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Factors influencing the quality of clinical trials on traditional Chinese medicine—Qualitative interviews with trial auditors, clinicians and academic researchers

Xue-yan Han[a,b,1], Xun Li[a,1], Ning Liang[a], Yu-qian Yan[a], Ying Wang[a], Yu-tong Fei[a], Ying Zhang[a], Nicola Robinson[a,c], Jian-ping Liu[a,*]

[a] Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China
[b] School of Public Health, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China
[c] School of Health and Social Care, London South Bank University, London, UK

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ABSTRACT

Background: As clinical trials evaluating the efficacy of traditional Chinese medicine (TCM) therapies have increased, several empirical studies have shown that the quality of TCM trials is generally low in terms of risk of bias. This qualitative study aimed to investigate the factors influencing the quality of TCM clinical trials to provide strategic advice on trial quality improvement.

Methods: One focus group with clinical trial auditors (n = 4) and six in-depth semi-structured interviews with clinical research organization managers (n = 2), lecturers and researchers in TCM academic institutions (n = 2), a chief physician in a TCM oncology department and a PhD candidate specialized in non-pharmaceutical TCM interventions were conducted. The interviews were audio-recorded, transcribed verbatim and thematically analyzed.

Results: Factors that influenced the quality of TCM clinical trials emerged with the following 6 themes: trial design; trialists/participants; trial conducting; TCM specified problems; trial monitoring, and finally societal influences. The lack of expertise and time inputs of the trialists were repeatedly mentioned. Methodological difficulties experienced when conducting TCM trials including calculating sample size, analyzing the efficacy of TCM decoctions with multiple ingredients, blinding in trials investigating non-pharmaceutical TCM interventions were highlighted. Interviewees agreed that third-party monitoring can help improving trial quality and improve participant welfare, may accelerate recruiting processes and increase compliance; however more comprehensive regulations and funding requirements would be needed.

Conclusions: This study identified real-life issues influencing the quality of TCM clinical trials from design to reporting. In addition to mandatory training for TCM trial designers and coordinators, more effective institutional oversight is required. Future studies should explore specific measures to address the methodological problems in TCM trials and explore how the quality of TCM trials can affect further evidence synthesis and clinical practice.

1. Background

Traditional Chinese Medicine (TCM) therapies have been used in China for centuries and have attracted increasing attention in the world, yet lack of reliable evidence on its effectiveness and safety could be one of the impediments for its wider application. Although more and more TCM researchers acknowledge the importance of clinical trials [1,2], methodological appraisals and systematic reviews on the published TCM clinical trials suggest poor methodological and reporting quality [1,3,4], pointing out the need for quality improvement.

* Corresponding author. Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, 11 Bei San Huan Dong Lu, Chaoyang District, Beijing, 100029, China.

E-mail addresses: hanxueyan611@163.com (X.-y. Han), tina000341@163.com (X. Li), liangning229@163.com (N. Liang), tracyxing1214@163.com (Y.-q. Yan), 2232759289@qq.com (Y. Wang), yutong_fei@163.com (Y.-t. Fei), novelzhang@sina.com (Y. Zhang), nicky.robinson@lsbu.ac.uk (N. Robinson), jianping_l@hotmail.com, liujp@bucm.edu.cn (J.-p. Liu).

[1] Xue-yan Han and Xun Li contributed to the article equally.

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Table 1
Participant profile and interviewer information.

	Study ID	Academic Degree	Current Occupation	Years of work	Specialties	Professional title	Interviewer/conductor
Focus Group	FG	M.Sci.[a]	Clinical trial auditor	3	GCP audit	Junior[b]	XL
	FG	M.Sci.	Clinical trial auditor	3	Auditing and trial-site training	Junior	
	FG	B.Sci	Clinical trial auditor	2	GCP audit	Junior	
	FG	M.Sci.	Clinical trial auditor	6	Auditing and participant recruitment	Junior	
In-depth Interview	II-1	M.Sci.	CRO manager	7	Clinical trial auditing oversight	Middle	XL
	II-2	PhD	CRO manager	8	Auditing oversight and trial data management	Middle	XH
	II-3	M.D.	Researcher at China Academy of Chinese Medical Sciences	3	Design of clinical trials using integrative therapies	Senior	WY
	II-4	M.D.	Lecturer at BUCM	4	Laboratory and clinical studies on acupuncture	Middle	YY
	II-5	M.D.	Chief physician in tertiary TCM hospitals; clinical trials coordinator	10	TCM treatments in oncology; designing and coordinating multi-center trials	Senior	NL
	II-6	M.D.	PhD candidates studying at BUCM	NA	Non-pharmaceutical TCM treatments	Junior	XH

[a] M.Sci. stands for master of science.
[b] Junior means the participant is a junior title holder.

TCM clinical trials discussed in this study are clinical experiments intended to evaluate the efficacy/effectiveness and/or safety of interventions (medicinal or nonpharmacologic) based on TCM theories. There is an urgent need to ensure the quality of primary research, to ensure credibility and reliability of systematic reviews and which should be used to inform clinical guidelines on TCM treatments. Primary research, alone or synthesized eventually affects clinical practice.

Understanding the factors influencing the quality of TCM clinical trials would be the first step in formulating targeted strategies for improvement however the comprehensive research on this question is still rare. A few Chinese studies based on questionnaire surveys have reported that trial settings [5] and characteristics (such as age, professional titles, years of practice) of the researchers [6] have potential influence on trial quality. There are quite a few Chinese papers analyzing the influencing factors of trial quality but only based on author's experiences or opinions [7–13] rather than providing qualitative/quantitative evidence. Several qualitative studies outside China have tended to focus on a specific phase of clinical trials, e.g. trial design or enrollment [14–19] instead of the whole process.

Using qualitative research methods (focus group and in-depth interview), this study aimed to investigate factors influencing the quality of TCM clinical trials. By interviewing trial designers, key investigators, trial coordinators and trial auditors, more detailed information could be obtained to understand perceptions and potential barriers to trial quality.

2. Methods

2.1. Selection of participants

All participants were selected using the homogeneous convenience sampling method as described in Jager et al 2017 [20]. This approach limits the sample to a particular subgroup which gives a homogeneous population. Using this method, we restricted our participants to people who had taken part in at least one clinical trial on TCM in the previous 5 years and based in Beijing. XL was in charge of the recruitment.

2.2. Data collection

One focus group discussion (with 4 participants) and 6 in-depth interviews were conducted between March to April 2017. All participants provided written consent. All interviews were conducted at the workplaces of the participants. Ethical approval was obtained from the ethics committee of BUCM (No. 2017BZHYLL0303).

The semi-structured interview guide was developed after conducting a literature review and brainstorming. Three pilot interviews were conducted before the guide was finalized. Major questions in the interview guide were as follows:

1) Please describe a clinical trial that you are involved with currently or previously (no confidential information required).
2) From score 0 to 10, please rate a few clinical trials that you have been involved with or read about. Probe all the reasons for the rating.
3) Based on your own experience and understanding, what factors may affect the quality of clinical trials? Probe: Why?
4) What would you say are the main difficulties and problems that TCM trials are particularly faced with? What make TCM clinical trials different?
5) What might, in your opinion, improve the quality of TCM clinical trials?

2.3. Data analysis

All interviews and discussions were audio-recorded and transcribed

by the authors verbatim. Any private details concerning individual participants was anonymized. Thematic analysis was undertaken [21,22] and open coding was carried out by the authors independently. We then categorized the codes, merging redundant or unnecessary codes in the process and updated the codebook. Based on the finalized codes, all researchers reached an agreement on the coding and themes for the transcription. XH, XL and YF led several discussions in which themes were synthesized from the codes and quotations [23]. The computer software RQDA (R package for qualitative data analysis) was used for data storage and analysis.

3. Results

All the people (n = 10) we approached agreed to participate in the interview and became our participant. Detailed information of participants is presented in Table 1. The clinical trial auditor participants worked in a contract research organization (CRO) that focused on auditing TCM trials. One of the specialties for participants in the focus group was the Good Clinical Practice (GCP) audit. Participant II-3 and II-5 were masters student advisers, at a research institute and TCM hospital respectively.

From the focus group and individual semi-structured interviews, six major themes were identified. A total of 32 codes as influencing factors emerged (Table 2).

3.1. Trial design

To begin with, most interviewees emphasized that study design has major influence on the quality of clinical trials. Whether the trial was investigating a clinically important question and whether the methods chosen by the trialists were realistic and practical required serious consideration. Sometimes due to lack of funding or human resources, compromises and change of plans had to be taken into consideration. Sample size determination was also highlighted as one of the biggest challenges for designing TCM clinical trials.

> *"The reason why it is so hard to determine the sample size for TCM clinical trials is that the effectiveness rates of TCM interventions are hard to calculate. Some foreign experts suggest the rate should be around 7–8%, but in that way the sample size would be more than 1,400—too big for any government funded project." (II-5)*

In addition, the selection of trial centers (for multi-center and large-scale trials) and identifying appropriate personnel was of critical importance. It was also pointed out that when designing the trial, clinical trials should consider the inclusion of a management team, so that the quality, progress, financial affairs can be addressed.

> *"Actually, clinical trials may struggle with managing their schedules, regardless of their sources of funding. They always drag their feet at the beginning and when the deadline approaches, they would rush to the end. That is not helpful for quality assurance." (II-2)*

3.2. Trialists/participants

Interviewees remarked that Chinese doctors are often busy being both clinicians and trialists and that puts doctors under great pressure. The doctors' solution was usually to get their "juniors" to do the job. The juniors were usually postgraduate students working as interns in the hospitals. The interviewees all agreed that many clinical trials were actually conducted by these students. The problem is that students were shifting between departments and possibly lack of necessary training and the sense of responsibility. When the students ended their shift in the department, they left the trial duty behind and other people would have to take over. The transition process may create many problems.

> *"The postgraduate students are not professional trialists. When they tried*

Table 2
Factors influencing the quality of TCM clinical trials.

Themes						
1	2	3	4	5	6	
Trial design	**Trialists/participants**	**Trial conducting**	**TCM specified Issues**	**Monitoring and auditing**	**Societal influence**	
Codes						
1) Define research questions	1) Paperwork transition	1) Trial sites	1) "Unprofitable" interventions	1) Third-party monitoring	1) Media coverage	
2) Significance and influence of the question	2) Time and energy of the trialists	2) Clinical trial coordinators	2) Patient recruitment	2) Professionalism of the auditors	2) Patient's opinions on clinical trials	
3) Feasibility of the trial	3)Training of the staff	3) Data management	3) Herbal injections	3) Limitation of trial audit	3) Government funded projects	
4) Sample size calculation	4) Professionalism of the trialists	4) Statistical analysis	4) Syndrome differentiation	4) On-site audit	4) Regulations on the clinical trials	
5) Personnel/center selection	5) Patient compliance	5) Trial progress monitoring	5) Placebo selection			
6) Project management	6) Participant traits		6) Nonpharmacologic TCM treatments			
			7) "Subjective" diagnostic procedure			
			8) TCM decoction			

to recruit patients, they are not skillful in getting the informed consents. These untrained personnel can cause serious delay in participant recruitment and poor patient compliance. The quality and progress of the entire trial can be affected." (FG)

The characteristics of the potential participants also made the trial conduct extra challenging.

"The patients seeking medical attention nowadays are mostly people in their fifties or sixties. It's not uncommon for people at this age in China to have poor education level due to the Culture Revolution in the 1960s and 1970s. This makes communicating with them a harder job." (II-6)

Interviewees suggested that the clinical trials conducted in hospitals should add a research assistant position so that the pressure on the practitioners can be partly relieved.

3.3. Conducting the trial

Facilities and equipment at the trial sites can have huge influence on the trial too. Although a trial may be primarily conducted in one department, the characteristics of the entire research institute has a contextual effect on the research quality too. For example, whether the laboratory as well as the radiology and diagnostic imaging department in the hospital can provide timely results and offer repetitive tests on the trial participants. The administrative support and coordination of the entire trial facility can be vitally important in this regard.

"Hospitals in the rural areas or primary healthcare facilities are willing to conduct clinical trials, but those hospitals lack of the necessary equipment for many outcome measurements. Tertiary hospitals in metropolises are well equipped but provide a much larger service throughput, they can spare few resources for the trial." (FG)

Some interviewees mentioned that the trial data management and the statistical analysis process can be problematic too.

"I think we should regulate the data management process and integrate data collection with data analysis. There should be a system which can track every revision or modification on the original data and if there is any modification, a sound reason has to be provided." (II-2)

3.4. TCM specific issues

Comparing TCM trials with trials on conventional medicine, two kinds of problems should be considered. One was the problems caused by the lack of methodological guidance for TCM trials. Selecting placebos for TCM treatments and the statistical analyses of the effect of TCM decoctions (which tended to have multiple ingredients) were common concerns of the interviewees.

"Some TCM studies would stress the traditional ways of data collection, which involve quite subjective diagnostic approaches such as inspecting, listening, inquiring and pulse taking. There can be very little objective data to back up those diagnoses and therefore it's hard to control the quality of those data." (II-1)

"There are TCM treatments concerns nonpharmacologic TCM treatments, such as qigong or Tai Chi. Blinding in a clinical trial investigating these therapies is almost impossible." (II-6)

The other issue were the problems steming from the theoretical framework and clinical practice of TCM. For example, the TCM hospitals in China were not as mainstream as hospitals specialized in conventional medicine, small outpatient visits could translate to increased difficulties in participant recruitment. Furthermore, the lack of standards in syndrome differentiation and low adherence to clinical guidelines were not only problems in clinical trials but also troublesome in clinical practices. Some interviewees mentioned the fact that in clinical practice, some TCM interventions were not very "profittable" comparing to for example major surgery or western medicines, thus limiting the funding and motivation of conducting TCM trials.

"Syndrome differentiation is mentioned in many study protocols; however, in real practice, clinical practitioners are quite different in terms of experience and educational background. The patients from northern and southern parts of China can have different body constitutions. Thus, the syndrome differentiation can mean different things in different trials. That can be very confusing and problematic." (FG)

3.5. Monitoring and auditing

Both the trial auditors and the trialists that were being interviewed agreed that introducing a third-party audit team would be helpful for trial quality assurance. Nevertheless, the auditors had limitations themselves and the monitoring process needed the support and cooperation from the trialists.

"We (trial auditors) would see how passive some trialists can be. When a problem arises, you expect them to tell you as soon as possible, but in fact they won't even mention it until your next visit to the center. Many consequent issues are irreversible till then." (FG)

"Some trial auditors are not even that qualified themselves. They have not been properly trained." (FG)

Apart from relying on the third-party audit, the trial sites should develop a more rigorous level 1 quality control scheme.

"I noticed that there are quality control divisions in some of the trial sites but their monitoring is not very effective. They tend to focus more on the paperwork than actual quality assurance." (II-6)

3.6. Societal influence

Societal factors can have direct impact on patients' view on clinical trials and compliance. Several interviewees mentioned the influence of media coverage.

"I saw some news agencies describe clinical trials as some evil human experience and compare trial participants to lab mice. I think that is not a very objective portrait and it certainly would mislead the public to a certain degree." (FG)

Some requirements in the government funded projects brought serious difficulties in the design and conduct of the clinical trials.

"I think it's fair to say that if the patients can get more concrete benefits from participating the trial, the progress on recruitment and the patient compliance would be improved significantly. Some free tests or medications or monetary compensations would help a lot." (FG)

"Some projects require the research to improve the curative rate of a disease by how much percentage. That's not a realistic aim for any study, how to measure it for example? And sometimes the government is in a big hurry to make progress, asking the clinical trials to produce results in 3 years or less. Nobody cares about the follow-up issues for trials on chronic diseases." (II-1; II-5)

Almost all interviewees mentioned in their suggestions for quality improvement that there should be budgets granted to pay for research assistants and patient compensations in the trial funding. In addition, trial sites that are focused more on conducting research than on carrying out clinical duties maybe a better place to conduct clinical trials, as the trialists would have more time and energy for the research. If the trial needs to be conducted in hospitals and by clinicians, trial designers should consider balancing the clinical and trial duty for the doctors at the protocol developing stage.

4. Discussion

This study explored the factors that influence the quality of TCM clinical trials from the perspective of trialists and used a qualitative approach, i.e. focus group and in-depth interviews. We categorized the 32 factors identified into 6 themes covering the whole procedure of conducting a trial. The interviewees in the study, with experiences of different phases of TCM trials as well as various education and academic backgrounds, were involved in TCM trials in different ways and offered a wide range of opinions on topic.

Compared with the previous studies, this research used qualitative research methods instead of a questionnaire survey or theoretical analysis, which allowed us to focus on specific issues of using TCM therapies as trial intervention, such as the application of syndrome differentiation. The research also explored the designing, conducting, monitoring and analyzing clinical trials.

Clinical research on TCM is not so different from trials on conventional medicine in terms of the challenges and obstacles they faced [22]. Djurisic et al. summarized 6 barriers of conducting RCTs within all disease areas as “inadequate knowledge of clinical research and trial methodology, lack of funding, excessive monitoring, restrictive privacy and lack of transparency, complex regulatory requirements, and inadequate infrastructures” [23]. Those barriers are consistent with findings of our study except for “excessive monitoring”. Djurisic's study argued that the International Conference on Harmonization (ICH) good clinical practice (GCP) guidelines were not required by the law and may or may not improve the quality of the trial, yet added huge burdens to the trialists [23]. However, in our study the interviewees stressed the necessities of trial monitoring. We would recommend increasing monitoring and quality control measures over saving funds because the trials in China are often conducted without proper monitoring thus causing trial quality problems [4].

Most of our interviewees had found difficulties in designing TCM trials to test various research hypotheses as TCM interventions tend to be complex and individualized. Better understanding of TCM as well as clinical trial methodology was needed to work out the modality suitable for TCM trials and its phases. In designing the trial protocol, multidisciplinary coordination involving clinical, methodological as well as statistical expertise is important [24].

Lots of problems were mentioned by the interviewees regarding conducting TCM trials. Trialists called for more adequate planning prior to the commencement of the trial. Trial registry, as well as the preparation and publication of comprehensive protocol and the manual of operations should be the new norm among the researchers and these standardized procedures will need to be followed. Lack of the expertise in conducting trials and poor infrastructure of the trial sites are universal problems [25] and can be addressed through better multidisciplinary coordination. For TCM trials, profound understanding of TCM theories is additionally required.

Our interviewees strongly emphasized that data authenticity, quality, completeness, and timeliness would have significant impact on the trial quality. A 2016 report from China FDA pointed out that 80% of China's clinical trial data were fraudulent [26], indicating the gravity of this issue. We suggest a two-pronged strategy for the data management problem: one is to enhance the power of the institutional supervising body, building the Chinese equivalent of “Data Safety and Monitoring Board” or extend the responsibility of the Institutional Review Board or the Ethical Committee, now present in most hospitals and academic institutions in China. The institutional oversight can be the first line of defense in data integrity; the other is to tackle the incentives for data modification and that is related to reporting the trial results to the government and/or to the scientific community.

The limitation of this study was primarily the sample size. However, using convenience sampling, we managed to reach a group of participants who assumed diversified roles in clinical trials. This enabled us to investigate a group of interviewees with a different level of trial experience, different occupations and different roles in trials. Another problem with the sample was that since all the participants were recruited from Beijing, they may not be representative enough for the trialists in China. Nevertheless, Beijing is the capital of China and it has a lot of trial sites suitable to conduct clinical research. In addition, some trialists participated in this study did travel around the country to supervise the trial sites in other regions. Therefore, we consider this as a valid sample for study.

Trial reporting and publication is also important for trial quality as clinical evidence, but our study covered very little on this part as we mainly focused on the process of trial implementation, and our interview did not emphasize this issue. Future study should consider to include views from not only the trialists but also other personnel in the industry, such as experts on evidence syntheses and grading, editors of medical journals, officials who assess and approve funding and together the group may unveil more potential challenges and solutions pertaining to the quality improvement of clinical trials.

5. Conclusion

This study applied qualitative research methods to explore the experiences as well as the point of view of TCM clinical researchers. We have identified and categorized the influencing factors of TCM clinical trials into 6 themes: trial design; trialists/participants; trial conducting; issues for trials on TCM; monitoring and auditing as well as societal influences. The results of this research may attract attention on the need for TCM trial quality improvement, and provide a reference point for the prospective TCM clinical trials. Future studies may focus on exploring specific measures to address the various problems of TCM trials or discovering how the quality of TCM trials can affect further evidence synthesis and clinical practice.

Authors' contributions

XH, LN, YY, YW and XL participated in the research design and project implementation. YF, JL and YZ participated in pre-interviews. XH, LN, YY, YW and XL participated in the data analysis. XH wrote the original manuscript. XL, YF, JL and YZ all helped with revision. NR and JL were instrumental in the language editing and offered essential consultancy. All authors read and approved the final manuscript.

Ethic approval

The ethic approval was obtained from the ethic committee of Beijing University of Chinese Medicine (No. 2017BZHYLL0303)

Conflicts of interest

The authors declare that they have no competing interests.

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