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CONSORT extension for reporting N-of-1 trials for traditional Chinese medicine (CENT for TCM) : Recommendations, explanation and elaboration

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ABSTRACT

Background: N-of-1 trial is a desired and appropriate approach to assessing the efficacy and safety of traditional Chinese medicine (TCM) interventions. There have been an increasing number of N-of-1 trials for TCM published. However, a lack of preferred reporting guidance led in the general poor reporting quality of these trials. Due to the unique characteristics of TCM, the working group developed this CONSORT Extension for reporting N-of-1 Trials for Traditional Chinese Medicine (CENT for TCM) to assist TCM researchers in reporting N-of-1 trials for TCM.

Methods: We registered CENT for TCM at the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network (available at equator-network.org). The development was a comprehensive process through collection of the initial reporting items, two-round scientific Delphi consensus survey with 17 panelists, revision and formation of the final reporting checklist.

Results: The checklist includes 25 items within six domains, eight items in which were extended and elaborated on the items of the CENT 2015 checklist. Explanation of the items were listed adequately considering the nature of TCM, introducing the concept of TCM syndrome differentiation and TCM interventions.

Conclusions: CENT for TCM can be used to assess the completeness of the reporting of N-of-1 trials for TCM. The working group expect that CENT for TCM could be a practical tool to enhance the comprehensiveness and transparency of the design, implementation and reporting of N-of-1 trials for TCM.

1. Introduction

N-of-1 trials are multiple crossover trials conducted in a single patient,[1,2] involving switching treatments and systematic, repeated outcome assessments,[3] which are methodologically rigorous studies to determine the treatment effect and make evidence-based treatment decisions for the individual patient.[4,5] Since N-of-1 trial was formally proposed as a personalized method to solve the average effect generated by population-based parallel group randomized controlled trials (RCTs),[1] with the improvement of experimental methodology, there has

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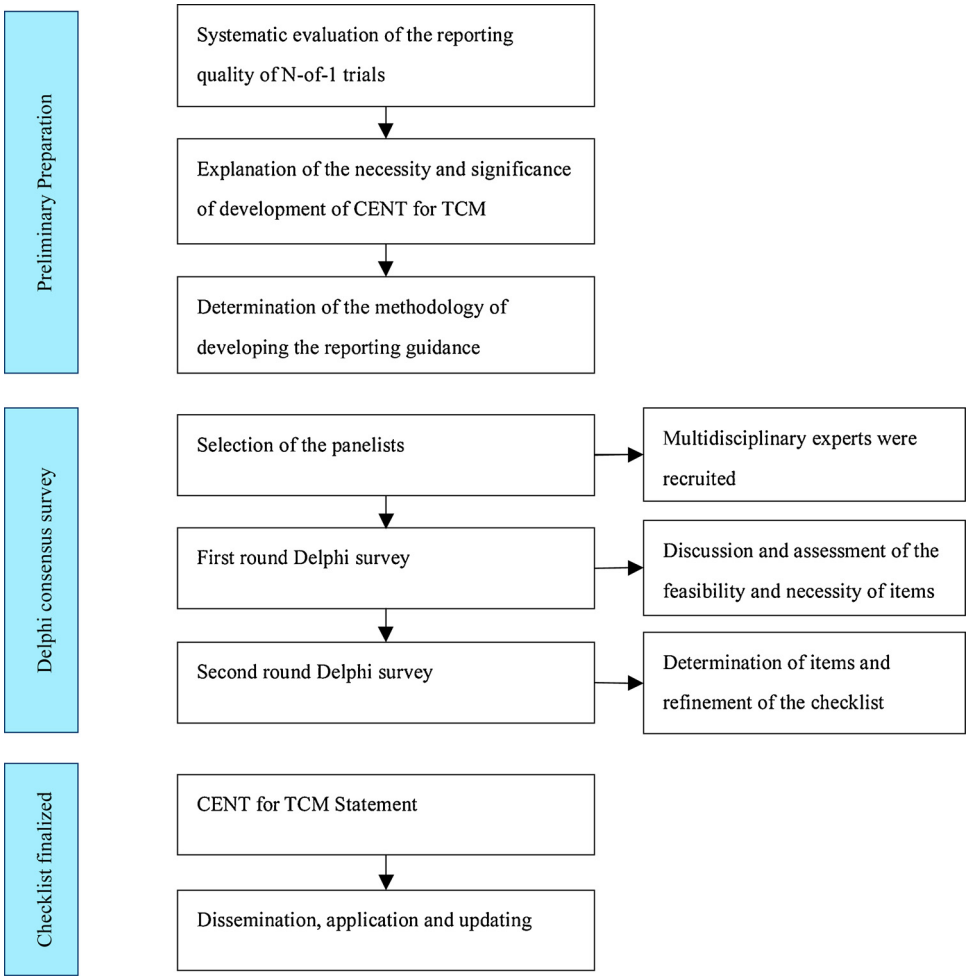

Fig. 1. Flow diagram of the development process.

been increasing number N-of-1 trials in evaluating a variety of health interventions for a wide range of medical disorders in both clinical practice and studies.[6] At present, N-of-1 trials is acknowledged as an useful tool for maximizing clinical benefits for individual patient and with great potential to provide effective information for all clinical fields.[7]

TCM, with a history of more than 2000 years,[8] is a unique, independent medical system with its own comprehensive theory. The key concepts of TCM are holism and treatment based on syndrome differentiation. In the clinical practice of TCM, practitioners determine the appropriate treatment based on TCM syndromes, which are in turn recognized by way of individual symptoms, clinical signs, and the constitution of the patient.[9] Patients with the same disease might be different in TCM syndromes and would accept separately individual interventions so that a scientific clinical research methodology which reflects the characteristics of individualized diagnosis and treatment of TCM is essential for assessing the efficacy. N-of-1 trials coincide naturally with the principle of crossover treatments based on the participants' clinical actual situation and are recognized as an attractive approach for TCM clinical trials.,[10,11]

In TCM N-of-1 trials, TCM intervention A or B is more beneficial to the specific patient with a TCM syndrome can be assessed through quantified analysis of crossing outcome measurement. Moreover, thinking of the temporal changes of TCM syndrome diagnosis, the design of N-of-1 trials makes it possible for clinical researchers tailoring individual TCM treatments in each alternation compared with corresponding placebo. TCM N-of-1 trial is the research method most consistent with TCM clinical diagnosis and treatment and has been paid great attention to.[12]

Recent years, an increasing number of N-of-1 trials using TCM interventions were published or conducted.[13–18] However, the reporting quality of these trials is disappointed.[19] In 2015, CONSORT extension for reporting N-of-1 trials (CENT) was developed to improve the reporting quality of N-of-1 trials.[5,20] Nevertheless, items in CENT are not fully suitable for reporting N-of-1 trials of TCM, because the CENT guidelines do not include the unique characteristics of TCM.

To address this gap, CONSORT Extension for reporting N-of-1 Trials for Traditional Chinese Medicine (CENT for TCM) was developed based on the relevant reporting guidelines.[5,21,22] CENT for TCM is targeted at researchers of TCM clinical trials. In the article, we present the methodology of the development process, the final reporting checklist and explanation.

2. Methods

This work was registered at the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network (www.equator-network.org). The development of CENT for TCM involved a multistep process followed the EQUATOR criteria.[23]

Specifically, we first obtained permission rights from the CENT group for a standard translation of Chinese version of CENT. Based on (1) the normative implementation,[3,6,24] of N-of-1 trials, (2) systematic review of published trials[19] and (3) the reporting items emphasized by CENT,[5,20] 42 items in 6 domains were included in an initial reporting list combined with the diagnostic and therapeutic specificity of TCM.

Second, following the principles of representativeness and

universality,[25,26] seventeen panelists were recruited for the Delphi consensus survey, including two biomedicine statistics experts and one editor from America, one clinical trial methodology expert from Canada, thirteen researchers who have profound qualifications in the fields of clinical epidemiology, clinical medicine, evidence-based medicine and TCM from China. The Delphi survey questionnaire was designed based on the initial reporting list. Respondents were asked to rate each item on a Likert scale from 1 (completely irrelevant) to 5 (highly relevant). To accommodate both English and Chinese speakers, versions of the questionnaire were prepared in both languages. The Delphi process involved two rounds e-mail–based surveys. Panelists rated each item, assessed feasibility and necessity of the items and suggested new items in the first round. In the second round, items with consensus were reconfirmed and each item was elaborated.

After the Delphi consensus survey, the working group members discussed the results, undertook a comprehensive review of the respondents' feedback, refined each item, agreed on the final reporting list and gave explanation to the items. The flow diagram of the development of CENT for TCM is showed in Fig. 1.

3. Results

CENT for TCM checklist is the extension of the CENT 2015 items and comprises a total of 40 sub-items (Table 1). Item 1c, keywords, is new added. In Table 2, explanation and elaboration are given for items to assist researchers using the checklist.

Corresponding items related to the key concepts of syndrome differentiation, characteristics of TCM and different types of interventions are elaborated below.

3.1. Title, abstract and keywords

3.1.1. Item1a

Identify as an "N-of-1 trial for traditional Chinese medicine" in the title; for series: Identify as "a series of N-of-1 trials for traditional Chinese medicine" in the title.

A self-explanatory title reflects the study type and essential information. This item is recommended to ensure the study can be clearly identified as N-of-1 trial(s) for TCM, including the diagnosis, a specific TCM syndrome and the TCM interventions to be evaluated, such as CHM formulas or acupuncture.

3.1.2. Item1c

Determination of appropriate keywords, including "traditional Chinese medicine" and "(series of) N-of-1 trial(s)"

The name of TCM interventions in keywords can be Chinese Pinyin, acronym or an English translation,[22] which is difficult to determine whether the intervention is associated with TCM. Consequently, it would be appropriately indexed and easily identified after adding the keyword "traditional Chinese medicine".

3.2. Participant(s)

3.2.1. Item4a

Diagnosis of a Western medicine–defined disease and the TCM syndrome differentiation; For series: inclusion and exclusion criteria for participants

The diagnostic criteria and syndrome differentiation reference should be given to where detailed explanation can be found

TCM syndrome plays an important role in determining the TCM therapeutic principles,[22] however, clinical trials of TCM usually recruit participants using the diagnostic criteria of Western medicine-defined disease, an approach inconsistent with the emphasis on syndrome differentiation of the individual. So detailed reporting of the syndrome differentiation of participants is recommended in order to reflect the whole disorder characteristic of participants from the theory of TCM. Futhermore, the syndrome differentiation reference should be reported so as to identify how the researchers conducted the process of TCM syndrome differentiation. Although there is no gold standard for TCM syndrome differentiation currently, related references developed by professional organizations like *Chinese Association of Integrative Medicine* and *China Association of Chinese Medicine* are recognized in the TCM field in which the detailed explanation can be found. For a single N-of-1 trial, a detailed description of the patient's clinical symptoms, syndrome differentiation, disease progression, complications, and surgical history is essential[30] and for N-of-1 trial series, researchers should report the participants' demographic and clinical information comprehensively,[31–33] a table is recomended. Such information is necessary to interpret and reproduce the study.

3.3. Interventions

3.3.1. Item5

Statements of interventions, both treatments and controls for each period, with detailed description for different types of interventions, including Chinese herbal medicine (CHM) formulas and acupuncture. For specific guidance on reporting CHM formulas, see CONSORT − CHM Formulas 2017[22] (Table 3) and acupuncture see STRICTA 2010 Statement[21] (Table 4).

Indications and relevant clinical or mechanistic studies concerning the interventions should be reported if possible. As for CHM formulas, detailed description of the name, source, and dosage form etc. is indispensable. In CONSORT − CHM Formulas 2017, there is elaborate reporting standard for the interventions,[22] so when the N-of-1 trial is designed to evaluate CHM formulas, Item5 in CONSORT − CHM Formulas 2017 (Table 3) is recommended. In addition, the effectiveness of certain TCM techniques like acupuncture and massage mainly hinges on the experience of the practitioner, when the intervention of the N-of-1 trial(s) is acupuncture, we recommend to use the six items in STRICTA 2010[21] (Table 4) for reporting. Detailed reporting of the TCM interventions is a necessity for objective and scientific assessment of trial results and replication. Furthermore, researchers should state how participants learn of the interventions (e.g. through the informed consent). In placebo controlled N-of-1 trials, describing the features of placebo relative to the interventions (e.g. in terms of color, smell, taste, appearance, and packaging) will help readers assess their comparability.

3.4. Blinding

3.4.1. Item11a

Who (for example, participants, care providers, or those assessing outcomes) was blinded after assignment to interventions, and if the intervention cannot be blinded, state why.

3.4.2. Item11b

Description of the similarity of interventions, including placebo (for specific guidance on reporting controlled interventions, see Item5)

Triple blinding of patients, clinicians, and outcomes assessors is considered good research practice and would generate generalizable knowledge about the effects of treatment in clinical trials. In N-of-1 trial with even one participant, blinding could guarantee the effect evaluation objective and reliable. The similarity of the characteristics of interventions is stated as the evidence of the method of blinding.[35] As for the particularity of TCM interventions, placebo is relative difficult, which should be designed identical with the study drug by qualified pharmacists of TCM. In the N-of-1 trial for acupuncture, sham acupuncture is a desired approach of blinding.[36]

4. Discussion

Evidence from N-of-1 trials is demonstrating clinical progresss

Table 1
CENT for TCM Checklist; CENT 2015 checklist items with modifications or additions for TCM; empty items in CENT for TCM column indicate no modification from the CENT 2015 item.

Section/Topic	CENT 2015		CENT for TCM	
	No	Item	No	Item
Title, abstract and keywords				
	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	1a	Identify as an "N-of-1 trial for traditional Chinese medicine" in the title; for series: Identify as "a series of N-of-1 trials for traditional Chinese medicine" in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CENT guidance for abstracts[20])	1b	
			1c	Determination of appropriate keywords, including "traditional Chinese medicine" and "(series of) N-of-1 trial(s)"
Introduction				
Background	2a1	Scientific background and explanation of rationale	2a1	
	2a2	Rationale for using N-of-1 approach	2a2	Rationale and explanation of the necessity for using N-of-1 approach
objectives	2b	Specific objectives or hypotheses	2b	
Methods				
Trial design	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	3a	
	3b	Important changes to methods after trial start (such as eligibility criteria), with reasons	3b	
Participant(s)	4a	Diagnosis or disorder, diagnostic criteria, comorbid conditions, and concurrent therapies For series: Eligibility criteria for participants	4a	Diagnosis of a Western medicine–defined disease and the TCM syndrome differentiation; For series: inclusion and exclusion criteria for participants The diagnostic criteria and syndrome differentiation reference should be given to where detailed explanation can be found
	4b	Settings and locations where the data were collected	4b	
	4c	Whether the trial(s) represents a research study and if so, whether institutional ethics approval was obtained	4c	
Interventions	5	The interventions for each period with sufficient details to allow replication, including how and when they were actually administered	5	Statements of interventions, both treatments and controls for each period, with detailed description for different types of interventions, including Chinese herbal medicine (CHM) formulas and acupuncture. For specific guidance on reporting CHM formulas, see CONSORT-CHM Formulas 2017[22] (Table 3) and acupuncture see STRICTA 2010 Statement[21] (Table 4)
Outcomes	6a1	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6a1	Primary/secondary outcome measures, including outcomes with TCM syndrome
	6a2	Description and measurement properties (validity and reliability) of outcome assessment tools	6a2	
	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	Whether the order of treatment periods was randomized, with rationale, and method used to generate allocation sequence	8a	
	8b	When applicable, type of randomization; details of any restrictions (such as pairs, blocking)	8b	
	8c	Full, intended sequence of periods	8c	
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	who (for example, participants, care providers, or those assessing outcomes) was blinded after assignment to interventions, and if the intervention cannot be blinded, state why
	11b	If relevant, description of the similarity of interventions	11b	Description of the similarity of interventions, including placebo (for specific guidance on reporting controlled interventions, see *Item5*)

(*continued on next page*)

Table 1 (*continued*)

Section/Topic	CENT 2015		CENT for TCM	
	No	Item	No	Item
Statistical methods	12a	Methods used to summarize data and compare interventions for primary and secondary outcomes	12a	
	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[27])	12b	For series: methods of quantitative synthesis of individual trial data, including subgroup analyses (with the assessment of heterogeneity), Bayesian analysis, adjusted analyses (for specific guidance on reporting syntheses of multiple trials, please consult the PRISMA Statement,[27] for the guidance on reporting Bayesian analysis, see the ROBUST criteria[28])
	12c	Statistical methods used to account for carryover effect, period effects, and intra-subject correlation	12c	
Results				
Participant flow (a diagram is strongly recommended)	13a1	Number and sequence of periods completed, and any changes from original plan with reasons	13a	
	13a2	For series: The number of participants who were enrolled, assigned to interventions, and analyzed for the primary outcome	13b	
	13b	For series: Losses or exclusions of participants after treatment assignment, with reasons, and period in which this occurred, if applicable	13c	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	14a	
	14b	Whether any periods were stopped early and/or whether trial was stopped early, with reason(s)	14b	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	15	
Numbers analyzed	16	For each intervention, number of periods analyzed. In addition for series: If quantitative synthesis was performed, number of trials for which data were synthesized	16	
Outcomes and estimation	17a1	For each primary and secondary outcome, results for each period; an accompanying figure displaying the trial data is recommended	17a1	
	17a2	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	17a2	
	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 assessment of carryover effects, period effects, intra-subject correlation In addition for series: If done, results of subgroup or sensitivity analyses	18	
Harms	19	All harms or unintended effects for each intervention (for specific guidance see CONSORT for harms[29])	19	
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	21	Whether the trial findings applicable for other patients, state why
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	

Table 2
Explanation and elaboration of the CENT for TCM checklist.

Section/Topic	No	Item	Explanation and Elaboration
Title, abstract and keywords			
	1a	Identify as an "N-of-1 trial for traditional Chinese medicine" in the title; for series: Identify as "a series of N-of-1 trials for traditional Chinese medicine" in the title	Statement of the diagnosis, TCM syndromes and interventions in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CENT guidance for abstracts[20])	Description of background, trial design and statistical methods, results and conclusions in the abstract, What should be emphasized is the illustration of the specific TCM syndrome and interventions in methods.
	1c	Determination of appropriate keywords, including "traditional Chinese medicine" and "(series of) N-of-1 trial(s)"	N-of-1 trial(s) for TCM would be easily identified using the key words "traditional Chinese medicine" and "(series of) N-of-1 trial (s)".
Introduction			
Background	2a1	Scientific background and explanation of rationale	Statement of the rational for using N-of-1 trial to figure out why N-of-1 trial is the appropriate study type and how TCM theory informs the trial design; In stating the objectives, description of what interventions of TCM could be effective for which syndrome.
objectives	2a2	Rationale and explanation of the necessity for using N-of-1 approach	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	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	Detailed description of the trial design is essencial for the evaluation of the trial and replication. Since there is no universal methods to calculate the the onset time and half-time of Chinese herbal medicine, preliminary trials are suggested for determining the treatment duration and wash-out. Also, the periods could be determined by clinical experience and pharmacokinetic and pharmacodynamic studies, corresponding references should be cited.
	3b	Important changes to methods after trial start (such as eligibility criteria), with reasons	
Participant(s)	4a	Diagnosis of a Western medicine–defined disease and the TCM syndrome differentiation; For series: inclusion and exclusion criteria for participants The diagnostic criteria and syndrome differentiation reference should be given to where detailed explanation can be found	Rationale and how to diagnose the specific TCM syndrome, with references
	4b	Settings and locations where the data were collected	Detailed description of where the data were collected, such as community hospitals, hospital outpatient. Who diagnose, who recruit participants shoulb be introduced.
	4c	Whether the trial(s) represents a research study and if so, whether institutional ethics approval was obtained	According to Declaration of Helsinki, each clinical trial should first obtain the ethics approval before recruiting any participant and the ethics number should be reported.
Interventions	5	Statements of interventions, both treatments and controls for each period, with detailed description for different types of interventions, including Chinese herbal medicine (CHM) formulas and acupuncture. For specific guidance on reporting CHM formulas, see CONSORT-CHM Formulas 2017[22] (Table 3) and acupuncture see STRICTA 2010 Statement[21] (Table 4).	Detailed description of different interventions: name, properties, administration route and dosage of each Chinese herb, medical substances and dosage of Chinese herbal medicine formulas, the similarity of placebo with intervention if done, the quantity and experience of acupuncturists; the specific reporting guidance of the interventions see CONSORT-CHM Formulas 2017 and STRICTA 2010
Outcomes	6a1	Primary/secondary outcome measures, including outcomes with TCM syndrome	Completely define the outcomes (both primary and secondary) and description of how the objective outcome measures were assessed and whether training was conducted to improve reliability of subjective outcomes
	6a2	Description and measurement properties (validity and reliability) of outcome assessment tools	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	Sample size refers to the number of periods for a single N-of-1 trial and number of participants for series of n-of-1 trials, the "sample size" within a specific patient refers to the number of crossovers (repetitions) between treatments. Having more crossovers provides better precision for estimating treatment effect of the individual patient. A scientific calculation may help determine the sample size.[2]
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Explanation of any interim and stopping asked by participants
Randomisation:			
Sequence generation	8a	Whether the order of treatment periods was randomized, with rationale, and method used to generate allocation sequence	
	8b	When applicable, type of randomization; 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	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	who (for example, participants, care providers, or those assessing outcomes) was blinded after assignment to interventions, and if the intervention cannot be blinded, state why	

(*continued on next page*)

Table 2 (*continued*)

Section/Topic	No	Item	Explanation and Elaboration
	11b	Description of the similarity of interventions, including placebo (for specific guidance on reporting controlled interventions, see *Item5*)	The similarity of interventions with placebo has to be described in detail
Statistical methods	12a	Methods used to summarize data and compare interventions for primary and secondary outcomes	Detailed description of the most appropriate statistical methods (such as carryover effect, period effects, and intra-subject correlation)
	12b	For series: methods of quantitative synthesis of individual trial data, including subgroup analyses (with the assessment of heterogeneity), Bayesian analysis, adjusted analyses (for specific guidance on reporting syntheses of multiple trials, please consult the PRISMA Statement,[27] for the guidance on reporting Bayesian analysis, see the ROBUST criteria[28])	
	12c	Statistical methods used to account for carryover effect, period effects, and intra-subject correlation	
Results			
Participant flow (a diagram is strongly recommended)	13a1	Number and sequence of periods completed, and any changes from original plan with reasons	Detailed description of the number of participants who were enrolled in inclusion and exclusion, assigned to interventions, followed up and analyzed for the primary outcome, with reasons
	13a2	For series: The number of participants who were enrolled, assigned to interventions, and analyzed for the primary outcome	
	13b	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	
	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	Baseline characteristics of participants, such as stage of disease development, and in series of N-of-1 trials a table is recommended
Numbers analyzed	16	For each intervention, number of periods analyzed. In addition for series: If quantitative synthesis was performed, number of trials for which data were synthesized	Statement of the number of intervention periods
Outcomes and estimation	17a1	For each primary and secondary outcome, results for each period; an accompanying figure displaying the trial data is recommended	More than one outcome would be observed and analyzed in a trial, so establishing the primary outcome in advance is important for unbiased interpretation of results. When writing the trial paper, only primary outcomes occur in the abstract. Also, the unexpected or unplanned outcomes of the trial need to be explained in the paper
	17a2	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	
Ancillary analyses	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	Analyses of the effect size of group comparison (risk ratio, relative risk, odds ratio, difference of median and mean survival time)
Harms	19	All harms or unintended effects for each intervention (for specific guidance see CONSORT for harms[29])	What has to be emphasized is that the harms or unintended adverse effects of TCM interventions are usually not be detected in the short term, so long-term observation and comprehensive reporting is necessary
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Discussing limitations of the trial will help shape future researches
Generalizability	21	Whether the trial findings applicable for other patients, state why	N-of-1 trial results may not only suggest the best treatment options for the individual but may potentially extend to patients with similar conditions. However, since a lack of universal standard for TCM syndrome differentiation and treatment, it is quite difficult to assess the generalizability. In the discussion, whether there is generalization, the reasons should be stated, because researchers' analysis and thoughs would be valuable inspiration and reference for readers and future studies.
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	Clinical trials registration, as a fundamental reporting element, guards against publication bias and reduces confusion introduced by post-analysis.
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

objectively, supports better treatment planning and leads to better outcomes for the individual. In TCM field, N-of-1 trials are an innovative approach for effect estimation of the individualized treatments, like CHM formulas, acupuncture and massage etc. In fact, present N-of-1 trials have been used extensively to evaluate TCM therapeutic effectiveness. If well reported, the outcomes can be translated into useful clinical information by clinicians and decision-makers. For presenting objective and reliable evidence of the efficacy and safety

Table 3
Specific guidance on reporting CHM formulas (Item 5 of CONSORT – CHM Formulas 2017[22]).

Item (Sub-item)	Description(s) for different types of formulas should include the following:
5a. For fixed CHM formulas	1 Name, source, and dosage form (e.g. decoctions, granules, powders)
	2 Name, source, processing method, and dosage of each medical substance. Names of substances should be presented in at least 2 languages: Chinese (Pinyin), Latin, or English. Names of the parts of the substances used should be specified.
	3 Authentication method of each ingredient and how, when, where, and by whom it was conducted; statement of whether any voucher specimen was retained, and if so, where they were kept and whether they are accessible
	4 Principles, rationale, and interpretation of forming the formula
	5 Reference(s) as to the efficacy of the formula, if any
	6 Pharmacologic study results of the formula, if any
	7 Production method of the formula, if any
	8 Quality control of each ingredient and of the product of the formula, if any. This would include any quantitative and/or qualitative testing method(s); when, where, how, and by whom these tests were conducted; whether the original data and samples were kept, and, if so, whether they are accessible.
	9 Safety assessment of the formula, including tests for heavy metals and toxic elements, pesticide residues, microbial limit, and acute/chronic toxicity, if any. If yes, it should be stated when, where, how, and by whom these tests were conducted; if the original data and samples were kept; and, if so, whether they are accessible.
	10 Dosage of the formula, and how the dosage was determined
	11 Administration route (e.g., oral, external)
5b. For individualized CHM formulas	1 See recommendations 5a 1–11
	2 Additional information: how, when, and by whom the formula was modified
5c. For patent proprietary CHM formulas	1 Reference to publicly available materials, such as pharmacopeia, for the details about the composition, dosage, efficacy, safety, and quality control of the formula
	2 Illustration of the details of the formula, namely 1) the proprietary product name (i.e., brand name), 2) name of manufacturer, 3) lot number, 4) production date and expiry date, 5) name and percentage of added materials, and 6) whether any additional quality control measures were conducted
	3 Statement of whether the patent proprietary formula used in the trial is for a condition that is identical to the publicly available reference
5d. Control groups	Placebo control
	1 Name and amount of each ingredient
	2 Description of the similarity of placebo with the intervention (e.g., color, smell, taste, appearance, packaging)
	3 3 Quality control and safety assessment, if any
	4 Administration route, regimen, and dosage
	5 Production information: where, when, how, and by whom the placebo was produced
	Active control
	1 If a CHM formula was used, see recommendations 5a–5c
	2 If a chemical drug was used, see item 5 of the CONSORT Statement[34]

of TCM interventions, a high-quality standard is needed to guide reporting. Because syndrome differentiation underlies the clinical practice of TCM, CENT for TCM took account of TCM theory on the basis of CENT 2015 to promote the standardization of N-of-1 trials of TCM and provide enough information to judge the methodology and the reliability of outcomes.

CENT for TCM was developed based on the principles of transparency, consistency, and full disclosure, which was completed by an innovative group including clinical epidemiologists, TCM clinicians (physicians, acupuncturists, etc.) and pharmacists, clinical research methodologists, journal editors and statisticians.

CENT for TCM checklist consists of 25 items, 40 sub-items, within six domains. These recommendations are applicable to N-of-1 trials of different TCM interventions such as CHM formulas and acupuncture. In CENT for TCM, the syndrome differentiation are elaborated.

For optimizing N-of-1 trials of TCM, this reporting guideline ultimately depends on its use. CENT for TCM could assist researchers with scientific design, strict implementation and complete reporting of N-of-

Table 4
Specific guidance on reporting acupuncture (information for reporting acupuncture interventions in STRICTA 2010[21]).

Item	Detail
1. Acupuncture rationale	1a. Style of acupuncture (e.g. Traditional Chinese Medicine, Japanese, Korean, Western medical, Five Element, ear acupuncture, etc)
	1b. Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate
	1c. Extent to which treatment was varied
2. Details of needling	2a. Number of needle insertions per subject per session (mean and range where relevant)
	2b. Names (or location if no standard name) of points used (uni/bilateral)
	2c. Depth of insertion, based on a specified unit of measurement, or on a particular tissue level
	2d. Response sought (e.g. de qi or muscle twitch response)
	2e. Needle stimulation (e.g. manual, electrical)
	2f. Needle retention time
	2g. Needle type (diameter, length, and manufacturer or material)
3. Treatment regimen	3a. Number of treatment sessions
	3b. Frequency and duration of treatment sessions
4. Other components of treatment	4a. Details of other interventions administered to the acupuncture group (e.g. moxibustion, cupping, herbs, exercises, lifestyle advice)
	4b. Setting and context of treatment, including instructions to practitioners, and information and explanations to patients
5. Practitioner background	Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience)
6. Control or comparator interventions	6a. Rationale for the control or comparator in the context of the research question, with sources that justify this choice
	6b. Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for Items 1 to 3 above.

1 trials so as to generate high-quality evidence and to encourage subsequent meta-analysis of N-of-1 trials.

The CONSORT relevant checklists and CENT achieved great success in promoting changes in practice and improving the general quality of trials. For better dissemination, we will introduce CENT for TCM to all TCM practitioners, researchers, peer reviewers, and journal editors through publication of relevant articles and various workshops conferences. We also accept comments and feedback from those in research or clinical practice in order to ameliorate the reporting guidance.

In the development of CENT for TCM, we recruited 17 specialists for the Delphi survey, which was not universal enough. In future iterations of this guideline, the working group will convene a broader group of experts to obtain new concept to revise it. And the working group will update regularly and modify the checklist when valuable comments provided.

CENT for TCM highlights the features of TCM and provides a comprehensive and explicit guide for clinical researchers of the scientific, normative and transparent reporting of TCM N-of-1 trials. We hope it will promote rigorous evaluation of TCM interventions among TCM researchers and the broader scientific community alike.

5. Conclusions

Through rigorous and transparent research, we developed this CENT for TCM to guide more standard implementation and reporting of TCM N-of-1 trials. It is expected that TCM researchers would carry out high quality N-of-1 trials both in methodology and reporting with the assistance of CENT for TCM checklist, subsequently produce convicing evidence to promote TCM clinical practice.

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Declaration of competing interest

The authors declare no conflicts of interest.

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