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EXAMINATION OF CLINICAL TRIALS IN TRADITIONAL CHINESE MEDICINE: ENHANCEMENT OF THE ETHICAL PROCESSES

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ABSTRACT

There is a current rise in published clinical trials relating to traditional Chinese medicine (CTM). However, the opposite execution of clinical trial registration (CTR), ethical review (ER), and informed consent (IC) relating to TCM trials are not elucidated. The current study aimed to examine CTR, ER, and IC in TCM clinical trials. TCM clinical trials selected from ten high-standard Chinese journals published in 2016 formed the study sample. Data relating to CTR, ER, and IC associated with the respective publications were obtained for further interpretation; these were acquired through two researchers' independent reviews of the chosen papers. Six hundred fifty-nine clinical trials fulfilled the study's inclusion criteria and were subject to analysis. Data of CTR, ER, and IC were evident in 9 (1.4%), 156 (23.7%), and 502 (72.6%) articles, respectively, and were poorly implemented. In particular, CTR and ER of TCM clinical trials should be assiduously considered by scientists, physicians, and journal editors. Education on related methodology should be made more robust.

1. Introduction

The Helsinki Declaration states that clinical studies may only be commenced once endorsed by the relevant ethics committee [1]. Any protocol for a clinical trial is required to be entered into a database that has open access for the public prior to recruitment of any participants [1, 2]. The International Committee of Medical Journal Editors (ICMJE) has stipulated that clinical trial data can only be accepted for publication following registration with an international professional body [3, 4]. In 2006 in China, a Chinese Clinical Trial Registration and Publishing Collaboration (ChiCTRPC) was instituted, comprising 48 Chinese medical journals (now 52) and the Chinese Clinical Trial Registry (ChiCTR) [5, 6]. In 2007, ChiCTRPC member journals promulgated a policy indicating a favoured publication strategy towards clinical trials that had a distinct worldwide registration identifier [7-10]. Subsequently, in 2010, an approach incorporating both ER and CTR was suggested by the ChiCTRPC in order to improve clinical trials' standards [11]. However, although the requisite criteria were made public, the policy was not implemented in a satisfactory manner [12].

A cross-sectional study based on previous publications has therefore been designed in order to assess and to enhance the execution of CTR, ER and IC with respect to TCM clinical trials.

2. Methods

2.1. Journal Selection

The highest ten Chinese journals were selected as the study sample based on their impact factor (IF) as indicated in the Chinese Science Citation Database (CSCD). These are listed in order, from highest to lowest IF, and comprise: 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

Any prospective clinical controlled trials presented during 2016 in the chosen journals were deemed suitable for incorporation into the current study. Both randomised controlled trials (RCTs) and non-randomised controlled trials (NRCTs) relating to TCM were accepted. Papers where the study design was observational, retrospective or descriptive were discarded. The range of TCM interventions included in the sample encompassed: herbal decoction, Chinese patent medicine, acupuncture, electric acupuncture, moxibustion, massage, cupping, and herbs complementary to conventional

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treatments. No restrictions were placed on the spectrum of pathologies or interventions within the control cohort or in relation to study endpoints.

2.3. Data Extraction and Analysis

Publication screening and data gathering were performed by two researchers (Zhao and Yang) autonomously; any debate was arbitrated by a third author (Zhang). The definition of ER receipt was a statement that the study protocol had been endorsed by an ethics committee (EC) or international review board (IRB). If it were documented that study subjects had signed an IC, this was accepted as evidence of IC. Trial registration was considered to have occurred if the publication provided a registration platform or unique identifier. Computations with respect to the frequencies and percentages of these factors were performed in Microsoft Excel.

3. Results

3.1 Flow of Eligible Publications

5710 articles in total were printed in the selected journals during 2016. Following screening of the titles and abstracts, 4971 unrelated papers were discarded, with full text being perused if the pertinence of the article were unclear. The ultimate study sample comprised 659 articles, i.e. 630 and 29 RCTs and NRCTs, respectively (Figure 1).

3.2 Frequency of CTR, ER and IC According to Journal

Of the 659 clinical trials reviewed, only 9 (1.4%) RCTs provided any statement pertaining to CTR; these were printed by the China Journal of Chinese Materia Medica (n = 2), Chinese Journal of Integrative Medicine (n = 1), Journal of Traditional Chinese Medicine (n = 1), and the China Journal of Traditional Chinese Medicine and Pharmacy (n = 5).

Study registration with the ChiCTR was documented by 8 articles; one clinical trial reported registration with the website, clinicaltrials.gov. The data demonstrated that a regional linguistic CTR stage was straightforward to find and to utilise by scientists and could drive the progress of CTR forwards. The highest percentage, 16.7%, of papers indicating CTR were printed in Chinese Materia Medica (Table 1).

Data pertaining to ER were presented by 156 (23.7%) RCTs. These were particularly evident in 3 journals, i.e. Chinese Journal of Integrative Medicine (60.0%), China Journal of Chinese Materia Medica (58.3%), and Chinese Traditional and Herbal Drugs (56.3%). The remaining journals exhibited a low frequency of reference to ER (Table 1). The remaining journals exhibited a low frequency of reference to ER (Table 1).

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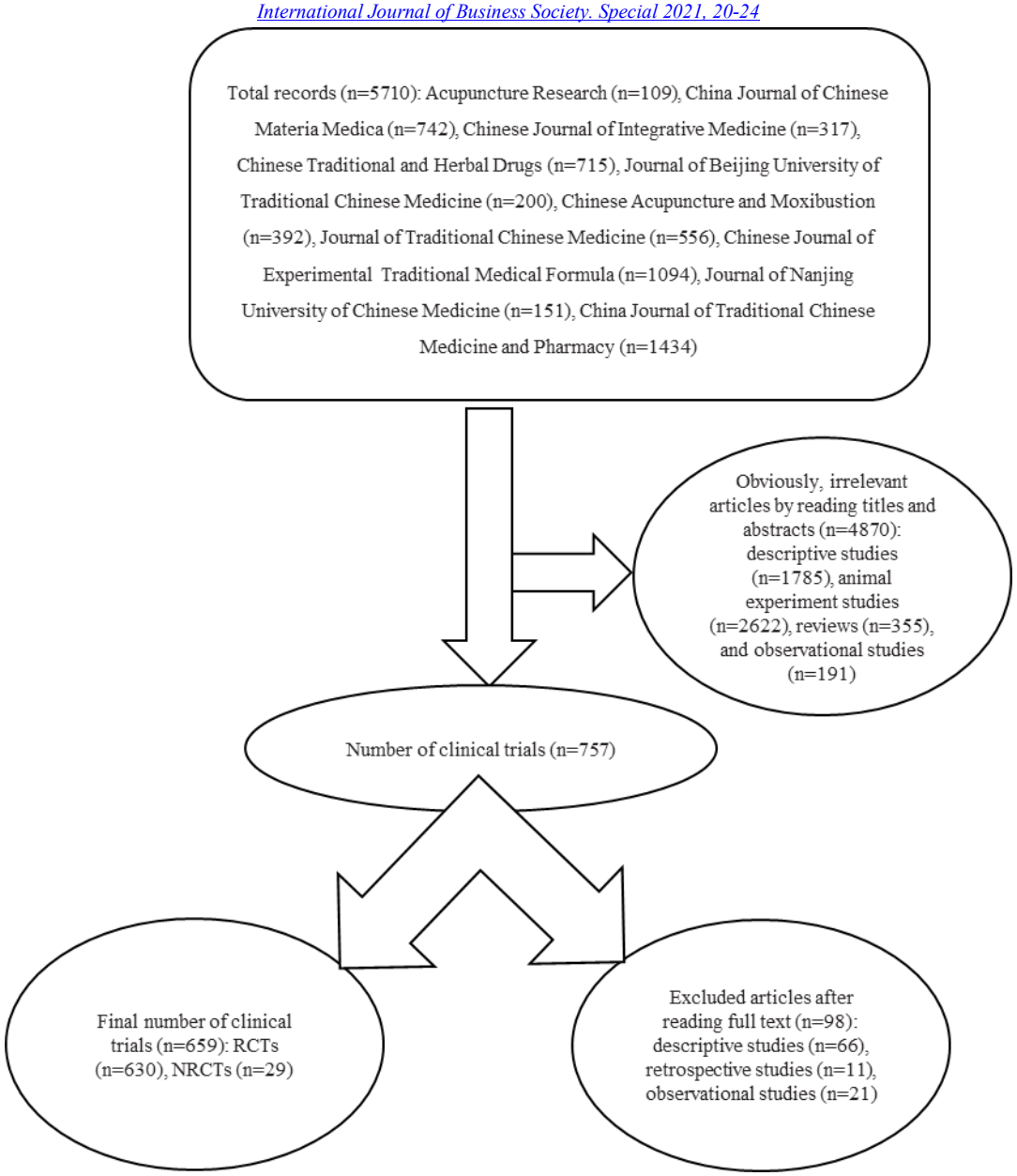

Figure: 1 Flowchart representing the eligible clinical trial selection process. NRCTs = non-randomised controlled trials, RCTs = randomised controlled trials.

Table: 1 Frequency of clinical trial registration (CTR), ethical review (ER) and informed consent (IC) according to journal (papers published in 2016). – indicates no available data.

Journal name	Number of clinical trials	CTR, n (%)	ER, n (%)	IC, n (%)
Chinese Journal of Experimental Traditional Medical Formulae	158	0 (–)	27 (17.1)	138 (87.3)
China Journal of Traditional Chinese Medicine and Pharmacy	119	5 (4.2)	15 (12.6)	67 (56.3)
Chinese Acupuncture and Moxibustion	103	0 (–)	16 (15.5)	93 (90.3)
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 (–)	6 (14.3)	21 (50.0)
Acupuncture Research	20	0 (–)	3 (15.0)	17 (85.0)

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Chinese Traditional and Herbal Drugs	16	0 (–)	9 (56.3)	13 (81.3)
Journal of Beijing University of Traditional Chinese Medicine	12	0 (–)	2 (16.7)	8 (66.7)
China 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)

Statements claiming that participants signed IC were made by 502 (76.2%) papers. Frequency of IC amongst the various journals ranged between 50% and 90.3% (Table 1).

3.3 Frequency of CTR, ER and IC According to Research Unit

The distribution of the main researchers amongst various institutions was as follows: allied hospitals of medical colleges (n= 273), municipal hospitals (n= 137), medical colleges (n= 131), provincial hospitals (n= 84), other primary units (n= 27), and research institutes (n= 7). When judged against the other sources, studies published by research institutes exhibited a higher frequency of referencing CTR, ER, and IC, i.e. 14.3%, 42.9% and 100.0%, respectively (Table 2).

3.4. Frequency of CTR, ER and IC According to Funding Status

508/659 (77.1%) of clinical trials had funding; these displayed frequencies for CTR, ER and IC of 1.6% (8/508), 23.4% (119/508) and 80.3% (408/508), respectively. In clinical trials without funding, the corresponding frequencies were comparable, i.e. 1.3% (2/151), 24.5% (37/151) and 62.3% (94/151), respectively. No associations between clinical trial funding status and references to CTR, ER or IC, respectively, were identified.

Table: 2 Frequency of clinical trial registration (CTR), ethical review (ER) and informed consent (IC) according to research unit. – indicates no available data.

Name of research unit	Total number	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%)	105 (80.2%)
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%)

Table: 3 Frequency of clinical trial registration (CTR), ethical review (ER) and informed consent (IC) according to funding status.

	All clinical trials	CTR	ER	IC
Funding	508 (77.1)	8 (1.6)	119 (23.4)	408 (80.3)
No funding	151 (22.9)	2 (1.3)	37 (24.5)	94 (62.3)

4. Discussion

Implementation of the policy about CTR, ER, and IC appeared suboptimal in the clinical trials included in the current review. CTR was only referenced by 1.4% of the tests in the sample; ER and IC information was provided in 23.7% and 75.7%, respectively. The data presented in this work are comparable to another publication for which the emphasis was on stable angina [13].

Several rationales can be postulated to explain these issues. Firstly, it is possible that the person carrying out the studies failed to appreciate the import of CTR, ER, and IC. The majority of the primary investigators were clinical specialists practising in China and were unaware of the prerequisites and ethics relating to study design and conduct. Studies performed in alone centre displayed a low CTR, ER, and IC frequency, owing to a shortfall in their appreciation of CTR and research processes.

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Secondly, the journals per se failed to apply rigid review criteria regarding data provided on CTR, ER and IC, potentially critiquing the factual content of the articles and not acknowledging whether CTR information was given. Survey data demonstrated that 50% of the journals adhering to the recommendations suggested by ICMJE and supporting the CONSORT declaration still failed to comply with the trial registration policy [14]. Registration details for clinical trials were only verified by a third of peer-reviewers and relayed to editorial personnel at the journal. An assertion regarding registration policy was only published on their journal website by two of the ten high IF journals in the current review [15, 16].

Lastly, the configuration of the IRB and EC process is not flawless. Although in China, IRBs and ECs are present in hospitals acknowledged by the Chinese Drug Administration, they are absent in other research institutions.

To overcome these issues, the following corrective strategies should be employed. Firstly, medical journals should emphasise trial registration data and adhere rigidly to the tenet of 'no CTR, no publication'. Information for authors in this regard could be published on the journal websites.

Secondly, researchers must acknowledge the import of CTR, ER, and IC. Education about these factors should be more robust for all clinical personnel, e.g. scientists, physicians, and training. In China, registered trials were acknowledged in regions where advances relating to evidence-based medicine have accelerated, e.g., Beijing, Shanghai, Guangzhou, Nanjing, Lanzhou, Sichuan, and Tianjin.

Finally, the standards of IRBs and ECs should be upgraded. To counter any weaknesses in ECs located in primary hospitals, an online publication platform for ER could be instigated.

5. Conclusion

In CTM clinical trials, it was established that CTR, ER, and IC were prominent actors but were frequently overlooked. Thus, it is recommended that scientists, editors, reviewers, and ECs promote standards and openness concerning clinical trials in China. Teaching and training on clinical trial principles and methods should be more robust to facilitate precise and rigorous research data.

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