Designing and implementing multicenter clinical randomized controlled trials on moxibustion with large samples

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Supported by the National "11th 5-year Plan" (2006BAI12B04-2); National Plan on Developing Key Basic Researches (973 Plan) (2009CB522902); State Natural Science Fund (30760320); and a project of Key Sci-tech Support Plan in Jiangxi

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Accepted: June 15, 2011

Abstract
Implementing clinical trials with large multicenter samples is an important way to scientifically evaluate and demonstrate the curative effect of moxibustion. At present, clinical trials on moxibustion with large multicenter samples are prospering in China. It is necessary for research units to have good research professionals and technical platforms as well as a highly standardized and scientifically feasible methodology of research. Taking tasks in the ongoing national 973 project and in the sci-tech support program of the "11th 5-year plan", for example, this research captures the characteristics of moxibustion, carries out deep analysis and introduces specific methods and the important significance of clinical research tasks on moxibustion in designing multicenter plans, implementing experiments, supervising quality and strengthening compliance.

INTRODUCTION
Scientifically evaluating and demonstrating the curative effect of moxibustion is the only way to realize its inheritance and creation and an important method for clinically explaining the scientific rationale of "when acupuncture does not work, moxibustion is appropriate". At present, because multicenter clinical trials on moxibustion with large samples in China are at their initial stage, it is necessary to steadily re-examine and perfect study design concepts and the implementation of details. On the one hand, designing clinical trials with high quality is important for scientifically verifying the curative effect of moxibustion. On the other hand, differing from traditional medicinal treatment, moxibustion has its own characteristics in discipline and clinical practice. Research units should follow the characteristics of moxibustion and work out suitable research plans without violating the basic principles of clinical trials. Therefore, a project of “research into treatment planning and evaluation of acupuncture and moxibustion” is specially set up in the national sci-tech support program of the “11th 5-year plan” to guide the design of a clinical research plan that both conforms to the characteristics of acupuncture and moxibustion and is acceptable to the academic cycle. The hospital affiliated with the Jiangxi Traditional Chinese Medicine (TCM) College is taking the lead in implementing the research into an optimized plan for treatment of chronic persistent asthma with heat-sensitive moxibustion. This is the only multicenter clinical trial in the project group to evaluate the curative effect of moxibustion, which has been registered as ChiC-
TR-TRC-09000599 at China’s clinical trial registration center. Taking this project as an example, this article outlines the characteristics of moxibustion, carries out deep analysis and introduces specific methods for multicenter clinical research tasks on moxibustion including designing plans, implementing trials, supervising quality and strengthening compliance. This study was approved by the appropriate ethics committees and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. All persons signed their informed consent prior to their inclusion in the study.

**FOLLOWING THE CHARACTERISTICS OF TRIAL DESIGN AND DISPLAYING THE CURATIVE EFFECT OF MOXIBUSTION IN CLINICAL PRACTICE**

**Central randomized system**

The optimized plan for treatment of chronic persistent asthma with heat-sensitive moxibustion is through multicenter clinical trials carried out by 12 units with large samples and a central randomized system. The China Academy of Chinese Medical Sciences is undertaking the central randomization and realizing data management.

**Blinding of evaluators**

The details of the clinical research plan and the restriction of manipulation in moxibustion present challenges for blinding. The blinding of evaluators used in the optimized plan on treatment of chronic persistent asthma with heat-sensitive moxibustion is accomplished by using evaluators who do not know the grouping condition when they evaluate patients.

**Control group of positive drug**

In the optimized plan on treatment of chronic persistent asthma with heat-sensitive moxibustion, it was not possible to select sham moxibustion as the control group, as only using a negative or ineffective measure to treat chronic asthma patients does not conform to ethical requirements. Therefore, the task group is using Shulida, an internationally accepted drug to control asthma, for the control group. According to the global proposal on preventing and treating asthma (GINA 2002), inhaled glucocorticoid hormone combined with a long acting \( \beta_2 \) receptor agonist is used as the initial plan for preventing and treating asthma. Shulida is confirmed as a standard drug with definite curative effects. It is a feasible control method in consideration of ethics, clinical practice and methodology.

**Repeatability**

Comparative research is generally divided into 3 types: superiority, non-inferiority and equivalence. Previous researches carried out by the task group showed that heat-sensitive moxibustion may be similar to Shulida in curative effect. Acupuncture and moxibustion take effect on the basis of regulating the whole body. Starting from clinical design, it is impossible for acupuncture and moxibustion to be superior to target-regulating drugs in curative effect. However, acupuncture and moxibustion have the superiority of regulating the whole body. Therefore, a non-inferiority experimental design is more suitable for objectively evaluating the curative effect of acupuncture and moxibustion.

In the optimized plan on treatment of chronic persistent asthma with heat-sensitive moxibustion, the sample size is estimated with the following formula involving 4 factors: the average effective rate \( P \) the active comparator effect mean, the experimental treatment effect mean and the non-inferiority critical value \( \delta \).

\[
n = 2 \times \frac{(U_\alpha + U_\beta)^2}{\delta^2} \times P(1 - P)
\]

In the formula, \( \alpha = 0.05 \) and \( \beta = 0.2 \). The average effective rate \( P \) is based on the data from clinical experiments of the International Asthma Alliance (GOAL). The asthma-controlling rate of Shulida can reach 71%. Selecting \( \delta \) is of vital importance. If too large a \( \delta \) is selected, drugs with inadequate medicinal effect are judged as non-inferior. If too small a \( \delta \) is selected, the clinical value of drugs may be underestimated. This value should not be larger than the effective difference \( \Delta \) of the effect confirmed by optimum effective experiments with a placebo control group. Therefore, the task group is selecting \( \delta = 0.15 \). The calculations indicate that each group needs 120 cases and the two groups need 240 cases in all. If the missed visit rate is controlled at 20\%, the total sample required is about 288 cases. In addition, it is necessary to point out that statistical deduction in non-inferiority experiments is different from traditional methods.

**Superiority in curative effect of moxibustion**

In its previous trials, the task group discovered that the treatment of chronic persistent asthma with heat-sensitive moxibustion can not only improve symptoms but also decrease complications such as oppressed feeling in the chest, reduce relapse rate and enhance patient quality of life. Therefore, when designing indices for measuring during trials, the task group selected a series of indices which can reflect the improvement of the quality of life of asthma patients. For example, the internationally used score for evaluating asthma control, the Asthma Control Test (ACT), is used to comprehensively test daily ability to function normally, level of asthma symptoms, frequency of rescue drug use and level of asthma control.

**IMPLEMENTING THE CONCEPT OF OPTIMIZED PLAN AND ENHANCING TOP LEVEL OF DESIGN**

Optimization, a concept of top design, requires researchers to repeatedly revise their plan in order to make it more strict, scientific and rational. In the
above-mentioned characteristics of experimental design, central randomization, blinding of evaluators, set-up of control and estimation of sample size are the result of the optimization of plan.

**Mode of experimental design**

In the initial plan of the task group, two factors of therapeutic dosage (A) and manipulator (B) and two levels of 60 minute dosage (A1) and disappearance of heat-sensitive phenomenon (A2) as well as doctor (B1) and subject (B2) were used in the experimental group. Shulida was used in the control group. Through discussion, the experts agreed that it is very difficult to make manipulations on subjects identical, as there are many uncontrollable factors, and that this method should be simplified. Therefore, the mode of design was simplified into a parallel comparison between two groups, with heat-sensitive moxibustion used in the experimental group.

**Defining the target population**

Included in the trial are patients who have the heat-sensitive phenomenon at the corresponding site and who can correctly express the sensation of moxibustion and coordinate their behavior. This creates the sensation of moxibustion, a nice warm feeling around the area. The following patients sensation suggested the heat-sensitive phenomenon: diathermanous sensation due to moxa-heat, defining as the heat sensation conducting from the moxa local skin surface into deep tissue, or even into the joint cavity; expand heat sensation due to moxa-heat, defining as the heat sensation spreading the surrounding little by little around the moxa point; transfer heat sensation due to moxa-heat, defining as the heat sensation transferring along some pathway or direction; non-heat sensation due to moxa-heat. Excluded are those who cannot tolerate the smoke of moxibustion, a nice warm feeling around the area. The above-mentioned characteristics of experimental design, central randomization, blinding of evaluators, set-up of control and estimation of sample size are the result of the optimization of plan.

Therefore, the task group is using the scores for evaluating asthma control (ACT), determinations of pulmonary function, and the scores for evaluating TCM symptoms to judge the curative effect of interventional measures in clinical practice.

**ESTABLISHING A SYSTEM OF SCIENTIFIC SUPERVISION AND STANDARDIZING THE MANAGEMENT OF CLINICAL TRIALS**

According to the standards of clinical research in acupuncture and moxibustion, clinical epidemiology, evidence-based medicine, GCP clinical research methods, requirements of international clinical experiments and the TCM standard of quality control and quality guarantee in clinical researches of China, a 3-level quality check system is being established.

**Appointing supervisors and identifying their qualifications**

Because the whole project will involve research at 12 centers, supervisors directly appointed by the quality supervision committee of the project will be responsible to the project office. Multicenter moxibustion trials are characterized by large samples and a long period of observation. Supervisors should have comprehensive knowledge and a professional background. Quality inspectors are appointed by the responsible person at each center and trained by the task group before task implementation.

**Drawing up the plan and procedure of supervision**

The supervision plan consists of the following: 1) the number of supervisors is planned according to the number of units undertaking the task; 2) the number of visits by supervisors is planned according to the clinical experimental plan and research speed; 3) the frequency of visits is regulated according to the progress and quality of the research.

**Common problems and their management**

Data in the case report platform (CRP)table carry the contents of the clinical trial. Supervisors have found that many research units inconsistently express onset frequency as 8 times per month or twice per week, and pulmonary function as absolute value or percentage or both. Therefore, the task group contacts the responsible persons at the centers as needed to fill in the table consistently. Accurately locating the application point for heat-sensitive moxibustion is a key factor for enhancing its curative effect. At the pre-test stage of the clinical experiment, having discovered that individual researchers at some centers were not skilled in accurately locating the application point for heat-sensitive moxibustion, the task group assigned supervisors to carry out on-the-spot or online instruction as needed.
The sensation-eliminating dose is the key to realizing the individual moxibustion dose in heat-sensation moxibustion[15]. At the pre-test stage of the clinical experiment, the task group discovered that when treating patients with heat-sensation moxibustion, individual researchers at some centers had not given enough moxibustion dosage. The time (30-90 min) of each treatment must make the heat-sensation phenomenon disappear at the point of moxibustion[19]. On-the-spot or online detailed explanations of the importance of giving enough moxibustion dosage enables researchers at the centers to appreciate its importance in order to achieve the best curative effect of heat-sensation moxibustion.

**ENHNCING COMPLIANCE OF SUBJECTS AND STRENGTHENING CONFIDENCE IN THE EXPERIMENTAL RESULT**

Good compliance of subjects is the key to guaranteeing the quality of clinical trials[17]. In clinical multicenter trials of moxibustion, a broad source for the included population, the characteristics of the interventional measures and a long period of observation make the compliance of subjects different from their compliance in general clinical trials.

**Course of treatment intervention**

Research shows that the compliance of patients is negatively correlated with the complexity of the interventional plan (such as the times, dosage and frequency of medication)[18]. Combined use of many drugs will reduce the compliance of patients. The longer the therapeutic time is, the poorer the compliance will be[19,20]. In the project, both the heat-sensation moxibustion and Shulida used in the two groups are interventional methods, particularly the Shulida used in the control group[21]. Shulida, a mixed dosage form of salmeterol and fluticasone propionate, as a powder inhalant, conforms to the interventional requirements of a compound drug for patients with chronic asthma and is convenient for subjects to use[19,20]. The two groups were treated for 3 months. In consideration of the characteristics of moxibustion, subjects should generally go to research units for treatment. Too frequent moxibustion treatments will inevitably influence the work or study of subjects and reduce compliance. Therefore, the task group used a method of management in sections. Subjects were treated for 8 days in a row from their first visit, once every day; 12 treatments were guaranteed in the last 22 days of the first month; and 15 treatments were guaranteed every month in the next two months (6 once every day).

**Safety of moxibustion and adverse drug reactions**

Although moxibustion is a green therapy without trauma, appropriate measures should be taken before treatment to guarantee the safety of moxibustion. Before moxibustion, the physician should put the subject in a calm environment and pay close attention to the burning condition of the moxa roll in order to avoid scalding.

**Effectively measuring compliance**

The interventional plan of the project consists of two completely different types of therapeutic measures: heat-sensation moxibustion and inhalant medication. The task group used different methods to evaluate subjects in the two groups. In the experimental group, moxibustion dosages were collected from physicians and subjects and their original data were checked at moxa-roll distribution centers to calculate the compliance of subjects. In the control group, researchers calculated the rate of medication use by subjects according to the surplus drug in the inhaler[24,25].

**CREATING A GOOD PHYSICIAN-PATIENT ENVIRONMENT**

In the project, because of the long period of observation, it is very difficult for some patients to persist in treatment once their symptoms have been improved. Therefore, it is necessary to establish a communication channel. All the researchers have a card for contact with subjects, on which the name, telephone number and address of the subjects are recorded. Researchers encourage patients to write a medication diary. A benign system for feeding back information among physicians, nurses and subjects is formed to make subjects feel safe and at ease during the process of the trials without dropout of cases due to the long periods between follow-up visits.

**SUMMARY**

Understanding the characteristics of research design and implementing progressive optimization of the research plan are two trends in the methodology of clinical research into acupuncture and moxibustion at present. We have earnestly sorted out, summed up and extracted the results of previous researches and the conditions of clinical practice, formed a preliminary clinical treatment plan according to the aims and demands of this research, reached consensus after full discussion by experts in the task group and participating units, absorbed proposals from well-known experts in methodology, statistics and clinical practice in reference to the latest research achievements at home and abroad, and optimized and perfected the experimental plan.

In order to guarantee the quality of the research task and the reliability of the research results, researchers must implement scientific and rational quality supervision. Although relevant standards for managing clinical trials can be used for reference, it is necessary for researchers to constantly re-examine the moxibustion tri-
al because of its unique characteristics. The project is a beneficial exploration to constantly perfect and optimize the supervision plan from application for the task, through proof by experts, to implementation of the task in order to strive to absolutely guarantee the reliability of the research results. In addition, multicenter clinical trials on moxibustion aim at objectively and accurately evaluating the curative effect and safety of moxibustion. It is necessary for designers to consider if moxibustion and non-moxibustion are correctly implemented in order to reduce the dropout rate and enhance the compliance of subjects. In short, in implementing multicenter clinical randomized controlled trials on moxibustion with high quality and large samples, it is necessary for research units to have good researchers, adequate technical platforms and a highly standardized, scientific and feasible methodology of research. The task group believes that scientifically designing the plan, optimizing the contents of plan, supervising quality and strengthening compliance are the key links.

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