Improve the ethical review of clinical trials on traditional medicine

A cross-sectional study of clinical trial registration, ethical review, and informed consent in clinical trials of Traditional Chinese Medicine

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Abstract
Recently, there is an increasing number of clinical trials on Traditional Chinese medicine (TCM) published, but the implementation of Clinical Trial Registration (CTR), Ethical Review (ER), and Informed Consent (IC) in clinical trials of TCM is unclear. This study aims to investigate the status of CTR, ER, and IC in clinical trials of TCM.

Clinical trials of TCM published in 10 high-quality Chinese journals in 2016 were selected as a sample. Information of clinical trial registration, ethical review, and informed consent of clinical trials was extracted for analysis. Two authors independently screened the literature and extracted the relevant information.

A total of 659 clinical trials met the criteria and were included for analysis. Only 9 clinical trials reported information of clinical trial registration (1.4%). The number for ethical review and informed consent were 156 (23.7%) and 502 (76.2%).

Trial registration, protocol approval, and informed consent were not well executed. Especially registration and ethical review of clinical trials in TCM should be carefully concerned by researchers, clinicians, and journal editors. Training on methodology of clinical trial should be strengthened.

Abbreviations: CTR = clinical trial registration, ER = ethical review, IC = informed consent, TCM = Traditional Chinese Medicine.

Keywords: clinical trial registration, ethical review, informed consent, Traditional Chinese medicine

1. Introduction
The Declaration of Helsinki claims that clinical study protocol can be implemented only after approved by Ethics Committee. All clinical trials’ protocol need to be registered in public accessible database before the first subject is enrolled. International Committee of Medical Journal Editors (ICMJE) also declared that the results of clinical trials could be published only after being registered in international institution.

In China, 48 Chinese medical journals and Chinese Clinical Trial Registration (ChiCTR) had developed a Chinese Clinical Trial Registration and Publishing Collaboration (ChiCTRPC) in 2006. From 2007, ChiCTRPC member journals (added to 52) implemented a policy that the clinical trials with the unique global registration ID can be preferentially published. In 2010, ChiCTRPC proposed establishing a system combined with the ER and CTR together to improve the quality of clinical trials. Although the related requirements had been released, it was unsatisfactory executed. To analyze and improve the implementation of CTR, ER, and IC in clinical trials of TCM, we developed a cross-sectional study based on literatures.

2. Methods
2.1. Selection of journals
According to their impact factors (IF) in 2016, top 10 Chinese journals cited in Chinese Science Citation Database (CSCD) were chosen as a sample. The top 10 journals (IF from high to low) are Acupuncture Research, China Journal of Chinese Materia Medica, Chinese Journal of Integrative Medicine, Chinese Traditional and Herbal Drugs, Journal of Beijing University of Traditional Chinese Medicine, Chinese Acupuncture and Moxibustion, Journal of Traditional Chinese Medicine, Chinese Journal of Experimental Traditional Medical Formula, Journal of Nanjing University of Chinese Medicine, China Journal of Traditional Chinese Medicine and Pharmacy.

2.2. Inclusion and exclusion criteria
All prospective clinical controlled trials published in the top 10 journals in 2016 were considered as eligible in this study, including
randomized controlled trials (RCTs) and nonrandomized controlled trials (NRCTs) of TCM. Other studies including observational study, retrospective study, and descriptive study were excluded. The intervention measures of TCM included herbal decoction, Chinese patent medicine, acupuncture, electric acupuncture, moxibustion, massage, cupping, herbs combined with conventional therapies. There were no limitations to the types of diseases and interventions in the control group and outcome measures.

2.3. Data extraction and analysis
Two authors (Zhao, Yang) screened literatures and extracted information independently, any disagreements were resolved by discussion with a third review author (Zhang). Trials reported that the study protocols have been reviewed by the Ethics Committees/Institutional Review Boards (ECs/IRBs) means the acquisition of ER. Trials reported “participants signed informed consents” were regard as the acquisition of IC. Trials reported registration platform and/or registration ID were regarded as registration. The quantities and proportions of CTR, ER, and IC were calculated with Microsoft excel.

3. Results
3.1. The flow of eligible literatures
There were 5710 all type of articles published in the top 10 Chinese journals in 2016. After reading titles and abstracts, 4971 irrelevant items were excluded. Full text would be read if we were not sure about the type of the article. The final study sample consisted of 659 records: 630 RCTs, 29 NRCTs (Fig. 1).

3.2. The situation of CTR, ER, and IC in clinical trials
Only 9 RCTs (1.4%) of the 659 clinical trials reported the information of CTR which were published in China Journal of Chinese Materia Medica (n=2), Chinese Journal of Integrative Medicine (n=1), Journal of Traditional Chinese Medicine (n=1), China Journal of Traditional Chinese Medicine and Pharmacy (n=5). Eight clinical trials were registered in Chinese Clinical Trial Registration (ChiCTR), one RCT was registered in Clinical trials. Gov. The results show that localized language CTR platform was easily recognized and used by local researchers and can propel the progress of CTR. RCTs published in Chinese Materia Medica had the highest proportion of reporting registration (16.7%) (Table 1).

There were 156 RCTs (23.7%) reported ER information. Clinical trials with high reporting rate of ER were 3 journals which were Chinese Journal of Integrative Medicine (60.0%), China Journal of Chinese Materia Medica (58.3%), Chinese Traditional and Herbal Drugs (56.3%). Other journals had a low reporting rate of ER (Table 1).

| Total records number (n=5710): | Acupuncture Research (n=109), China Journal of Chinese Materia Medica (n=742), Chinese Journal of Integrative Medicine (n=317), Chinese Traditional and Herbal Drugs(n=715), Journal of Beijing University of Traditional Chinese Medicine(n=200), Chinese Acupuncture and Moxibustion (n=392), Journal of Traditional Chinese Medicine(n=556), Chinese Journal of Experimental Traditional Medical Formula(n=1094), Journal of Nanjing university of Chinese medicine(n=151), China Journal of Traditional Chinese Medicine and Pharmacy (n=1434) |
| Obviously irrelevant articles by reading titles and abstracts (n=4870): | Descriptive studies (n=1785), Animal experiment studies (n=2622), Reviews (n=355) Observational studies (n=191) |
| The numbers of clinical trials (n=757) | |
| Excluded numbers after reading full text (n=98): | Descriptive studies (n=66), Retrospective studies (n=11), Observational studies (n=21) |
| The final numbers of clinical trials (n=659): RCTs (n=630), NRCTs (n=29) |

Figure 1. The flowchart of the selection of eligible clinical trials. NRCTs = Non-randomized controlled trials, RCTs = Randomized controlled trials.
There were 502 clinical trials (76.2%) reported that the subjects signed IC. For different journals, the informed consents of patients varied from 50% to 90.3% (Table 1).

### 3.3. The situation of CTR, ER, and IC in different research units

The principal investigators of 659 clinical trials were from different research units including the affiliated hospitals of medical college (n=273), municipal hospitals (n=137), medical colleges (n=131), provincial hospitals (n=84), other primary units (n=27), and research institutes (n=7). Clinical trials conducted by the research institutes had a higher rate in reporting CTR, ER, and IC (14.3%, 42.9%, and 100.0%) than other units (Table 2).

### 3.4. The situation of CTR, ER, and IC in clinical trials with or without funding

Among 659 clinical trials, 508 (77.1%) were supported with funding and the rates of CTR, ER, and IC were 1.6% (8/508), 23.4% (119/508), and 80.3% (408/508) in them. It was similar with the rate of CTR (1.3% [2/151]), ER (24.5% [37/151]), and IC (62.3% [94/151]) in no-funding trials. It seems that there was no relationship between funding and CTR/ER/IC (Table 3).

### 4. Discussion

The execution of CTR, ER, and IC in clinical trials of TCM was poor in this study. Only 1.4% trials reported CTR, and the number was 23.7% and 75.7% for ER and IC. The results of this study were similar to another study focused on stable angina.\(^{[5]}\)

There were several possible reasons causing these problems. First, the researchers did not recognize the importance of CTR, ER, and IC. Most of the principal investigators of trials are clinical practitioners in China, they did not clearly know the requirements and principles for design and managing. CTR, ER, and IC were not well completed in many single site trials due to the shortage of knowledge in clinical trial registration and research methods. Second, the journals did not strictly review the information of CTR, ER, and IC. Editors and peer reviewers may only review the contents and format of clinical trial papers, they did not review whether the RCTs were registered or not. A survey showed that half of the journals following ICMJE’s Recommendations and/or endorsing the CONSORT statement did not adhere to trial registration policy.\(^{[6]}\) Only one-third of peer reviewers checked registration information of clinical trials and reported to journal editors.\(^{[7]}\) Of the top 10 journals in this study, only 2 declared registration statement on their website.\(^{[8]}\) Third, the construction of IRBs/ECs system is not perfect. In China, all hospitals certified by the Chinese drug administration for clinical trial had IRBs/ECs, while other research units were lack of the construction of IRBs/ECs.

To deal with current problems, the counter measures should be taken. First of all, medical journals should pay more attention to information of trial registration, and strictly follow the principle of “No CTR, NO publication”. Statements should be declared in the websites of journals to inform authors. Second, it is necessary for researchers to recognize the importance of CTR and IC. Professional training related to clinical trial registration and ethics review should be strengthened for researchers and clinicians and medical students. In China, the trials with registration were implemented in where the Evidence Based Medicine (EBM) developed rapidly, such as Beijing, Shanghai, Guangzhou, Nanjing, Lanzhou, Sichuan, Tianjin. Therefore, it is

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### Table 1

| Journals’ name                                                                 | The number of clinical trials | CTR, n (%) | ER, n (%) | IC, n (%) |
|-------------------------------------------------------------------------------|------------------------------|-----------|-----------|-----------|
| Chinese Journal of Experimental Traditional Medical Formulae                   | 158                          | 0 (1.2)   | 27 (17.1) | 138 (87.3) |
| China Journal of Traditional Chinese Medicine and Pharmacy                    | 119                          | 5 (4.2)   | 15 (12.6) | 90 (76.3)  |
| Chinese Acupuncture and Moxabustion                                            | 103                          | 0 (0.0)   | 16 (15.5) | 87 (83.0)  |
| Journal of Traditional Chinese Medicine                                       | 92                           | 1 (1.1)   | 20 (21.7) | 68 (73.9)  |
| Chinese Journal of Integrative Medicine                                       | 85                           | 1 (1.2)   | 51 (60.0) | 68 (80.0)  |
| Journal of Nanjing University of Chinese Medicine                             | 42                           | 0 (0)     | 6 (14.3)  | 21 (50.0)  |
| Acupuncture Research                                                          | 20                           | 0 (0)     | 3 (15.0)  | 17 (85.0)  |
| Chinese Traditional and Herbal Drugs                                          | 16                           | 0 (0)     | 9 (56.3)  | 13 (81.3)  |
| Journal of Beijing University of Traditional Chinese Medicine                 | 12                           | 0 (0)     | 2 (16.7)  | 8 (66.7)   |
| Chinese Journal of Chinese Materia Medica                                    | 12                           | 2 (16.7)  | 7 (58.3)  | 9 (75.0)   |
| Total                                                                         | 659                          | 9 (1.4)   | 156 (23.7) | 502 (76.2) |

\(\text{CTR} = \text{clinical trial registration}; \text{ER} = \text{ethical review}; \text{IC} = \text{informed consent}.\)

### Table 2

| Name of research units       | Total numbers | CTR   | ER     | IC     |
|------------------------------|---------------|-------|--------|--------|
| Affiliated hospital of medical college | 273           | 5 (1.5%) | 57 (20.9%) | 201 (73.6%) |
| Municipal hospital           | 137           | 1 (0.7%) | 32 (23.4%) | 104 (75.9%) |
| Medical college              | 131           | 2 (1.5%) | 36 (27.5%) | 95 (70.2%)  |
| Provincial hospital          | 84            | 1 (1.2%) | 24 (28.6%) | 62 (73.8%)  |
| Others                      | 27            | 0 (-)   | 4 (14.8%)  | 23 (85.2%)  |
| Research institute           | 7             | 1 (14.3%) | 3 (42.9%)   | 7 (100.0%)  |
| Total                       | 659           | 9 (1.4%) | 156 (23.7%) | 502 (76.2%) |

\(\text{CTR} = \text{clinical trial registration}; \text{ER} = \text{ethical review}; \text{IC} = \text{informed consent}.\)

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### Table 3

| All clinical trials | CTR   | ER     | IC     |
|---------------------|-------|--------|--------|
| Funding             | 508   | 8 (1.6%) | 119 (23.4%) | 408 (80.3%) |
| No funding          | 151   | 2 (1.3%) | 37 (24.5%)  | 94 (62.3%)  |

\(\text{CTR} = \text{clinical trial registration}; \text{ER} = \text{ethical review}; \text{IC} = \text{informed consent}.\)
necessary to strengthen the education of EBM and clinical research methods for researchers around the country. Third, the function of IRBs/ECs should be improved. Online publication platform for ethical review can be established to compensate the deficiency of the ethical review committee in primary hospitals.

5. Conclusions
Clinical trial registration, ethical review and informed consent played important roles but had received little attention in clinical trials of TCM. Therefore, we suggest that researchers, editors, reviewers, along with ethics committees be involved in the process of improving the quality and transparency of clinical trials in China. Education and training on methodology of clinical trial should be strengthened to ensure accurate and reliable scientific results.

Author contributions
Conceptualization: hongjie Zhao, Junhua Zhang.
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