SPIRIT extension and elaboration for n-of-1 trials: SPENT 2019 checklist

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Randomised clinical trials are the preferred method for establishing average intervention effects for groups. Using key methodological elements of these trials, n-of-1 trials provide rigorous evidence of intervention effects for individuals. N-of-1 trials are particularly useful for situations where randomised clinical trials are not always feasible or appropriate, such as for individuals with rare diseases, comorbid conditions, or using concurrent treatments. N-of-1 trials enhance precision when intervention effects are heterogeneous between individuals. Here, we describe an extension to the SPIRIT (standard protocol items: recommendations for interventional trials) guideline, SPENT (SPIRIT extension for n-of-1 trials), to improve the completeness and transparency of n-of-1 trial protocols. SPENT is also aligned with the CONSORT (consolidated standards of reporting trials) extension for n-of-1 trials (CENT). The guideline development group followed the development strategy for reporting guidelines endorsed by the EQUATOR Network. SPENT began with a systematic review for n-of-1 protocol recommendations. After analysis to identify possible SPENT items, a three round Delphi process was implemented, with international participation involving researchers, patient advocates, and other stakeholders. This was followed by in-person meetings and email discussion of the SPENT group to achieve consensus. SPENT has 14 extension items specific to n-of-1 trials, a checklist for n-of-1 trial protocol abstracts, and additional guidance for eight SPIRIT items where trialists could encounter issues specific to n-of-1 trials. This paper describes the rationale and development process, and provides examples and explanations for each SPENT checklist item.

SUMMARY POINTS

We have developed SPENT (SPIRIT extension for n-of-1 trials), a 14 item extension of SPIRIT for n-of-1 trial protocols, a checklist for n-of-1 protocol abstracts, and additional guidance for eight SPIRIT items where trialists could encounter issues specific to n-of-1 trials

This reporting guideline is to improve the completeness and transparency of n-of-1 trial protocols

SPENT is also aligned with the CONSORT (consolidated reporting items for trials) extension for n-of-1 trials (CENT) to create concordance between the reporting of a trial's protocol and its results

N-of-1 trials

Well conducted, randomised clinical trials create the evidence base that informs modern medical practice, guidelines, and regulatory decisions.[1] However, these trials estimate average treatment effects, providing little information about heterogeneity and no information about individual treatment effects.[2 3] Randomised clinical trials are not always feasible, are rarely conducted on rare diseases, and often exclude individuals with comorbid conditions or concurrent treatments even though these individuals constitute the majority of patients.[2 4 5] Based on the methodology of randomised clinical trials, n-of-1 trials can rigorously measure intervention effects for individuals, either singly or in a series.[6]

In an n-of-1 trial, each individual receives both intervention and comparator in a multiple crossover design, allowing the effect of the treatment to be measured separately for each individual. N-of-1 trials work best for conditions that are stable over the period of evaluation, using interventions with a relatively quick onset of action and quick termination of effect

when discontinued, although they are robust for use in many non-ideal situations.[2 5 7] N-of-1 trials can also be a useful tool for gaining insight into individual variation with regards to intervention effect.[6 8] A systematic review of n-of-1 trials showed their use across many health conditions and for many interventions, both pharmacological and non-pharmacological; the use of these trials is slowly increasing over time.[9]

N-of-1 trials provide opportunities to enhance care that is both patient centred and evidence based.[6 7 10] N-of-1 trials can more easily accommodate patient preferences, goals, and outcomes (eg, through the use of the MYMOP (measure your medical outcome profile) tool[11]) and can enhance shared decision making between individuals and their healthcare providers. For example, the PREEMPT (personalised research for monitoring pain treatment) study allowed individuals to choose their own treatment comparisons.[12] N-of-1 trials can also be used to evaluate ongoing effectiveness of chronic treatments as well as reduce ineffective polypharmacy (especially when multiple treatments are used for one indication). The incorporation of patient preferences, ongoing treatment and measurement engagement, and provision of all treatment options suggest that the n-of-1 design offers multiple opportunities to maximise adherence, both during the trial and for post-trial care.[13-15] Finally, n-of-1 trials build useful evidence when the best intervention option for an individual is unclear, including potential off-label use and lack of applicable evidence.

Box 1: Methodological terminology typical in n-of-1 trial reports

N-of-1 trial

An experimental clinical study design to determine the effect of an intervention in one study participant. SPENT is intended to be used to report protocols for repeated challenge-withdrawal (that is, ABAB) trials, commonly used in medicine, in which multiple crossovers between interventions and control (placebo, standard care, alternate treatment) are continued for a prespecified amount of time or until intervention effectiveness is determined. More than two intervention alternatives might be compared to each other or control (that is, ABCABC).

Period

The time during which one intervention (A or B) is administered. Period length is typically determined a priori and can vary within a trial. The order of periods within a pair or intervention block may be randomised. In behavioural analysis, the analogous term is "condition."

Block or pair

A repeated unit of a set number of periods in n-of-1 trials is referred to as a block, in which the sequence of periods may or may not be randomised (eg, three blocks of four periods might be AABB BBAA ABAB). By convention, when the repeated unit contains only two periods (eg, three sequential two-period units might be AB BA BA), the unit is conventionally referred to as a pair.

Cycle

Each pair or block within a sequence is often termed a cycle.

Sequence

Multiple pairs or blocks comprise an entire sequence. The sequence is the consecutive set of blocks, and may or may not indicate the number of periods within the repeated unit.

Washout period

A period in which no intervention is administered. A washout might be administered between different intervention periods or might act as a period in itself, as in a reversal design (to wash out the effects of an intervention before it is readministered).

Run-in period

A prespecified duration of time before a trial begins, during which trial interventions might be initiated (eg, to get to a stable therapeutic dose), to determine potential participant compliance with study regimens or to wash out the effects of a drug taken by a participant before the trial.

Terminology

Research with a single person has a long history within both social and medical sciences.[16] To facilitate accurate interpretation, we will use the term "n-of-1" in accordance with modern nomenclature—that is, to refer to multiple crossover trials in one individual.[17] SPENT (SPIRIT extension for n-of-1 trials) is specific and restricted to the n-of-1 trial, as opposed to other designs of single person trials. In older articles, "n-of-1" could have referred to any form of research in a single person or a case report, while actual n-of-1 trials might not have used the n-of-1 designation. N-of-1 terminology, originally published in the CONSORT (consolidated reporting items for trials) extension for n-of-1 trials (CENT) guidelines, is reproduced in box 1.[18]

Protocol reporting guidelines

Reporting guidelines promote transparent, accurate, standardised reporting.[19 20] They define a minimum set of expected components, facilitating accountability and comparability between trials. A research protocol, the written summary of all key aspects of a planned research project, enhances a study's planning, ethical oversight, execution, evaluation, and results dissemination.[19] Many people use the protocol: the investigators and staff who implement the trial processes, monitor progress, and evaluate the data; scientific review boards who assess the quality and thoroughness of the research design; and the ethics and monitoring boards who ensure participant safety and care throughout the trial and through to peer review and publication. Thus, a thorough protocol facilitates transparency, clarity of process, and reproducibility of the research, while limiting publication bias such as selective outcome reporting.[21 22] To ensure quality in the development of randomised clinical trials, the SPIRIT (standard protocol items: recommendations for interventional trials) statement was developed using recommended methods.[19 20 23] The purpose of developing the SPIRIT extension for n-of-1 trials reporting guideline and checklist (SPENT) was to provide guidance on the development and publishing of n-of-1 trial protocols.

Methods to develop SPENT

Previous work has identified problems with n-of-1 trial reporting (CENT relative to CONSORT),[18 24] and gaps in n-of-1 protocol recommendations relative to SPIRIT.[9] Using a recommended process, members

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from the SPIRIT and CENT teams have developed the international, consensus based, SPENT guideline. This extension deals with protocol issues specific to n-of-1 trials, and ensures alignment with the parallel reporting issues in CENT.

The development process followed the recommended process framework from members of the Enhanced Quality and Transparency of Reporting (EQUATOR) Network's executive group.[20] The primary SPENT authors, with experience from SPIRIT (A-WC), CENT (RLK, CHS, LS, SV), clinical n-of-1 trials (AO, SP, PR), and the project coordinator (AJP), began with a systematic review of n-of-1 trial protocol recommendations (AJP, SP).[25] The search included both medical and psychosocial databases (Medline, Embase, PsycINFO, CINAHL, Cochrane Methodology Register, CENTRAL, and the United Kingdom's health service) to increase the identification of relevant articles. Public and private medical research organisations from Australia, Europe, and North America were asked for n-of-1 protocol guidelines; none had any available. The search results, consisting of 18 detailed n-of-1 implementation guides (no reporting guidelines), were analysed by use of a matrix to compare their recommendations with the SPIRIT and CENT reporting items. The analysis highlighted several n-of-1 trial design differences relative to the SPIRIT and CENT checklists (eg, intervention choices, modification and stopping criteria, statistical methods, and safety and data monitoring), and emphasised the opportunities for participant input into the trial design. From this matrix, a preliminary set of SPENT items was created on the basis of SPIRIT, with CENT wording when possible. SPENT also takes into account the ethical principles and considerations for protocols mandated by the 2008 Declaration of Helsinki.[19]

The preliminary checklist was refined through three rounds of a Delphi consensus process.[26] This work involved input from 53 international panellists from Australia, Canada, China, France, Germany, Greece, South Africa, UK, and the United States. They included 34 healthcare professionals and trialists, 28 methodologists, six statisticians, five representatives from government and private funding organisations, four patient representatives, three health technologists, three medical and trial managers, two journal editors, one ethicist, and one medical insurance organisation representative (roles not mutually exclusive). Twenty three individuals had been involved in the development of other reporting guidelines.

In all rounds, the panellists rated each item on an eight point scale (definitely reject; probably reject; maybe reject; undecided; maybe keep, probably keep, must keep; and no judgment) and provided comments and suggested new items. Summaries of votes, comments, and suggestions were included in subsequent Delphi rounds; after discussions in rounds 1 and 2, changes to items were made for round 3. After the third round, items with a median score of six (maybe keep) or above were kept, items with a median score of two (probably reject) or less were excluded. Two discussion meetings were held with the 18 SPENT group members to achieve consensus on the remaining items and discuss refinements to the wording of the final guideline items based on Delphi comments. Discussions continued until consensus was reached on all items.

With the SPENT checklist drafted, this statement was written, with oversight and input from the primary writing group. The principles considered here are largely derived from SPIRIT and CENT, with additional input from the SPENT development participants. The draft checklist and statement were then reviewed and finalised by the entire SPENT group. The SPENT checklist and extension documents will be made available through the SPIRIT website (www.spirit-statement.org) and the EQUATOR library of reporting guidelines (www.equator-network.org).

Increasingly, published protocols include an abstract, although protocol abstract guidelines have not been published. However, CENT includes recommendations for abstracts,[18] based on the CONSORT statement,[24] and these were adapted using the SPENT checklist items by consensus of the SPENT group. Reference to the abstract guideline was added as an additional SPENT item (item 1b).

SPENT checklist

The SPENT checklist is a formal extension of SPIRIT, with 14 items specifying adaptations or considerations specific to n-of-1 trial protocols (appendix table 1). It is also aligned with CENT, using CENT wording as much as possible for similar reporting items. This alignment will create a cohesive continuum from protocol to completed trial report that will facilitate both the researcher's production of the trial report, and any assessment of the final report's adherence to the protocol (fig 1).

About 60% of n-of-1 trial publications report on a series of trials in more than one participant.[9] Thus, as appropriate and as specified, SPENT items include recommendations for both single and prospectively planned series of n-of-1 trial protocols. SPENT

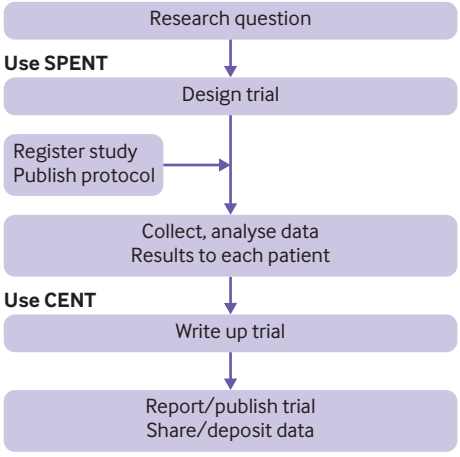

Fig 1 | Research and reporting flow

also considers the emerging emphasis on patient participation in the research development processes.

Each SPENT item includes an example and explanation of the issue considered by the new or updated item. An additional eight items (identified below as "SPIRIT (no change)") detail n-of-1-specific considerations for those SPIRIT items. Describing the details recommended in the 14 SPENT checklist items and addressing the additional n-of-1 considerations will ensure the needed transparency and thoroughness for n-of-1 protocol reporting, and enhance reproducibility and accountability in research reporting.

Applying the SPENT checklist

Explanations are provided here for all n-of-1-specific protocol considerations identified in the development process. Some SPENT items are minor modifications, others are major revisions or are new relative to SPIRIT. The SPENT items are meant to be used instead of SPIRIT, unless indicated (that is, specified here with "SPENT extension (in addition)" or if SPENT specific commentary is provided ("SPIRIT (no change)" items)). In most cases, a general SPENT item applies to both single and series trials (including individual trials within a series), unless the phrases "for series" or "in addition for series" specifically refer to issues not applicable to individual participants or trials. Consulting the explanations and examples for each checklist item will provide additional insight, guidance, and rationale for each item.

Many trial design and reporting issues explained in the SPIRIT explanation and elaboration (E&E) document are relevant, as written, to n-of-1 trials.[22] Thus, for all items, readers should refer to that SPIRIT document for insight and explanation of the item. Similarly, some n-of-1 topics are thoroughly explained in the CENT E&E document, and for those topics readers will be directed to that document.[21] As per SPIRIT, empirical evidence was used when possible to inform explanations. The n-of-1 research base is significantly less developed than for randomised clinical trials with a parallel group design; in some instances, the inclusion of some items or their explanations are based on a strong pragmatic or ethical rationale, but examples of good reporting could not be found in the published n-of-1 literature. When available, examples from n-of-1 protocols reflect n-of-1 context and interpretation of the item. Some examples effectively illustrate a specific component of the checklist item, others refer to all key aspects of the item.

Patients as contributors and collaborators

The importance of the patient voice in clinical research has received growing recognition; patients might engage as participants in the trial, in an advisory role, or as study collaborators and coinvestigators.[27-29] The Patient-Centered Outcomes Research Institute in the US encourages patient input in all aspects of the research process, including research design.[27] The n-of-1 trial focus on determining intervention effectiveness for an individual patient provides several opportunities for patient involvement in n-of-1 protocols; patients can and should be involved in determining specific issues such as possible interventions or comparators, as well as the trial's goals and choice of outcomes.[7 21] For a series of n-of-1 trials, the desire to aggregate results could impose some restrictions on designs options, which might reduce opportunities for patient input. Acknowledgment of patient involvement in protocol development and implementation should occur with appropriate informed consent and awareness of the potential impacts on participant confidentiality and anonymity.

Use of SPENT for n-of-1 trials for personal/clinical care

Although SPENT was developed for research application, n-of-1 trials can be undertaken for research, clinical care, or other health purposes (eg, response to environmental factors, self-efficacy), or to achieve a combination of these goals.[2 30] When undertaking an n-of-1 trial primarily to guide an individual patient's healthcare decision, clinicians can consult SPENT's checklist and explanation items relevant to individual trials; item explanations include commentary on care issues when appropriate. While SPENT recommendations include best practices and possible ethical issues for research,[2 31] clinical practice and healthcare assessments might not require the same processes recommended in some items (eg, background and rationale (item 6a), research ethics approval from a research ethics council or institutional review board (item 24)). Chapter 2 of the Agency for Healthcare Research and Quality's guide to n-of-1 trials includes a detailed discussion of issues about clinical care versus research when using n-of-1 trials.[32]

Section 1: Administrative data

Title—item 1a

SPIRIT: Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym.

SPENT extension (in addition): Descriptive title including "n-of-1 trial" and "protocol." For series: Descriptive title including "a series of n-of-1 trials" and "protocol."

Example

"Ephedrine as add-on therapy for patients with myasthenia gravis: protocol for a series of randomised, placebo-controlled n-of-1 trials."[33]

Explanation

For easy and rapid identification of relevance of a protocol during any search, the title should prominently focus on key, recognisable terminology. There are often conflicting demands on published protocol titles, including potential character limitations, but a good title should convey information about the topic, treatments, trial acronym (if any), and trial design as an n-of-1 trial or series of trials. Additionally, it should alert readers that the document is a trial protocol.

Abstract—item 1b

SPIRIT: None (new for SPENT).

SPENT extension: Structured summary (see SPENT guidance for abstracts (appendix table 2).

Example

"Central nervous system stimulants for secondary attention deficit-hyperactivity disorder after paediatric traumatic brain injury: a rationale and protocol for single patient (n-of-1) multiple cross-over trials

"Background: It is estimated that 22 800 children were living with an Acquired Brain Injury (ABI) (0.6% of children aged under 15 years) in Australia during 2003. Many children after a traumatic brain injury will experience difficulties with attention and concentration; a condition termed secondary Attention Deficit-Hyperactivity Disorder [ADHD]. There is conflicting evidence on whether treatment with stimulant therapy with medications such as methylphenidate or dexamphetamine will improve the attention and behaviour of children with this condition.

"Methods and analysis: Single patient trials (n-of-1s or SPTs) evaluate the effect of titrated doses of psychostimulants methylphenidate or dexamphetamine compared to placebo on attention and behaviour, in children with TBI [traumatic brain injury] and secondary ADHD. The aggregation of multiple SPTs will produce a population estimate of the benefit. Forty-two children will be registered into the trial through rehabilitation services at three large children's hospitals in Australia. Patients will complete up to 3 cycles of treatment. Each cycle is 2 weeks long comprising seven days each of treatment and placebo, with the first two days of each cycle considered a washout period and the data not analysed. The order of treatment and placebo is randomly allocated for each cycle. The Conners' Parent Rating Scales long forms will be employed to measure change in attention-deficit/hyperactivity and related problems of the child, and the primary outcome measure is the Conners' Global Index Parent Version. Secondary outcomes include the teacher and child (if aged >12 years) Conners' Rating Scales, the Behaviour Rating Inventory of Executive Function among other measures. This study will provide high-level evidence using a novel methodological approach to inform clinicians about the most appropriate treatment for individual children. Through aggregation of individual trials, a population estimate of treatment effect will be provided to guide clinical practice in the treatment of children with secondary ADHD after a traumatic brain injury.

"Discussion: This study employs an innovative methodological approach on the effectiveness of CNS [central nervous system] stimulants for secondary ADHD from a brain injury. The findings will both guide clinicians on treatment recommendations, and inform the concept and acceptance of SPTs in paediatric research.

"Trial registration number: Australian New Zealand Clinical Trials Registry. ACTRN12609000873224."[34]

Explanation

Abstracts should be an efficient summary of the document, enabling readers to quickly assess key points of the article, including the design type (n-of-1) and document purpose (eg, protocol, results). With protocol publication increasingly being encouraged, the SPENT recommendations were used to adapt the CENT abstract recommendations, focused on key items relevant to n-of-1 protocols.

Section 2: Introduction

Background and rationale—item 6a

SPIRIT: 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.

SPENT extension: 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, and rationale for using n-of-1.

Example

"Background and rationale: Oral mucositis is inflammation and necrosis of the oropharyngeal mucosa, resulting in pain, erythema and ulceration. Mucositis may be caused by a multitude of agents including chemotherapy, irradiation and microorganisms such as herpes simplex virus (HSV). It is a common consequence of chemotherapy, occurring in approximately 40% of standard-dose chemotherapy regimens.[1] Mucositis is an important sequela of cancer therapy for many reasons. First, it is painful and decreases the quality of life for affected patients. Second, this pain may be sufficiently severe to require hospitalization for alimentation, hydration or parenteral analgesia. This increased health care utilization increases the costs of cancer treatment, with the presence of mucosal ulcers being associated with $42,749 higher mean hospital charges (compared to the absence of ulcers) in one economic analysis.[1] Third, as chemotherapeutic regimens have become more intense, oral mucositis has become a major dose-limiting toxicity. Consequently, mucositis may limit delivery of anti-cancer therapy, possibly decreasing the chance of cancer-free survival. Finally, mucositis represents a breach of the oral mucosal integrity, allowing entry of oral microflora with subsequent bacteremia and sepsis . . .

"Vitamin E is a fat-soluble essential vitamin. Vitamin E may augment the chemotherapeutic index of doxorubicin by protecting against doxorubicin-induced normal tissue damage while improving anticancer activity. This apparently paradoxical activity has been explained by Myers who suggested that doxorubicin has two mechanisms of cellular injury that differentially affects normal and tumour cells.[14] One mechanism involves tissue toxicity via oxidative damage; this mechanism is preferentially responsible for normal tissue damage and is blocked by vitamin E. The second involves binding of doxorubicin to DNA with resultant DNA fragmentation and inhibition of DNA synthesis.

This mechanism is preferentially responsible for anti-tumour activity and is not antagonized by vitamin E.[14]

"We plan to study the efficacy of topical vitamin E in the prevention of chemotherapy induced oral mucositis. Although a standard double-blind RCT [randomised controlled trial] might be feasible in adults with cancer, there are significant limitations to this design in paediatric patients. [These include access to population, and wide inter-patient variability in the incidence and severity of mucositis] . . .We have chosen instead to use an innovative trial design. Our method involves combining multiple n-of-1 trials using Bayesian meta-analysis. With this technique, repetition of the chemotherapeutic agent for a minimum of 2 cycles is required . . . This manoeuvre reduces variability of the outcome of interest and consequently improves the power of the study compared to a traditional RCT. Only children receiving at least 2 cycles and preferably 4 cycles of doxorubicin administered in an identical fashion (doxorubicin dose and concurrent chemotherapy) will be included." (Unpublished protocol by Sung L et al, personal communication, 2015.)

Explanation

The rationale for the choice of the n-of-1 design should be included, and clearly fit with the research question. Not all readers are familiar with the n-of-1 design, why it would be considered, and when it is appropriate. Guyatt et al proposed guidelines for undertaking clinical n-of-1 trials[7]; reporting which relevant criteria were considered in the decision to use an n-of-1 trial would be helpful for evaluating the protocol.

Individual n-of-1 trials should, at a minimum, undertake a review of the literature as part of the trial protocol development. For all n-of-1 trials, it is strongly recommended that an up-to-date systematic review be summarised and cited in the protocol.[35] The importance of such reviews is explained in the SPIRIT E&E document.[22]

Background and rationale—item 6b

SPIRIT (no change): Explanation for choice of comparators.

Commentary: For active controls and usual or standard care, refer to SPIRIT item 6b.[19] Some of the concerns about the use of a placebo as comparator[19 36 37] are mitigated by the use of the n-of-1 design, because participants receive all comparator interventions. That does not lessen the necessity of careful consideration of the use of a placebo relative to the value of other potential active comparators.

Trial design—item 8

SPIRIT: Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory).

SPENT extension: Description of the trial design as either an n-of-1 trial or series of trials, allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory). In addition for series: Explanation of the series design including whether the design will be tailored to each participant.

Examples

"Given the contradictory findings in the literature, and the potential benefits to children if effective, this protocol will describe a study that identifies both the children who will benefit and those who will not on a case-by-case basis and provides a population estimate of treatment effect using an aggregated n-of-1 trial design . . . The study drug to be tested is Methylphenidate or Dexamphetamine versus Placebo. The dose to be trialled will be individually titrated to each child as per accepted clinical practice, before randomisation (see below)."[34]

"This is a TE [therapeutic equivalence] study using n-of-1 trails or tests. Each n-of-1 test will be a randomized, partially blind, multiple-crossover study designed to simulate the routine clinical practice of switching a patient between generic and brand forms of enalapril."[38]

Explanation

The trial design should be stated early on because it creates the context for the methods. For n-of-1 trials, an early statement about the use of the n-of-1 design (or series of n-of-1 trials) is appropriate. The framework of the design sets many choices, including the study methods, choice of comparator, conduct, analysis, and interpretation; it is also important for auditing and accountability. The framework should therefore always be clearly stated.

N-of-1 trials might be tailored to each participant, adjusting factors such as period length, dosing, number of crossovers, or response-adaptive designs.[39] Planned types of individualisation should be documented, and relevant details included in other aspects of the protocol, such as interventions (item 11a), modification (item 11b), analysis (items 20a1 and 20a2), and monitoring (item 21a).

N-of-1 trial protocols might be developed for non-pharmacological (practitioner-dependent) interventions. SPENT recommends that for such interventions, authors should also refer to the CONSORT extension for trials assessing non-pharmacological treatments.[40]

Section 3A: Methods—participants, interventions, and outcomes

Eligibility criteria—item 10

SPIRIT: Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists).

SPENT extension (in addition): Diagnosis/disorder, diagnostic criteria, comorbid conditions, and concurrent treatments. For series: Same as SPIRIT item 10.

Example

"Study participants include patients as well as their regular treating clinicians. Clinicians are recruited

first, and must have completed residencies in internal medicine, family medicine, or pain medicine or be practicing nurse practitioners or physician assistants. Patients, recruited from the practices of consenting clinicians, are required to meet the following criteria: English speaking adults between 18 and 75 years old who have experienced on-going musculoskeletal pain for 6 weeks or longer; own an eligible iOS or Android smartphone or tablet; have a pain score of 4 or higher (on a 0 to 10 scale where 10 is the 'worst pain imaginable') on at least 1 of 3 items from the PEG pain scale[30 31] and in the judgment of the treating clinician, have pain potentially amenable to treatment with acetaminophen, NSAIDs [non-steroidal anti-inflammatory drugs], low-dose opioids, tramadol, a complementary/alternative treatment such as massage or meditation, or a combination of these treatments (since these treatments are among those offered on the Trialist 'menu' [the study is about the feasibility of the Trialist programme]). Patients are excluded if they are pregnant or breastfeeding; have undergone surgery, radiation or chemotherapy treatment for cancer in the past 5 years; or have other medical conditions or behaviors, such as bipolar disorder or current alcohol or prescription drug abuse, rendering them unsuitable for the trial. (See Table 1 for a complete list of patient inclusion and exclusion criteria.)"[12]

Explanation

For single participants, inclusion and exclusion criteria are not usually used; instead, the particular participant's demographics are described, as per the SPENT inclusion. CENT 2015 E&E items 4a (participants) and 15 (baseline data) discuss the reasons for reporting this information, and describe the appropriate data to include for both single and series n-of-1 trials.[21] SPIRIT 2013 E&E item 10 also provides details on series reporting.[22]

Interventions—item 11a

SPIRIT: Interventions for each group with sufficient detail to allow replication, including how and when they will be administered.

SPENT extension: Interventions for each period with sufficient detail to allow replication, including how and when they will be administered, planned number of periods and crossovers, and duration of each period (including run-in and washout details, if applicable). In addition for series: How the design will be tailored to each participant, if applicable.

Examples

"This study is a series of randomised, double-blind, placebo-controlled, multi-centre, single patient (N-of-1) Trials [SPTs]. In this SPT, the participant undergoes 3 pairs of treatment periods. As [Methylphenidate hydrochloride (MPH)] has a short half-life (4 hours), the clinical effect is achieved quickly and a steady state is reached after 5 half-lives (i.e., 20 hours). This allows a treatment period of 3 days (and 6 days for each treatment pair), making a total of 18 days for patients to complete the full trial. No assessment of efficacy is taken on the first day of each 3-day period to allow for medication wash-out. In each cycle, drugs are randomly allocated to patients with both investigators and patient blinded (fig 1). At the end of the trial, the order of medications within each of the three cycles is unmasked. Repeated results from the outcome assessments in the same direction favouring the treatment can be reported in terms of a probability that the result is true."[41]

"Allowable n-of-1 trials will last a total of 4 to 12 weeks depending on the trial parameters selected. Trial parameters include the duration a patient is on each treatment before switching treatments (7 or 14 days), and the number of treatment pairs (cycles) they complete (2, 3, or 4). At least two cycles (for example, ABAB, BABA, ABBA, or BAAB) are required for a valid n-of-1 trial. (Table 2 shows examples of possible trial configurations.) The clinician and patient jointly select a start date for the n-of-1 trial, allowing for time to fill prescriptions. The n-of-1 trial parameter bounds were selected to provide a compromise between greater precision (for example, increasing number of cycles), and practicality (that is trial lengths that maintain patient interest)."[12]

Explanation

SPIRIT 2013 E&E item 11a provides a thorough discussion about reporting intervention descriptors.[22] Additionally, authors should refer to the reporting recommendations of the Template for Intervention Description and Replication (TIDieR) reporting guideline.[42]

The SPENT extension item additions reflect the need to document aspects of n-of-1 trial design needed for transparency and replication. As multiple crossover trials, this includes the number and length of the periods, and details of run-in or washout periods including their rationale and length.[43] Any details about how trial design components might be tailored to individual participants (eg, dosing, period length, choice of number of crossovers, response-adaptive design components, washout period) should be described.[39]

If used at the start of a trial, a run-in period can help to document a stable baseline state, determine tolerability, assess potential study regime adherence, or wash out any pretrial interventions if needed.[44-46] A run-in period might also occur at the beginning of any period of an intervention in a trial, if the intervention requires ramping up to the trial's therapeutic dose. Although measurements taken during such ramping-up periods are documented, they are not typically included or analysed with the main trial results.

Washout periods are added at the end of intervention periods to give time for the effects of the intervention in a period to wear off before instigating the next intervention, thus limiting potential carry-over of the intervention effects into that next period.[43] Similar to run-in periods, measurements might be taken during the washout period but would not be included in

analyses; some measurements at the beginning of the next period might also be excluded, depending on the washout time length and the trial design. Chapter 4 of the Agency for Healthcare Research and Quality's guide to n-of-1 trials provides more detail about the design and analytical considerations of washout issues.[8]

Interventions—item 11b (modifications)

SPIRIT (no change): 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).

Commentary: The SPIRIT 2013 E&E document discusses the general importance of documenting modification or discontinuation criteria.[22] Authors should consider modifications specific to the n-of-1 trial design, such as period length or the potential for early stopping. This item is specific to preplanned stopping or modifying criteria for each individual within an n-of-1 trial, a topic explained further by CENT 2015 E&E item 14b.[21] Item 21b addresses stopping criteria for the entire trial, particularly relevant for series trials.

Although n-of-1 trials can be tailored to the participant, to maximise validity of the trial design, whenever possible, any plans for individualisation should be outlined a priori in the relevant protocol sections (items 8, 11b, 18b, 20a, 20b, 21b).

Sample size—item 14

SPIRIT: Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations.

SPENT extension: Estimated number of intervention periods and measurements or observations within each period needed to achieve study objectives within an individual n-of-1 trial. In addition for series: Estimated number of participants needed to achieve study objectives. For both individual and series trials: Describe how these numbers were determined, including the clinical and statistical assumptions.

Example

"The [Quantitative Myasthenia Gravis test (QMG)] test results in a numerical score between 0 and 39, with higher scores indicating more severe disease. The estimated SD [standard deviation] of repeated measures for a single person is 2.95 based on our clinical observations and an earlier trial.[37] An average decrease in QMG score of 3.5 points is considered clinically relevant.[38 39] A linear model with fixed effects for treatment and patient will be fitted to the repeated QMG measurements. Our sample size computations are based on the test of significance of the treatment effect in this model (see 'Analysis' section). Monte Carlo simulations were used to compute the power with three cycles (i.e., 6 measurements) per patient for 3, 4, and 5 patients, which was 0.648, 0.772 and 0.862, respectively. In light of the availability of eligible patients, time and resources, we chose a sample size of 4 patients, achieving approximately 77% power."[47]

Explanation

SPIRIT 2013 E&E item 14 provides a general discussion about sample size calculations and reporting.[22] N-of-1 trials are a specific form of crossover trial and have additional sample size factors involved in increasing power and accuracy:

- The number of observations per period
- The number of blocks (number of crossovers)—generally three blocks are considered minimal, and four or more blocks are preferred to increase confidence in the results
- The number of participants.

Specific issues, including the modelling assumptions (eg, random *v* common effects) must be clarified in order to choose the most relevant calculations.[48] The SPENT extension also recommends reporting how the number of intervention periods and measurements to be made during each trial were established, providing clarity and rigour for related items (items 12, 13, and 18a). This topic is explained further in CENT 2015 E&E item 7a.[21]

Recruitment—item 15

SPIRIT: Strategies for achieving adequate participant enrolment to reach target sample size.

SPENT extension: For series: No change from SPIRIT item 15.

Example

"Recruitment: Clinicians are recruited via flyers, Emails, letters and presentations. Once clinicians indicate interest, informed consent is obtained detailing their responsibilities and soliciting their consent to have their patients recruited into the study.

"Two methods are used for patient recruitment. First, clinicians can ask patients directly if they are interested in the study. Clinicians provide interested patients with a study flyer that provides research staff contact information. Second, patients of enrolled clinicians who have been seen within the past 2 to 12 months for a chronic painful condition (as indicated by appropriate International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes) are sent an informational letter informing them about the study and inviting them to contact research staff if interested in learning more. Both patient recruitment methods rely on patients initiating contact with PREEMPT study research staff. (See Figure 1 for the participant flow diagram and Additional file 1 for the ICD-9 codes.)

"Screening: Patients are screened for eligibility over the telephone. Research staff explain the study and ask initial screening questions to assess pain levels and determine that the patient has an eligible device. At this time, permission is obtained from the patient to contact his/her clinician for medical history screening.

If permission is granted, the patient's clinician is contacted via secure email and/or telephone to verify that the patient is an appropriate candidate for the study. Eligible patients are then re-contacted by telephone or email, notified of eligibility, and asked the date and time of their next clinic appointment. Once a patient is deemed eligible, a consent packet is mailed or emailed with the study consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form. Informed consent will be obtained from all participants included in this study."[12]

Explanation

Enrolment issues are not relevant for single-participant trials, and this item is only relevant for an n-of-1 trial series. SPIRIT 2013 E&E item 15 and CENT 2015 E&E item 14a provide information about recruitment for series.[21 22]

Section 3B: Methods (assignment of interventions for controlled trials)

Allocation—item 16a (sequence generation)

SPIRIT: 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 enrol participants or assign interventions.

SPENT extension: Method of generating the allocation sequence (eg, computer-generated random numbers, counterbalancing). To reduce predictability of a random sequence, details of any restrictions (eg, pairs, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions. In addition for series: List of any factors for stratification.

Examples

"Randomisation will be carried out for each individual n-of-1 trial by the dispensing hospital pharmacy to ensure patient and physician blinding, and will be performed in MS Excel. Ephedrine and placebo treatments will be randomised in a 1:1 ratio per cycle over the three cycles of the n-of-1 trial (e.g., AB-BA-BA)."[47]

"Patients are randomized to Trialist versus usual care. Randomization is stratified by clinician; each clinician's patients are randomized in blocks of size 4 (90% of blocks) or 6 (10% of blocks) in order to balance the numbers of participants per clinician and to minimize selection bias. Patients assigned to usual care will receive the usual course of care as prescribed by their clinician. The allocation sequence are generated by the study statisticians (CS and JS) and provided to the study coordinator (MM) in a format that allows for clinician block size to be masked until the study is completed and for patient randomization allocation to be masked until completion of the enrollment procedures."[12]

Explanation

For details regarding sequence generation in general, see SPIRIT 2013 E&E item 16a.[22] Details regarding the importance and process of randomisation in n-of-1 trials, including considerations regarding pair and block randomisation and the need for alternatives such as counterbalancing,[2] have been described in detail in CENT 2015 E&E items 8a and 8b.[21]

Regardless of the form of randomisation or sequence allocation used to assign the intervention sequence, all factors and the rationale (particularly for non-random allocations) for setting the intervention sequence should be described. Potential period effects (eg, progressive deterioration or improvement) should be accounted for.[2 21]

Allocation—item 16b (concealment mechanism)

SPIRIT (no change): 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.

Commentary: In n-of-1 trials, participants receive all interventions, mitigating one important reason for assignment concealment: preventing knowledge of potential assignment. Thus, concerns about allocation to only one intervention (usually the control arm) affecting a participant's decision to join or withdraw from the trial, or a recruiter's decision to try and enrol a patient in a trial, are less relevant to n-of-1 trials. However, because of the multiple crossover nature of n-of-1 trials, allocation concealment is coupled to blinding (masking; item 17) if it is being used; allocation concealment usually applies to the entire sequence of interventions set for each participant, and applies even if blinding does not.

Section 3C: Methods—data collection, management, and analysis

Statistical methods—item 20a1 (outcomes)

SPIRIT: Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.

SPENT extension: Statistical methods for analysing primary and secondary outcomes for each individual. Reference to where other details of the statistical analysis plan can be found, if not in the protocol. In addition for series: If planned, proposed methods of quantitative synthesis of individual trial data, and how heterogeneity between participants will be assessed.

Examples

"For each individual patient, QMG [quantitative myasthenia gravis test] scores, scores for secondary outcome measures, and adverse effects reported during the ephedrine and placebo periods will be described in an individual patient report. This report will be discussed by the patient and their physician during the evaluation phase of the n-of-1 trial and may be used to guide individual therapeutic decisions."[47]

"Data preparation and descriptive reporting will follow that recommended by the CONSORT statement. For each cycle, data from day 1 will be discarded to allow for a wash-out period, and data from days 2 and 3 will be analysed. All patients with at least one completed treatment cycle will be included in analyses. An effect size will then be calculated between active medication cycles and placebo, thus providing a population measure of effect commensurate with an RCT [randomised controlled trial].

"Both individual and population treatment differences will be estimated using hierarchical Bayesian methods and employing noninformative priors using the methods described in Zucker et al.,[33] and Schluter and Ware.[34] The likelihood distributions for each model will be assessed for violations and data transformations undertaken, where necessary. Conventional burn-in periods, model convergence and stability diagnostics, and residual checks will be employed.[35] WinBUGS[35] will be used for the Bayesian analysis.

"To describe participants' overall response, three types of Bayesian results will be presented: (i) the mean of the posterior distribution of the mean difference between placebo and stimulant scores, which gives the best estimate of the overall effect size difference between treatments; (ii) the associated 95% credible region, which give intervals of uncertainty (in this case the 2.5 and 97.5 percentile) of the posterior distributions used in (i); and (iii) the posterior probability of the mean difference that stimulant scores were better than placebo scores, which describes the likelihood that the patients will favour the active treatment in future cycles[34]. A patient will be defined to be a 'responder' when these estimated values exceed predefined threshold values."[34 33]

Explanation

SPIRIT 2013 E&E statistical methods and item 20a (outcomes) provide a summary regarding the need for preplanning and specifying all planned evaluation methods in a protocol.[22] However, n-of-1 trials require more specificity, and CENT items 12a, 12b, and 12c describe the reporting n-of-1 analyses in detail. One key difference for n-of-1 trials is that each participant's personal trial results are usually shared with that participant (always when it is a single- participant trial; see also item 31a (dissemination policy)), and are also aggregated for a series of trials. Furthermore, similar to standard crossover trials, issues concerning crossover analysis are particularly relevant (see also SPENT item 20a2).

All statistical methods planned—from visual representation to meta-analysis—should be described in the protocol.[8] Visual representation of the data can be used to provide an overview of data to readers (see CENT E&E items 12a and 17a1 for context and issues).[21] Frequentist and Bayesian statistical analyses on an individual's data can be planned, particularly if the data might be used for future clinical decision making or published and used by future researchers (eg, for meta-analysis).[49] These analyses could include, for example, estimating the size of effects (magnitude and direction), the means for an outcome (per period, or per intervention for the entire trial), or the variance.

For both single trials and series, planned approaches for determining estimates of the size of effects are important. Related items such as statistical significance, clinical significance values, and measures of variability or uncertainty (eg, confidence intervals) should be described. This applies to both continuous and discrete data. Similarly, if sensitivity analyses are planned, the relevant parameters should be described in the protocol.

The crossover nature of n-of-1 trials requires methods for synthesising or aggregating a series of n-of-1 trial data that are distinct from standard randomised clinical trials (see also item 20a2 (crossover specific considerations)).[50-54] Both Bayesian and frequentist approaches are used. Generally, models are multilevel mixed models with participants as the grouping variable and predefined model parameters (eg, significance, confidence levels, time trends, carryover, correlation, and prior distributions for Bayesian models; see also item 20a2). When an n-of-1 trial includes a more heterogeneous range of individuals than might be recruited in a standard randomised clinical trial, results could vary substantially between, and possibly within, individuals, particularly if the number of observations is small. Therefore, statistical methods to explore the relative heterogeneity, both within and between individuals, should be planned.[8] SPENT item 20b addresses planning for the assessment of possible differences between participants in subgroup or sensitivity analyses.

Statistical methods—item 20a2 (correlation)

SPIRIT: None (new for SPENT).

SPENT extension: Statistical methods to account for correlation, and carryover, period, or sequence effects introduced by the repeated measures and crossover design of n-of-1 studies.

Examples

"For each cycle, data from day 1 will be discarded to allow for a wash-out period, and data from days 2 and 3 will be analysed."[33]

"N-of-1 trials will be combined using a Bayesian multilevel random effects model. This model will return posterior estimates of overall treatment effect as well as the effect in each individual participant, informed by the results on other participants. The Bayesian model constructs a separate regression model incorporating serial correlation that relates longitudinal outcomes to treatment and other covariates for each participant. These regression models are then connected through a second-level random effects model which postulates that the subject-specific regression coefficients are related through a probability distribution centered about the average coefficients. The variability of these random effects represents the variability in the

individual treatment effects. The posterior estimates of the individual treatment effects represent weighted averages of the individual's measurements and the average effect. Ultimately, these individual posterior estimates may be used to inform individuals of their response to treatment in light of how others have responded."[55]

Explanation

Many statistical models assume independence of samples and measurements. However, as a multiple crossover study design, n-of-1 trials use multiple measurements over time on the same individual and so usually will induce autocorrelation.[8] Assuming the independence of data points will misestimate standard errors and result in incorrect confidence intervals leading to inaccurate statistical inferences.[56] Similar to correlation, washout (as described in items 11a and 13) and time trends (the change that would have occurred over time regardless of intervention [43]), can also bias estimates of intervention effects. Therefore, the relevance of correlation or washout/period effects in the planned analysis must be considered, particularly for aggregation or meta-analysis, and described in the protocol. Depending on the choice of intervention and outcome measures, correlation, washout, and period effects might not be an issue.[8] Chapter 4 of the Agency for Healthcare Research and Quality's guide to n-of-1 trials provides more detail about design and analytical considerations of washout issues.[8]

Statistical methods—item 20b (additional analyses)

SPIRIT: Methods for any additional analyses (eg, subgroup and adjusted analyses).

SPENT extension: For series: No change from SPIRT Item 20b.

Example

"Important confounding variables, such as anticholinergic load and cause of xerostomia (e.g. prior radiotherapy), will [be] included in adjusted analyses and report treatment effects (or success differences) over the various variable stratifications and combinations, following the method advocated by Zucker and colleagues[33]."[33]

Explanation

SPENT item 20b is about subgroup and adjusted analyses that are specific to n-of-1 trial series, and not to single-participant trials. Many trials examine whether intervention effects vary between subgroups of the trial populations, which can help determine if any heterogeneity in the results (higher or lower response to intervention effect) can be attributed to specific population features (eg, sex, genetic marker, medical history).[22] Because of the potential to increase knowledge about the intervention effects, inclusion of a few subgroup analyses can be useful. Due to the small size of n-of-1 trials, and the limited number of data points, only a limited number of subgroup analyses might be possible, especially those of within-participant factors. If they are being considered, the SPIRIT guideline provides subgroup recommendations and describes potential problems with subgroup analyses. Similar to standard trials, post-hoc analyses should be explicitly labelled as exploratory owing to their high degree of spurious findings.[57] No specific n-of-1 trial recommendations currently exist for adjusted analyses; the SPIRIT E&E document can provide some guidance.[22]

Statistical methods—item 20c (additional analyses)

SPIRIT: Definition of analysis population relating to protocol non-adherence (eg, as-randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation).

SPENT extension: Statistical methods to handle missing data (eg, imputation). In addition for series: Definition of analysis population relating to protocol non-adherence (eg, as-randomised analysis).

Example

"When no endpoint is available (for example, no pain measurements available at the 6-month time interval to calculate the outcome of change from baseline), we will use different approaches. In one, we will assume that no change has occurred and impute a change of zero. This will permit simple conservative assessments of single time point analyses. Longitudinal models can accommodate missing outcomes by ignoring them under the assumption that data are missing at random. We will also use multiple imputation to permit comprehensive analyses with missing covariates and interactions."[12]

Explanation

See SPIRIT 2013 E&E item 20c.[22]

Section 3D: Methods (monitoring)

Data monitoring—item 21a (formal committee)

SPIRIT (no change): Composition of data monitoring committee; 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 data monitoring committee is not needed.

Example

"The study will be overseen by the Trial steering committee (TSM), which is comprised of the Principal Investigator, co-investigators, research coordinator, and study statistician. The TSM will be responsible for ensuring that the study is conducted within appropriate and professional ethical guidelines, ensuring the good clinical practice guidelines are observed at all times. Furthermore, the DSMB [data safety monitoring board], which consists of three members with clinical, methodological, and NHP [natural health product] expertise who are independent of the trial will review all documented harms during the study and adjudicate them with regard to causality.

"Any significant amendments to the protocol will be submitted to Health Canada, Therapeutic Goods Australia, and to the University of Alberta and University of Queensland ethics committees for approval. Trial registries will also be notified of any major amendments."[55]

Explanation

SPIRIT 2013 E&E item 21a provides an excellent overview of data and safety monitoring, and the value of data monitoring committees (exact name might vary by region) in research.[22] The SPIRIT E&E document notes that not all studies have or need data monitoring committees. Single n-of-1 trials, small series of n-of-1 trials, and n-of-1 trials of short duration might also not need data monitoring committees. However, plans for data and safety monitoring (item 22) should be described in all protocols.

Data monitoring—item 21b (interim analysis)

SPIRIT (no change): 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.

Commentary: For a single participant n-of-1 trial, interim analyses are not typical, but could occur. Item 21b is particularly relevant for delineating planned interim analyses and the related conditions under which a series of n-of-1 trials—the study as a whole—would be terminated. Item 11b addresses stopping or modification criteria for single participants in a trial.

Harms—item 22

SPIRIT (no change): Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct.

Commentary: SPIRIT 2013 E&E item 22 describes the importance of harms monitoring and recommendations on when or how it can be incorporated into a protocol (eg, monitoring protocols, as a secondary outcome).[22] CENT 2015 E&E item 19 also describes how n-of-1 trials might be undertaken specifically to assess harms, assess potential harms, and assist in reduction of polypharmacy in individual patients.[21]

Section 4: Ethics and dissemination

Research ethics approval—item 24

SPIRIT (no change): Plans for seeking research ethics council or institutional review board approval.

Example

"Written approvals have been obtained from relevant Hospital Research Ethics Committees (Royal Children's Hospital and Health Service District Ethics Committee, Queensland Health; The Children's Hospital at Westmead HREC, Sydney) and The University of Queensland Medical Research Ethics Committee prior to study commencement. Approval was obtained from Education Regulatory Authorities in Queensland and NSW (Queensland Government Dept. of Education and Training, Catholic Education Archdiocese of Brisbane, New South Wales Government of Education and Communities, Catholic Education Office Sydney)."[34]

Commentary

SPIRIT 2013 E&E item 24 provides detail on the importance of ethical oversight.[22] For any research project involving humans, ethical review and oversight is mandatory, and n-of-1 research trials for individuals or series are no exception. Chapter 2 of the Agency for Healthcare Research and Quality's guide to n-of-1 trials includes a detailed discussion of issues about clinical care versus research when using n-of-1 trials.[32]

Confidentiality—item 27

SPIRIT (no change): 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.

Example

"All study data will only be identified by a unique identification number and participant initials. Identifiable data (e.g., contact details) will be stored in the research assistant's office onsite in a locked cabinet. De-identified data will be securely stored online on the WCHRI [Women's and Children's Health Research Institute] servers. The master list linking identifying participant information and ID numbers will be maintained in a locked cabinet, separate from the participant database. Master lists will be held at each participating site. Data will be analyzed according to ID number only."[55]

Commentary

SPIRIT 2013 E&E item 27 addresses general confidentiality issues.[22] Planning for confidentiality management during an n-of-1 trial will usually be the same as for any research trial. However, for some n-of-1 trials, maintaining confidentiality during the trial or in reporting might be difficult because of the small number of people participating in a trial combined with potentially revealing information (demographic information, study setting, comorbidities, rare diseases). Study setting (item 9), eligibility criteria and participant descriptors (item 10), data management (item 19), access to data (item 29), and dissemination plans (items 31a and 31c), could all include confidentiality issues. Item 27 is—at a minimum—a reminder that these aspects (items) must be reviewed together from a confidentiality perspective, necessitating a careful balancing of reporting and confidentiality. Under some circumstances, it might be difficult to fully protect participant confidentiality owing to particular participant or setting characteristics; in some situations, participants might choose to and consent to participate or disseminate their results non-anonymously. These situations must be discussed with the participant, who should not be forced to choose between confidentiality and access to a trial; privacy must be maintained in accordance with

participant consent. For such situations, consultation with the local research ethics council or institutional review board is recommended.

Dissemination policy—item 31a

SPIRIT: Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions.

SPENT extension: Plans for investigators to communicate each individual's results to the participant. Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions.

Examples

"Each participant's N-of-1 data will be communicated back to each participant's physician by fax directly, thereby fulfilling our obligation to all participants without biasing staff (i.e., project manager, research assistants, and study statistician will not be informed of the trial results as they accrue)."[55]

"At the end of the study, the study team will finalise a report on the study. This report will be discussed with members of regulatory organisations involved in market approval and reimbursement of treatment. In addition, a lay summary of the overall findings of the study will be made available to the study participants. Anonymised results of the study will be published in a peer-reviewed journal, and will be presented at academic meetings and scientific conferences."[47]

Explanation

N-of-1 trials are focused on the individual, and healthcare providers should review individual results with each participant.[2] Methods to enhance participant understanding of their trial results are actively underway. Trial results might also become part of the participant's record, and participants should be aware that other healthcare providers might see their results when reviewing their file; these issues should be included in the confidentiality considerations (item 27). SPIRIT 2013 E&E item 31a on dissemination addresses the sharing of trial results with any other party.[22]

Discussion

SPENT aims to improve the quality of protocol content by detailing the items needed for completeness and transparency of n-of-1 trial protocol reporting. The writing and publication of high quality n-of-1 protocols affects protocol review, trial conduct and appraisal, and the final reporting of n-of-1 trials. In conjunction with SPIRIT, the SPENT statement will also be a practical resource for clinicians, investigators, and trial staff, describing key elements needed to design and run an n-of-1 trial. We strongly recommend that stakeholders and reviewers adopt the use of the SPENT checklist to increase the standardisation of format, completeness of content, and comparability between n-of-1 trial protocols, thus improving the assessment and review of protocols, as well as alignment between the original protocol and the final trial report. Clinicians using n-of-1 trials for clinical and healthcare decisions should also review SPENT to ensure that relevant trial details have been considered.

SPIRIT was developed using a thorough, internationally recognised process for reporting guideline development, and the recommendations and explanations are, when possible, evidence based from the published literature. Many aspects of n-of-1 trials are no different from those of randomised clinical trials with a parallel group design, and the evidence based information informing SPIRIT applies equally to SPENT. Like SPIRIT, SPENT is not meant to prescribe how a trial should be designed or conducted, and is not a validated tool for appraising reporting quality. Nor does it cover all facets of what can and cannot be included; instead, the SPENT guideline represents the minimum content for reporting the needed components of an n-of-1 protocol. The primary limitation to the development of SPENT is the limited n-of-1 literature as a whole: no previous publication guidelines (only clinical recommendations) other than CENT for reporting trial results and only a few reviews of studies are available. The literature base of n-of-1 trials for research is growing, and methodological evaluations will become feasible, providing further support for, and possible revision of, future versions of this guideline. Feedback and recommendations from users of the guideline will also ensure the continued strength and applicability of SPENT.

Most journals now require trial registration; standardised n-of-1 protocol reporting should increase transparency and consistency of n-of-1 trial registration data. Several trial registries accept n-of-1 trial protocols. We will collaborate with the CENT team to continue to facilitate the increased registration of n-of-1 trials with the primary registries within the World Health Organization's International Trials Registry Network (www.who.int/ictrp/network/primary/en/index.html), and clinicaltrials.gov. Registration increases the transparency of trial reporting and facilitates comparison of what was planned for a trial to what was eventually done and found. This can help to detect potential reporting biases (eg, outcome reporting bias) in trial reports and facilitate detection of publication bias of trials that were done and never published.

With the publication of the SPENT statement and checklist, we will begin next steps of making SPENT available through reporting guideline resources, particularly the SPIRIT (www.spirit-statement.org) and EQUATOR (www.equator-network.org) websites. We will inform stakeholders of the establishment of SPENT. Through widespread knowledge and accessibility of this reporting guideline, we hope to increase its uptake and use for the purpose of improving the completeness

and quality of n-of-1 trial protocols, thus improving the subsequent review and use of the protocols—and the resulting trials—by all stakeholders.

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Appendix: Supplementary tables