knowledge synthesis. However, recommendations on what outcome-specific information should be included are diverse and inconsistent. To improve reporting practices promoting transparent and reproducible outcome selection, assessment, and analysis, a need for specific and harmonized guidance as to what outcome-specific information should be addressed in clinical trial protocols exists.

OBJECTIVE To develop harmonized, evidence- and consensus-based standards for describing outcomes in clinical trial protocols through integration with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement.

EVIDENCE REVIEW Using the Enhancing the Quality and Transparency of Health Research (EQUATOR) methodological framework, the SPIRIT-Outcomes 2022 extension of the SPIRIT 2013 statement was developed by (1) generation and evaluation of candidate outcome reporting items via consultation with experts and a scoping review of existing guidance for reporting trial outcomes (published within the 10 years prior to March 19, 2018) identified through expert solicitation, electronic database searches of MEDLINE and the Cochrane Methodology Register, gray literature searches, and reference list searches; (2) a 3-round international Delphi voting process (November 2018-February 2019) completed by 124 panelists from 22 countries to rate and identify additional items; and (3) an in-person consensus meeting (April 9-10, 2019) attended by 25 panelists to identify essential items for outcome-specific reporting to be addressed in clinical trial protocols.

FINDINGS The scoping review and consultation with experts identified 108 recommendations relevant to outcome-specific reporting to be addressed in trial protocols, the majority (72%) of which were not included in the SPIRIT 2013 statement. All recommendations were consolidated into 56 items for Delphi voting; after the Delphi survey process, 19 items met criteria for further evaluation at the consensus meeting and possible inclusion in the SPIRIT-Outcomes 2022 extension. The discussions during and after the consensus meeting yielded 9 items that elaborate on the SPIRIT 2013 statement checklist items and are related to completely defining and justifying the choice of primary, secondary, and other outcomes (SPIRIT 2013 statement checklist item 12) prospectively in the trial protocol, defining and justifying the target difference between treatment groups for the primary outcome used in the sample size calculations (SPIRIT 2013 statement checklist item 14), describing the responsiveness of the study instruments used to assess the outcome and providing details on the outcome assessors (SPIRIT 2013 statement checklist item 18a), and describing any planned methods to account for multiplicity relating to the analyses or interpretation of the results (SPIRIT 2013 statement checklist item 20a).

CONCLUSIONS AND RELEVANCE This SPIRIT-Outcomes 2022 extension of the SPIRIT 2013 statement provides 9 outcome-specific items that should be addressed in all trial protocols and may help increase trial utility, replicability, and transparency and may minimize the risk of selective nonreporting of trial results.

JAMA. 2022;328(23):2345-2356. doi:10.1001/jama.2022.21243
Published online December 13, 2022.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Nancy J. Butcher, PhD, Peter Gilgan Centre for Research and Learning, The Hospital for Sick Children, 686 Bay St, Toronto, ON M5G 0A4, Canada (nancy.butcher@sickkids.ca).

Trial protocols describe objectives, designs, methods, planned analyses, organization, and amendments of randomized clinical trials. Trial protocols are used by trial investigators, trial staff, funding and regulatory agencies, health technology assessment bodies, ethics review boards, systematic reviewers, academic journals, and more. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement[1-3] provided a checklist of 33 reporting items to be included in trial protocols. The SPIRIT 2013 statement encompassed trial protocol items recommended by the International Conference on Harmonisation good clinical practice guidance.[4] Even though a SPIRIT extension for reporting patient-reported outcomes is available,[5] no evidence-based guideline exists for reporting outcome-specific information applicable to all systematically collected outcome types, populations, and trial designs.

Complete reporting of outcome-specific information in trial protocols is important for obtaining ethical and regulatory approvals, and ensuring the trial is conducted in accordance with predetermined aims and methods. Although a clearly described trial protocol promotes the transparency of an individual trial's methods and facilitates the reporting and interpretation of the trial results, a recent scoping review[6] revealed that recommendations on how to prospectively report the selection, assessment, and analyses of trial outcomes in trial protocols by academic, regulatory, and public sources are diverse, inconsistent, and dispersed across a large number of documents. Even though the SPIRIT 2013 statement[1,2] provides general guidance on how to report trial outcomes, well-documented problems in reporting trial outcomes persist.[7-11] These reporting problems can affect the conclusions of systematic reviews and meta-analyses, contributing to ongoing research waste.[12,13]

The aim of the SPIRIT-Outcomes 2022 extension was to develop harmonized, evidence- and consensus-based outcome reporting standards for trial protocols.

Key Points

Question What outcome-specific information should be included in a clinical trial protocol?

Findings Using an evidence-based and international consensus–based approach that applied methods from the Enhancing the Quality and Transparency of Health Research (EQUATOR) methodological framework, 9 outcome-specific reporting items to be addressed in clinical trial protocols were identified.

Meaning Inclusion of these items in clinical trial protocols may enhance trial utility, replicability, and transparency and may help limit selective nonreporting of trial results.

Methods

The SPIRIT-Outcomes 2022 extension was developed as part of the Instrument for Reporting Planned Endpoints in Clinical Trials (InsPECT) project[14] in accordance with the Enhancing Quality and Transparency of Health Research (EQUATOR) methodological framework for reporting guideline development.[15] Ethics approval was not required as determined by the research ethics committee at The Hospital for Sick Children. Specific guidance for the content of statistical analysis plans has been published.[16] The development of the SPIRIT-Outcomes 2022 extension occurred in parallel with the Consolidated Standards of Reporting Trials (CONSORT)–Outcomes 2022 extension for clinical trial reports.[17]

Key Development Phases

First, we created an initial list of recommendations relevant to reporting outcomes for randomized clinical trials that were synthesized from consultation with experts and a scoping review of existing guidance for reporting trial outcomes (published within the 10 years prior to March 19, 2018) identified through expert solicitation, electronic database searches of MEDLINE and the Cochrane Methodology Register, gray literature searches, and reference list searches as described.[6,18] Second, a 3-round international Delphi voting process took place from November 2018 to February 2019 to identify additional items and assess the importance of each item using a 9-point Likert scale and completed by 124 panelists from 22 countries (eTable 1 in the Supplement). Third, an in-person expert consensus meeting was held (April 9-10, 2019), which was attended by 25 panelists from 4 countries, including a patient partner and a public partner, to identify the set of essential items relevant to reporting outcome-specific information in trial protocols and establish dissemination activities. Selection and wording of the items was finalized at a postconsensus meeting by executive panel members and via email with consensus meeting panelists.

Other Information

The detailed methods describing development of the SPIRIT-Outcomes 2022 extension appear in eAppendix 1 in the Supplement, including the number of items evaluated at each phase and the process toward the final set of included items (eFigure in the Supplement). The scoping review trial protocol and findings have been published[6,18] and appear in eAppendix 1 in the Supplement and the search strategy appears in eAppendix 2 in the Supplement. The self-reported characteristics of the Delphi voting panelists and the consensus meeting panelists appear in eTables 1-2 in the Supplement. Details regarding the involvement of the patient partner and public partner appear in eAppendix 1 in the Supplement.

Results

In addition to the inclusion of the SPIRIT 2013 statement checklist items, the SPIRIT-Outcomes 2022 extension recommends that descriptions of a minimum of 9 outcome-specific reporting items should be included prospectively in trial protocols, regardless of trial design or population. The scoping review and consultation with experts identified 108 recommendations relevant to outcome-specific reporting to be addressed in trial protocols, the majority (72%) of which not were not included in the SPIRIT 2013 statement. All recommendations were consolidated into 56 items for Delphi voting; after the Delphi survey process, 19 items met the criteria for further evaluation at the consensus meeting and possible inclusion in the SPIRIT-Outcomes 2022 extension. The SPIRIT 2013 statement checklist items and the 9 outcome-specific reporting items added by the SPIRIT-Outcomes 2022 extension appear in **Table 1**.[19]

Table 1. Recommended Checklist Items to Address in a Clinical Trial Protocol From the SPIRIT 2013 Statement and the SPIRIT-Outcomes 2022 Extension[a]

Section	Item No.	SPIRIT 2013 statement	Item No.	SPIRIT-Outcomes 2022 extension
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym		
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry		
	2b	All items from the World Health Organization Trial Registration Data Set		
Protocol version	3	Date and version identifier		
Funding	4	Sources and types of financial, material, and other support		
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors		
	5b	Name and contact information for the trial sponsor		
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities		
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see item 21a for data monitoring committee)		
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention		
	6b	Explanation for choice of comparators		
Objectives	7	Specific objectives or hypotheses		
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)		
Methods: participants, interventions, and outcomes				
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained		
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists)		
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (for specific guidance see TIDieR checklist and guide)[19]		
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)		
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)		
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial		
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12.1	Provide a rationale for the selection of the domain for the trial's primary outcome
			12.2	If the analysis metric for the primary outcome represents within-participant change, define and justify the minimal important change in individuals
			12.3	If the outcome data collected are continuous, but will be analyzed as categorical (method of aggregation), specify the cutoff values to be used
			12.4	If outcome assessments will be performed at several time points after randomization, state the time points that will be used for the analysis
			12.5	If a composite outcome is used, define all individual components of the composite outcome

(continued)

Table 1. Recommended Checklist Items to Address in a Clinical Trial Protocol From the SPIRIT 2013 Statement and the SPIRIT-Outcomes 2022 Extension[a] (continued)

Section	Item No.	SPIRIT 2013 statement	Item No.	SPIRIT-Outcomes 2022 extension
Participant timeline	13	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)		
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14.1	Define and justify the target difference between treatment groups (eg, the minimal important difference)
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size		
Methods: assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions		
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned		
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions		
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how		
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial		
Methods: data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18a.1	Describe what is known about the responsiveness of the study instruments in a population similar to the study sample
			18a.2	Describe who will assess the primary outcome (eg, nurse, parent)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols		
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol		
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20a.1	Describe any planned methods to account for multiplicity in the analysis or interpretation of the primary and secondary outcomes (eg, coprimary outcomes, same outcome assessed at multiple time points, or subgroup analyses of an outcome)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)		
	20c	Definition of analysis population relating to protocol nonadherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)		
Methods: monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed		
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial		
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct		
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor		

(continued)

Table 1. Recommended Checklist Items to Address in a Clinical Trial Protocol From the SPIRIT 2013 Statement and the SPIRIT-Outcomes 2022 Extension[a] (continued)

Section	Item No.	SPIRIT 2013 statement	Item No.	SPIRIT-Outcomes 2022 extension
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval		
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)		
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see item 32)		
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial		
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site		
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators		
Ancillary care and care after the trial	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation		
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions		
	31b	Authorship eligibility guidelines and any intended use of professional writers		
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code		
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates		
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable		

Abbreviations: SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; TIDieR, Template for Intervention Description and Replication.

[a] It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 statement guidelines[1,2] for important clarification on the checklist items. The SPIRIT 2013 statement checklist is distributed under the terms of the Creative Commons license.

A fillable version of the checklist appears in eTables 3-4 in the Supplement and on the SPIRIT website.[3] When using the updated checklist, users should refer to definitions of key terms in the glossary[20-37] (**Box**) because variations in the terminologies and definitions exist across disciplines and geographic areas. The 5 core elements of a defined outcome (with examples) appear in **Table 2**.[38,39]

Application of these new checklist items from the SPIRIT-Outcomes 2022 extension, in conjunction with SPIRIT 2013 statement, ensures trial outcomes will be comprehensively defined prospectively in trial protocols and reported in trial reports. The estimated list of key users, their proposed actions, and the consequential potential benefits of implementing the 9 SPIRIT-Outcomes 2022 extension checklist items appears in eTable 5 in the Supplement and was generated from the consensus meeting's knowledge translation session. Examination and application of these outcome reporting recommendations may be helpful for trial authors, journal editors, peer reviewers, systematic reviewers, patients, the public, and trial participants (eTable 5 in the Supplement).

This report contains a brief explanation of the 9 checklist items generated from the SPIRIT-Outcomes 2022 extension. Guidance on how to report the existing checklist items can be found in the SPIRIT 2013 statement,[1] in Table 1, and in an explanatory guideline report.[2] Additional items that may be useful to include in some trial protocols or in associated trial documents (eg, the statistical analysis plan) appear in eTable 6 in the Supplement, but were not considered essential reporting items for all trial protocols.

SPIRIT-Outcomes 2022 Extension Checklist Items for the Descriptions of the Outcomes

Item 12.1. Provide a Rationale for the Selection of the Domain for the Trial's Primary Outcome

This item expands on SPIRIT 2013 statement checklist item 12 to prompt authors to report on the rationale underlying the selection of the outcome domain for use as the primary outcome, which includes its clinical relevance. At a broad conceptual level, the outcome's domain refers to the name or concept used to describe an

Box. Glossary of Terms Used in the SPIRIT-Outcomes 2022 Extension

Composite outcome: A composite outcome consists of ≥2 component outcomes (eg, proportion of participants who died or experienced a nonfatal stroke). Participants who have experienced any of the events specified by the components are considered to have experienced the composite outcome.[20,21]

CONSORT 2010: Consolidated Standards of Reporting Trials (CONSORT) statement that was published in 2010.[22,23]

CONSORT-Outcomes 2022 extension: Additional essential checklist items describing outcome-related content that are not covered by the CONSORT 2010 statement.

Construct validity: The degree to which the scores reported in a trial are consistent with the hypotheses (eg, with regard to internal relationships, the relationships of the scores to other instruments, or relevant between-group differences) based on the assumption that the instrument validly measures the domain to be measured.[33]

Criterion validity: The degree to which the scores of a study instrument are an adequate reflection of a gold standard.[33]

Minimal important change: The smallest within-patient change that is considered important by patients, clinicians, or relevant others.[24,25] The change may be in a score or unit of measure (continuous or ordinal measurements) or in frequency (dichotomous outcomes). This term is often used interchangeably in health literature with the term *minimal important difference*. In the SPIRIT-Outcomes 2022 extension, the minimal important change conceptually refers to important intrapatient change (item 12.2) and the minimum important difference refers to the important between-group difference. Minor variants of the term, such as minimum instead of minimal, or the addition of the adjective clinically or clinical are common (eg, the minimum clinically important change).[26]

Minimal important difference: The smallest between-group difference that is considered important by patients, clinicians, or relevant others.[24,27-29] The difference may be in a score or unit of measure (continuous or ordinal measurements) or in frequency (dichotomous outcomes). Minor variants of the term, such as minimum instead of minimal, or the addition of the adjective clinically or clinical are common (eg, the minimum clinically important difference).[26]

Outcome: Refers to what is being assessed to examine the effect of exposure to a health intervention.[30] The 5 core elements of a defined outcome appear in Table 2.

Primary outcome: The planned outcome that is most directly related to the primary objective of the trial.[5] It is typically the outcome used in the sample size calculation for trials with the primary objective of assessing efficacy or effectiveness.[31] Many trials have 1 primary outcome, but some have >1. The term *primary end point* is sometimes used in the medical literature when referring to the primary outcome.[6]

Responsiveness: The ability of a study instrument to accurately detect and measure change in the outcome domain over time.[25,32] Distinct from an instrument's construct validity and criterion validity, which refer to the validity of a single score, responsiveness refers to the validity of a change score (ie, longitudinal validity).[33]

Secondary outcomes: The outcomes prespecified in the trial protocol to assess any additional effects of the intervention.[5]

Smallest worthwhile effect: The smallest beneficial effect of an intervention that justifies the costs, potential harms, and inconvenience of the interventions as determined by patients.[34]

SPIRIT 2013: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement that was published in 2013.[1,2]

SPIRIT-Outcomes 2022 extension: Additional essential checklist items describing outcome-related trial protocol content that are not covered by the SPIRIT 2013 statement.

Study instrument: The scale or tool used to make an assessment. A study instrument may be a questionnaire, a clinical rating scale, a laboratory test, a score obtained through a physical examination or an observation of an image, or a response to a single question.[35]

Target difference: The value that is used in sample size calculations as the difference sought to be detected on the primary outcome between intervention groups and that should be considered realistic or important (such as the minimal important difference or the smallest worthwhile effect) by ≥1 key stakeholder groups.[36,37]

Validity: The degree to which a study instrument measures the domain it purports to measure.[33]

outcome (eg, pain).[13,38] The word domain can be closely linked to and sometimes used equivalently with the terms *construct* and *attribute* in the literature.[39] Even though a complete outcome definition is expected to be provided in the trial protocol (as recommended by SPIRIT 2013 statement checklist item 12),[2] the rationale for the choice of the outcome domain for the trial's primary outcome is also essential to communicate because it underpins the purpose of the proposed trial.

Important aspects for the rationale may include (1) the importance of the outcome domain to individuals involved in the trial (eg, patients, the public, clinicians, policy makers, funders, or health payers), (2) the expected effect of the intervention on the outcome domain, and (3) the ability to assess it accurately, safely, and feasibly during the trial. It also should be reported whether the selected outcome domain originated from a core outcome set (ie, an agreed standardized set of outcomes that should be measured in all trials for a specific clinical area).[40-44]

Item 12.2. If the Analysis Metric for the Primary Outcome Represents Within-Participant Change, Define and Justify the Minimal Important Change in Individuals

This item expands on SPIRIT 2013 statement checklist item 12. In cases in which the participant-level analysis metric for the primary outcome represents intraindividual change from an earlier value (such as those measured at baseline), a definition and justification of what will be considered the minimal important change (MIC) for the relevant study instrument should be provided. In the SPIRIT-Outcomes 2022 extension, the MIC was defined as the smallest within-patient change that is considered important by patients, clinicians, or relevant others (common alternative terminologies appear in the Box).[24,25,27] The MIC is important to report for all trials that use a within-participant change metric, such as those that plan to analyze the proportion of participants showing a change larger than the MIC value in each treatment group (eg, to define the proportion who improved)[45] or in n-of-1 designs.[46]

Table 2. The 5 Core Elements of a Defined Outcome[a]

Element No.	Element term	Definition used	Example 1	Example 2	Example 3
1	Domain[b]	Title or concept to describe ≥1 outcomes	Blood pressure	Depression	Death
2	Measurement variable or specific measurement	Corresponds to the data collected directly from trial participants; description includes the instrument used to assess the outcome domain			
		• Descriptive name	Systolic blood pressure measured with Omron upper arm blood pressure monitor	MADRS	All-cause mortality per hospital database
		• If applicable, the total score or the subscales that will be analyzed	Not applicable	MADRS total score	Not applicable
3	Specific metric	Participant-level unit of measurement (eg, change from baseline, final value or a value at a time point, time to event) for analysis	Value at a time point	Change from baseline	Time to event
4	Method of aggregation	The procedure for estimating the treatment effect			
		• If the outcome will be treated as a continuous, categorical, or time-to-event variable	Continuous variable	Binary variable	Time to event
		• For continuous variables, a measure of central tendency (eg, mean value); for categorical and time-to-event data variables, proportion with an event and, if relevant, the specific cutoff values or categories compared	Mean value	Proportion of participants with ≥50% decrease	Incidence density and between-group incidence density rate
5	Time point	The timing of follow-up measurements			
		• When outcome measurements will be obtained	2, 4, and 12 wk after randomization	2, 4, 6, and 8 wk after randomization	Daily
		• Which of the outcome measurements will be analyzed	12 wk after randomization	8 wk after randomization	End of follow-up

Abbreviation: MADRS, Montgomery-Åsberg Depression Rating Scale.

[a] Content adapted from Zarin et al,[38] Mayo-Wilson et al,[13] and Chan et al.[2]

[b] An explicit and specific description of the outcome domain should be provided in the trial protocol, as appropriate, when defining the trial outcome. If an outcome domain is broad, such as pain, a specific protocolized domain definition might be the daily average of the intensity of the sensation of pain expressed on a range from no pain to worst pain imaginable over a 24-hour window during an average day.[39]

Trialists and those involved with trials may be interested in the MIC itself as the benchmark or, alternatively, in a value larger than the known MIC. If the MIC is unknown for the study instrument with respect to the planned trial population and setting, this should be reported along with any efforts planned to determine the MIC as part of the trial. Describing the justification for the selected MIC in the trial protocol is important because there can be numerous MICs available for the same study instrument, with varying clinical relevance and methodological quality depending on how and in whom they were determined.[47-51]

Item 12.3. If the Outcome Data Collected Are Continuous, but Will Be Analyzed as Categorical (Method of Aggregation), Specify the Cutoff Values to Be Used

This item expands on SPIRIT 2013 statement checklist item 12 to prompt authors to prospectively describe the cutoff values to be used and that any outcome data collected on a continuous (or ordinal) scale should be converted into a categorical variable for their analyses.[2,13,52] Providing an explanation of the rationale for the choice of the cutoff value is recommended. The cutoff values selected are most useful when they have clear clinical relevance.[53] Failure to include cutoff values in the trial protocol (and in the statistical analysis plan)[16] facilitates undetectable multiple testing (known as "p-hacking"), data cherry-picking, and selective nonreporting of results in the trial report.[7,13,54]

Item 12.4. If Outcome Assessments Will Be Performed at Several Time Points After Randomization, State the Time Points That Will Be Used for the Analysis

This item expands on SPIRIT 2013 statement checklist item 12 to prompt authors to specify the time point to be used in the main analysis if outcome assessments are planned to be performed at multiple time points after randomization (eg, trial will assess blood pressure daily for 12 weeks after randomization). Specifying the preplanned time points of assessment for the analyses will help limit the possibility of unplanned analyses of multiple time points for assessment and the selective nonreporting of time points that did not yield large or significant results.[2,38] Providing a rationale for the choice of time point is encouraged (eg, based on the expected clinical trajectory after the intervention or the duration of treatment needed to achieve a clinically meaningful exposure to treatment). The length of follow-up should be appropriate to the management decision the trial is designed to inform.[55]

Item 12.5. If a Composite Outcome Is Used, Define All Individual Components of the Composite Outcome

A composite outcome consists of 2 or more component outcomes that may be related. Participants who have experienced any 1 of the defined component outcomes comprising the composite outcome are considered to have experienced the composite outcome.[20,21] When used, composite outcomes should be prespecified, justified, and fully defined in the trial protocol,[53] which includes a complete definition of each individual component outcome (SPIRIT 2013 statement checklist item 12 and SPIRIT-Outcomes 2022 extension checklist items 12.1-12.4) and a description of how those outcomes will be combined (eg, what analytic steps define the occurrence of the composite outcome). The use and interpretation of composite outcomes are complex, debated in the literature, and are an important trial design consideration.[21,56]

Item 14.1. Define and Justify the Target Difference Between Treatment Groups (eg, the Minimal Important Difference)

This item expands on SPIRIT 2013 statement checklist item 14 describing sample size calculations to prompt authors to specify an a priori target between-group treatment difference at the specific time point for the analysis. The target difference is the value used in sample size calculations as the difference sought to be detected in the primary outcome between the intervention groups at the specific time point for the analysis that should be considered realistic or important by 1 or more key stakeholder groups.[36] The Difference Elicitation in Trials project has published extensive evidence-based guidance on selecting a target difference for a trial, sample size calculation, and reporting.[36,37] The target difference may be the minimal important difference (the smallest difference between patients perceived as important by patients, clinicians, or relevant others)[24,28,29] or the smallest worthwhile effect (the smallest beneficial effect of an intervention that justifies the costs, harms, and inconvenience of the interventions as determined by patients).[34]

Reporting the target difference is essential at the trial protocol stage for (1) grant peer reviewers to determine whether a trial will have sufficient plausibility and clinical effect to warrant allocation of funding, and (2) ethics boards, regulators, and other reviewers evaluating whether there is an adequate benefit to harm ratio to approve the trial, and whether the trial will be adequately powered to detect a clinically important difference. Because there can be different pragmatic or clinical factors informing the selected target difference (eg, the availability of a credible minimal important difference for the study instrument used to assess the primary outcome),[47] and numerous different options available (eg, 1 of several minimal important differences or values based on pilot studies),[47] it is important to explain why the chosen target difference was selected.[26,48,49]

SPIRIT-Outcomes 2022 Extension Checklist Items for the Descriptions of the Data Collection, Management, and Analysis

Item 18a.1. Describe What Is Known About the Responsiveness of the Study Instruments in a Population Similar to the Study Sample

This item expands on SPIRIT 2013 statement checklist item 18, which asks for a description of the reliability and validity of the study instruments (eg, questionnaires, laboratory tests), to also report on the responsiveness of the study instruments. Responsiveness refers to the ability of evaluative instruments (ie, those that measure longitudinal change and typically the effects of treatment)[57] to accurately detect and measure change over time in the health outcome being assessed.[25,32,33] Responsiveness is less relevant to discriminative instruments (eg, diagnostic tests), for which diagnostic accuracy is important. Describing whether measurement properties (such as responsiveness) have been evaluated in a population similar to the study sample (or at least not substantively different from the study sample) is helpful because measurement properties of study instruments are context specific and cannot be assumed to be generalizable between different populations (eg, with different health problems or with different age groups) in the absence of evidence.[58] If measurement properties are unknown for the study population (eg, use of a scale developed for adults in a trial studying adolescents), this should be stated with a rationale as to why it is expected that this instrument is still useful and preferable to other available options and whether there are any other instruments that could be used.

Item 18a.2. Describe Who Will Assess the Primary Outcome (eg, Nurse, Parent)

This item expands on SPIRIT 2013 statement checklist item 18 to describe who will assess the primary outcome as part of the description of plans for the assessment and collection of outcome data. Blinding of the outcome assessor to the patient's treatment assignment and to the emerging trial results is covered under SPIRIT 2013 statement checklist item 17a. Substantially different responses, and therefore different trial results, can be obtained for many types of outcomes (eg, behavioral, psychological outcomes), depending on who is assessing the outcome of interest. This variability may result from differences in assessors' training or experience, different perspectives, or patient recall.[59-61] Assessments of a clinical outcome reported by a clinician, a patient, or a nonclinician observer or through a performance-based assessment are correspondingly classified by the US Food and Drug Administration as clinician-reported, patient-reported, observer-reported, and performance outcomes.[62] For outcomes that could be assessed by various people, an explanation for the choice of outcome assessor made in the context of the trial should be provided. For outcomes (eg, plasma cholesterol levels) that are not influenced by the assessor, this information is less relevant.

Item 20a.1. Describe Any Planned Methods to Account for Multiplicity in the Analysis or Interpretation of the Primary and Secondary Outcomes (eg, Coprimary Outcomes, Same Outcome Assessed at Multiple Time Points, or Subgroup Analyses of an Outcome)

This item expands on the SPIRIT 2013 statement checklist item 20a to prompt authors to describe any planned methods to account for multiplicity relating to the analysis or interpretation of the outcomes. Outcome multiplicity issues are common in trials and deserve particular attention when there are coprimary outcomes, multiple possible time points resulting from the repeated assessment of a single outcome, multiple planned analyses of a single outcome (eg, interim or subgroup analysis, multigroup trials), or numerous secondary outcomes for analysis.[63] The planned methods used to account for such forms of multiplicity include statistical methods (eg, family-wise error rate approaches) or descriptive approaches (eg, noting that the analyses are exploratory, placing

the results in the context of the expected number of false-positive outcomes).[63,64] Decisions around whether and how to account for multiplicity may be informed by the outcome type (ie, primary vs secondary), the design of the trial (ie, exploratory vs confirmatory), and local or national regulatory requirements.[53,64] Such information may be briefly described in the trial protocol or described in more detail in the statistical analysis plan.[16]

Discussion

The SPIRIT-Outcomes 2022 extension provides evidence- and consensus-based guidance for reporting outcome-specific information in trial protocols, extending the SPIRIT 2013 statement checklist with 9 additional reporting items and harmonizing reporting recommendations with guidance from the CONSORT-Outcomes 2022 extension.[17] Alignment across these 2 extension guidelines creates a cohesive continuum of reporting from the trial protocol to the completed trial report that will facilitate both the researchers' production of the trial protocol and trial report and, importantly, enable assessment of researchers' adherence to the trial protocol.

Similar to the SPIRIT 2013 statement,[1,2] the SPIRIT-Outcomes 2022 extension applies to the content of the trial protocol, regardless of trial design or population. The current recommendations are similarly not prescriptive regarding how information should be included, which varies depending on local requirements, the purpose and audience for which a trial protocol is intended (eg, submission to a regulatory agency vs an academic journal for publication), and the public availability of related trial documents (eg, the statistical analysis plan[16]).

When other documents are available, the trial protocol should briefly describe or outline the checklist item components and refer to the separate documents such as the statistical analysis plan so that their existence, location, and accessibility are known. To maximize the usefulness and effect of the SPIRIT-Outcomes 2022 extension, it can be used in conjunction with the CONSORT-Outcomes 2022 extension.[17] In addition, inclusion of SPIRIT-Outcomes 2022 extension checklist items in trial registry entries (eg, ClinicalTrials.gov) may increase implementation. Endorsement and implementation of the SPIRIT-Outcomes 2022 extension by publishers and editors for their authors could also increase uptake. The information described in the trial protocol should be consistent with the information reported in trial registrations and statistical analysis plans. Trial protocols should be freely and prospectively accessible (eg, via publication or a permanent online repository).

Users of the SPIRIT-Outcomes 2022 extension should note that these additional checklist items represent the minimum essential outcome-specific reporting items and are being added to the SPIRIT 2013 statement guidelines to promote trial transparency, replication, and critical appraisal, and to limit selective nonreporting of results (eTable 5 in the Supplement). In some cases, it may be important to report additional outcome-specific information in the trial protocol such as those in eTable 6 in the Supplement or refer to the SPIRIT-PRO extension[5] for guidance in describing patient-reported outcomes in trial protocols. Some of the SPIRIT-Outcomes 2022 extension checklist items that achieved consensus as essential reporting items only for the primary outcome may nevertheless be important to report for other trial outcomes. Authors adhering to the SPIRIT-Outcomes 2022 extension should specify why any items are not relevant to their trial when completing the checklist. For example, this extension checklist, which is for reporting systematically assessed outcomes, might not be applicable to outcomes that are not systematically collected or prespecified such as spontaneously reported adverse events.

We anticipate that the key users of the SPIRIT-Outcomes 2022 extension will be trial protocol authors, ethics review boards, and journal editors. Use of this SPIRIT-Outcomes 2022 extension by these groups may help improve trial utility and transparency and may help reduce the risk of selective nonreporting of results in trial reports when used in conjunction with the CONSORT-Outcomes 2022 extension.[17] Patient and public engagement was successfully embedded into a consensus meeting for a methodologically complex topic, a rarity in reporting guideline development to date. Future reporting guideline development should engage patients and members of the public throughout the process. The SPIRIT-Outcomes 2022 extension will be disseminated as outlined previously,[14] including through the EQUATOR Network and the SPIRIT website. End users can provide their input on the content, clarity, and usability online,[65] which will inform any future updates.

Limitations

This study has several limitations. First, the included checklist items are appropriate for systematically collected outcomes, including most potential benefits and some harms; however, other items might be applicable for reporting harms not systematically assessed.[66]

Second, because these checklist items are not yet integrated in the main SPIRIT checklist, finding and using multiple checklists may be considered burdensome by some authors and editors, and implementation might be affected because of these obstacles.[67] Future efforts to integrate these additional items in the main SPIRIT checklist might promote implementation in practice.

Third, although a large, diverse, international group of experts and end users was involved in the development of these recommendations with the aim of increasing usability among the broader research community, the Delphi voting results could have been affected by a nonresponse bias because panelists were self-selecting (ie, interested individuals signed up to take part in the Delphi process).

Fourth, the consensus meeting panelists were purposively sampled based on their expertise and roles relevant to randomized clinical trial conduct, oversight, reporting, and use of trial results. The views of individuals not well represented by the consensus meeting panelists (eg, trialists outside North America and Europe) might differ. The systematic and evidence-based approach[14,15] used to develop this guideline, including a rigorous scoping review of outcome reporting guidance,[6,18] may help mitigate the potential effect of these limitations.

Conclusions

This SPIRIT-Outcomes 2022 extension of the SPIRIT 2013 statement provides 9 outcome-specific items that should be addressed in all trial protocols and may help increase trial utility, replicability, and transparency and may minimize the risk of selective nonreporting of trial results.

ARTICLE INFORMATION

Accepted for Publication: October 28, 2022.

Published Online: December 13, 2022. doi:10.1001/jama.2022.21243

Author Affiliations: Child Health Evaluative Sciences, The Hospital for Sick Children Research Institute, Toronto, Ontario, Canada (Butcher, Monsour, Mew, Chee-A-Tow, Baba, Saeed, Farid-Kapadia, Ungar, Offringa); Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (Butcher, Monga); Department of Chronic Disease Epidemiology, School of Public Health, Yale University, New Haven, Connecticut (Mew); Department of Medicine, Women's College Research Institute, University of Toronto, Toronto, Ontario, Canada (Chan); Centre for Journalology, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada (Moher); School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada (Moher, Tugwell); Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill (Mayo-Wilson); Amsterdam University Medical Centers, Vrije Universiteit, Department of Epidemiology and Data Science, Amsterdam, the Netherlands (Terwee); Department of Methodology, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands (Terwee); public panel member, Toronto, Ontario, Canada (Gavin); Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada (Grimshaw); Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada (Grimshaw, Tugwell); Department of Pharmacology and Therapeutics, University of Manitoba, Winnipeg, Canada (Kelly); Children's Hospital Research Institute of Manitoba, Winnipeg, Canada (Kelly); Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada (Thabane); NHMRC Clinical Trials Centre, University of Sydney, Sydney, New South Wales, Australia (Askie); patient panel member, Ottawa, Ontario, Canada (Smith); MRC-NIHR Trials Methodology Research Partnership, Department of Health Data Science, University of Liverpool, Liverpool, England (Williamson); Cundill Centre for Child and Youth Depression, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Szatmari); Department of Psychiatry, The Hospital for Sick Children, Toronto, Ontario, Canada (Szatmari, Monga); Bruyère Research Institute, Ottawa, Ontario, Canada (Tugwell); Ottawa Hospital Research Institute, Ottawa, Ontario, Canada (Tugwell); Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Golub); Departments of Pediatrics and Psychiatry, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada (Vohra); Clinical Trials Ontario, Toronto, Canada (Marlin); Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada (Marlin); Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada (Ungar, Offringa); Division of Neonatology, The Hospital for Sick Children, Toronto, Ontario, Canada (Offringa).

Author Contributions: Dr Butcher had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Butcher.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Monsour.
Obtained funding: Offringa.
Administrative, technical, or material support: Monsour, Mew, Baba.
Supervision: Butcher, Offringa.

Conflict of Interest Disclosures: Dr Butcher reported receiving grant funding from CHILD-BRIGHT and the Cundill Centre for Child and Youth Depression at the Centre for Addiction and Mental Health (CAMH) and receiving personal fees from Nobias Therapeutics. Ms Mew reported receiving salary support through a Canadian Institutes of Health Research doctoral foreign study award. Dr Grimshaw reported holding a Canada research chair in health knowledge transfer and uptake and receiving funding from the Ontario Ministry of Health, the Ottawa Hospital Academic Medical Organization, the National Institute of Health Research, and the National Health and Medical Research Council. Dr Kelly reported receiving funding from the Canadian Cancer Society, Research Manitoba, the Children's Hospital Research Institute of Manitoba, Mitacs, and the SickKids Foundation. Dr Askie reported being a co-convenor of the Cochrane Prospective Meta-Analysis Methods Group. Dr Farid-Kapadia reported currently being an employee of Hoffmann La-Roche and holding shares in the company. Dr Williamson reported chairing the COMET initiative management group. Dr Szatmari reported receiving funding from the CAMH. Dr Tugwell reported co-chairing the OMERACT executive committee; receiving personal fees from the Reformulary Group, UCB Pharma GmbH, Parexel International, PRA Health Sciences, Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Eli Lilly, Genentech, Roche, Genzyme, Sanofi, Horizon Therapeutics, Merck, Novartis, Pfizer, PPD Inc, QuintilesIMS (now IQVIA), Regeneron Pharmaceuticals, Savient Pharmaceuticals, Takeda Pharmaceutical Co Ltd, Vertex Pharmaceuticals, Forest Pharmaceuticals, and Bioiberica; serving on data and safety monitoring boards for UCB Pharma GmbH, Parexel International, and PRA Health Sciences; and receiving unrestricted educational grants from the American College of Rheumatology and the European League of Rheumatology. Dr Monga reported receiving funding from the Cundill Centre for Child and Youth Depression at CAMH; receiving royalties from Springer for *Assessing and Treating Anxiety Disorders in Young Children*; and receiving personal fees from the TD Bank Financial Group for serving as a chair in child and adolescent psychiatry. Dr Ungar reported being supported by the Canada research chair in economic evaluation and technology assessment in child health. No other disclosures were reported.

Funding/Support: This work, project 148953, received financial support from the Canadian Institutes of Health Research.

Role of the Funder/Sponsor: The Canadian Institutes of Health Research had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimers: Dr Golub is Executive Deputy Editor of *JAMA*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance. This article reflects the views of the authors, the Delphi panelists, and the consensus meeting panelists and may not represent the views of the broader stakeholder groups, the authors' institutions, or other affiliations.

Additional Contributions: We gratefully acknowledge the additional contributions made by the project core team, the executive team, the operations team, the Delphi panelists, and the international consensus meeting panelists (eAppendix 3 in the Supplement). We thank Andrea Chiaramida, BA, for administrative project support and Lisa Stallwood, MSc, for administrative manuscript support (both with The Hospital for Sick Children). We thank Petros Pechlivanoglou, PhD, and Robin Hayeems, PhD, for piloting and providing feedback on the format of the Delphi survey (both with The Hospital for Sick Children). None of these individuals received compensation for their role in the study.

Additional Information: The project materials and data are publicly available on the Open Science Framework at https://osf.io/arwy8/.

REFERENCES

1. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-207. doi:10.7326/0003-4819-158-3-201302050-00583

2. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586. doi:10.1136/bmj.e7586

3. SPIRIT. SPIRIT statement website. Accessed April 13, 2021. https://www.spirit-statement.org/

4. International Conference on Harmonisation. E6: good clinical practice. Accessed November 22, 2022. https://www.ich.org/page/efficacy-guidelines

5. Calvert M, Kyte D, Mercieca-Bebber R, et al; the SPIRIT-PRO Group. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO extension. *JAMA*. 2018;319(5):483-494. doi:10.1001/jama.2017.21903

6. Butcher NJ, Mew EJ, Monsour A, Chan A-W, Moher D, Offringa M. Outcome reporting recommendations for clinical trial protocols and reports: a scoping review. *Trials*. 2020;21(1):620. doi:10.1186/s13063-020-04440-w

7. Page MJ, McKenzie JE, Forbes A. Many scenarios exist for selective inclusion and reporting of results in randomized trials and systematic reviews. *J Clin Epidemiol*. 2013;66(5):524-537. doi:10.1016/j.jclinepi.2012.10.010

8. Yordanov Y, Dechartres A, Atal I, et al. Avoidable waste of research related to outcome planning and reporting in clinical trials. *BMC Med*. 2018;16(1):87. doi:10.1186/s12916-018-1083-x

9. Chan AW, Pello A, Kitchen J, et al. Association of trial registration with reporting of primary

outcomes in protocols and publications. *JAMA*. 2017;318(17):1709-1711. doi:10.1001/jama.2017.13001

10. Kampman JM, Sperna Weiland NH, Hollmann MW, Repping S, Hermanides J. High incidence of outcome switching observed in follow-up publications of randomized controlled trials: meta-research study. *J Clin Epidemiol*. 2021;137:236-240. doi:10.1016/j.jclinepi.2021.05.003

11. Monsour A, Mew EJ, Patel S, et al. Primary outcome reporting in adolescent depression clinical trials needs standardization. *BMC Med Res Methodol*. 2020;20(1):129. doi:10.1186/s12874-020-01019-6

12. Glasziou P, Altman DG, Bossuyt P, et al. Reducing waste from incomplete or unusable reports of biomedical research. *Lancet*. 2014;383(9913):267-276. doi:10.1016/S0140-6736(13)62228-X

13. Mayo-Wilson E, Fusco N, Li T, Hong H, Canner JK, Dickersin K; MUDS investigators. Multiple outcomes and analyses in clinical trials create challenges for interpretation and research synthesis. *J Clin Epidemiol*. 2017;86:39-50. doi:10.1016/j.jclinepi.2017.05.007

14. Butcher NJ, Monsour A, Mew EJ, et al. Improving outcome reporting in clinical trial reports and protocols: study protocol for the Instrument for reporting Planned Endpoints in Clinical Trials (InsPECT). *Trials*. 2019;20(1):161. doi:10.1186/s13063-019-3248-0

15. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Med*. 2010;7(2):e1000217. doi:10.1371/journal.pmed.1000217

16. Gamble C, Krishan A, Stocken D, et al. Guidelines for the content of statistical analysis plans in clinical trials. *JAMA*. 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556

17. Butcher NJ, Monsour A, Mew EJ, et al. Guidelines for reporting outcomes in trial reports: the CONSORT-Outcomes 2022 extension. *JAMA*. 2022;328(22):2252-2264. doi:10.1001/jama.2022.21022

18. Butcher NJ, Mew EJ, Saeed L, et al. Guidance for reporting outcomes in clinical trials: scoping review protocol. *BMJ Open*. 2019;9(2):e023001.

19. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: Template for Intervention Description and Replication (TIDieR) checklist and guide. *BMJ*. 2014;348:g1687. doi:10.1136/bmj.g1687

20. Ferreira-González I, Permanyer-Miralda G, Busse JW, et al. Methodologic discussions for using and interpreting composite endpoints are limited, but still identify major concerns. *J Clin Epidemiol*. 2007;60(7):651-657. doi:10.1016/j.jclinepi.2006.10.020

21. Cordoba G, Schwartz L, Woloshin S, Bae H, Gøtzsche PC. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. *BMJ*. 2010;341:c3920. doi:10.1136/bmj.c3920

22. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c869. doi:10.1136/bmj.c869

23. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC Med*. 2010;8(1):18. doi:10.1186/1741-7015-8-18

24. Mokkink LB, Terwee CB, Patrick DL, et al. COSMIN checklist manual. Accessed February 28, 2022. https://fac.ksu.edu.sa/sites/default/files/cosmin_checklist_manual_v9.pdf

25. de Vet HCW, Terwee CB, Mokkink LB, Knol DL. *Measurement in Medicine*. Cambridge University Press; 2011. doi:10.1017/CBO9780511996214

26. Cook JA, Hislop J, Adewuyi TE, et al. Assessing methods to specify the target difference for a randomised controlled trial: DELTA (Difference ELicitation in TriAls) review. *Health Technol Assess*. 2014;18(28). doi:10.3310/hta18280

27. Johnston BC, Ebrahim S, Carrasco-Labra A, et al. Minimally important difference estimates and methods: a protocol. *BMJ Open*. 2015;5(10):e007953. doi:10.1136/bmjopen-2015-007953

28. de Vet HC, Beckerman H, Terwee CB, Terluin B, Bouter LM. Definition of clinical differences. *J Rheumatol*. 2006;33(2):434-435.

29. de Vet HC, Terwee CB. The minimal detectable change should not replace the minimal important difference. *J Clin Epidemiol*. 2010;63(7):804-805. doi:10.1016/j.jclinepi.2009.12.015

30. COSMIN. Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) is an initiative of an international multidisciplinary team of researchers. Accessed April 13, 2021. https://www.cosmin.nl/

31. Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *BMJ*. 2010;340:c723. doi:10.1136/bmj.c723

32. Mokkink L, Terwee C, de Vet H. Key concepts in clinical epidemiology: responsiveness, the longitudinal aspect of validity. *J Clin Epidemiol*. 2021;140:159-162. doi:10.1016/j.jclinepi.2021.06.002

33. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol*. 2010;63(7):737-745. doi:10.1016/j.jclinepi.2010.02.006

34. Ferreira ML, Herbert RD, Ferreira PH, et al. A critical review of methods used to determine the smallest worthwhile effect of interventions for low back pain. *J Clin Epidemiol*. 2012;65(3):253-261. doi:10.1016/j.jclinepi.2011.06.018

35. Prinsen CAC, Mokkink LB, Bouter LM, et al. COSMIN guideline for systematic reviews of patient-reported outcome measures. *Qual Life Res*. 2018;27(5):1147-1157. doi:10.1007/s11136-018-1798-3

36. Cook JA, Julious SA, Sones W, et al. Practical help for specifying the target difference in sample size calculations for RCTs: the DELTA^2 five-stage study, including a workshop. *Health Technol Assess*. 2019;23(60):1-88. doi:10.3310/hta23600

37. Cook JA, Julious SA, Sones W, et al. DELTA^2 guidance on choosing the target difference and undertaking and reporting the sample size calculation for a randomised controlled trial. *BMJ*. 2018;363:k3750-k3750. doi:10.1136/bmj.k3750

38. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database–update and key issues. *N Engl J Med*. 2011;364(9):852-860. doi:10.1056/NEJMsa1012065

39. OMERACT. OMERACT domain resources. Accessed May 19, 2022. https://omeract.org/domain-selection/

40. Williamson P, Altman D, Blazeby J, Clarke M, Gargon E. Driving up the quality and relevance of research through the use of agreed core outcomes. *J Health Serv Res Policy*. 2012;17(1):1-2. doi:10.1258/jhsrp.2011.011131

41. Gargon E, Gorst SL, Williamson PR. Choosing important health outcomes for comparative effectiveness research: 5th annual update to a systematic review of core outcome sets for research. *PLoS One*. 2019;14(12):e0225980. doi:10.1371/journal.pone.0225980

42. Williamson PR, Altman DG, Bagley H, et al. The COMET Handbook: version 1.0. *Trials*. 2017;18(suppl 3):280. doi:10.1186/s13063-017-1978-4

43. Kirkham JJ, Davis K, Altman DG, et al. Core Outcome Set-STAndards for Development: the COS-STAD recommendations. *PLoS Med*. 2017;14(11):e1002447. doi:10.1371/journal.pmed.1002447

44. Gorst SL, Prinsen CAC, Salcher-Konrad M, Matvienko-Sikar K, Williamson PR, Terwee CB. Methods used in the selection of instruments for outcomes included in core outcome sets have improved since the publication of the COSMIN/COMET guideline. *J Clin Epidemiol*. 2020;125:64-75. doi:10.1016/j.jclinepi.2020.05.021

45. Collister D, Bangdiwala S, Walsh M, et al. Patient reported outcome measures in clinical trials should be initially analyzed as continuous outcomes for statistical significance and responder analyses should be reserved as secondary analyses. *J Clin Epidemiol*. 2021;134:95-102. doi:10.1016/j.jclinepi.2021.01.026

46. Kravitz RL, Duan N; DEcIDE Methods Center N-of-1 Guidance Panel, eds. *Design and Implementation of N-of-1 Trials: A User's Guide*. Agency for Healthcare Research and Quality; 2014.

47. Carrasco-Labra A, Devji T, Qasim A, et al. Minimal important difference estimates for patient-reported outcomes: a systematic survey. *J Clin Epidemiol*. 2021;133:61-71. doi:10.1016/j.jclinepi.2020.11.024

48. Woaye-Hune P, Hardouin JB, Lehur PA, Meurette G, Vanier A. Practical issues encountered while determining minimal clinically important difference in patient-reported outcomes. *Health Qual Life Outcomes*. 2020;18(1):156. doi:10.1186/s12955-020-01398-w

49. Mouelhi Y, Jouve E, Castelli C, Gentile S. How is the minimal clinically important difference established in health-related quality of life instruments? review of anchors and methods. *Health Qual Life Outcomes*. 2020;18(1):136. doi:10.1186/s12955-020-01344-w

50. Devji T, Carrasco-Labra A, Guyatt G. Mind the methods of determining minimal important differences: three critical issues to consider. *Evid Based Ment Health*. 2021;24(2):77-81. doi:10.1136/ebmental-2020-300164

51. Devji T, Carrasco-Labra A, Qasim A, et al. Evaluating the credibility of anchor based estimates of minimal important differences for patient reported outcomes: instrument development and reliability study. *BMJ*. 2020;369:m1714. doi:10.1136/bmj.m1714

52. Mayo-Wilson E, Fusco N, Li T, Hong H, Canner JK, Dickersin K; MUDS investigators. Harms are

assessed inconsistently and reported inadequately part 1: systematic adverse events. *J Clin Epidemiol*. 2019;113:20-27. doi:10.1016/j.jclinepi.2019.04.022

53. International Conference on Harmonisation. Harmonised Tripartite Guideline: statistical principles for clinical trials E9: current step 4 version. Accessed November 19, 2022. https://database.ich.org/sites/default/files/E9_Guideline.pdf

54. Mayo-Wilson E, Li T, Fusco N, et al. Cherry-picking by trialists and meta-analysts can drive conclusions about intervention efficacy. *J Clin Epidemiol*. 2017;91:95-110. doi:10.1016/j.jclinepi.2017.07.014

55. Butcher NJ, Mew E, Monsour A, et al. A scoping review of outcome-reporting recommendations for clinical trial protocols and reports. Accessed April 26, 2022. https://osf.io/6f5x7/

56. Freemantle N, Calvert M. Weighing the pros and cons for composite outcomes in clinical trials. *J Clin Epidemiol*. 2007;60(7):658-659. doi:10.1016/j.jclinepi.2006.10.024

57. Hankins M. How discriminating are discriminative instruments? *Health Qual Life Outcomes*. 2008;6(1):36. doi:10.1186/1477-7525-6-36

58. Mokkink LB, Prinsen CAC, Patrick DL, et al. COSMIN methodology for systematic reviews of Patient-Reported Outcome Measures (PROMS): user manual: version 1.0. Published 2018. Accessed November 14, 2022. https://cosmin.nl/wp-content/uploads/COSMIN-syst-review-for-PROMs-manual_version-1_feb-2018.pdf

59. De Los Reyes A, Augenstein TM, Wang M, et al. The validity of the multi-informant approach to assessing child and adolescent mental health. *Psychol Bull*. 2015;141(4):858-900. doi:10.1037/a0038498

60. Cohen SB, Strand V, Aguilar D, Ofman JJ. Patient- versus physician-reported outcomes in rheumatoid arthritis patients treated with recombinant interleukin-1 receptor antagonist (anakinra) therapy. *Rheumatology (Oxford)*. 2004;43(6):704-711. doi:10.1093/rheumatology/keh152

61. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. *J Natl Cancer Inst*. 2009;101(23):1624-1632. doi:10.1093/jnci/djp386

62. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) resource. Accessed May 19, 2022. https://www.ncbi.nlm.nih.gov/books/NBK338448/

63. Li G, Taljaard M, Van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. *Int J Epidemiol*. 2017;46(2):746-755. doi:10.1093/ije/dyw320

64. European Medicines Agency. Guideline on multiplicity issues in clinical trials. Accessed February 8, 2022. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-multiplicity-issues-clinical-trials_en.pdf

65. REDCap Research. SPIRIT-Outcomes feedback form. Accessed February 28, 2022. https://redcapexternal.research.sickkids.ca/surveys/?s=7N847LCEJF

66. Qureshi R, Mayo-Wilson E, Li T. Harms in systematic reviews paper 1: an introduction to research on harms. *J Clin Epidemiol*. 2022;143:186-196. doi:10.1016/j.jclinepi.2021.10.023

67. Howick J, Webster R, Knottnerus JA, Moher D. Do overly complex reporting guidelines remove the focus from good clinical trials? *BMJ*. 2021;374:n1793. doi:10.1136/bmj.n1793