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CONSORT extension for reporting N-of-1 trials (CENT) 2015 Statement

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N-of-1 trials provide a mechanism for making evidence based treatment decisions for an individual patient. They use key methodological elements of group clinical trials to evaluate treatment effectiveness in a single patient, for situations that cannot always accommodate large scale trials: rare diseases, comorbid conditions, or in patients using concurrent therapies. Improvement in the reporting and clarity of methods and findings in N-of-1 trials is essential for reader to gauge the validity of trials and to replicate successful findings. A CONSORT extension for N-of-1 trials (CENT 2015) provides guidance on the reporting of individual and series of N-of-1 trials. CENT provides additional guidance for 14 of the 25 items of the CONSORT 2010 checklist and recommends a diagram for depicting an individual N-of-1 trial and modifies the CONSORT flow diagram to address the flow of a series of N-of-1 trials. The rationale, development process, and CENT 2015 checklist and diagrams are reported in this document.

Although randomised controlled trials are the ideal for establishing treatment efficacy, they have limitations.[1 2] In particular, even the most rigorous and clearly reported randomised controlled trial cannot predict if a given intervention will be effective in a specific individual. For this reason, N-of-1 trials have been placed, by some, on the pinnacle of the evidence hierarchy for making decisions about treatment benefits and harms.[3 4] They use key methodological elements of group clinical trials to evaluate treatment effectiveness in a single patient, for situations that cannot always accommodate large scale trials: rare diseases, comorbid conditions, or in patients using concurrent therapies.

N-of-1 trials have been used to evaluate a range of health conditions—including mental and behavioural disorders and diseases of the nervous, respiratory, circulatory, musculoskeletal, and digestive systems[5]—and are appropriate for a range of interventions, pharmacological or non-pharmacological, including complementary or alternative therapies. However, N-of-1 trials are not applicable for all health conditions or interventions. They are ideal for chronic stable conditions and for therapies with a relatively quick onset of action after initiation and quick termination of effect after discontinuation.

In an era that promotes patient centered research, comparative effectiveness, and personalised medicine, N-of-1 trials allow clinicians and patients to evaluate health interventions in a rigorous fashion and to re-evaluate chronic therapies to ensure therapeutic effectiveness is still achieved. N-of-1 trials are a unique tool to elicit patient preferences and to facilitate shared decision-making, hence evidence-based medicine, in real clinical practice. In addition, N-of-1 trials may also be used to assess causality of potential adverse effects. By reducing ineffective polypharmacy, N-of-1 trials may help promote patient safety.

N-of-1 methodology and reporting

N-of-1 trials provide a methodologically rigorous evaluation of treatment effectiveness in a single individual at a time, thereby helping to close the gap between evidence and practice. Unlike randomised controlled trials, which often exclude patients with comorbid conditions or concurrent therapies, N-of-1 trials allow a more flexible approach. Patients may be included as long as their health and concurrent therapies are stable during the period of evaluation; caution is necessary if combining results of N-of-1 trials because of heterogeneity between patients. As in group crossover trials, the potential for confounding by covariates is eliminated in N-of-1 trials given that each patient serves as his or her own control. The use of multiple crossovers in N-of-1 trials also increases confidence in the reliability of the results.

A recent systematic review of 100 trial reports indicates that the reporting of N-of-1 trials is largely inadequate.[5] As an example, 79% of reports included in the review did not indicate which outcome was considered to be primary. Another 64% of reports did not comment on the presence or absence of adverse

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events. If N-of-1 trials are to be useful, these and other essential pieces of information must be included.

Among the first initiatives aiming to improve the completeness of reporting of research studies was the Consolidated Standards of Reporting Trials (CONSORT) guideline, which first emerged in 1996[6] and has been revised twice, most recently in 2010,[7 8] to keep in line with evolving evidence and methodological standards for trials. Extensions to the main CONSORT document have been developed to address the reporting of variations in trial designs,[9-11] interventions,[12-14] and data.[15-17] The CENT guideline provides a set of items, modified from the CONSORT 2010 guideline to facilitate complete reporting of N-of-1 trials. The development of CENT 2015 is in line with recent, international efforts to improve the reporting of research overall.[18]

For convenience, throughout this document, we refer to treatments and patients, although we recognise that not all interventions evaluated in N-of-1 trials are technically treatments and that participants are not always patients.

Terminology and scope of CENT

The single case experimental design, including N-of-1 trials, has a long history in the behavioural sciences.[19 20] In the medical literature, the term "N-of-1 trial" is used to describe a prospectively planned, multiple crossover trial in a single individual—often challenge-withdrawal-challenge-withdrawal, also described as "ABAB".[20] CENT restricts itself to this use of the term "N-of-1", rather than all possible single case experimental designs (fig 1), for which a separate reporting guideline is under development.[21] Consisting of repeated units of treatment comparisons (see box 1), N-of-1 trials may compare an active treatment against placebo, more than one active treatment, or perhaps multiple doses of a single treatment. The comparison depends on the question that is being asked. Definitions of methodological terminology specific to N-of-1 trials are provided in box 1.

Since approximately 60% of N-of-1 trial publications report on results from more than a single patient,[5] the CENT reporting guidelines have been designed to facilitate the reporting of both a single N-of-1 trial or a prospectively planned series of multiple N-of-1 trials. Readers may also wish to use the checklist to facilitate the critical appraisal of published N-of-1 trial reports for completeness and transparency. This guidance is not intended to be applied by those reporting systematic reviews in which N-of-1 trials are included; future such guidance is planned.

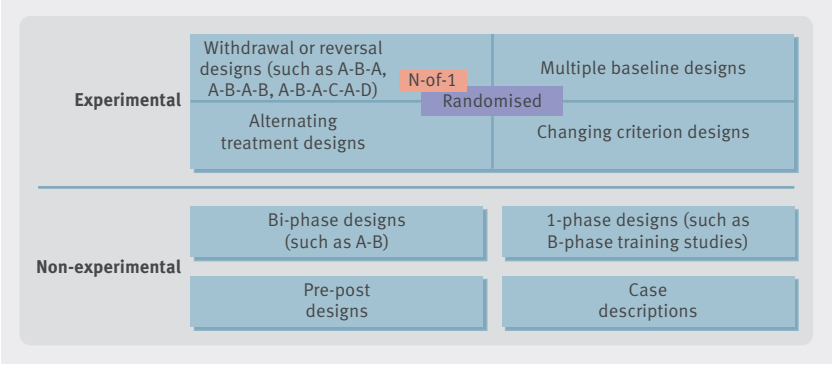

Fig 1 | Common single case designs. CENT is applicable to a subset of the "Withdrawal/reversal designs" category, which may or may not include the use of randomisation, designated by the red "N-of-1" box (adapted from [27])

Developing the CENT Statement

An international steering committee (DGA, Nick Barrowman, CB, GG, DM, JN, MS, RT, SV) comprising members with wide experience in clinical trial methodology and reporting guideline development, together with the project coordinator (LS), led the development of CENT. Two members of the team are practising physicians (SV and JN), and two others are members of the CONSORT and EQUATOR (Enhanced Quality and Transparency of Reporting) Network executive (DGA and DM). The EQUATOR Network is a group dedicated to "improving the reliability and value of medical research literature by promoting transparent and accurate reporting of research studies" (www.equator-network.org). The CENT Statement was developed in

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 a single study participant. CENT is intended to be used to report repeated challenge-withdrawal (that is, "ABAB") trials, commonly used in medicine, in which multiple crossovers between treatment(s) and control (placebo, standard care, alternate treatment) are continued for a pre-specified amount of time or until treatment effectiveness is determined. More than two treatment alternatives may be compared to each other or control (that is, "ABCABC")
- *Period*—The time during which a single treatment (A or B) is administered. Period length is typically determined a priori and may vary within a trial. The order of periods within a pair or treatment block may be randomised.
- *Block or pair*—A repeated unit of a set number of period in N-of-1 trials is referred to as a block, in which the sequence of periods may or may not be randomised (for example, three repeating blocks of four periods may look like "AABB BBAA ABAB"). By convention, when the repeated unit contains only two periods (for example, three repeating pairs may look like "AB BA BA"), it is conventionally referred to as a pair.
- *Sequence*—Multiple pairs or blocks comprise an entire sequence. The sequence is the consecutive set of periods, which may or may not indicate size of the repeated unit.
- *Washout period*—A period in which no intervention is administered. A washout may be administered between different treatment periods or may act as a period in itself, as in a "reversal" design (to "wash out" the effects of a treatment before it is re-administered).
- *Run-in period*—A pre-specified duration of time before a trial begins, during which trial treatments may be initiated (for example, to get to a stable therapeutic dose), to determine potential patient compliance with study regimens, or to allow for washout of a medication(s) a patient may have been taking before the trial.

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accordance with the process developed by members of EQUATOR executive group.[22]

Pre-meeting activities

In order to assess whether a reporting guideline for N-of-1 trials was indeed warranted, members of the CENT group (CB, MS, LS, SV) undertook a systematic review to assess the design and reporting of N-of-1 trials in the medical literature.[5] This work confirmed the heterogeneity in N-of-1 trials, and large inadequacies in their reporting, as described above.

Between February 2009 and April 2009, a modified Delphi process was carried out to seek consensus on a set of potential reporting items (n=55) for N-of-1 trials. This initial list was developed based on the characteristics of published trials guided by our systematic review and reporting elements from the CONSORT 2010 checklist.[7] A two-round survey was sent out to 56 international experts of N-of-1 trialists, biostatisticians, clinical epidemiologists, reporting guideline developers, biomedical journal editors, and health research funders, of whom 75% and 62% responded in rounds 1 and 2, respectively. Participants were asked to rank the importance of each potential checklist item on a 1 to 10 scale. After both rounds of surveying, items with a mean ranking of ≤5 were excluded from further consideration on the CENT checklist. Items ranking ≥6 or for which there was a large discrepancy between participants were carried forward for further discussion at the CENT consensus meeting.

CENT consensus meeting

In May 2009, a two day, in person meeting was convened in Banff, Canada, during which 23 experts in N-of-1 methodology, guideline development, N-of-1 study funders, and journal editors came together to further discuss and refine proposed checklist items. Discussion at the meeting yielded agreement on a set of essential concepts to be included in the guidelines; nuances of wording were not discussed at the meeting.

Post-meeting activities

After the CENT meeting, wording and organisation of concepts into checklist items was carried out and refined within the steering group and approved by meeting participants. A second round of circulation solicited feedback from those invited to the meeting but unable to attend. A flow diagram subcommittee was formed (NBG, JN, DRZ) to lead development of the CENT flow diagrams.

CENT 2015 checklist

The final CENT 2015 checklist is an extension of 14 items of the 25 CONSORT 2010 (table 1) and contains a total of 44 sub-items, some of which are modifications of a standard CONSORT 2010 item and some of which are in addition. For item 1b, pertaining to the abstract, recommendations specific for N-of-1 trials are proposed in table 2. Since N-of-1 trials may be conducted for an individual or a series of individuals, where pertinent, the checklist indicates specific items where different or additional information is required for series of N-of-1 trials. The recommendations within CENT may require more words or space than N-of-1 trialists are accustomed to. Providing detailed descriptions for some trials will facilitate transparency and future reproducibility, in line with emerging journal policies aimed at facilitating reproducibility.[23]

We recognise that improved reporting must be balanced against patient confidentiality in situations when the condition is rare. Authors must be mindful of this, and if there is any doubt as to whether complete reporting could be identifying, they should seek consultation with their institutional ethics board. This issue is of heightened importance in N-of-1 trials of rare conditions or when the potential societal stigma is high. Caution should be taken when reporting a combination of identifying information pertaining to CENT items 4a, 4b, 14a, and 15.

CENT diagrams

Diagrams have been developed to help authors visually depict both an individual participant's progress through an N-of-1 trial (fig 2, CENT trial pictorial) and the flow of multiple participants through a series of trials (fig 3, CENT flow diagram). Authors are encouraged in include the relevant diagram(s) in their N-of-1 reports. Specific guidance on the information that should be included in each diagram is provided in the CENT Explanation and Elaboration document.[24]

CENT 2015 Explanation and Elaboration (E&E) document

Once the CENT checklist was drafted, the steering committee and members from the larger CENT group prepared a rationale and examples of good reporting for the final set of checklist items. These can be found in the CENT 2015 Explanation and Elaboration (E&E) document.[24] The principles addressed in this document were largely derived from existing literature, the CONSORT 2010 E&E document[8] where applicable, and from discussions at the CENT meeting, which was recorded and summarised.

We strongly recommend that authors preparing N-of-1 trial reports and those charged with reviewing them use the CENT 2015 checklist to guide or assess their reporting. Authors are urged to read and use the CENT 2015 E&E document together with the checklist, as it provides examples of good reporting and evidence and consensus based rationale and guidance on how to report each item.[24]

Post-publication activities

Post-publication activities are planned around CENT 2015, including collecting feedback from the broader scientific community on the CENT initiative and specific checklist items. We also plan to seek endorsement from medical journals known to publish N-of-1 trials (see below). The CENT 2015 Checklist, Statement, and E&E documents are available through the CONSORT website

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Table 1 | CENT 2015 checklist*; CONSORT 2010 checklist items with modifications or additions for individual or series of N-of-1 trials; empty items in the CENT 2015 column indicate no modification from the CONSORT 2010 item

	CONSORT 2010		CENT 2015	
Section/Topic	**No**	**Item**	**No**	**Item**
Title and abstract				
	1a	Identification as a randomised trial in the title	1a	Identify as an "N-of-1 trial" in the title *For series:* Identify as "a series of N-of-1 trials" in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1b	For specific guidance, see CENT guidance for abstracts (table 2)
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	2a.1	
			2a.2	Rationale for using N-of-1 approach
	2b	Specific objectives or hypotheses	2b	
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3a	Describe trial design, planned number of periods, and duration of each period (including run-in and wash out, if applicable) *In addition for series:* Whether and how the design was individualized to each participant, and explain the series design
	3b	Important changes to methods after trial start (such as eligibility criteria), with reasons	3b	
Participant(s)	4a	Eligibility criteria for participants	4a†	Diagnosis or disorder, diagnostic criteria, comorbid conditions, and concurrent therapies. *For series:* Same as CONSORT item 4a
	4b	Settings and locations where the data were collected	4b†	
			4c	Whether the trial(s) represents a Research Methods & Reporting study and if so, whether institutional ethics approval was obtained
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5	The interventions for each period with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6a.1	
			6a.2	Description and measurement properties (validity and reliability) of outcome assessment tools
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6b	
Sample size	7a	How sample size was determined	7a	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	7b	
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence	8a	Whether the order of treatment periods was randomised, with rationale, and method used to generate allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8b	When applicable, type of randomisation; details of any restrictions (such as pairs, blocking)
			8c	Full, intended sequence of periods
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	11a	
	11b	If relevant, description of the similarity of interventions	11b	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12a	Methods used to summarize data and compare interventions for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12b	*For series:* If done, methods of quantitative synthesis of individual trial data, including subgroup analyses, adjusted analyses, and how heterogeneity between participants was assessed *(for specific guidance on reporting syntheses of multiple trials, please consult the PRISMA Statement)*
			12c	Statistical methods used to account for carryover effect, period effects, and intra-subject correlation

(*Continued*)

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Table 1 | (Continued) CENT 2015 checklist*; CONSORT 2010 checklist items with modifications or additions for individual or series of N-of-1 trials; empty items in the CENT 2015 column indicate no modification from the CONSORT 2010 item

	CONSORT 2010		CENT 2015	
Section/Topic	**No**	**Item**	**No**	**Item**
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	13a.1	Number and sequence of periods completed, and any changes from original plan with reasons
			13a.2	*For series:* The number of participants who were enrolled, assigned to interventions, and analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons	13c	*For series:* Losses or exclusions of participants after treatment assignment, with reasons, and period in which this occurred, if applicable
Recruitment	14a	Dates defining the periods of recruitment and follow-up	14a†	
	14b	Why the trial ended or was stopped	14b	Whether any periods were stopped early and/or whether trial was stopped early, with reason(s).
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	15†	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	16	For each intervention, number of periods analysed. *In addition for series:* If quantitative synthesis was performed, number of trials for which data were synthesized
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	17a.1	For each primary and secondary outcome, results for each period; an accompanying figure displaying the trial data is recommended.
			17a.2	For each primary and secondary outcome, the estimated effect size and its precision (such as 95% confidence interval) *In addition for series:* If quantitative synthesis was performed, group estimates of effect and precision for each primary and secondary outcome
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	17b	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	18	Results of any other analyses performed, including assessment of carryover effects, period effects, intra-subject correlation *In addition for series:* If done, results of subgroup or sensitivity analyses
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	19	All harms or unintended effects for each intervention. *(for specific guidance see CONSORT for harms)*
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	21	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	22	
Other information				
Registration	23	Registration number and name of trial registry	23	
Protocol	24	Where the full trial protocol can be accessed, if available	24	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	25	

*It is strongly recommended that this checklist be read in conjunction with the CENT 2015 Explanation and Elaboration[24] for important clarification on the items. The copyright for CENT (including checklist) is held by the CENT Group and is distributed under a Creative Commons Attribution (CC-BY 4.0) license.
†Caution should be taken when reporting potentially identifying information pertaining to CENT items 4a, 4b, 14a, and 15.

(www.consort-statement.org) and accessible through the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network library of reporting guidelines (http://www.equator-network.org/resource-centre/library-of-health-research-reporting/).

Endorsement

The CONSORT Statement is likely the best known reporting guideline. It has been well received by several scientific organisations (including the International Committee of Medical Journal Editors, Committee on Publication Ethics, and World Association of Medical Editors) and many biomedical journals, over 600 of which currently endorse CONSORT. Endorsement is typically demonstrated by way of an editorial statement in a journal's "Instructions to authors" section, supporting the use of one or more reporting guidelines. Following this model, we plan to seek endorsement from journals that publish N-of-1 trials and work with these journals to ensure author adherence to reporting CENT 2015 items. To help journals ensure optimal use of the CENT 2015 by authors, we propose the following wording:

> "[This journal] requires a completed CENT 2015 checklist as a condition of submission of reports of individual N-of-1 trials or a series of N-of-1 trials. We recommend that, while completing this form, you consider amending your manuscript to ensure your article, at a minimum, addresses each item listed on the CENT 2015 checklist. Taking the time to ensure your manuscript meets these basic reporting requirements will greatly improve your manuscript, potentially enhancing its chances for eventual publication."

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Table 2 | CENT abstract considerations (modifications or additions to CONSORT Statement for Abstracts)

Item	CONSORT for abstracts	Extension for N-of-1 designs
Title	Identification of the study as randomised	Identification of the study as an N-of-1 trial or series of N-of-1 trials in the title
Authors*	Contact details for the corresponding author	
Trial design	Description of trial design (such as parallel, cluster, non-inferiority)	Description of trial design, number of periods, and period duration
Methods:		
Participant(s)	Eligibility criteria for participants and the settings where the data were collected	For individual trial, clinical condition under study For series, eligibility criteria for participants
Interventions	Interventions intended for each group	Interventions intended for each period
Objective	Specific objective or hypothesis	
Outcome	Clearly defined primary outcome for this report	
Randomisation	How participants were allocated to interventions	
Blinding (masking)	Whether participant(s), care givers, and those assessing the outcomes were blinded to group assignment	
Results:		
Numbers randomised	Number of participants randomised to each group	For individual N-of-1 trial, the number and sequence of periods completed For series, number of individual trials carried out
Recruitment	Trial status	Not applicable
Numbers analysed	Number of participants analysed in each group	For individual N-of-1 report, number of periods analysed for each intervention For series, the number of participants analysed
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	
Harms	Important adverse events or side-effects.	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register, if applicable	
Funding	Source of funding	

*For conference abstracts.

Registering N-of-1 trials

N-of-1 trials can be prospectively registered in existing trial registries (albeit with some modifications). Eventually, we plan to work with clinicaltrials.gov and all of the primary registries within the WHO Registry Network (www.who.int/ictrp/network/primary/en/index.html), in accordance with the International Clinical Trials Registry Platform, to enable a broader audience to more easily register their N-of-1 trials. This will help to increase the transparency of N-of-1 trial reporting and facilitate appraisal of trial reports for potential biases (selective reporting). Although it is possible to register N-of-1 trials in existing registries few published N-of-1 trials have been registered or indicate being registered in their published report.

Evaluation

As with other reporting guidelines, the impact of CENT can be evaluated by comparing the completeness of reporting of checklist items between N-of-1 trial reports published in journals endorsing and not endorsing the CENT checklist as well as before versus after endorsement in endorsing journals. This approach reflects methods previously used to evaluate CONSORT and other reporting guidelines.[25 26]

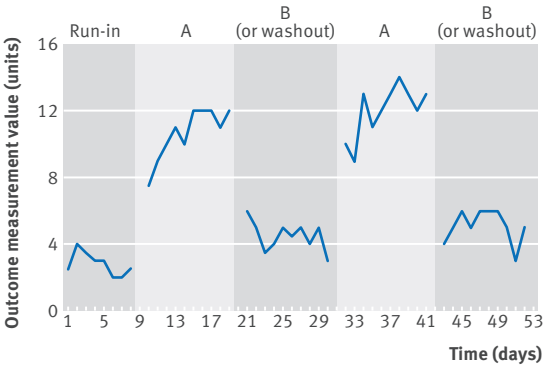

Fig 2 | N-of-1 trial pictorial; suggested visual representation of data from an individual N-of-1 trial

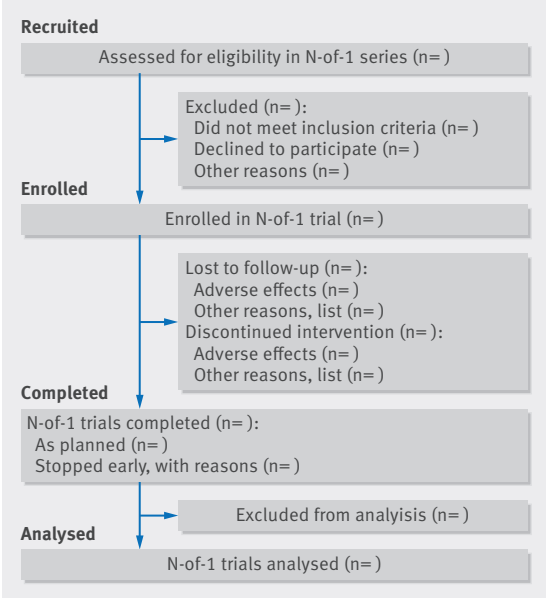

Fig 3 | CENT flow diagram; suggested representation of the flow of participants in a series of N-of-1 trials

Conclusions

N-of-1 trials offer a pragmatic approach to evidence based clinical practice. Rather than forcing patients into an all or none fit with a rigid parallel group-based trial protocol, N-of-1 trials can be flexible and adapt around the individ-

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ual to help assess treatment effectiveness under real world circumstances. They facilitate shared decision making between patients and practitioners, thereby bringing evidence based medicine into real clinical practice. While N-of-1 trials can be flexible enough for clinical use, they can also be standardised for the purpose of research, which may allow outcomes to be combined for population estimates. By improving the clarity of N-of-1 trial reporting, the CENT 2015 guidelines offer an opportunity to improve the interpretation and usefulness of N-of-1 trials.

The CENT 2015 guideline is primarily intended to be used by authors and reviewers who report and assess N-of-1 trials, respectively. It may also be helpful earlier in the research process as researchers design protocols for N-of-1 trials.

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Contributors: SV, LS, MS, DGA, and DM conceived of this paper. SV and LS drafted the article and all authors critically revised it for important intellectual content. All authors approved the final version of this article. SV is the guarantor of this work.

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