Research Methodology Guidelines for
Acupuncture Randomized Controlled Trial

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1. Purpose

This guideline addresses the methodology for acupuncture clinical research by organizing the essential elements for consideration in the design, preparation, and reporting of acupuncture randomized controlled trial (RCT).

2. Background

Acupuncture has been used for thousands of years in China. It spread to other Asian countries in the sixth century [1] and was gradually introduced into the western societies in the seventeenth century [1-3]. Acupuncture became popular worldwide in 1970s when a journalist, James Reston, wrote an article in the New York Times on his experience with acupuncture. According to a survey by the World Federation of Acupuncture-Moxibustion Societies, acupuncture was being used in 183 countries by 2015 [4]. Along with the popularization of acupuncture in the West, scientific evaluation on the effects of acupuncture has been conducted by researchers in many countries. In the past few decades, increasing number of clinical studies were conducted to evaluate the safety and efficacy of acupuncture for various diseases/conditions, using the gold standard research design of RCT. In 1995, the World Health Organization (WHO) published the Guidelines for Clinical Research on Acupuncture [5], in which the basic elements for clinical research on acupuncture are elaborated.

Due to the subjective and complex nature of acupuncture practice, designing a high quality RCT with rigorous scientific methodology remains challenging [6-8]. This guideline aims to provide advice on the scientific methodology on acupuncture research, particularly on choosing the control treatment in acupuncture RCTs. We systematically reviewed acupuncture trials on pain [9] and non-pain conditions from 2004 to 2014. The design of control group used in these studies were categorized to form the basis of this guideline on acupuncture trial design. The principles of RCT are followed and adapted to the unique nature of acupuncture in clinical trial. The guidelines consist
of the key elements of designing, conducting, and reporting acupuncture RCTs. They can be primarily applied to design, conduct, and analyze RCTs for traditional needling acupuncture, as well as other acupuncture modalities such as acupressure, laser acupuncture, and ear acupuncture.

3. Guidelines for designing scientific RCT on acupuncture

3.1 Principles of RCT

Well-designed RCTs have been considered as a gold standard to evaluate the effect of interventions by randomly assigning subjects to the intervention arm(s) or the control arm(s) to reduce bias. The randomization process control for confounding variables contributed by the baseline characteristics of the patients.

In the control arms of a RCT, subjects are exposed to the conditions of the experiment but not the intervention under study. A control is used to determine the true effect of an intervention by excluding placebo or non-specific effects in the treatment. A blank (waitlist or non-intervention group) or a sham control is often employed. A control can also be used to determine the treatment effectiveness by comparing with other conventional treatments. Many controls have been developed for acupuncture RCTs. The choice of control can be determined by the specific aim of an acupuncture trial as shown in Figure 1.

3.2 Identification of research question

When designing a trial, the investigator must take the perspectives of science, ethics, and legal compliance into full consideration. The trial should be conducted in a reasonable and evaluable way. In scientific research, the investigator first develops a research question by identifying the research gap between existing knowledge and unsolved problems. Such a question may, for example, be as follows:

i. Is acupuncture treatment more effective in pain reduction compared to conventional medication?
ii. Does acupuncture overcome flaws or minimize side effects of current treatment?

iii. Can additional acupuncture enhance the effectiveness of a conventional treatment?

Research questions can be generated from literature reviews, clinical experience, pilot studies or by encountering clinical problems. They are usually formulated in terms of PICO (population, intervention, comparison, and outcome) in the practice of evidence-based medicine [10, 11].

3.3 Hypothesis and aims

A clinical trial is designed and conducted to answer a specific primary research question. The study hypothesis contains a statement with a tentative answer to a research question. A study can have more than one hypothesis and they are usually less formally phrased than the statistical hypothesis which is the basis for statistical analysis. For instance, a study hypothesis can be “this intervention may relieve a specific disorder/disease”. The intervention used in an acupuncture RCT can be a general acupuncture treatment, a special style of acupuncture therapy/needle manipulation, treatment on a set of experienced acupoints, a special needle device or acupuncture treatment as an adjunct to conventional regimens.

A hypothesis is often elaborated as several study objectives. To illustrate, the hypothesis “acupuncture is able to reduce chronic neck pain intensity, and improve neck pain disability and health-related quality of life compared to sham acupuncture” could be tested through three studies with specific aims: (1) to determine whether acupuncture could reduce pain intensity on the Visual Analogue Scale more than sham acupuncture, (2) to determine if acupuncture relieves neck pain disability in the Northwick Park Neck Pain Questionnaire more than sham acupuncture, and (3) to determine if acupuncture improves the health-related quality of life in Short form-36 compared to sham acupuncture. Figure 1 shows how a hypothesis and specific aims of a study guide the trial design and choice of controls.
3.4 Essential elements in an acupuncture trial protocol

A study protocol is a pre-designed plan which contains the fundamental elements of the trial. Such elements include subjects, sample size, randomization, blinding, setting, control or comparator, outcome assessment, follow-up schedule, intervention protocol, data management, statistical analysis, and other relevant elements.

3.4.1 Subjects (patients)

A clinical trial is conducted within a defined population. When designing a trial, the eligibility of subjects are considered. Considerations include age, gender, race, disease severity or disease duration, comorbidities, and so on. Inclusion and exclusion criteria are set for the selection of subjects bearing the scientific and ethical considerations. Inclusion criteria are set to identify specific subjects for the study (e.g. population characteristics, stage of diseases), while exclusion criteria are used to exclude participants who contain possible confounders to the study or for safety reasons.

3.4.2 Sample size

Sample size is estimated at the planning stage of the study, which ensures sufficient subjects for assessing treatment efficacy and safety. A qualified statistician is strongly recommended for professional sample size calculation. Before performing the estimation, the following needs to be specified: (a) primary study hypothesis (e.g. superiority, non-inferiority or equivalence of the treatment) and hypotheses, (b) primary endpoint and the statistical methods to be applied for the primary outcome analysis in the study, (c) effect size, the clinically important / meaningful difference in the treatment effect, (d) significance level (probability of a type I error) and power (1–probability of a type II error), and (e) treatment allocation ratio. Mathematical formula for sample size estimation varies with the statistical test of the hypothesis, which is based on the statistical method to analyze the primary outcome and its data type (e.g. binary, ordinal, continuous, time-to-event). Softwares for sample size estimation (e.g. G*power which is free of charge and PASS) and
statistical analysis (e.g. SPSS, SAS, and R) can perform tests for a wide range of data types and analytical methods. Adjustment of sample size with the expected attrition rate is usually required to account for the loss to follow-up.

Selecting the effect size for sample size calculation is not always straightforward. Findings from pilot studies or previous similarly designed studies with the same endpoint can provide valuable information on the mean and variance of the primary outcome in the population studied. With the comparability of the study settings evaluated, one can adopt or adjust previous findings to derive an effect size for the current study. When prior finding is unavailable, clinical judgments and experts’ opinion can serve as the basis of decision.

3.4.3 Randomization

Randomization refers to randomly allocating the study subjects into the intervention arm and the control arm(s). Its purpose is to minimize the selection bias and balance baseline characteristics in the study arms [12]. Commonly used methods of randomization include simple randomization, block randomization, and stratified randomization. The random sequence is generated by a statistical software. Allocation concealment is strictly implemented to prevent foreknowledge of treatment assignment. The assignment mechanism is secured through central randomisation or numbered opaque sealed envelopes in RCTs.

3.4.4 Blinding

Blinding is intended to prevent study findings being affected by the awareness of treatment assignment by the participants and personnel involved, particularly during outcome assessment, patient or investigator’s decision making, and the analyses and interpretation of results [13]. Adequate blinding minimizes performance bias, ascertainment bias, and detection bias when conducting an acupuncture RCT. However, challenge of blinding rises from the unique nature of acupuncture treatment. Acupuncture treatment does not only involve a device but also a complex acupuncture process, such as needle insertion and needle manipulations (lifting, thrusting, twisting
and rotating) which induces de qi sensation. These render the blinding of practitioner impossible, thus most of the trials on needling acupuncture are single blinded.

To minimize the ascertainment bias of subjects, implementation of intervention is carefully designed to achieve effective blinding to the subjects. For example, a screen can be used to block the view of the subjects when the acupuncturist performs real or sham acupuncture at low extremities. Certain postures of the subjects, for instance, receiving acupuncture on their back in prone position, also aid the masking. Since subjects’ expectation and subject-acupuncturist relationship could lead to potential bias [14, 15], acupuncturists are advised to communicate with the subjects in a neutral manner when carrying out acupuncture and control treatment.

Outcome assessor should also be blinded to the treatment assignment so as to reduce detection bias in the study. The statistician involving in data analysis is blinded to group assignment so that the data is appropriately analyzed and interpreted without bias.

3.4.5 Setting

Setting refers to the place where the clinical trial is conducted, e.g. public hospital, local community, university clinics, primary care center or multiple centers. To ensure smooth running of the trial, feasibility of conducting the trial at the study site, including the capacity for subject recruitment, availability of essential equipment and facilities, logistics and so on, should be evaluated.

3.4.6 Control groups or comparison groups

The selection of control type is determined by the specific aim of a trial as shown in Figure 1. One of the commonly used controls in acupuncture trials is the waiting list or non-intervention control. Patient in this control group receive the same concomitant treatments but not the study intervention [16-20]. This type of control is used to control for the natural course of disease. Other common types of controls are the non-insertion sham control [21-25], which is used to control for
the placebo effect, and the needle-insertion at sham or real acupoints [16, 26-29], which is used to control for the placebo effect and non-specific effect.
Figure 1 Flowchart for choosing a control for an acupuncture trial

Waiting list/non-treatment control

Aims: (i) to control for remission in the natural disease process and nocebo effect; (ii) to establish an adequate dose (treatment parameters) and collect preliminary data for a large RCT, such as:
   a) Identifying appropriate acupoints
   b) Selecting proper outcomes
   c) Choosing a follow-up time
   d) Measuring safety
   e) Determining total number of treatments and treatment duration

Limitation: does not control for placebo effects

Positive control (standard medication/usual care)

Aims:
   (i) to identify the effectiveness of an acupuncture treatment compared to a conventional treatment or an adjunct effect to a conventional treatment or standard care, so as to provide clinical and healthy policy decision-making
   (ii) to examine the safety and cost-effectiveness of acupuncture treatment.

Limitation: cannot blind patients or practitioners

Non-insertion sham control (for studying pain-related symptom/disorders)

Aims: to eliminate non-specific effect of needling

Limitation: (i) difficult to implement in long-term studies; (ii) may be effective only for acupuncture-naïve patients; (iii) does not test for specificity of acupoints

Needling-insertion sham acupuncture control (for studying pain-irrelevant symptom/disorders)

Aims: to test the specific effect of acupoints

Limitation: likely to produce non-specific physiological effects of needling

Combined insertion and non-insertion control

Aims: to maximize the blinding to subjects

Limitation: (i) difficult to implement; (ii) likely to produce non-specific physiological effect
(i) Control groups

Waiting list/non-intervention control

Under the waiting list control group, subjects receive no intervention in the waiting period. The study intervention is provided to the subjects after the study period for compensation and to motivate them to participate in the study. In the non-intervention control, subject receive no intervention to be tested or any sham treatments of the intervention in the study. Usual care or rescue medication is provided to subjects in the non-intervention control. This type of control has been used in knee osteoarthritis (KOA) [30] and low back pain study [31]. The waitlist control/non-intervention control is utilized to determine whether acupuncture is more effective than no intervention (i.e. whether the outcome in the study is from spontaneous recovery or not). Disadvantage of the waitlist/non-intervention control setting is that it is unable to differentiate between the placebo effect and therapeutic effect of acupuncture. It is shown that trials using waitlist/non-intervention control often overestimated the treatment effects [32]. Our study showed that acupuncture RCT publications with the waitlist/non-intervention control had a higher proportion of positive conclusions in acupuncture studies for pain conditions. Similar findings were found in acupuncture RCTs for non-pain conditions (Appendix I, Table 1).

The waitlist/non-intervention control is recommended for studying the efficacy of acupuncture in early stage (Stage I) of a study. It is used to establish an adequate dose of acupuncture (e.g. identifying appropriate acupoints, selecting proper outcomes, measuring safety) or to collect preliminary data for a large scale trial. However, ethical issues should be fully considered when applying the waiting list/non-intervention control to a clinical trial. The researcher should carefully consider the potential risk and benefit for the subjects. The waiting list/non-intervention control might not be applied in some studies, for example, trials on end stage of cancer.
**Non-insertion sham control**

The non-insertion control resembles the real acupuncture needling procedure but without skin penetration. It helps to control for the psychological effects (placebo effect) of acupuncture. Types of non-insertion control used in acupuncture trials include empty guiding tube, semi-blunt needling, toothstick, and non-penetrating needle devices [21-25]. However, patients with acupuncture experience may be able to distinguish between real acupuncture and sham control. Alternatively, patient with no or minimal acupuncture experience could be recruited. Another disadvantage of non-insertion sham control is a short-term blinding effect. Patients might acquire experience on real acupuncture experience from other acupuncturists or patients during a long-term study. This was demonstrated in a study with successful blinding of subjects of real or sham acupuncture treatment at week 4 but failed at week 26 [30]. The non-insertion sham control is recommended for short-term clinical trials or trials recruiting patients with little acupuncture experience. The blinding credibility of the non-insertion sham acupuncture should be evaluated. Evaluation could be conducted via post-intervention interviews. For example, after patients have received all interventions, questions like “as you were informed, participants would receive real acupuncture or placebo acupuncture. Which acupuncture do you think you received in the study?” can facilitate the assessment of blinding effectiveness [33]. Approximately half of the published acupuncture RCTs with non-insertion sham control showed positive conclusions in the acupuncture studies for pain conditions and non-pain conditions (Appendix I, Table 2). It is also highly recommended to conduct a pilot study to validate the effectiveness of the blinding methods before commencing an acupuncture trial.
Needle-insertion sham acupuncture control

The needle-insertion sham acupuncture control penetrates the skin at non-acupoints or the acupoints which are believed to have no specific effect [16, 26-29]. It is used to measure non-specific effect of needling and placebo effect of acupunctures/acupoints.

The advantage of needle-insertion sham acupuncture control is its resemblance to real acupuncture. The sham needling procedures are well blinded to subjects. However, few points needled in the sham arm are well validated so that potential therapeutic effect of the sham needling cannot be excluded. In addition, this type of control produces non-specific physiological effects such as alternations at blood circulation and neural pathways (e.g. the diffuse noxious inhibitory controls [34]) upon skin penetration. These effects are considered a confounding factor.

In order to minimize the non-specific physiological effects of needling, a superficial needling at non-acupoints, distal points or irrelevant points is used in the control arm of acupuncture trials [16, 26-29]. Needle manipulation is generally not applied as minimal manipulation may cause non-specific effect. More importantly, validation of the control to ensure little physiological effect prior to the study is highly recommended. The disadvantage of this control is that it is not completely inert, thus the physiological effect should be considered for adjusting the expected difference between acupuncture and sham control group for sample size estimation.

Our study showed that the acupuncture RCTs with needle-insertion sham control for non-pain conditions had higher proportion of positive conclusions (Appendix I, Table 3). Since most studies used the adjacent points (1 - 1.5 cm from acupoint) as the sham points, the findings indicated higher specificity of acupoint treatment for non-pain conditions than that in the treatment for pain conditions. It is likely that superficial needling at non-acupoint did not exert significant therapeutic dose when needle-insertion was used as the sham control group for non-pain conditions. Needle-insertion sham
control is recommended for non-pain acupuncture trials. However, superficial needling at non-acupoint was likely to exert therapeutic dose when needle-insertion was used as the sham control groups for pain conditions. This might be caused by the non-specific analgesic effects of acupuncture or the small sample size. It is thus recommended to minimize the non-specific analgesic effects when conducting acupuncture RCT for pain conditions and enlarge the sample size if needed. This recommendation is further supported by findings in the validated blinding studies (Appendix I, Table 6 & 7). For studies on non-pain conditions, the use of non-insertion sham control had the highest proportion of positive conclusion (100%), and the use of needle-insertion sham control also had high proportion of positive conclusion (71.4%). In contrast, for studies on pain conditions, the use of non-insertion sham control had higher positive proportion (28.6%) but the use of needle-insertion sham control had 0% of positive conclusion. Trials on non-pain conditions are more likely to obtain positive conclusions compared to those on pain conditions.

**Combined controls**

To enhance the blinding effectiveness, combined controls with both non-insertion and needle-insertion sham acupuncture may be used. In a successful study on acupuncture as adjunctive therapy in KOA, the treatment group consisted of real needling at 5 local points and 4 distal points and tapping plastic guiding tube at 2 sham points (non-insertion placebo control), and the sham group consisted of inserting 2 needles at sham points (needle-insertion sham control) and tapping at 9 real points (non-insertion placebo control) [30]. The combined controls have the following advantages: 1) enhanced blinding in both groups because the two treatments are comparable in appearance, and 2) enhanced blinding in the real acupuncture group because the sham points may render the real treatment appear less real while the control treatment more real [30]. However, combined controls also have limitations such as the difficulty in implementation and likelihood of producing non-specific physiological effect.
(ii) Comparison groups

Different treatment options such as conventional medications, physiotherapy, radio-chemotherapies, or complementary and alternative therapies are available for a certain disease. However, the benefits and limitations of these treatment options should be evaluated by comparing different treatments so as to make clinical or health policy decisions [35]. Witt et al. has published a guidance document on effectiveness for conducting acupuncture trials [35]. According to the document, effectiveness is “a measure of the extent to which an intervention, when deployed in the field in routine circumstances, does what it is intended to do for a specific population” while efficacy refers to “a measure of the extent to which a specific intervention is beneficial under ideal conditions” [35, 36].

With increasing data variance in effectiveness studies, a larger sample size than that of efficacy studies is needed. Our study showed that acupuncture RCT publications had a higher proportion of positive conclusions in acupuncture treatments compared to other comparative treatments (such as physiotherapies, medications, other alternative therapies) (Appendix I, Table 4). This type of control is recommended to address the following research questions: (1) specific effect of acupuncture needling, acupoints, and other acupuncture parameters; (2) effect of acupuncture as a therapy compared to other therapies, and (3) safety and costs [35]. A double dummy design could be used in a comparison study to keep the blinding of a clinical trial where the two treatments cannot be made identical.

3.4.7 Outcome assessments

The outcomes have to be measurable. They can be objective instruments (e.g. laboratory index) or subjective instruments (e.g. symptom questionnaires, quality of life or self-report feelings). Validated instruments should be used for measuring these outcomes. The choice of outcome instruments should be in line with the study question. For example, The Western Ontario and
McMaster Universities Arthritis Index is commonly used to assess the efficacy of acupuncture on KOA and is available in several languages [16, 22, 30, 37-40].

The primary and secondary outcomes should be clearly defined in the study protocol. The primary outcome is the most important measurement which addresses the major objective of the study. It is often limited to one or two parameters. Secondary outcomes are other relevant measures. The number of secondary outcome instruments to be used depends on the investigator’s interest.

3.4.8 Follow-up schedule

Time interval of the follow-up period will affect the determination of the true intervention effect. Negative result will likely be obtained if the time of follow-up exceeds the therapeutic duration. The appropriate time of follow-up could be determined by the pilot study. The time of follow-up is also determined by the study aim. If the study aims to evaluate the immediate effect of acupuncture, the follow-up can be carried out within several weeks. On the contrary, to evaluate the long-term effect of acupuncture, the follow-up can be as long as several months to a year.

3.4.9 Intervention protocol

Intervention protocol provides the details on the acupuncture or control procedures to be performed in the subjects. A well-designed intervention protocol ensures a consistency in intervention implementation and reliability of results from the trial. Key elements such as acupuncture rationale, acupoint selection, needling manipulation, needling retention, electrical stimulation, and experience of an acupuncturist are specified. The Standards for Reporting Interventions in Clinical Trials of Acupuncture ( STRICTA) has been developed to improve the completeness and transparency on the reporting of interventions in acupuncture controlled trials. It documents the essential items in designing intervention trials [41]. With reference to STRICTA, the intervention protocol should contain the acupuncture rationale (e.g. styles of acupuncture, rationale of acupoint selection), details of needling
(e.g. the length, diameter, and brand of needles), choice of acupoints, depth of needle insertion, and retention time of needles. Details on the needling technique such as manual manipulation (e.g. lifting, rotating), electrical stimulation (frequency and intensity), or de qi (needle sensation) are also documented. Treatment schedule (e.g. number of treatment sessions, frequency and duration of acupuncture treatment) are also specified. The investigator should determine the use of concurrent regimen, usual care or rescue medications during the study. The efficacy of acupuncture is nonetheless affected by the experience of acupuncturist, which includes the educational background, years of acupuncture practice, acupuncturist’s specialty, and communication style with subjects.

3.4.10 Data management

Data management includes data collection and processing. The accuracy and security in data usage should be fully considered. Key issues of data collection, such as person responsible for data collection, method of data storage and security, and protocol for handling missing data, should be specified.

3.4.11 Statistical analysis

Method of statistical analysis is planned prior to data analysis by statisticians. The plan includes the general principles and direction of analysis, and the statistical methods to be applied to analyse the primary and secondary outcomes and other data generated from the study. Alternative statistical methods may also be used if there is sound justification of such methods.

3.5 Other relevant elements in a trial

3.5.1 Research team

A research team should consist of members from different disciplines (e.g. acupuncturist, disease specialist, clinical trial expert, and biostatistician) in order to secure the operation of a clinical trial, and to ensure good quality in designing, conducting, analyzing, and reporting of the trial. For
example, in a study on arthritis pain, a research team may consist of an acupuncturist, a rheumatologist, research assistants, and a statistician. In addition, junior investigators are advised to receive adequate training prior to participating in the research.

3.5.2 Facilities

Sufficient facilities are essential for successfully conducting an acupuncture trial. In the study protocol, the facilities need to be well planned. Facilities should include equipment for outcome measurements, storage of specimen, and capacity for patient recruitment.

3.5.3 Institutional Review Board/Ethics Committee (IRB/EC)

IRB is an independent ethics committee designated to approve, monitor, and review clinical research involving humans. The IRB ensures the protection of the rights, safety, and well-being of all patients involved in a trial. The members of IRB will review the documents from investigators such as the study protocol/amendment(s), written informed consent form, subject recruitment procedures (e.g., advertisements) to approve, disapprove, or require modification of the trial. The members of IRB also make decision on termination or suspension of a trial if unanticipated adverse effects are reported.

3.5.4 Data and Safety Monitoring Board (DSMB)

DSMB is an independent group of experts that offers advice to both the funding agency and the study investigators. The members of the DSMB serve in an independent capacity to provide their expertise and recommendations. They periodically review and evaluate the accumulated study data for participants’ safety, study conduct and progress, and scientific validity and integrity of the trial.
4. Preparing the acupuncture RCT

4.1 Ethical approval

The research protocol and essential documents (informed consent form, case report form, advertisement and posters) are prepared and submitted to ethics committee for approval before commencement of a clinical trial. These documents may be amended in regard to the reviewers’ comments. The clinical trial is conducted following the approved protocol. Any amendments made in the protocol are subjected to further approval from the ethics committee.

4.2 Trial registration

Registration of acupuncture RCT prior to enrollment of subjects is considered to be a scientific, ethical, and moral responsibility. It reduces publication bias, improves the quality of trial, avoids duplication of clinical trials, and promotes the efficient allocation of research funds [42, 43]. The International Committee of Medical Journal Editors (ICMJE) requires trial registration as a prerequisite for publishing clinical trial results. The WHO International Clinical Trials Registry Platform has established registry networks (http://www.who.int/ictrp/network/primary/en/) to provide the public with information on the design, conduct, and administration of clinical trials (http://www.who.int/ictrp/network/trds/en/). Registration can be done via appropriate online registries:

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(From http://www.who.int/ictrp/network/trds/en/)

4.3 Research team and training

Guidelines such as ICH E6 Good Clinical Practice guidelines (http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html) have been developed to ensure good quality in clinical trials. The research team involved in the clinical trial, e.g. principal and co-investigators, outcome assessor, acupuncturists and other investigators, is recommended to receive good clinical practice training. Equally important, knowledge on local regulations should be incorporated into the training materials. Many organizations and universities provide training courses locally or via internet to serve such purposes.

4.4 Research funding

Research funding is fundamental to a successful trial. Investigators may seek funding from research agencies, government, donations, and from companies. However, they are required to disclose any conflict of interests in the study.

5. Reporting the acupuncture RCT

5.1 Key elements in reporting

To enhance the quality of clinical trials reporting, a Consolidated Standards of Reporting Trials (CONSORT) Statement were published in 1996 and updated regularly. Hundreds of journals listed in Pubmed have endorsed the CONSORT [44]. The CONSORT stated 25 key elements for reporting in a trial. The Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)
guideline was published in 2010 as an extension of the CONSORT Statement [41]. The STRICTA particularly highlights 6 key items in reporting according to the unique nature of acupuncture, including acupuncture rationale, details of needling, treatment regimen, additional components of treatment, practitioner background, and control or comparator interventions [41].

5.2 Avoiding publication bias

Research findings from trials need to be interpreted appropriately and investigators should be aware of publication bias. Results should be reported using the outcome measurements pre-specified in the study protocol and not selecting out positive results for publications. It has been appealed that not only the positive results but also the negative results should be published. Publishing both results have demonstrated values for other investigators or patients, such as on avoiding repeating the trial, improving the design for future studies, and allocating the appropriate medical resources for patients.

6. Overcome challenge in acupuncture RCT

6.1 Considering the unique feature of acupuncture in RCT

To overcome the challenges in acupuncture RCT design, the unique nature of acupuncture treatment should be considered. Firstly, the subjective performance, attitude or experience of the acupuncturist may influence the acupuncture treatment [14, 15, 45]. Training on standardized acupuncture intervention should be provided to acupuncturists prior to the trial so that they are capable of maintaining the quality and consistency of intervention provided to the subjects. Secondly, needle penetration causes multiple uncertain biological effects. Findings from previous studies have indicated that both placebo and specific effects are found in acupuncture trials [34]. The control design should be validated prior to the trial in order to avoid bias from placebo and non-specific effects. Thirdly, the treatment effect attributed by the needling at a set of acupoints should be considered. Selection of
acupoints should be based on literature review or clinical observation. Lastly, the patient’s experience of acupuncture might affect the compliance of patients in the control groups.

6.2 Answering clinical questions in stages

Given the above unique features of acupuncture, no single trial can address all clinical questions. Different trials are designed to answer specific clinical questions [46]. In addition, many clinical trials failed due to a lack of data from pilot studies, which is important to determine sample size and feasibility of the study. Similar to drug development, the efficacy or effectiveness of acupuncture on a certain disease could be tested in stages. For example, in a stage I study, a small number of subjects can be recruited to test the feasibility and tolerance without the control [47]. This early stage trial can establish an adequate dose for later stage trials and provide preliminary information such as the number of treatments, treatment duration, acupoint, and acupuncture manipulation. Pilot study also contributes information on selecting outcome instruments, choosing a follow up time, measuring the safety and providing training for acupuncturist for the later stage trials. In a stage II trial, a larger trial can be initiated to measure the efficacy of acupuncture by choosing appropriate controls. A number of parameters can be determined from the data obtained in the previous stage I trial. In later stage trials, the control should be specially designed to examine the specific effect, such as acupoint specificity.
7. Summary of recommendations

**Waiting list control**
*Recommended for:* efficacy study of acupuncture in Stage I (early stage)
*Purpose:* • to establish adequate dose of acupuncture (e.g. identifying appropriate acupoints, selecting proper outcomes, measuring safety), or
• to collect preliminary data for a larger scale trial

**Non-insertion sham control**
*Recommended for:* • short-term clinical trials or trials enrolling patients with little acupuncture experience.
• pain acupuncture trials
• for Stage II study
*Purpose:* • In order to minimize the non-specific physiological effects of needling, a superficial needling at non-acupoints, distal points or irrelevant points is often used in the control arm of acupuncture trials.
• Needle manipulation should not be applied. More importantly, validation of the control to ensure little physiological effect prior to the study is highly recommended.

**Needle-insertion sham control**
*Recommended for:* • non-pain acupuncture trials
• for Stage II study

**Combined sham control (Non-insertion and needle-insertion sham acupuncture)**
*Recommended for:* enhancing the blinding effectiveness

**Positive comparator (conventional treatment)**
*Recommended for:* testing the safety and cost-effectiveness of treatment
*Purpose:* to assess the effect of acupuncture or adjunct effect compared to conventional treatment
References


Appendix I – The proportion of positive conclusions in acupuncture RCTs using different controls

A systematic search of acupuncture RCTs was conducted to evaluate the proportion of positive conclusions in RCTs using different controls.

(a) Search strategy

The databases included in the search were Medline, AMED, Cochrane libraries, EMBASE, PsycINFO, Clinicaltrials.gov, and CAB Abstracts.

#1    acupuncture*
#2    acupoint*
#3    acupress*
#4    meridian*
#5    needling*
#6    sham acupuncture
#7    placebo acupuncture
#8    “control acupuncture” or “acupuncture control”
#9    #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#10   Filter: Randomized control trial; SCI (English)
#11   #10 AND pain*
#12   #10 NOT pain*

(b) Inclusion and exclusion criteria

Inclusion criteria

- randomized controlled trial
- contain pain score as the outcome
- needing acupuncture (traditional acupuncture, electro-acupuncture as the major intervention, including auricular acupuncture and scalp acupuncture as the secondary intervention
- publications from 2004 to 2014
- SCI papers
**Exclusion criteria**

- bee venom acupuncture as the intervention
- acupoint injection as the intervention
- poor quality design (unclear randomization method, incorrect concealment and individual assessment), if low risk items less than 5 of 7 (Risk bias Assessment, Cochrane hand book) or Jadad score < 3
- active treatment of any acupuncture modalities (e.g. active acupuncture, auricular acupuncture, etc.) as the control

The retrieved RCTs were categorized into the two types of studies: (1) RCTs with acupuncture for the pain condition, and (2) RCTs with acupuncture for non-pain condition.

(c) **Definition for positive/negative conclusion in RCTs with acupuncture for pain conditions**

Positive conclusion (+) indicated that acupuncture was significantly superior to the control \((P < 0.05)\) in the primary outcome of clinical studies. If no primary outcome was stated in the studies, the general conclusion of the study was judged as positive conclusion when it indicated acupuncture was better than the control.

Negative conclusion (−) indicated that acupuncture was not significantly superior to the control \((P \geq 0.05)\) in the primary outcome of clinical studies. If no primary outcome was stated in the studies, the general conclusion of article was judged as negative conclusion when it indicated acupuncture was not better than the control.

Positive/negative conclusion (+/−) indicated that acupuncture was significantly superior to the control in some primary outcomes but not in all primary outcomes. If no primary outcome was stated in the studies, the general conclusions of the study was as +/− when it indicated acupuncture was somewhat better than the control but not in all outcomes.

(d) **Definition for positive/negative conclusion in RCTs with acupuncture for non-pain conditions**

Positive conclusion (+) indicated that acupuncture was significantly superior to the control \((P < 0.05)\) in the primary outcome of clinical studies. If no primary outcome was stated in the studies, the general conclusion of the study was judged as positive conclusion when it indicated acupuncture was better than the control.
Negative conclusion (−) indicated that acupuncture was not significantly superior to the control ($P \geq 0.05$) in the primary outcome of clinical studies. If no primary outcome was stated in the studies, the general conclusion of article was judged as negative conclusion when it indicated acupuncture was not better than the control.

Positive/negative conclusion (+/−) indicated that acupuncture was significantly superior to the control in some primary outcomes but not in all primary outcomes. If no primary outcome was stated in the studies, the general conclusions of the study was as +/− when it indicated acupuncture was somewhat better than the control but not in all outcomes.

Findings revealed that three major types of controls were commonly used in the acupuncture RCTs: (1) waitlist controls/non-intervention control, (2) non-insertion sham control, and (3) needle-insertion sham controls. The remaining studies used comparisons as the control, which usually are not procedures or intervention identical to real acupuncture (e.g. physiotherapies). The findings are shown in Table 1, 2, 3 and 4.

Table 1. The proportion of positive/negative conclusions in studies with the waitlist controls/non-intervention controls (2004-2014)

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Pain conditions</th>
<th>Counts</th>
<th>%</th>
<th>Non-pain conditions</th>
<th>Counts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td></td>
<td>43</td>
<td>84.3</td>
<td>55</td>
<td>64.0</td>
<td></td>
</tr>
<tr>
<td>–</td>
<td></td>
<td>6</td>
<td>11.8</td>
<td>30</td>
<td>34.9</td>
<td></td>
</tr>
<tr>
<td>+/-</td>
<td></td>
<td>2</td>
<td>3.9</td>
<td>1</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>51</td>
<td>100</td>
<td>86</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. The proportion of positive/negative conclusions in studies with the non-insertion sham controls (2004-2014)

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Pain conditions</th>
<th>Counts</th>
<th>%</th>
<th>Non-pain conditions</th>
<th>Counts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td></td>
<td>16</td>
<td>53.3</td>
<td>21</td>
<td>45.7</td>
<td></td>
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<tr>
<td>–</td>
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<td>13</td>
<td>43.3</td>
<td>25</td>
<td>54.3</td>
<td></td>
</tr>
<tr>
<td>+/-</td>
<td></td>
<td>1</td>
<td>3.3</td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>30</td>
<td>100</td>
<td>46</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. The proportion of positive/negative conclusions in studies with the needle-insertion sham controls (2004-2014)

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Pain conditions</th>
<th>Non-pain conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>14</td>
<td>37.8</td>
</tr>
<tr>
<td>–</td>
<td>20</td>
<td>54.1</td>
</tr>
<tr>
<td>+/-</td>
<td>3</td>
<td>8.1</td>
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<tr>
<td>Total</td>
<td>37</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4. The proportion of positive/negative conclusions in studies with the different comparisons (2004-2014)

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Pain conditions</th>
<th>Non-pain conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>26</td>
<td>56.5</td>
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<tr>
<td>–</td>
<td>16</td>
<td>34.8</td>
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<tr>
<td>+/-</td>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>100</td>
</tr>
</tbody>
</table>

(e) The correlation of conclusion and blinding efficacy

A total of 22 studies reporting the blinding test or treatment credibility were further analyzed. Twenty-one studies indicated successful blinding while one study indicated successful blinding at early stage but failed in later stage of the trial. The studies having successful blinding were analyzed.

As shown in Table 5, the proportion of positive conclusions is similar in studies with non-insertion sham controls or needle-insertion sham controls. For non-pain conditions, the use of non-needle insertion sham control had highest proportion of positive conclusion (100%) and the use of needle-insertion sham control also had high proportion of positive conclusion (71.4%) (Table 6). In contrast, for pain conditions, the use of non-insertion sham control had highest positive proportion but the use of needle-insertion sham control had 0% of positive conclusion (Table 7).
Table 5. The proportion of positive/negative conclusions in studies with non-insertion sham controls or needle-insertion sham controls (2004-2014)

<table>
<thead>
<tr>
<th>Conclusion Group</th>
<th>Conclusion</th>
<th>+</th>
<th>–</th>
<th>+/-</th>
<th>Sub</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Non-insertion sham control</td>
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<td>4</td>
<td>44.4</td>
<td>1</td>
<td>11.1</td>
</tr>
<tr>
<td>Needle-insertion sham control</td>
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<td>41.7</td>
<td>7</td>
<td>58.3</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table 6. The proportion of positive/negative conclusions in studies with the non-pain conditions (2004-2014)

<table>
<thead>
<tr>
<th>Conclusion Group</th>
<th>Conclusion</th>
<th>+</th>
<th>–</th>
<th>+/-</th>
<th>Sub</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Non-insertion sham control</td>
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<td>100</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Needle-insertion sham control</td>
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<td>71.4</td>
<td>2</td>
<td>28.6</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table 7. The proportion of positive/negative conclusions in studies with pain conditions (2004-2014)

<table>
<thead>
<tr>
<th>Conclusion Group</th>
<th>Conclusion</th>
<th>+</th>
<th>–</th>
<th>+/-</th>
<th>Sub</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Non-insertion sham control</td>
<td>2</td>
<td>28.6</td>
<td>4</td>
<td>57.1</td>
<td>1</td>
<td>14.3</td>
</tr>
<tr>
<td>Needle-insertion sham control</td>
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<td>0.0</td>
<td>5</td>
<td>100</td>
<td>0</td>
<td>0.0</td>
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</table>
## Appendix II – Useful websites

<table>
<thead>
<tr>
<th>International guidelines related to RCT design and reporting</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. The Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)</td>
<td><a href="http://www.stricta.info/">http://www.stricta.info/</a></td>
</tr>
</tbody>
</table>