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Methodology guideline for clinical studies investigating traditional Chinese medicine and integrative medicine Executive summary☆

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ABSTRACT

This guideline aims to provide a methodological guidance for clinical studies in TCM and integrative medicine in terms of study design, execution, and reporting. The commonly used methods including experimental and observational methods were introduced in this guideline such as randomized clinical trials, cohort study, case-control study, case series, and qualitative method which can be incorporated into above quantitative methods. The guideline can be used for the evaluation of therapeutic effect of TCM therapies or their combination with conventional therapy. TCM therapy refers to one of the followings or their combination: herbal medicine, acupuncture, moxibustion, cupping, Taichi/Qigong, and Guasha, Tuina (therapeutic massage). It is also suitable for research and development of ethnopharmaceuticals or folk medicine.

1. Background and scope

The system of Traditional Chinese Medicine (TCM) is one of the whole- systems complementary and alternative medicine approaches. Clinical practice is typically based on pattern differentiation, prescription of herbal formulations or acupuncture regimen. Thus, clinical research of TCM should reflect its characteristics as a therapeutic system. Currently, there are three clinical research models. The first one is called 'disease-pattern model', where the international classification of diseases (ICD-10) in conjunction with TCM pattern differentiation is used for diagnosis. The second one is the 'TCM defined disease or symptom model' and the third one is the 'pattern model', which involves the targeting of a specific pattern rather than a disease or a symptom. TCM clinical practice, is based on a holistic approach, and the intervention includes dietary advice, behavior/life style change, as well as the herbal and/or acupuncture treatment. It is considered to be a complex intervention. Furthermore, in China, different TCM therapies are often integrated with conventional therapies and medications in what is also referred to as integrative health care.

This guideline aims to provide a methodological guidance for clinical studies of TCM and integrative healthcare including TCM in terms of study design, execution, and reporting. The role of commonly used experimental and observational methods are discussed in this guideline. These methods include randomized clinical trials, cohort studies, case-control studies, case series, as well as qualitative methods which can also be 'nested' into the above-mentioned quantitative methods. This guideline can be used for the evaluation of the therapeutic effects of TCM, either on a standalone basis or as used in conjunction with conventional therapy. TCM refers to one of the following treatment modalities or their combination: herbal medicine, acupuncture, moxibustion, cupping, Taichi/Qigong, Guasha, and Tuina (therapeutic massage).

2. Essentials for design of clinical studies in traditional Chinese medicine and integrative medicine

2.1. Clinical question formulation

The most important aspect of a clinical research project is the formulation of a clear and answerable research question. The research question should be formulated based on a comprehensive review of the literature as well as on clinical experience, and

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it should be clinically relevant, feasible, innovative, ethical and of scientific research value.[1]

2.2. Well defined objective

The objective should be well defined in a structured way, and include reference to the subjects with the disease or condition, the intervention, reference treatment(s) if appropriate, and outcome. Secondly, it should be clarified if the study is exploratory or confirmatory.

2.3. Design

The research design is determined by the research question(s)[2]:

Questions relating to the efficacy of a TCM therapy in treating a particular condition can adopt an design such as placebo controlled, randomized clinical trial (RCT).

Questions relating to the effectiveness of TCM therapy in clinical practice can adopt a pragmatic design such as comparative effectiveness research.

Questions relating to the efficacy of TCM (including individual treatment) will require observational studies and/or a small sample exploratory pilot trial (feasibility study) before the conduct of larger confirmatory trials.

2.4. Population

The selection of subjects should be based on research purpose. In clinical trials, we should determine uniform diagnostic criteria (including western medicine disease and TCM syndromes), develop inclusion and exclusion criteria for the subjects. Well defined inclusion and exclusion criteria can help to recruit eligible participants and to avoid confounding bias.[3]

2.5. Sample

In clinical trials, a minimum sample size is required to test the hypothesis by a predefined statistical power. For exploratory studies in early stages of clinical research, sample size calculation may not be required. The sample size is calculated mainly based on the primary outcomes (depending on efficacy and/or safety endpoint), and other factors such as design, comparisons, testing hypotheses, type I and type II error parameters, should be considered as well.[4]

2.6. Intervention

In protocol of clinical trials, the definition of tested intervention should include name and definition of the tested intervention, dosage, administration, course of treatment, and any co-intervention. The dosage of TCM therapy is generally determined based on past experience of clinical use and preclinical research. Treatment course should be determined considering the development of the disease and the characteristics of the intervention. Co-interventions (if any) should be predefined; otherwise it will affect the efficacy and safety evaluation.[3,5]

2.7. Comparator/reference treatment

The reference treatment should be selected in accordance with the study objective. In a comparative effectiveness study, we usually choose therapies that are commonly used in clinical practice as control to determine comparative effect for the subjects. In equivalence trials, standard western medicine therapy or medication could be used as control. In a dose–response study, different doses are compared. When investigating the specific effects of TCM therapy, a placebo should be used if the ethical approval for this is aquired.[3,5]

2.8. Outcome measure

Outcome assessment includes the effect and safety, and sometimes cost- effectiveness. The effectiveness evaluation of TCM involves the specific outcomes related to disease and change of TCM syndromes. Depending on the study objectives, primary outcomes can be clinical endpoints, patient- related outcomes, and the secondary outcomes can be quality of life, or other surrogate outcomes such as biomarkers for disease. For evaluation of TCM syndromes, clinical symptoms scales or instruments with validated reliability and validity are preferred. Safety should be evaluated considering the target indications of the intervention, characteristics of the target population, treatment duration, administration, known target organ toxicity, TCM theories (herb matching) and previous experience of clinical use. For rare adverse events, long-term exposure data and sufficient numbers of participants are needed.[6]

2.9. Follow-up

TCM is commonly used in chronic diseases; hence a sufficient follow-up time should be ensured for evaluating the outcomes of TCM. The follow-up length and intervals depend on the purposes of the trials and on the characteristics of different TCM interventions.

3. Randomized clinical trials for TCM and integrative medicine

3.1. Introduction

RCTs are commonly used to evaluate the effect of medical interventions, health education or management.[7] Since known or unknown confounding factors are controlled in RCT design, a cause-effect association can be established by comparing the outcomes between groups post-treatment. Consequently, the RCT is accepted as a 'gold standard' for evaluating therapeutic effects of specific drugs or procedures.[8]

However, limitations exist when conducting classical placebo-controlled RCTs for TCM therapies. Therapeutic effects can be influenced by factors other than the efficacy of the interventions themselves; such factors may include patient preference, practitioner preference, and the patient-practitioner relationship among others. Also, the absence of an ideal placebo control for most TCM treatments limits the application of the classical RCT model. Thus, some modified research models of RCT such as N of 1 trial, pragmatic trials, add-on design, expertise-based trials were introduced for assessing therapeutic effect of TCM therapies (including herbal medicine, acupuncture, moxibustion, cupping therapy, etc.).

3.2. Types of RCTs

3.2.1. Explanatory RCT

Explanatory RCTs test the efficacy in a research setting with highly selected participants and under highly controlled conditions.[9] This design maximizes the balancing of any confounders, both observed and unobserved, with a view to evaluating the efficacy of the intervention compared to placebo or active drug. Explanatory RCTs are designed to test causal hypotheses, and evaluate the efficacy of the intervention which is strictly enforced in "ideal" setting. Standardized herbal extracts can be tested in this type of design. However, when interventions are complex or flexible, explanatory RCT may result in lower external validity therefore limiting its application.

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