Chapter 2
Methodology for Clinical Study
Investigating Chinese Medicine

Hui-juan Cao and Jian-ping Liu

Abstract Background A new clinical trial guideline for Chinese Medicine (CM) was published in 2015, which incorporates the characteristics of traditional approaches of practice with the practical recommendations of rigorous research methodology. Objectives This chapter aimed to introduce the research methodology for CM practice and the key considerations that need to address in relation to the characteristics of CM as a whole system. Details This chapter includes the introduction of basic study design, key issues on planning, implementing, and analyzing and reporting a clinical study of CM. The principles of clinical study design, basic research methods for interventional studies (e.g., randomized controlled trial), observational studies (e.g. cohort study, case-control study, case series study and case report), and systematic reviews were introduced in the first section. For each type of study, research model, scope of application, merit and weakness were addressed in accordance with the characteristics of CM. In the second section, we introduce details of methods of planning (research question, study protocol, sample size, study settings, participants, comparisons, and outcome measures), implementing (allocation sequence generation, blinding method, ethical approval, bias control, data management and monitoring), and analyzing (statistical methods, analysis and interpretation of results) a CM clinical study. Adequate examples from previous publications are shown to give clues and deepen understanding on each issue. Conclusions It is our hope that this chapter will encourage a thoughtful and meticulous process of investigation to provide reliable evidence for CM therapies for better health care.

Keywords Study methodology · Chinese medicine

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2.1 Introduction to Basic Study Design

2.1.1 Principles of Clinical Study Design

2.1.1.1 Control

Regarding the natural course of disease, spontaneous fluctuations and regression to mean phenomenon, the results of a study are hard to interpret without a strict control. “Control” means that a sample of participants with consistent diagnosis and baseline characteristics are divided into several groups receiving different kinds of treatment, to demonstrate the differences in the results between the experimental and control groups. The group of patients who receive nonexperimental treatment is usually called control group. The overall finding is that a study without an appropriate control is more likely to report positive results of the treatment. With a control group(s), we could compare the outcomes of the experimental and control groups and find the difference between them to determine the treatment effect.

Commonly used “control group” include blank control (no treatment for this group), placebo (ineffectual treatment) control, standard (effective treatment with evidence) control, mutual control (a comparison of two different doses or different routes of administration for treatment), self control (participants may accept two therapies one after another), paired control (subjects of the experimental group are matched with the control group according to the non-test factors), and historical control (to compare the current patients with previous patients who had received standard treatment) [1]. For different purpose of research, we may choose different type of comparisons (Table 2.1). Among them, placebo control is unlikely to be successful in trial assessing traditional Chinese medicine (TCM) due to the absence of ideal placebo for most of the Chinese medicine therapies, especially the non-pharmaceutical treatment such as acupuncture, cupping therapy, etc. We may further discuss this in the sections below.

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<th>Type of effect assessed</th>
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<td>Specific effect (efficacy)</td>
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2.1.1.2 Equalization

Equalization aims to make sure the comparability of characteristics of participants between groups, and besides matching and stratifying, the most popular method to fulfill equalization is randomization. Randomization, whenever during sampling from general population or allocating samples into different groups, is a method to ensure each individual of the sample/population has equal opportunity to be selected/divided to the treatment or control group. The purposes of randomization are (a) to avoid selection bias caused by choosing patients with preference; and (b) to meet the basic requirements of statistical analysis such as significance tests.

Although historically “manual” randomization techniques (such as throwing dice, flipping coin, and drawing straws) were used, statistical software (such as SPSS and SAS) are now commonly used to generate the random numbers [2].

2.1.1.3 Replication

Replication may test the internal and external validity of the study. There are two implications: one is to reproduce the study results under the same test condition; the other is to observe appropriate sample size of participants within the study. The reproducibility of the results indicates that it is not caused by chance. And the stable result seems more reliable.

On the other hand, in clinical trials it is crucial to be able to differentiate a chance from a true effect. Statistical methods should be used to determine the sample size of the study.

2.1.1.4 Blinding

In any clinical study, if neither the patient himself, practitioner nor outcome assessor is aware of which treatment the patient is receiving, it is called a blinding study. Physicians may pay more attention to the patients in placebo group and enhancing the placebo effect; participants may seek to other treatments when they were allocated to control group; outcome assessors may check the data of treatment group carefully to detect bias. The purpose of “blinding” is to avoid the performance bias, detection bias, or reporting bias due to subjective factors.

Blinding would be feasible if the following aspects are met: (a) ethics, the double-blind procedure as well as the application of placebo control should not result in any harm or undue risk to a patient; (b) practicality, as we mentioned before, for some non-pharmaceutical Chinese medicine treatment (such as acupuncture, cupping therapy, moxibustion, qigong, etc) it would be infeasible to arrange a double-blind trial due to the lack of ideal placebo control as well as
patient previous experience of the treatment; (c) avoidance of bias, researchers need to assess just how serious the bias might be without blinding; and (d) compromise, in some cases only partial blinding (e.g., independent blinded evaluators) would be sufficient to minimize the potential bias [3].

2.1.1.5 Ethics

For every clinical study, ethics issue should be concerned throughout the design and conduct period according to the Declaration of Helsinki issued by the World Medical Association in 1964 and revised in 2013. Depending on the content of the study, getting approval from the ethics committee (or IRB, institutional review board) can be challenging and time consuming. The following documents should be prepared at the beginning of the study to get approval from ethics committee.

1. Study protocol
2. Written informed consent form
3. Patient information leaflet
4. Case report form (CRF) during the study
5. Patient recruitment procedures, including advertisements
6. Safety information for intervention treatment, including drugs or nondrug treatment
7. Investigators’ current curriculum vitae and/or other documentation providing evidence of qualifications and competence.

2.1.2 Basic Research Methods for Observational Studies

Descriptive studies and analytic studies are the two types of observational studies. Descriptive studies describe distribution characteristics of disease in relation to variables such as person, place, and time. The data provided by descriptive studies are essential for public health administrators as well as epidemiologists. The ultimate goal of an analytic study is to determine a particular exposure causes or developing preventive procedures for the specific disease. Common descriptive studies are case reports, case series studies, and cross-sectional studies; and frequently used analytic studies are case-control studies and cohort studies.

2.1.2.1 Case Reports/Case Series Studies

A single case study is an observational study of an individual patient who exposes to certain interventions which produced meaningful results. A case report usually
concerns about clinical diagnosis, demographic characteristics, details of treatment, prognosis, and follow-up of the case. The purpose of the study is to explore the potential relationship between specific intervention and outcomes through the individual’s detailed medical information or records. However, due to the large variation of an individual person, the results of a case report may only provide weak evidence of clinical experience for the clinicians. Usually, case reports can represent and document the first clues in the identification of a new disease or the adverse effects of exposures in unusual medical occurrences. Key points on designing a single case study include (a) developing the protocol according to research purpose; (b) calculating a sample size; (c) identifying appropriate patient through strict diagnostic, inclusion and exclusion criteria; (d) collecting data precisely and completely; and (e) evaluating the outcomes objectively and independently by all the researchers.

The results of a case series are collected from a number of individual cases, which may occur within a fairly short period of time. The collection of a case series can mean the difference between formulating a useful hypothesis and merely documenting an interesting medical oddity (Table 2.2).

Table 2.2 Results of uncontrolled observational studies

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<th>Exposure/intervention</th>
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Merits of case reports and case series studies:

1. This design can be used for the studies in which control is unavailable due to ethics issue;
2. This kind of studies can be used to observe the patients who do not meet the inclusion criteria of clinical controlled trials, and provide the potential evidence for those patients;
3. This kind of studies can be used to observe a special disease (tumor, AIDS, atypical pneumonia, etc.), rare or chronic disease, complications and adverse reactions; and
4. This kind of studies cost less and is easy to carry out.

Demerits of case reports and case series studies:

1. While case reports and case series are very good for generating hypotheses, they are not applicable to verifying hypotheses;
2. Their external validity is not determined; and
3. These two types of studies are usually considered to have many potential confounding factors, and more likely to overestimate the effect under observation.
Example 2.1 [4]

Introduction: To evaluate the therapeutic effect of traditional medicinal cupping for treatment of fibromyalgia.

Methods: A prospective case series was conducted in 30 consecutive patients with fibromyalgia at an outpatient department in a hospital in Beijing. Patients were diagnosed according to the criteria of 1990 by American College of Rheumatology. The bamboo cup, boiled in herbal decoction for 5 min, was applied to Ashi (tender) points for 10 min once daily for 15 sessions. Visual analog scale (VAS, 0–10 cm) for pain and the number of tender points were recorded at the baseline, 5, 10, 15 days, and followed up at 2 weeks after the treatment.

Results: The average score of VAS in 30 patients was 2.63 sessions. Visual analog scale (VAS, 0–10 cm) for pain and the number of tender points were recorded at the baseline, 5, 10, 15 days, and followed up at 2 weeks after the treatment. The bamboo cup, tender points was reduced from 12.57 ± 2.25 at 5 days, 11.2 ± 2.50 at 10 days, to 9.33 ± 2.89 at 15 days. Compared with baseline, VAS score was reduced 52.27 %, and the number of tender points was reduced 30.86 %. 29 patients were followed up to 2 weeks and the VAS and tender points sustained (1.24 ± 0.67 for VAS; 9.07 ± 2.96 for pain points). There was no serious adverse effect occurred during the treatment.

Conclusions: Medicinal cupping therapy appears to relieve pain in patients with fibromyalgia in terms of VAS and number of tender points, and the promising effect deserves to be tested in clinical trials.

2.1.2.2 Cross-Sectional Studies

Cross-sectional studies, also called surveys, usually provide information about the frequency and characteristics of a disease by furnishing a snapshot of the health experience of the population at a specified time. Within a survey, potential exposure and disease/health status are assessed simultaneously among individuals in a well-defined population. The results from cross-sectional studies can help public health administrators to assess the health status and healthcare needs of a population. On the other hand, cross-sectional studies can also be used to provide information on the prevalence of disease or other health outcomes in certain occupations.

There are two key points of cross-sectional study: (a) Exposure and disease status are assessed at a single point in time, it is impossible to determine whether the exposure is the cause of the disease or an outcome of the development of the disease; and (b) Since prevalence rather than incidence must be considered in
cross-sectional study, the data obtained will always reflect determinants of survival as well as etiology.

Merits of cross-sectional studies:

1. A cross-sectional study is population-based study, which may have strong external validity;
2. The concurrent control is formed naturally during the survey, therefore, the comparability between groups is stronger;
3. A variety of factors can be observed at the same time.

Demerits of cross-sectional studies:

4. Disease and factors exist at the same time, it is difficult to refer the causal relationship;
5. Incidence rate cannot be calculated in cross-sectional study;
6. Latent period and remission patients are easy to be misdiagnosed; and
7. It is generally applicable to the study of chronic disease.

Only in one case, a cross-sectional study can be considered as a special type of analytic study and used to test hypotheses. This can occur only when the current values of the exposure variables are unmodifiable over time, thus representing the value present at the beginning of the disease. However, in most cross-sectional study, the exposures may be subject to alteration subsequent (or even consequent) to the development of disease. Under these circumstances, the data can be used to describe characteristics of individuals with the disease and to formulate hypotheses, but not to validate them.

Example 2.2 [5]

Background: The prevalence of chronic kidney disease is high in developing countries. However, no national survey of chronic kidney disease has been done incorporating both estimated glomerular filtration rate (eGFR) and albuminuria in a developing country with the economic diversity of China. We aimed to measure the prevalence of chronic kidney disease in China with such a survey.

Methods: We did a cross-sectional survey of a nationally representative sample of Chinese adults. Chronic kidney disease was defined as eGFR less than 60 mL/min per 1.73 m² or the presence of albuminuria. Participants completed a lifestyle and medical history questionnaire and had their blood pressure measured, and blood and urine samples taken. Serum creatinine was measured and used to estimate glomerular filtration rate. Urinary albumin and creatinine were tested to assess albuminuria. The crude and adjusted prevalence of indicators of kidney damage were calculated and factors associated with the presence of chronic kidney disease analyzed by logistic regression.
Findings: 50,550 people were invited to participate, of whom 47,204 agreed. The adjusted prevalence of eGFR less than 60 mL/min per 1.73 m² was 1.7% (95% CI 1.5–1.9) and of albuminuria was 9.4% (8.9–10.0). The overall prevalence of chronic kidney disease was 10.8% (10.2–11.3); therefore the number of patients with chronic kidney disease in China is estimated to be about 119.5 million (112.9–125.0 million). In rural areas, economic development was independently associated with the presence of albuminuria. The prevalence of chronic kidney disease was high in north (16.9% [15.1–18.7]) and southwest (18.3% [16.4–20.4]) regions compared with other regions. Other factors independently associated with kidney damage were age, sex, hypertension, diabetes, history of cardiovascular disease, hyperuricaemia, area of residence, and economic status.

Interpretation: Chronic kidney disease has become an important public health problem in China. Special attention should be paid to residents in economically improving rural areas and specific geographical regions in China.

2.1.2.3 Case-Control Studies

A case-control study is a retrospective study, in which subjects are selected on the basis of whether they do (cases) or do not (controls) have a particular disease/outcome under study. Its basic principle is to compare the proportion having a history of an exposure or characteristic of interest between the cases and controls to evaluate the association between the exposure and a disease/outcome. This type of study design is more commonly used in the early exploration of the relationship between disease and its possible etiological factors.

For a case-control study to verify the association between an exposure and disease, comparability of cases and controls is essential (Table 2.3). The aspects of comparability that must be considered include factors such as their baseline risk of developing the disease other than from the exposure under study, as well as the accuracy and completeness of data. Consequently, the major issues to be considered in designing and conducting a case-control study are the selection of the study groups and the sources of information about exposure and disease.

Table 2.3 Results of case-control studies

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Example 2.3 [6]
Ethnopharmacological relevance: Our previous study indicated that the TCM formula Liu-Wei-Di-Huang-Wan, which consists of six types of herbs, namely Rehmannia glutinosa (Gaertn.) DC., root, dried; Cornus officinalis Siebold & Zucc., fructus, dried; Dioscorea oppositifolia L., root, dried; Alisma plantago-aquatica subsp. orientale (Sam.) Sam., tuber, dried; Paeonia × suffruticosa Andrews, bark, dried; Poria cocos (Fr.) Wolf., sclerotium, dried, is the most frequently prescribed herbal formula used to treat type 2 diabetes patients. The aim of the study was to evaluate the integration of TCM into diabetes care in terms of how it reduces the risk of developing kidney failure.

Materials and methods: The Taiwan’s National Health Insurance Research Database (NHIRD) provided detailed information of healthcare services for each patient and covers 98% of all Taiwan residents as of 2007. Case and control subjects were selected from the NHIRD. Two multivariable logistic regression models were constructed in order to explore two types of exposure assessments including prescription of TCMs (model 1) and prescription of different estimated dosages of Liu-Wei-Di-Huang-Wan (model 2).

Results: Using logistic regression model 1, having used TCMs was independently associated with a decreased risk of kidney failure by multivariable analysis (OR = 0.69, 95% CI 0.61–0.77). Using logistic regression model 2, there was no difference between non-Liu-Wei-Di-Huang-Wan TCM users and Liu-Wei-Di-Huang-Wan TCM users in terms of the risk of developing kidney failure. Furthermore, there was also no linear dose-response trend when we used exposure to prescribed Liu-Wei-Di-Huang-Wan as a continuous variable (for non-Liu-Wei-Di-Huang-Wan TCM users, OR = 0.68, 95% CI 0.60–0.77; for TCM users consuming 1–30 g of Liu-Wei-Di-Huang-Wan, OR = 0.69, 95% CI 0.54–0.87; for >30 g of Liu-Wei-Di-Huang-Wan, OR = 0.84, 95% CI 0.49–1.44).

Conclusions: Integrating TCM health care into diabetes care was found to be associated with a decreased risk of developing kidney failure. Having recognized the use of TCM, exploring any potential interactions and adverse effects, and integrating both technologies into a holistic treatment system may be beneficial to the relief of diabetic nephropathy on patients with type 2 diabetes.

Merits of case-control studies:
1. As a retrospective study, outcome measurement of this kind of studies is easy to meet the ethical requirements;
2. With a small sample size, it is commonly used for etiology research of rare disease and the special long latency disease;
3. By asking the history of the exposure, most of the research are short-term study which saves manpower and material resources and easy to draw conclusions; and
4. Case-control study is able to explore a variety of potential etiologic exposures that might relate to the specific disease as well as the internal connections among these factors.

Demerits of case-control studies:

1. It is insufficient for the evaluation of rare exposures, unless the attributable risk is high, and in some situations, it is difficult to establish the temporal relationship between exposure and disease;
2. Selection bias can occur whenever the inclusion of cases or controls into the study depends in some way on the exposure of interest, which is a problem in case-control study;
3. Recall bias, which related to differences in the ways exposure information is recalled or reported by cases and what truly happened, exist in every case-control study and should be considered carefully in the design as well as in the interpretation of published results;
4. Observation bias, or information bias in gathering information from participants, may also be a particular problem in a case-control design; and
5. Cannot directly compute morbidity rate of disease in both groups, unless the study is population based.

### 2.1.2.4 Cohort Studies

In a cohort study, the observed individuals are grouped by whether or not they are exposed to a certain kind of suspected risk factor for a disease. Cohort studies have great advantages for evaluating the association between risk factors and disease. (a) participants exposure are determined when the disease has not yet occurred, thus, the time sequence of the exposure and disease can be more clearly established; (b) this type of study is more suitable for assessing effects of rare exposures, especially those arise in occupational settings; and (c) cohort studies allow for the test of multiple effects of a single exposure.

Cohort studies are generally classified into prospective or retrospective cohort studies or two-way cohort studies. In retrospective cohort studies, both exposures and outcomes of interest have already occurred when the study is initiated. In prospective studies, the diseases have certainly not yet occurred, regardless whether or not the relevant exposures have occurred at the time when the study begun. Consequently, participants must be followed into the future to assess incidence rates of disease after the selection of the cohort (Table 2.4). Ambidirectional cohort study

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is mixed of the prospective and retrospective studies, which is usually most useful for exposures having both short-term and long-term effects.

Merits of cohort studies:

1. Cohort studies can test multiple effects of a single exposure;
2. For etiology study, the incidence or mortality of the exposed group and control group can be obtained directly, and the cause of the disease can be directly analyzed; and
3. The prospective cohort study which minimizes bias in the ascertainment of exposure, can interpret temporal relationship between exposure and disease.

Demerits of cohort studies:

1. Cohort studies are insufficient for the evaluation of rare diseases, unless the attributable risk is high;
2. Prospective cohort study can be extremely costly, while retrospective cohort study requires the sufficient records; and
3. Validity of the results can be seriously affected by missing data.

Example 2.4 [7]

Background: Chinese medicine is commonly used and covered by health insurance to treat symptoms of uterine fibroids in Taiwan. This retrospective cohort study compared the consumption of conventional western medicine and medical cost between CM users and nonusers among patients with uterine fibroids.

Methods: We extracted 44,122 patients diagnosed with uterine fibrosis between 1996 and 2010 from the National Health Insurance reimbursement database, which is a population-based database released by a government-run health insurance system. Multivariate linear regression models were used to find association between using CM and the consumption of conventional medicine, and between using CM and medical cost.

Results: The total fibroid-related conventional western medicine consumed by CM users was less than that by nonusers ($\beta = -10.49$, $p < 0.0001$). Three categories of conventional medicines, including antianemics ($-3.50$ days/year/patient, $p < 0.0001$), hemostatics ($-1.89$ days/year/patient, $p < 0.0001$), and hormone-related agents ($-3.13$ days/year/patient, $p < 0.0001$), were used less in patients who were CM users. Moreover, although using CM increased 16.9 USD per patient in CM users annually ($p < 0.0001$), the total annual medical cost for treating fibroid was 5610 USD less in CM users than in nonusers ($p < 0.0001$).

Conclusions: Our results suggested that CM reduced the consumption of conventional medicine, and might be a potential therapeutic substitute for conventional western medicines to treat uterine fibroids with low cost.
Intervention studies, or clinical trials, are generally considered either therapeutic or preventive. The therapeutic trials are conducted on the patients with a particular disease to determine the ability of a therapy to eliminate symptoms, prevent recurrence, or reduce mortality from that disease. The preventive trials are to assess whether a procedure avoids the occurrence of disease among those free from that condition at enrollment.

### 2.1.3.1 Randomized Controlled Trials

Randomized controlled trials (RCT) are commonly used to evaluate the effects of medical interventions, health education or management. Since random allocation is the basis of designing RCT, which means the eligible participants would be randomly allocated to the experimental group or control group, cause–effect relationship could be evaluated according to the results from RCT due to the comparability between baseline characteristics of two groups and well-controlled confounding factors during the treatment. Consequently, RCT is generally accepted as the golden standard study model for assessing therapeutic effects of specific drugs/procedures.

In a randomized controlled trial, participants, regardless of random sampling or not, must be identified through accepted diagnostic criteria and met the inclusion and exclusion criteria of the study. They would then be randomly assigned to the experimental or control group to receive corresponding treatments. Outcomes are measured before, during, and after the treatment. According to the types of data, appropriate statistical methods would be used to analyze the reliably observed effect of the intervention and the differences between groups (Table 2.5).

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**Example 2.5 [8]**

Background: Perennial allergic rhinitis (PAR) has a high and increasing prevalence worldwide. Ear acupressure (EAP) is a noninvasive semi-self-administered form of acupuncture. Previous studies indicated that EAP could be effective and safe for AR symptom management. However, there was insufficient evidence to confirm this. This study investigated whether EAP, a noninvasive clinical alternative to acupuncture, is effective and safe for PAR.
Methods: This is an international, multicenter, randomized, single-blind, sham-controlled trial. The trial was conducted at two centers: Royal Melbourne Institute of Technology University (Melbourne, Australia) Clinical Trial Clinic and Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China. PAR participants were randomized to receive real or sham EAP treatment once a week for 8 weeks and then were followed up for 12 weeks. Participants were instructed to administer EAP stimulation three times daily. Symptom severity and quality of life (QoL) were evaluated. Adverse events (AEs) were also monitored. Intention-to-treat analysis on change of symptom scores and QoL was applied.

Results: Two hundred forty-five participants were randomly assigned to real ($n = 124$) and sham EAP ($n = 121$) groups. Twenty-five participants discontinued during treatment and 15 participants dropped out during follow-up. At the end of treatment and follow-up periods, changes of global QoL score were significantly greater in the real EAP group compared with the sham group. At the end of follow-up, scores for total nasal symptom, runny nose, and eye symptoms in the real EAP group had a greater reduction compared with the sham group. Overall, both real and sham EAP were well tolerated. Two severe AEs were reported but were not considered related to the EAP procedures.

Conclusions: In conclusion, EAP showed short-term and extended benefit for improving PAR symptoms and QoL for PAR patients.

Merits of randomized controlled trials:
1. If the treatments are allocated at random in a representative sample of sufficiently large size, RCT has the potential to provide a degree of assurance about the validity of a result that is simply not possible with any observational study; and
2. Results of RCT can provide the strongest and most direct epidemiologic evidence that the basis of whether an observed association is a causal judgment.

Demerits of randomized controlled trials:
1. RCT cost more than most observational studies;
2. Ethical considerations hold back the assessment of many treatments or procedures in RCT; and
3. There is a more strict inclusion criterion for those who participate in RCT compare to other observational studies or pragmatic studies, the external validity is therefore comparatively limited.

According to the purpose of the study, there are several types of randomized controlled trials including explanatory RCT (which tests efficacy in a research setting with highly selected participants and under highly controlled conditions), pragmatic RCT (which design is closer to the “real world” clinical circumstances and conditions), crossover trial (a type of longitudinal study in which subjects
receive a sequence of different interventions), N-of-1 trial (which is considered as a crossover randomized controlled trial with only one subject), dose-response study (which is a valid research design to determine the best dose of the intervention product), factorial design (which allows researchers to assess more than one intervention in a single trial), etc. Among those different types of RCTs, explanatory RCT is commonly used to evaluate the efficacy of the intervention (drugs), ideally there should be reasonable placebo control for the intervention. Pragmatic RCT is more often to focus on the comparison of the effectiveness between different interventions, thus it can be classified into the category of comparative effectiveness research (see Sect. 2.1.4).

2.1.3.2 Nonrandomized Controlled Trials

A well-designed nonrandomized comparative study may have higher external validity compared to randomized trial, and the recruitment of that kind of study is much easier than for randomized trial due to patients’ strong preference. What we need to concern when designing nonrandomized trial are taking baseline differences into account, and adjusting analyses for imbalances.

Example 2.6 [9]
Background: One of five children visiting a homoeopathic physician is suffering from atopic eczema.

Objective: To examine the effectiveness, safety, and costs of homoeopathic versus conventional treatment in usual care.

Methods: In a prospective multicentre comparative observational nonrandomized study, 135 children (homoeopathy n = 48 vs. conventional n = 87) with mild to moderate atopic eczema were included. The primary outcome was the SCORAD (Scoring Atopic Dermatitis) at 6 months. Further outcomes at 6 and 12 months also included quality of life of parents and children, use of conventional medicine, treatment safety and disease-related costs.

Results: The adjusted SCORAD showed no significant differences between the groups at both 6 months (homoeopathy 22.49 ± 3.02 [mean ± SE] vs. conventional 18.20 ± 2.31, p = 0.290) and 12 months (17.41 ± 3.01 vs. 17.29 ± 2.31, p = 0.974). Adjusted costs were higher in the homoeopathic than in the conventional group: for the first 6 months EUR 935.02 versus EUR 514.44, p = 0.026, and for 12 months EUR 1524.23 versus EUR 721.21, p = 0.001. Quality of life was not significantly different between both groups.

Conclusions: Taking patient preferences into account, homoeopathic treatment was not superior to conventional treatment for children with mild to moderate atopic eczema.
In some cases, randomization may not be appropriate even if the control group is available. First, the patients who visit TCM or integrative medicine hospital seeking to Chinese medicine therapies usually prefer to Chinese medicine treatments. This may increase the difficulty of recruiting appropriate patients for a randomized controlled trial. Also, randomization is not necessary to find out whether treatment effects are very different if the study is well done in other respects. Moreover, randomization is also not appropriate for the comparison of anthroposophical and conventional care if we are primarily interested in the differences regarding preferences, experiences, processes, and compliance.

2.1.4 Basic Research Methods for Comparative Effectiveness Research

Efficacy is the specific effects which are due to the active ingredient of the treatment, while effectiveness is both of the specific and nonspecific effects, latter are those due to psychological or psycho-physiological effects associated with the act of treatment (such as placebo effect). Placebo control and appropriate blinding methods are needed to investigate the efficacy of the components; otherwise, the specific effect could not be validated. However, challenges exist when conducting RCTs for traditional nondrug therapies (e.g. acupuncture, cupping therapy, and moxibustion). Therapeutic effects can be influenced by patient preference, practitioner preference, and patient–practitioner relationship, among others, rather than the efficacy of the interventions themselves. Thus, placebo control could be extremely difficult for nondrug therapies, specific study design such as comparative effectiveness research (CER) could be used to investigate the effectiveness of such therapies [10].

CER, which is defined as “conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat, and monitor health conditions,” is aimed to assist patients, practitioners, purchasers, and policy makers to make informed decisions which may improve health care at both the individual and population levels. Design models of CER could be like majority of the observational studies, some of the experimental studies (especially pragmatic randomized controlled trials) and research synthesis (such as systematic review, see Sect. 2.1.5). Observational studies are more likely to be chosen to evaluate the effectiveness of the interventions since their implementation conditions are closer to the environment of the real world.

On the other hand, the primary and secondary outcomes of the CER are more concerned with the patient-centered outcomes, which are selected as the core of the patients’ interests [11]. Consequently, CER is also called ‘patient-centered outcome research’.
2.1.5 Basic Research Methods for Systematic Review and Meta-analysis

Different from the above original studies, systematic review is a kind of secondary study. Systematic review, defined as a kind of study which acquire, appraise, and synthesis evidence from scientific studies in order to provide informative, empirical answers to the research questions, is considered the ‘gold standard’ for assessing the effectiveness of a treatment or intervention. In another word, systematic review brings together all available research evidence with critical appraisal of the quality of the studies. This information can then be combined with your clinical judgment to make decisions about how to deliver the best care to your patients.

Meta-analysis [12], which also called quantitative systematic review, looks at data from multiple studies of the same clinical question and uses a variety of statistical techniques to integrate their findings. A systematic review may or may not have meta-analysis within it, if a systematic review did not conduct meta-analysis due to the potential heterogeneity among included studies, it would be called qualitative or descriptive systematic review.

The Cochrane collaboration is an independent, nonprofit, nongovernmental organization consisting of a group of more than 31,000 volunteers in more than 120 countries, which conducts systematic reviews of mainly randomized controlled trials of healthcare interventions and published them in the Cochrane Library. The Cochrane Handbook [13] outlines eight general steps for preparing a systematic review:

1. Defining the question and formulating the inclusion and exclusion criteria;
2. Literature searching;
3. Screening and selecting studies, then extracting data;
4. Assessing methodological qualities of included studies;
5. Analyzing and pooling the data;
6. Addressing reporting biases;
7. Presenting results and “summary of findings” tables; and
8. Interpreting results and drawing conclusions.

Merits of systematic review:

1. Systematic review could identify the heterogeneity among studies and merge those trials with acceptable homogeneity;
2. Minimize or eliminate the bias of included studies and achieve the currently ‘best evidence’;
3. Weakness of systematic review;
4. Grade of evidence of systematic review is depending on the quality of original studies included; and
5. Misuse of systematic review or meta-analysis may overestimate the effect of interventions or controls.
Example 2.7 [14]

Objective: Cupping as a traditional therapy is used to treat a myriad of health conditions, including pain. This systematic review assessed the effectiveness and safety of cupping for different types of pain.

Methods: Thirteen databases and four trial registries were searched for randomized clinical trials. Meta-analysis of data was conducted if there was nonsignificant clinical and statistical heterogeneity (measured by \( I^2 \) test) among trials.

Results: Sixteen trials with 921 participants were eligible and included. Six trials were assessed as low risk of bias, another six trials were of unclear risk of bias, and the remaining four trials were of high risk of bias. Pain was related to three acute and seven chronic diseases. Meta-analysis showed a beneficial effect of cupping compared to wait-list control (visual analogue scale (VAS), MD 1.85 cm, 95 % CI 2.66–1.04) and heat therapy (numerical rating scale, MD 2.05 cm, 95 % CI 2.93–1.17). Cupping combined with acupuncture was superior to acupuncture alone on posttreatment pain intensity (VAS, MD 1.18 cm, 95 % CI 1.68–0.68), however, no difference was found between this comparison based on changes in pain intensity (difference of VAS, MD 0.16 cm, 95 % CI 0.54–0.87). Results from other single studies showed significant benefit of cupping compared with conventional drugs or usual care. Hematoma and pain at the treated site, increasing local pain or tingling were reported as mild adverse effects of cupping.

Conclusion: This review suggests a potential positive short-term effect of cupping therapy on reducing pain intensity compared with no treatment, heat therapy, usual care, or conventional drugs.

Currently, hundreds of the CM systematic reviews are published annually. However, findings from 70 Cochrane reviews [15] related to herbal medicine and acupuncture showed insufficient evidence to support or to refute the intervention due to either poor methodology quality or small sample size of the included trials. It is important to direct future research by two ways based on the Cochrane review conclusions, one is to address how to shape the research questions in relation to traditional CM (see Sect. 2.2.1.1), and the other is how to design clinical trials to raise the quality.

2.2 Key Issues in Planning, Implementing, Analyzing, and Reporting a Clinical Study

2.2.1 Planning

2.2.1.1 Defining a Research Question

Raising a research question is the first and important part of whole research program. A clear research question is the precondition for deciding which choice of
design makes sense, which patients should be included, which interventions and controls should be discussed and which outcomes should be measured. That is the reason why posing the research question appropriately is absolutely fundamental.

After translating clinical problems into questions (no matter background question or foreground question), these questions should be further structured as PICO (S):

1. P: patients, or what kind of population would be concerned in the research;
2. I: intervention, or exposure you interest;
3. C: comparison;
4. O: outcomes that would be primary or secondary measured and reported in the research; and
5. S: study type, which would be determined according to the study purpose.

Once the research question is formulated, you should search online (at least through PubMed, http://www.ncbi.nlm.nih.gov/pubmed or CNKI, cnki.net) to find out whether the similar studies have already been conducted or ongoing. You may further revise or redefine your research question according to the current evidence. During this process, the specific research objectives would be confirmed.

2.2.1.2 Drafting the Study Protocol

Study protocol is a document that describes the objectives, type of research model, methodology, statistical methods, and procedures of a clinical study. Developing the study protocol is a process that goes hand in hand with planning the study. The protocol describes the whole study in detail before the study started.

One should probably draft the study protocol cover the following items:

1. Study objectives and background

In this section, researchers should state the rational of the study clearly, including the importance of subject area, review of relevant literature, study justification, relevant research questions and how will the research results be used.

2. Research team

Principle investigator (PI) is the person responsible for the implementation and quality control of clinical trial, who must be qualified to ensure the quality of clinical trial. Research team would be constituted by persons whose expertise in methodology, statistics, clinical study and the relevant majors.

3. Overview of research design

To clarify what kind of study model it may employ, and describe the details of the study design. For observational studies, methods of selecting participants, defining exposure, measuring outcomes, and analyzing data should be fully addressed. And
for intervention studies, methods of randomization and blinding are quite important in the protocol.

4. The inclusion criteria, exclusion criteria of the participants

Researchers should describe the characteristics of participants and disease clearly, study setting, as well as the procedures of recruitment, advertising plan, and recruitment materials.

If the aim of the study is to determine a specific effect of intervention, using adequate placebo control is required, and to ensure blinding and to minimize bias the placebo should be indistinguishable from the study intervention. As mentioned before, there was no ideal placebo control for most of the TCM therapies. In fact, placebos could be easily used in drug trial, if placebo and drugs have indistinguishable in appearance, smell, and taste. Therefore, for herbal medicine, capsules could be an option. For nondrug Chinese medicine therapies, sham acupuncture is the contention. Neither standard needles inserted at inappropriate sites nor non-penetrating needles were impure placebo. And for cupping therapy, massage, tai chi, or other type of meditation therapy, placebo control seems difficult to simulate. For assessing those kinds of interventions, comparative effectiveness research could be considered.

5. Sample size estimation

Total number and number in each group, including all assumptions as recalculation might be necessary. To determine the size of a study, researchers should consider the main purpose of the study, type of primary outcome measures, methods of statistics, and potential difference of effect between groups.

6. Details of the intervention and control

Details of intervention and control should be thorough enough to make sure that other researchers could repeat the study step by step according to your protocol.

7. Clinical observation and outcome measures

All patients should be regularly followed up, and examined at a certain interval of time. Time of each observation and inspection should be clearly reported in the protocol, and if available, in the case report form (CRF) as well. Primary and secondary outcomes should be outlined.

8. Design of case report form

The CRF is used to record the data in clinical trials, in which how patient response to the drug along with their general information should be noted. At meanwhile, the baseline condition of the patients should also be recorded.

9. Adverse events and severe adverse events

10. Data management and statistical analysis
Data management includes establishing the database, inspection and verification the data, and statistical analysis. In the protocol, plan of statistical analysis should be mentioned, such as the basic statistical methods, types of hypothesis (superiority, equivalence or non-inferiority test) etc.

11. Quality control of clinical trials

It is advisable at a very early stage to plan how to handle trial results as they materialize. Monitoring the trial is to ensure the clinical trials conducted following the predefined way and get the accurate records/data. Methods of monitoring should be stated clearly in the protocol.

12. Publishing the research

The belonging of the research findings (including the publications) should be clarified in the protocol.

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Example 2.8 [16]

Background: Conducting randomized controlled trials on traditional Chinese nondrug therapies has been limited by factors such as patient preference to specific treatment modality. The aim of this study is to investigate the feasibility of applying a partially randomized patient preference (PRPP) trial model in evaluating the efficacy of two types of TCM therapies, acupuncture and cupping, for fibromyalgia while accounting for patients’ preference of either therapeutic modality.

Methods: This protocol was approved by the Institutional Ethics Committee of affiliated Dongfang Hospital, Beijing University of Chinese Medicine (approval number: 2013052104-2). One hundred participants with fibromyalgia will be included in this study. Diagnosis of fibromyalgia will be based on the American College of Rheumatology criteria. Before treatment, participants will be interviewed for their preference toward acupuncture or cupping therapy. Fifty participants with no preference will be randomly assigned to one of the two groups and another 50 participants with strong preference to either acupuncture or cupping will receive what they choose. For acupuncture and cupping therapy, the main acupoints used will be tender points (Ashi). Treatment will be three times a week for 5 consecutive weeks with a follow-up period of 12 weeks. Outcome measures will be qualitative (patient expectation and satisfaction) and quantitative (pain intensity, quality of life, depression assessment).

Trial registration number: NCT01869712 (in clinicaltrials.gov, on 22nd May 2013).
2.2.1.3 Registering the study

After getting an approval from the Ethics Committee, and before starting recruitment, we suggest that the researchers should register the study online. International Medical Journal editorial board requires all clinical trials to be internationally registered before publishing, regarding to ethical aspect (Table 2.6). The readers or other researchers are allowed to check the study plan and make their own decisions.

<table>
<thead>
<tr>
<th>Name of registries</th>
<th>Abbreviations</th>
<th>Country</th>
<th>Website</th>
<th>Date established</th>
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<tr>
<td>Brazilian Clinical Trials Registry</td>
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<td>India</td>
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<td>EU-CTR</td>
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<td>The Netherlands National Trial Register</td>
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<td><a href="http://www.trialregister.nl/">http://www.trialregister.nl/</a></td>
<td>2004</td>
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</table>
on the methodological quality of the study. According to a study [17] which investigated the inconsistent between registered protocol and final report of the study, particularly inconsistent reporting of primary outcomes is a major violation of trial design for confirmatory studies. This may introduce a potential high risk of reporting bias, and downgrade the internal validity and evidence of the study results.

When the investigators register their trials with the above registries, they should provide the following information: study title, program code, funding resources, study type, settings, diagnostic/inclusion/exclusion criteria for participants, details of intervention and control, outcome measurements, timing of the study and contact information.

2.2.2 Implementing

2.2.2.1 Study Management

Study management is process containing plans, it organizes and manages to allow successful completion of specific project objectives. Initiation, planning, execution, monitoring/controlling, and completion are all need to be managed in a clinical study. Challenges of study management include: (a) to achieve all of these objectives within the limits of the known constraints of the project such as scope, time and budget; and (b) to optimize the allocation of resources to meet the objectives as efficiently as possible.

Commonly more months are spent running a trial than planning it or analyzing its data. A schedule with certain timelines of the study would be really helpful to control the study process. Besides, finances, roles, and functions in study team, monitoring (as we mentioned in ‘drafting study protocol’ section) are also important on managing study. Sometimes, taking notes (using checklist or mind mapping) in a structured way is helpful.

2.2.2.2 Data Management

All data should be collected, double checked, and organized before analysis. The appropriate forms for each patient should be arranged and distributed to each investigator at the beginning of the trial. It should be clarified who is responsible for completing each form. The handling of clinical trial data at the coordinating center requires administrative and clerical skills which should not be the priority of clinicians or statisticians. In addition, a specially trained data manager whose job is to get all trial data in good shape ready for statistical analysis is needed. For most cases, a data monitoring committee (DMC) will also be required by local standards.
For each form arriving at the coordinating center, the DMC should carry out a series of checks:

1. General checks, to make sure that all forms have been sent at the right time and received with matched patient number;
2. Missing data;
3. Range checks, to ensure that no items fall within the appropriate range of replies; and
4. Logical checks, to find out any inconsistencies in replies to different questions.

Any problems identified by these checks should be conveyed back to the local institution so that corrections can be made. Data managers will also have concerns with the subsequent data processing which often requires use of computer software (such as EpiData).

2.2.3 Analyzing

2.2.3.1 Steps of Data Analysis

With a specific research question and clarified protocol, we could predefine a statistical analysis plan (SAP) of the study, and this actually should be more detailed than the relevant part of protocol.

1. To analyze the data, you should first define the analysis populations and the handling of missing values. If no data are present for the variable in the current time point, appropriate statistical methods (such as last value carried forward or multiple imputations for a continuous variable, and the worst/best case scenario for a categorical variable) should be used to deal with missing data.
2. Then, people should choose suitable statistical methods, which depend on the variable types and sample size. Statistical methods may include methods for descriptive analysis, confirmatory analysis and multiple testing.
3. The next step is performing the statistical analysis. The researchers may need to use statistical software and become fully conversant with the software. Do not forget to check the data and the results for plausibility and recalculate the important results. Any document of the statistical analysis including notes, USB sticks, or mobile hard drives should be clearly labeled and safely stored for at least five years after termination of the study.
4. The last key step is to interpret the results and draw conclusions. Remember that the conclusions should be clearly based on your study question and should consider the potential limitations of the study.
2.2.3.2 Basic Principles of Statistical Analysis

For each patient in a clinical trial one collects three types of data: (a) which treatment the patient assigned to and actually received; (b) the patient’s response to the treatment including adverse events; and (c) details of the patient’s initial condition and previous history before entry into the trial.

When describing the data, one should describe the basic three types of response data in clinical trials, which are qualitative response, quantitative response, and time to relapse. Frequencies or constitution ratios could be reported as qualitative response, and it is essential to record the total number of patients on each treatment; otherwise, one cannot reliably interpret the results. For quantitative data, the simplest summary is to compute the mean response with the confidence interval for the patients on each treatment. Thus, one can check if the values are clinically feasible and valid to reduce the possibility of erroneous extreme results.

Significant tests have become the most commonly used methods of statistical inference in clinical trials, and both statistical and clinical significance should be assessed and interpreted.

2.2.4 Reporting

Through publication, research findings can be spread worldwide. Researchers who are concerned with a similar topic may repeat the study or test its conclusions. On the other hand, the publication may help others to avoid wasting time and resources to do redundant work. It may provide the current ‘best evidence’ for some specific interventions and help clinicians to make decisions.

2.2.4.1 Early Preparation for Publication

One should decide on a number of basic issues as early as possible.

1. Defining the aims;
2. Deciding on authorship;
3. Selecting a journal;
4. Checking instructions for authors; and
5. Checking general guidelines for reporting.

When selecting the journal, researchers may consider the field of research topics, impact factors (which reflect the impact of the journal), and the quality of the journal (such as its PubMed list or peer review system). Each journal may have its own instructions for authors. Different journals may have different ways to list author names, format the abstract, or cite references. That is the reason why people
should read the instructions and find out which format the journal prefers before drafting.

### 2.2.4.2 Writing the Manuscript

Reports of original clinical research and systematic reviews are usually structured: introduction/background (why did you start), objectives (what’s the main purpose), methods (what did you do), results (what did you find), discussions (what does it mean), and conclusions (what you finally concluded).

High-ranking journals often require authors to follow standard recommendations for the publications of a given type of study. Following the guidelines in Table 2.7 is not only a prerequisite for getting a study accepted but also useful advice to help authors in writing.

Among the items in the guideline for drafting manuscripts, one of the vital things is to critically evaluate the study and interpret the results accordingly. A useful preliminary task is to carefully read the title and abstract of the report to decide if the trials’ findings are relevant and hence to determine whether the report is trustworthy. Furthermore, the real test trial’s validity lies in careful look through the methods section. The design of a trial largely determines whether an unbiased and objective therapeutic comparison can be made. In the discussion of the report, the strengths and weaknesses of the study as compared to other studies should be addressed.

<table>
<thead>
<tr>
<th>Name of the statement</th>
<th>Applicable study type</th>
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<td>Randomized controlled trials for acupuncture</td>
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<tr>
<td>STROBE</td>
<td>Observational studies</td>
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<tr>
<td>MOOSE</td>
<td>Systematic review of observational studies</td>
<td>JAMA 2008, 283 (15) [18]</td>
</tr>
</tbody>
</table>
2.2.4.3 Publishing the Manuscript

After submitting the manuscript to a journal, the authors should wait for the first decision made by editors on whether the manuscript merits external peer review. The first decision may take days or weeks. Hopefully, the manuscript would be sent to two or more external peer reviewers and the peer review process may take months. There are three possibilities to the submission, be accepted, be requested to have revision, or be rejected. If the decision letter requests a revised version of the manuscript, one should forward the decision letter to all coauthors. Besides amending the manuscript, a response letter is needed for resubmission. It is acceptable not to follow all recommendations if you explain why. Each question/point raised by peer reviewers in the response letter should be answered/addressed in a cooperative and unambiguous manner. Even if the submission were rejected by the journal, authors should try to consider rationally the problems and the chances of getting the manuscript accepted elsewhere.

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References


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