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E-mail: cjim_en@cjim.cn

Regulation and Guideline

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

DAI Liang[1,2], CHENG Chung-wah[1], TIAN Ran[1], ZHONG Linda LD[1], LI You-ping[3], LYU Ai-ping[1], CHAN An-wen[4], SHANG Hong-cai[5], BIAN Zhao-xiang[1] for the SPIRIT-TCM Extension 2018

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

1. Hong Kong Chinese Medicine Clinical Study Centre, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong SAR, China; 2. Institute of Digestive Diseases, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai (200032), China; 3. Chinese Evidence-Based Medicine Centre, Sichuan University, Chengdu (610041), China; 4. Women's College Research Institute, Women's College Hospital, University of Toronto, Toronto, Ontario (M5G 1N8), Canada; 5. Key Laboratory of Chinese Internal Medicine of Ministry of Education and Beijing, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing (100007), China
Correspondence to: Prof. BIAN Zhao-xiang, E-mail: bzxiang@hkbu.edu.hk
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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