Chinese Journal of Integrative Medicine
Available online at link.springer.com/journal/11655
Journal homepage: www.cjim.cn/zxyjhen/zxyjhen/ch/index.aspx
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Regulation and Guideline

Standard Protocol Items for Clinical Trials with Traditional Chinese Medicine 2018: Recommendations, Explanation and Elaboration (SPIRIT-TCM Extension 2018)

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ABSTRACT Traditional Chinese Medicine (TCM) is one of the oldest systems of medicine. More and more attention has been paid to TCM application, but the variable quality of clinical trials with TCM impedes its widespread acceptance. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement has established guidelines for designing clinical trials to ensure that the trial results are accurate and reliable. However, there are difficulties when applying SPIRIT 2013 Statement to trials with TCM, due to the unique theory and the characteristic of TCM intervention. An Extension to the original SPIRIT was developed to ensure the quality of trial design with TCM. As Chinese herbal formulae, acupuncture and moxibustion are common and representative interventions in TCM practice, the executive working group determined that the SPIRIT-TCM Extension focus on these three interventions. Extension was developed through initiation, 3 rounds of Delphi consensus survey, and finalizing expert meeting. Seven items from the SPIRIT 2013 Statement were modified, namely, "title", "background and rationale", "objectives", "eligibility criteria", "interventions", "outcomes", and "data collection methods". The Extension includes the introduction of the concept of TCM pattern and 3 major TCM interventions, with examples and explanations. The SPIRIT-TCM Extension 2018 provides suggestion for investigators in designing high quality TCM clinical trials. It is expected that wide dissemination and application of this extension ensure continuous improvement of TCM trial quality throughout the world.

KEYWORDS SPIRIT, traditional Chinese medicine, clinical trial, extension, recommendation

Traditional Chinese medicine (TCM) is one of the oldest medical systems in the world, it is widely utilized in China and other East Asian countries, and increasingly throughout the rest of the world.[1] It is unique in both theory and therapeutic practices. Since the first TCM randomized controlled trial (RCT) was published in 1982,[2] a huge number of clinical trials have been conducted to evaluate the efficacy and safety of TCM.[3] However, the questionable quality of trial design and reporting undermines acceptance of the results from the trials. The quality of clinical trial reporting has been addressed by the publication of the Consolidated Standards of Reporting Trials (CONSORT), and it did improve the quality of trial reporting.[4] Based on this initiative, some TCM related reporting recommendations have been developed, including Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA),[5] Reporting Interventions in Clinical Trials of Moxibustion (STRICTOM),[6] and Consolidated Standards of Reporting Trials for Chinese Herbal Medicine Formulae 2017 (CONSORT-CHM extension 2017).[7] As these recommendations are implemented, the quality of reporting of TCM trials is expected to improve.

With regard to trial design, the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement 2013 was developed, published and disseminated.[8] Currently, this Statement has been

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DOI: https://doi.org/10.1007/s11655-018-2999-x

Chin J Integr Med 2019 Jan;25(1):71-79

endorsed by numerous journals, regulators, funders/ industries, trial groups, academic institutions, contract research organizations, and patient groups.[9] Several translations have been published, including Chinese, Italian, Korean, and Spanish, while French and Portuguese translation are in progress.[10] Further, academic community of TCM strongly encourages researchers to follow the recommendation of the SPIRIT 2013 Statement for TCM clinical trial design.[11-14] However, the application of the SPIRIT 2013 Statement to TCM trial protocol is not easy because the requirements of recommendations do not directly apply to the unique features of TCM. For example, the SPIRIT 2013 Statement requires that "interventions for each group (be described) with sufficient details to allow replication, including how and when they will be administered";[8] however, it is difficult for researchers to define how much should be described about the intervention of Chinese herbal medicine (CHM), acupuncture or moxibustion. Secondly, some TCM clinical studies' protocol has been developed based on the CONSORT and/or STRICTA, but both of which were developed for trial reporting not for design.[15,16] It is understandable that reporting standards may help in protocol design, but they cannot represent the requirements of protocol design. Reporting requirements emphasize the transparent, accurate recording of what has been done, but the design focus on how to plan a high quality and practical trial. Thirdly, even some of reporting guideline can be used as reference for trial design, but some of features of TCM are not included in reporting. For example, STRICTA does not mention the pattern concept,[5] which is fundamental to TCM theory both in diagnosis and treatment. To be useful, protocol design guidelines need to tell the reader how TCM patterns are described, distinguished and diagnosed. In addition, some of factors such as acupuncture rationale, needling details, etc, should be included not just in the trial reporting,[17] but also in the trial design. Therefore, given the increasing number of clinical trials involving TCM, both in China and elsewhere, a SPIRIT-TCM Extension is needed to ensure that trials are designed properly.

DEVELOPMENT OF THE SPIRIT-TCM EXTENSION 2018

First Draft

The SPIRIT-TCM Extension was developed using the same process as was used for SPIRIT. The composition of the executive working group is shown in Appendix 1. It included experienced TCM practitioners, the SPIRIT development initiator, TCM researchers and clinical research methodologists. Considering that CHM formulae, acupuncture and moxibustion are the three common and representative TCM interventions in clinical practice and research, the executive working group decided to develop the SPIRIT-TCM Extension focusing on three treatment modalities. The items of the SPIRIT 2013 checklist were thoroughly scrutinized, and the content of 7 items, namely "title", "background and rationale", "objectives", "eligibility criteria", "interventions", "outcomes" and "data collection methods", were revised to accommodate the unique characteristics of TCM interventions. The first draft of the SPIRIT-TCM Extension Checklist was formed accordingly. After that, the Delphi survey process was initiated.

Delphi Survey Process

The Delphi survey process is shown in Figure 1. Based on the first draft of the SPIRIT-TCM Extension Checklist, a survey questionnaire was developed by the executive working group. Next, 33 active TCM researchers were invited to participate, including TCM investigators, clinical research methodologists, statisticians and clinical trial coordinators. The full list of survey participants is shown in Appendix 1. All of them have doctorate degrees and actively participate in clinical research. Questionnaires were distributed personally or through e-mail. The objectives and workflow of the SPIRIT-TCM Extension Checklist Delphi process were thoroughly explained in the invitation letters. Anonymity and confidentiality of responses were ensured. Five weeks were taken for each round of survey, comprising 1 week for testing, 3 weeks for acquiring responses, and 1 week for summarizing results and preparing the questionnaire for the next round.

Every suggested item in SPIRIT-TCM Extension Checklist was rated using a 10-point scale, with increasing significance from "1" to "10". Experts were required to explain their reason(s) for the rating chosen. In Round 1, demographic information about the invited experts (organization, post, degree and specialty) was collected. In addition, all experts were encouraged to provide comments or additional items that should be included in the SPIRIT-TCM Extension Checklist. In Round 2, the initial items were modified based on the responses from Round 1. For each item, the median and interquartile range of Round 1 scores were presented along with anonymous comments. All experts were asked to re-rate the items after

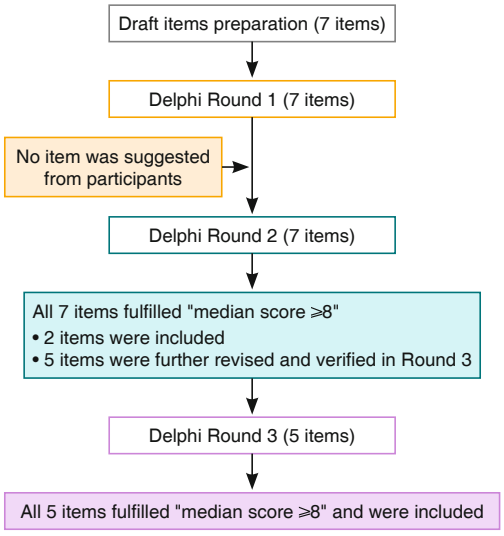

Figure 1. Flow of SPIRIT-TCM Extension 2018 for Delphi Survey

reviewing the scores and comments from Round 1, and they were informed that consensus would be defined by the mean of median score in 2 rounds (⩾8 = included, ⩽5 = excluded). After 2 rounds, all nominated items obtained a mean of median score ⩾8, and no new items had been suggested. Further, based on the comments acquired from Round 2, the executive working group prepared items for the 3rd-round survey. The 3rd survey questionnaire was presented in two parts. Part 1 contained revised items requiring further feedback. Part 2 presented items that had reached consensus in Rounds 1 and 2 and would therefore be included in the final checklist. After 3 rounds, the items were fixed, and the checklist of SPIRIT-TCM Extension 2018 was finally formed.

Consensus Meeting

After the Delphi survey, the executive working group prepared the the manuscript of the SPIRIT-TCM Extension 2018. After that, a face-to-face consensus meeting (full name list of participants in Appendix 1) was organized in July 2017 in Lanzhou, China, to review the survey results and criticize the manuscript. Based on this meeting, the executive working group finalized the manuscript.

Unique Characteristics

Pattern

Pattern, also known as syndrome or Zheng, is a vital concept in TCM theory. It is the theoretical foundation of diagnosis and treatment in TCM.[18] Corresponding to the concept of biomedical disease, TCM pattern could be considered as an alternative standard for patient categories. It is the summary of the specific pathogenesis at a certain stage of a disease, identified from a comprehensive collection and evaluation of clinical information obtained through four main diagnostic TCM methods (inspection, listening and smelling, inquiry, and palpation).[19,20] The same biomedical disease (i.e., in Western medical terms) may present with different patterns, while the same pattern may be identified as diverse biomedical diseases.[18] Since the 1980s, multiple diagnostic criteria for specific diseases and patterns have been developed, such as Syndrome Diagnosis Criteria and Therapeutic Schedule for Depression,[21] and Syndrome Diagnosis Criteria for Common Cold.[22] Currently, these standards have been utilized in clinical research as references for inclusion and exclusion criteria relating to an eligible pattern. In the SPIRIT-TCM Extension, it is strongly suggested that if a pattern will be involved in the study, the pattern should be described in the title (Item 1b), background and rationale (Item 6a), objectives (Item 7), eligibility criteria (Item 10a), outcomes (Item 12), and data collection methods (Item 18).

TCM Interventions

TCM interventions are different from that in Western medicine (WM). The most common interventions in TCM are CHM formulae, acupuncture and moxibustion. As for CHM formulae, the intervention could be one single herb, a mixed herbs (formula), or a proprietary preparation of herbs. In order to guarantee the composition and quality of a CHM formula and to allow its replication for use in trials, the SPIRIT-TCM Extension strongly recommends that sufficient details (e.g., source of herbs, place of manufacture if a proprietary formula, method of preparation) should be provided (Item Interventions 11a.1A). Similarly, details about acupuncture and moxibustion administration should be described in detail.

The choice of comparator groups affects the interpretation of trial results. An appropriate comparator facilitates an assessment of whether the observed effect of the experimental intervention resulted from the intervention itself, natural disease progression, or participants' and researchers' expectations.[23] Therefore, the SPIRIT-TCM Extension strongly suggests that comparator interventions should be fully described based on Item Interventions 11a.2. Full details will enable readers and reviewers to evaluate how the trial was designed.

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Finalized Items

The finalized SPIRIT-TCM Extension 2018 is presented in Appendix 2. Model examples for each revised item from the published literature, where available, are attached in Appendix 3.

R1. Title

1a. Specify the patient population in terms of 1) a WM-defined disease, 2) a WM-defined disease with a specific TCM pattern, or 3) a TCM pattern.

1b. Specify the intervention, in terms of 1) CHM formula, 2) acupuncture, 3) moxibustion, or 4) other TCM therapy(s).

Explanation: The title provides the first description of a protocol to reviewers and readers. Thus, accurate, transparent and detailed information should be presented in title. It is strongly recommended that the target disease and/or pattern and specific intervention should be included.

R2: Background and Rationale

6a.1. Provide the background and rationale of the research question with TCM theory.

Explanation: TCM has its own theoretical basis which is different from WM. In order to preserve the unique characteristics of TCM, the rationale based on TCM theory should be reported in addition to any WM principles.

6a.2. Describe the rationale of the utilized TCM interventions with references.

Explanation: Knowing the rationale is the first step for reviewers and readers to understand the intervention. For CHM formulae, acupuncture or moxibustion, it is important to describe whether the rationale for the intervention selection is based on biomedical science evidence, TCM theory or both. For CHM formulae, it is better to include the principles, rationale, and prescription analysis of the formula, as well as the available data on efficacy, safety and pharmacology. For acupuncture and moxibustion, the description should include the rationale for treatment protocol, whether it is from historical context, available studies, and/or consensus methods. Corresponding references should also be provided.

6a.3. Provide the rationale of adding experimental TCM interventions if WM intervention is used as basic or combined remedy. If possible, the potential interaction between WM intervention and TCM intervention (especially for CHM) should also be explained with related reference(s).

Explanation: In practice, some TCM clinical trials may include WM intervention. Generally, the aim of this type of trial is to illustrate the superior efficacy of the combined interventions compared with WM intervention alone. Therefore, the SPIRIT-TCM Extension recommends that investigators should not only explain the background and rationale of every intervention, but also include the reasons for the additional TCM intervention. Moreover, considering the potential interaction(s) between WM and TCM (especially for CHM), it would be desirable to describe the impact and implications. Unfortunately, an example of a protocol in which the interaction between WM and TCM was described cannot be found.

6b. Describe the rationale and principle(s) for selecting comparators corresponding to certain interventions (i.e. CHM formulae, acupuncture, moxibustion or other TCM interventions), considering 1) comparable with tested intervention; 2) success of blinding.

Explanation: The selection of the comparator influences the interpretation of trial outcomes. An adequate comparator enables comprehensive analysis of the observed effect, which results from the experimental intervention itself, natural disease progression, or patients' and investigators' expectations. Therefore, the type of the chosen comparator group and its rationale should be clarified. Unfortunately, no optimal example for moxibustion comparator is available from the published trial protocols.

R3. Objectives

7. State the objectives or hypotheses regarding the specific TCM intervention for 1) a WM-defined disease, 2) a WM-defined disease with a specific TCM pattern or 3) a TCM pattern.

Explanation: TCM pattern is a unique concept which reflects the specific pathogenesis at a certain stage of a disease in terms of Chinese concepts, not physical parameters as measured by laboratory tests. It is categorically, intrinsically different from a

WM definition of a disease. Hence, TCM clinical trials should state the specific intervention targets: a WM-defined disease, WM-defined disease with a specific TCM pattern, or a TCM pattern. Clear identification of pattern in the objectives would facilitate an understanding of research aims and targets.

R4. Eligibility Criteria

10a. State whether participants with a specific TCM pattern will be recruited, in terms of 1) diagnostic criteria, and 2) inclusion and exclusion criteria. All criteria utilized should be universally recognized, or reference(s) where detailed explanations can be found should be given.

Explanation: As pattern is a core concept of TCM, clinical trials which involve pattern as one qualified condition should comprehensively describe the diagnostic criteria of the specific pattern as part of the eligibility criteria. This information is necessary for appropriate and accurate interpretation, appraisal, and replication of the trial.

10b. Descriptions of the roles, qualifications and other relevant experience of the researchers (e.g., participant screeners, care providers, outcome assessors, data analysts) in TCM research are recommended.

Explanation: Some clinical trial protocols define the eligibility criteria for participants but ignore the criteria for the practitioners. This may lead to variable or lower quality of administration of the interventions because of the technical skill and experience needed, particularly for acupuncture and moxibustion. Hence, for the qualification, it is recommended that the working experience and other relevant clinical or research experience of practitioners in TCM studies should be prescribed and reported in the protocol.

10c. Descriptions of the qualification and relevant experience of study center(s) involved in a TCM trial are recommended.

Explanation: The qualification and relevant experience of research center(s) will give the confidence to readers about their results, otherwise, readers may have concerns about the quality of their results. Detailed information about clinical center(s), especially for multi-centre trials, could be helpful for readers to understand how the trial will be implemented.

R5. Interventions

11a.1. Interventions for the experimental group(s) with sufficient detail to allow replication.

Explanation: The description of interventions is one of the most important parts of a protocol. The protocol should contain enough accurate details for readers to repeat the intervention. A complete and detailed description of the intervention is also essential for its subsequent application in clinical practice and further research.

Compared with WM drug interventions, the quality of CHM formulae is affected by many more factors. For instance, researches have demonstrated that factors such as the plant species, location of collection, and processing method can influence the pharmacological function of herbs.[24-27] Therefore, for CHM and every single herb, location of collection, authentication of species and processing method should be given, while for every formula, description of composition, processing and quality control should be given (Box 1).

Acupuncture and moxibustion are externally-administered, procedural therapies of TCM that are also complex in nature. Multiple factors such as participant posture, treatment environment, response sought, and operation techniques can impact the efficacy and even, in some cases, safety.[28-30] Thus, complete information about these procedures should also be stated (Box 2, 3).

11a.2. Describe interventions for the control group(s) with sufficient detail to allow replication.

Explanation: Similar to the experimental intervention, investigators should provide comprehensive and detailed information about the control (comparator) interventions. For CHM formulae, in general, there would be three categories: 1) placebo control, 2) same intervention with different dose or regimen, and 3) active control.[23] For placebos, there are still no recognized methods to make them with the identical color, smell, taste and texture as CHM formulae. Therefore, it is necessary to describe transparently the name and dosage of each ingredient, similarity of intervention, production methods, administration route, regimen and dosage, and any quality control or safety assessments

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Box 1. Recommended Items for CHM Formulae as Experimental Interventions

11a.1A. CHM Formulae

For Fixed CHM Formulae

1. Name, source and dosage form (e.g., decoction, granules, powder, pills).
2. Name, source, processing method and dosage of each medical substance. Name of all substances should be presented in at least two types of 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, by whom it will be conducted.
4. Production method of the formula.
5. Quality control of each ingredient and the whole formula.
6. Safety assessment of the formula, containing heavy metals and toxic elements test, pesticide residue test, microbial limit test, acute/chronic toxicity test.
7. Dosage of the formula, and how the dosage was determined.
8. Administration route (e.g., oral, external).

For Individualized CHM Formulae

1. As for fixed CHM formulae, refer to Fixed CHM Formulae Points 1–8.
2. Additional information: how, when and by whom the formula will be modified.

For Patent Proprietary CHM Formulae

1. Reference to a publicly available material(s), 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: i) the proprietary product name (i.e. brand name), ii) name of manufacturer, iii) lot number, iv) production data and expiry date, v) name and content of added materials, and vi) whether any additional quality control procedures will be conducted.
3. Statement of whether the patent proprietary CHM formula utilized in the study is identical to the publicly available reference.

Box 2. Recommended Items for Acupuncture as Experimental Intervention

11a.1B. Acupuncture

1. Treatment environment and participant posture.
2. Number of needle insertions per subject per session (mean and range if possible).
3. Names and location of acupoints (uni/bilateral). Name of all acupoints should be presented in Chinese (Pinyin) and international code.
4. Angle and depth of insertion, which should be presented in a specified unit of measurement or on a particular tissue level.
5. Response sought (e.g., de qi or muscle twitch response).
6. Needle stimulation (e.g., manual, electrical). If electroacupuncture apparatus will be utilized, the brand, manufacturer and frequency should be indicated.
7. Needle retention time.
8. Needle type, including diameter, length, manufacturer and material, etc.
9. Number of treatment sessions.
10. Frequency and duration of treatment sessions.

Box 3. Recommended Items for Moxibustion as Experimental Intervention

11a.1C. Moxibustion

1. Treatment environment and participant posture.
2. Number of moxibustion units per subject per session (mean and range if possible).
3. Names and location of acupoints (uni/bilateral). Name of all acupoints should be presented in Chinese (Pinyin) and international code.
4. Procedure and technique of moxibustion (e.g., direct/indirect, warming/sparrow-pecking technique, warming needle, moxa box).
5. Response sought (e.g., warm feeling, skin reddening, burning pain).
6. Moxibustion retention time.
7. Materials used for moxibustion (e.g., moxa floss, moxa cone, moxa stick, herbal patches, and their sizes and manufacturers).
8. Number of treatment sessions.
9. Frequency and duration of treatment sessions.

that will be conducted to assure the appropriateness and replication of the comparator. For active control, the requirements of CHM formulae are the same as the recommendations in Item 11a.1A, while those of chemical drugs are as in Item 11 of the SPIRIT 2013 Statement (Box 4).[8]

Box 4. Recommended Items for Control Intervention of CHM Formulae

11a.2A. CHM Formulae

Placebo Control

1. Name and dosage of each ingredient.
2. Description of the similarity of placebo with intervention (e.g., color, smell, taste, appearance, packing).
3. Quality control and safety surveillance, if any.
4. Administration route, dosage and regimen.
5. Production information: when, where, how and by whom the placebo will be produced.

Active Control

1. If a CHM formula will be used, refer to the recommendations of 11a.1A.
2. If a chemical agent will be used, the name, administration route, dosage and regime should be included.

There are different considerations about control design for the trials with acupuncture and moxibustion. For no-treatment or waiting-list controls, the SPIRIT-TCM Extension recommends that researchers include any special arrangements in pre-treatment, treatment and post-treatment periods corresponding to the experimental intervention. The details of acupuncture-like or moxibustion-like controls should also be described in strict accordance with Item Interventions 11a.1B and Item 11a.1C (Box 5, 6). The

SPIRIT-TCM Extension also highly recommends the use of well-established models for placebo controls in acupuncture and moxibustion clinical trials. The use of sham acupuncture is widely accepted as an appropriate placebo control in clinical trials of acupuncture.[31] Similarly, a sham moxibustion device has been reported in moxibustion trials.[32]

Box 5. Recommended Items for Control Intervention of Acupuncture

11a.2B. Acupuncture *Blank/Waitlist Control* • State any special arrangements in pre-treatment, treatment and post-treatment periods corresponding to the experimental intervention (e.g., examinations in pre-treatment period, unaltered lifestyle and medication in treatment period, and compensatory interventions in post-treatment period). *Sham Acupuncture or Acupuncture-Like Control* • State the comparability of the sham acupuncture or acupuncture-like control and comprehensively provide details as for the recommendations of Intervention 11a.1B.

Box 6. Recommended Items for Control Intervention of Moxibustion

11a.2C. Moxibustion *Blank/Waitlist Control* • State any special arrangement(s) in pre-treatment, treatment and post-treatment periods corresponding to the experimental intervention (e.g., examinations in pre-treatment period, unaltered lifestyle and medication in treatment period, and compensatory interventions in post-treatment period). *Sham Moxibustion or Moxibustion-Like Control* • State the comparability of the sham moxibustion or moxibustion-like control and comprehensively provide details as for the recommendations of Intervention 11a.1C.

11d.2. Descriptions of other interventions that will be administrated to experimental and/or control groups are recommended (e.g., rescue interventions), with enough details to allow replication.

Explanation: Except for the experimental interventions and corresponding comparators, clinical trials may also contain other interventions not involved in the outcomes assessment. The descriptions of other interventions such as general treatments and rescue interventions should meet ethical requirements and ensure the integrity of the experimental interventions.

R6. Outcomes

12a. Provide the rationale of TCM-related indexes as outcomes (e.g. the change of degree and scope of symptoms and signs related to pattern differentiation).

12b. Provide the details of the TCM-related outcomes assessment, including i) the measuring methods and standard (e.g. frequency, severity rating scale of symptoms and signs, verified pattern questionnaire, time points for assessment and corresponding rationale), ii) assessor qualification (e.g. relevant assessment experience, years in clinical practice), iii) methods used to enhance the quality of assessment (e.g. multiple repeated observation, training of assessors), and iv) related reference(s).

Explanation: Trial outcomes reflect the efficacy and safety of the interventions. In RCTs of TCM, the outcome variables can be categorized into WM-specific and TCM-specific.[33,34] The former is measured with objective biomedical markers or standard subjective measures, while the latter is frequently evaluated with changes in the degree and nature of a pattern. The outcome of pattern trials should be fully detailed including the evaluation methods and rationale. Unfortunately, examples are not available.

R7. Data Collection Methods

18a. When trial targeting TCM pattern, or a WM-defined disease with a specific TCM pattern, baseline data about TCM pattern should be provided.

Explanation: The pattern is repeatedly emphasized because it is vital in TCM clinical trials. As the pattern is a unique characteristic of certain TCM trials, recording pattern information in baseline data collection is necessary. It can enhance the completeness of a TCM protocol, facilitate outcome evaluation, and benefit future trial reporting. Thus, the SPIRIT-TCM Extension strongly recommends that baseline data include TCM pattern information, especially for those trials which utilize pattern as one category of outcomes. No examples are available.

DISCUSSION

The SPIRIT 2013 Statement, which was developed based on evidence from systematic reviews, international guidelines, and a Delphi consensus process, serves as an important tool for investigators to use in developing high-quality protocols for interventional clinical trials. The unique characteristics of TCM, both in diagnosis according to pattern and treatment using acupuncture, moxibustion, and CHM, however, call for special consideration. The SPIRIT-TCM Extension includes the detailed information that should

be included in TCM trial protocol. It was developed based on extensive discussion and consultation with epidemiologists, journal editors, clinical methodologists, clinical research specialists, and TCM practitioners. It is expected that this initiative can guide TCM clinical trial protocol development as it gives researchers a precise checklist to use in designing their protocols—a checklist that ensure the high quality of their results.

Consistency between trial protocol and final reporting are one of the concerns about the quality of clinical studies. In 2015, the China Food and Drug Administration released the Announcement of Self-Examination and Inspection of Drug Clinical Trial Data, in which one of the major focuses is to examine whether the trial results were generated according to the trial protocol.[35] The SPIRIT-TCM Extension could be used for trials of new TCM drugs, and help improve the quality of new drug trials with CHM.

In order to illustrate items in the SPIRIT-TCM Extension, we provide examples for most protocol items. However, there are some items for which we could not find examples, such as the authentication method, quality control and safety surveillance for CHM formulae, and control group design for acupuncture and moxibustion. A lack of examples among published protocols reflect the need for this checklist of recommendations. Adoption and implementation of the SPIRIT-TCM Extension, as expected, will improve the quality of TCM clinical trial protocol design.

Multiple strategies will be applied to better disseminate and promote the SPIRIT-TCM Extension. Firstly, the SPIRIT-TCM Extension is being published in a leading international medical journal to bring it to the attention of TCM investigators around the world, and thereby increase its potential impact. The SPIRIT-TCM Extension will also be translated into Chinese and other languages, and published in local medical journals and on related websites. In addition, various educational activities including academic lectures, scientific workshops and conference presentations will be scheduled to introduce the SPIRIT-TCM Extension to researchers and clinicians. Meanwhile, comments and feedback will be collected, discussed, and evaluated for future updates.

In conclusion, the SPIRIT-TCM Extension 2018 was developed through a rigorous systematic process. Its items encompass 3 major interventions: CHM formulae, acupuncture and moxibustion. This Extension is expected not only to help investigators develop high-quality clinical trial protocols, but also improve the quality of clinical trials with TCM.

Author Contributors

All authors provided a substantial contribution to the development of SPIRIT-TCM Extension 2018. Bian ZX initiated and lead this project. Dai L and Tian R conducted the Delphi survey and analyzed the data. Dai L, Tian R, Cheng CW, Zhong LD and Bian ZX drafted the manuscript. Lyu AP, Li YP, Chan AW, Shang HC provided critical comments on the manuscript, and Bian ZX finalized the manuscript.

Acknowledgement

We thanks David Moher for his critical comments about this project. Special thanks for Dr. Martha Dahlen for her help in polishing this manuscript.

Electronic Supplementary Material: Supplementary material is available in the online version of this article at https://doi.org/10.1007/s11655-018-2999-x.

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(Accepted September 16, 2018, First Online November 27, 2018)
Edited by YUAN Lin