The Use of Pattern Differentiation in WHO-Registered Traditional Chinese Medicine Trials – a systematic review

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ABSTRACT

Introduction: Pattern differentiation is a critical component for traditional Chinese medicine (TCM) diagnosis and treatment. However, the issue of whether pattern differentiation is appropriately applied in TCM interventional trials, including Chinese herbal medicine (CHM) interventions and non-herbal TCM interventions, is unclear. The aim of this study was to i) systematically review the current status of pattern differentiation used in WHO-registered clinical trials for different types of TCM interventions; and ii) provide suggestions for improving the use of pattern differentiation in future clinical trial design.

Methods: The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) database was searched for all TCM interventional trials registered up to 31 December 2017. In this systematic review trials with a TCM pattern differentiation in their design were included. Descriptive statistics were collated to demonstrate the characteristics of pattern differentiation applied for different TCM interventional trials.

Results: Among 2,955 TCM interventional trials registered during 1999-2017, 376 (12.7%) trials included pattern differentiation. Of 376 trials, the use of pattern differentiation was identified in –title (30.6%), objective (50.5%), participants inclusion

(100%), outcomes (43.6%) and study background (12.5%). Further, 85.4% reported the specific name of the TCM intervention, 10.6% provided the intervention's targeted pattern, 83.8% reported the specific name of the TCM pattern, 7.2% presented diagnostic criteria for the pattern studied, and 19.1% adopted a pattern-related outcome as primary outcome for evaluation.

Conclusion: The reporting and application of pattern differentiation in TCM trials were inadequate and confusing, which was mainly due to lack of clarity regarding study design, objectives, diagnostic criteria and outcomes.

Key words: Pattern differentiation; Clinical trial registration; Traditional Chinese medicine; Chinese medicine interventions; WHO registries; Systematic review

1. Introduction

Traditional Chinese medicine (TCM) is one of the oldest medical systems in the world, it is widely used in China and other East Asian countries, and increasingly throughout the rest of the world. It is perhaps the most widely practiced system of traditional east Asian medicine in many of those countries. It has long been thought to offer the possibility of offering an individualized approach to treatment [1]. The advent of personalized medicine with its tailored and individualized approach to diagnosis and treatment of disease may further demonstrate the importance, unique features and impact of pattern differentiation as applied in the clinical practice of TCM [2]. More recently, the WHO has released the new International Classification of Diseases (ICD-11), which includes new chapters, including one on traditional medicine conditions (e.g., This chapter refers to disorders and patterns which originated in ancient Chinese Medicine and are commonly used in China). Although

millions of people use traditional medicine worldwide, the diagnostic categories for traditional medicines have never been classified in this system [3]. Currently, TCM's impact worldwide is increasing and there is a pressing need to further develop the unique aspects of its clinical practice [4]. There exists a variety of TCM interventions, such as Chinese herbal medicines (CHM), acupuncture, moxibustion, tuina (massage), cupping, guasha (scraping), Qigong, Tai Chi, etc.; however, the success in deciding on a TCM intervention depends on an accurate pattern diagnosis known as *Bian-Zheng-Lun-Zhi* (e.g. treatment based on pattern differentiation) [5]. According to TCM theory, a TCM pattern (also termed a syndrome or *Zheng*) is a pathological cluster or summary of signs and symptoms at a certain stage of a disease. Dependent on the pattern, the pattern may include the cause, pathological feature, properties and the relationship between the pathogens and the body's resistance [6]. The patterns are named according to a cluster of associated signs and symptoms described in terms of yin, yang, exterior, interior, cold, heat, deficiency and excess, etc. A "pattern" (*Zheng*) is obtained through analyzing the "symptoms", while the "disease" (*Bing*) comprises the whole morbid process and may include several different patterns [7]. Specifically, pattern differentiation refers to the analysis and summarization of the clinical symptoms obtained through the four diagnostic methods of TCM (inspection, auscultation and smell, inquiry, and pulse taking and palpation), after which TCM practitioners can accordingly determine the treatment based on the patient's current essential pattern [8]. Accurate TCM pattern differentiation is critical and provides a diagnostic label as well as guiding the choice of TCM treatment using CHM and/or non-CHM interventions, utilizing the theory of correspondence between formula and pattern (e.g., *Fang-Zheng-Dui-Ying*) [9-10].

The reliable evidence to support how TCM treatment is based on pattern differentiation, usually depends on well-designed clinical trials, such as randomized controlled trials (RCTs) [11]. The first RCT using a TCM pattern differentiation design

was published in 1983 to examine the efficacy of CHM in primary liver cancer [12]. Since then, increasingly attention has been paid to the use of pattern differentiation in clinical trials [13-14]. Many TCM trials have preferred to adopt the model of integration of western medical (WM) disease and TCM pattern differentiation, for which the eligible participants are screened using both a WM disease criterion and TCM pattern diagnostic criterion [15-16]. TCM patterns have been used for many diseases in clinical trials, including irritable bowel syndrome [17], stroke [18], diabetic nephropathy [19], chronic obstructive pulmonary disease [20], and cancer [21]. Many scholars have suggested that patients with different diseases will benefit from TCM treatment according to pattern differentiation [22-23]. In practice, one disease may include several different TCM patterns, and conversely, different diseases may exhibit the same TCM pattern in the course of their development. Thus, the application of *Bian-Zheng-Lun-Zhi* may “treat the same diseases with different methods”, or it may “treat different diseases with the same therapeutic method” [24]. Up to now, the debate on the standardization of patterns, such as diagnostic criteria, common patterns of a disease, etc. still continues [25]. Specific diagnostic criteria of the pattern or the identification of the patterns of specific diseases continue to develop [26-27], however, many studies still do not report the diagnostic criteria of a pattern, or present different pattern criteria of the same disease, so the results from different studies cannot be compared [28-29]. For different types of TCM interventional studies, the use of pattern differentiation varies. Compared to CHM (i.e. fixed or individualized CHM formulas), the lack of pattern differentiation in Chinese proprietary medicine (CPM), acupuncture, cupping or other non-CHM treatment is evident in many clinical trials [30-32]. Liu has pointed out that the evaluation of TCM clinical trials have mainly been conducted according to the efficacy assessment of TCM pattern differentiation (e.g. pattern-related outcomes), although how to properly incorporate treatment based on pattern differentiation into a clinical trial remains complex [33].

There are no data on how many clinical trials using TCM intervention protocols have been based on pattern differentiation. In addition, it is unclear whether *Bian-Zheng-Lun-Zhi* has been rigorously applied across different types of intervention studies, as the theory of correspondence between formula and pattern is fundamental in correctly applying pattern differentiation [34]. For clinical research, the registration of a clinical trial is an important first step, and the study design of a trial should be reported at registration with a clear and transparent manner [35]. Given the importance of including the *Bian-Zheng-Lun-Zhi* in TCM trial design, the primary aim of this study was to examine TCM trials in WHO registries to identify specific features and common problems associated with the reporting of pattern differentiation design in trial registration records. A secondary aim was to provide suggestions for improving the quality of pattern differentiation design for future clinical trials.

2. Materials and methods

2.1. Data source

The database of the ICTRP (http://apps.who.int/trialsearch/) was searched on 15 January 2018 for all TCM trials that had been registered up to 31 December 2017. There are 17 Registries in the ICTRP which include the Australian New Zealand Clinical Trials Registry (ANZCTR), Chinese Clinical Trial Register (ChiCTR), ClinicalTrials.gov, EU Clinical Trials Register (EU-CTR), International Standard Randomized Controlled Trial Number Register (ISRCTN), the Netherlands National Trial Register (NTR), Brazilian Clinical Trials Registry (ReBec), Clinical Trials Registry-India (CTRI), Clinical Research Information Service-Republic of Korea (CRiS), Cuban Public Registry of Clinical Trials (RPCEC), German Clinical Trials Register (DRKS), Iranian Registry of Clinical Trials (IRCT), Japan Primary Registries Network (JPRN), Pan African Clinical Trial Registry (PACTR), Sri Lanka Clinical Trials

Registry (SLCTR), Thai Clinical Trials Register (TCTR), and the Peruvian Clinical Trials Registry (REPEC).

2.2. Search strategy

A standard Search, provided by WHO ICTRP (ICTRP Search Portal, http://apps.who.int/trialsearch/) was selected and the search strategy was undertaken using the terms 'Chinese medicine OR traditional Chinese medicine OR Chinese materia medica OR Chinese herbal medicine OR acupuncture OR moxibustion OR tuina OR massage OR cupping OR guasha', without any restrictions.

2.3. Inclusion and exclusion criteria

Firstly, Firstly, this study focused on TCM clinical trials that registered up to 31 December 2017, and did not examine other forms of traditional East Asian medicine such as those found in Japan, Korea, and thus does not reflect those systems. Thus, the following kinds of trials were excluded: Conventional Physical Therapy (CPT) or other Complementary Alternative Medicine (CAM) rather than TCM; Swedish/Thai/ice/aroma massage; Korean medicine which clearly identified that the theoretical basis of the trial did not utilize Chinese medicine theory as basis for the study. For example, trials with non-CHM interventions in Japanese/Korean were excluded because of clear indication of the use of specific Japanese massage therapy (e.g., Anma therapy) or Korean acupuncture medical (e.g., Sasang theory) as the basis in the registered information.

Secondly, among the TCM trial registrations, TCM interventional studies were identified according to the information of 'study type' (e.g. interventional, observational, etc.) and the type of 'intervention' (e.g. CHM, acupuncture, cupping, etc.). Non-interventional studies (e.g. observational studies, case studies, etc.) were excluded. The scope of TCM interventions included Chinese herbal medicines (e.g. single herb,

compound formula, Chinese proprietary medicines, etc.), acupuncture (electro-acupuncture, auricular acupuncture, etc.), moxibustion, tuina (massage), cupping, guasha (scraping), Qigong, etc.

Finally, after screening the full-text of the registered records, we included TCM intervention trials that had a diagnosis of pattern differentiation as participant inclusion criteria. There were no limitations in the comparisons and outcomes. Finally, we excluded TCM interventional studies without any pattern differentiation design. For example, although some trials reported the diagnostic criteria of disease studied according to both WM and TCM, there was no detailed information on TCM pattern differentiation in any of the registration information.

2.4. Data extraction and analyses

Using a predefined data extraction table, two authors (XZ and RT) extracted the data from each trial independently. Disagreements were resolved by consensus. If needed, a third author (CZ) was consulted. The content of the data extraction forms was comprised of two parts: I. Characteristics of pattern differentiation used in the trial (e.g. diseases and patterns studied, type of TCM intervention, study objective, study design, sample size of pattern differentiation group, and outcomes, etc.); and II. Assessment on whether the *Bian-Zheng-Lun-Zhi* was appropriately applied in the trial or not. This decision was based on seven questions (Box 1) related to the theory of correspondence between formula and pattern. Following this TCM theory could provide some guarantee that if the patients (or participants) have a specific TCM pattern, they will receive the correct matched treatment. All data were collected and tabled in Microsoft Office Excel (Version 2016). Categorical data is presented as number (n) and percent (%).

Box 1. Seven questions on correspondence between formula and pattern

Q1: For TCM intervention(s), was a specific name(s) reported (e.g. not a generalized name of treatment determination on pattern differentiation)?

Q2: For TCM intervention(s), was the definite applicable pattern(s) reported?

Q3: For TCM pattern(s) studied in a trial, was the specific name(s) reported?

Q4: For TCM pattern(s) studied in a trial, was the diagnostic criteria for each pattern reported?

Q5: For different patterns belonging to the same category of pattern classification (e.g. category of deficiency pattern includes Qi deficiency, Yang deficiency and Yin deficiency, etc.), was the same intervention entirely adopted, such as only one CHM studied in the trial?

Q6: For different patterns belonging to a different categories of pattern classification (e.g. deficiency of both Qi and Yin, deficiency of kidney Qi, stagnation of Qi and blood, etc), was the same intervention entirely adopted, such as only one CHM studied in the trial?

Q7: With reference to the above six answers, was the concept of correspondence between formula and pattern reflected in the study design?

3. Results

3.1. Search

The initial search identified 4,326 records. Preliminary screening excluded 987 records due to them being non-TCM trials. After examination of the remaining 3,339 TCM clinical trials, 2,955 interventional studies were chosen for further screening, which included 889 CHM trials and 2,066 non-CHM trials (Figure 1). Finally, a total of 376 trials (12.7%, 376/2,955) were eligible for inclusion because they appeared to have information related to pattern differentiation in their design. Among them, 78.7% were CHM trials (n=296) and 21.3% were non-CHM trials (n=80). An ID list of all included records is provided in Supplementary 1 (S_1).

3.2. Distribution of years and registries

The 376 TCM intervention trials that included pattern differentiation design were registered between 2003 and 2017. The first clinical trial of TCM using pattern differentiation was registered in 2003, and the number of trial registrations showed a steady increase from 2013, then a further exponential increase during 2016-2017, which accounted for 52.1% (196/376) of the total numbers (Figure 2). Among the 17 registries in the ICTRP, all the trials were identified in only 3 registries (17.6%, 3/17), including ChiCTR (332), ClinicalTrials.gov (41), and ISRCTN (3). The majority (88.3%, 332/376) were registered in ChiCTR (i.e. China) (Figure 3).

3.3. Descriptive characteristics of included trials

As presented in Table 1, the included trials were classified as utilizing either WM and/or TCM (e.g., *Bian Bing*) diseases and TCM pattern (e.g., *Bian Zheng*) diagnostic criteria (99.2%, 373/376) or only single TCM pattern diagnostic criteria (0.8%, 3/376). The three most common body systems studied were diseases of the circulatory system (14.4%, 54/376), genitourinary system (13.0%, 49/376) and respiratory system (12.5%, 47/376). Various types of TCM interventions were utilized in the 376 trials, of which CHM comprised the largest proportion (78.7%, 296/376), followed by acupuncture (8.2%, 31/376). However, 5.6% (21/376) of the included trials adopted more than one intervention (e.g. multiple interventions such as acupuncture plus moxibustion). For the CHM intervention, the most common design utilized a fixed standardized CHM formula (71.3%, 211/296), and the major dosage were granules (35.1%, 104/296).

The most common study design was the RCT (97.9%, 368/376). Of 376 included trials, 367 (97.6%) trials had both a treatment group and a control group, of which most had a placebo control arm (29.4%, 108/367). This was followed by trials where a conventional drug (21.8%, 80/367) or an add-on design (17.7%, 65/367) was utilized.

For the treatment group that used pattern differentiation, the most common sample size utilized was 1-100 participants (67.8%, 255/376).

3.4. Characteristics of pattern differentiation application in TCM interventional studies

As shown in Table 2, for included CHM trials, the use of pattern differentiation was reported in the study objective (55.7%, 165/296), outcomes (45.3%, 134/296), title (33.8%, 100/296) and study background (12.8%, 38/296). For non-CHM trials, the reporting rate of pattern differentiation were lower than those in CHM trials: outcomes (37.5%, 30/80), study objective (31.3%, 25/80), title (18.8%, 15/80) and study background (11.3%, 9/80). Of all included TCM trials, only 7.2% (27/376) provided a clearly defined diagnostic criteria basis or reference for the pattern differentiation. Furthermore, 43.6% (164/376) adopted pattern-related outcomes in the trial and 43.9% (72/164) of them were primary outcomes.

3.5. Assessment on pattern differentiation design in TCM interventional studies

Of 376 included trials, 14.6% (55/376) gave no specific name for the intervention, 89.4% (336/376) did not report the applicable pattern scope of the intervention, 16.2% (61/376) gave no specific name for the pattern, while 92.8% (349/376) failed to provide the diagnostic criteria of the pattern. In addition, nearly 5% of the included trials adopted the same intervention (e.g.one intervention) to treat different types of TCM patterns, either in the same or different categories. This incomplete reporting led to uncertain judgement of most included trials (>90%) of whether the correspondence between formula and pattern were correctly applied in clinical trials. When comparing CHM trials with non-CHM trials, the reporting rate of patterns without a specific name was higher in non-CHM trials (33.8%) than in CHM trials (11.5%). Further details are provided in Table 3.

4. Discussion

The concept of *Bian-Zheng-Lun-Zhi* (treatment based on pattern differentiation) is a fundamental and historically defined principle of TCM as well as offering guidance for the associated treatment. However, in this study, of 2,955 TCM intervention trials, only 12.7% (376/2,955) eligible trial registrations (namely TCM interventional trials with pattern differentiation design) were identified between 2003 and 2017, while the remaining 87.3% (2,579/2,955) trials were targeting diseases only. In addition, of the 17 registries provided by WHO ICTRP, only 3 registries contained TCM intervention trial registrations that used pattern differentiation in their design. The largest number of the 376 included trials were registered with the Chinese registry, ChiCTR (88.3%, 332/376), while the remaining trials were registered with the US registry (41 trials) and UK registry (3 trials), ClinicalTrials.gov and ISRCTN respectively. Of 2,955 TCM interventional trials, the number of non-CHM interventional trials (69.9%, 2,066/2,955) was much higher than that of CHM interventional trials (30.1%, 889/2,955). However, the use of pattern differentiation was more common in CHM interventional trials (78.7%, 296/376) than non-CHM interventional trials (21.3%, 80/376).

Unfortunately, for most of the included trials it was difficult to confirm whether the study design of *Bian-Zheng-Lun-Zhi* was properly applied or not, due to the inadequate reporting of registered information. This included 14.6% which did not report the specific name of the TCM intervention, 89.4% which did not provide an applicable pattern scope of the intervention studied, 16.2% which did not report specific name of the TCM patterns and 92.8% which did not present diagnostic criteria of the pattern studied. Approximately 5% of the included trials adopted the same intervention (e.g. one intervention) to treat different types of TCM patterns (e.g. deficiency pattern and excess pattern). The key issue in the practice of using the *Bian-Zheng-Lun-Zhi* is whether there was alignment/correspondence between the formula

and the pattern (“formula” included different types of TCM interventions in this study) [36-37]. This review, unfortunately, found that more than 90% of the included trials failed to reflect a correspondence between formula and pattern in their design. There were however some characteristics within the design and application of pattern differentiation in TCM clinical trials. These included (1) standardization of TCM pattern; (2) CHM interventions based on pattern differentiation; (3) non-herbal TCM interventions based on pattern differentiation; (4) group of pattern differentiation and its controls; (5) pattern-related outcome evaluation; and (6) usage of pattern differentiation in RCT.

4.1. Standardization of TCM pattern

In this study, apart from the single TCM pattern design in 3 trials (0.8%, 3/376), most trials (99.2%, 373/376) included diagnosis of both disease and pattern in participant’s inclusion and exclusion criteria. However, only 27 trials (7.2%) clearly reported the diagnostic criteria of the TCM pattern. In reporting guidelines such as CONSORT extension for CHM formulas 2017 [38], it is important to choose patterns with well-recognized diagnosis criteria, and list the criteria in the trial publication, which is the same requirement as for trial registration [39]. Commencing from the 1980's, more and more specific diagnostic criteria for TCM patterns and pattern of specific diseases have been developed [40-42], but the application of standardized pattern was limited. As a result, identifying patterns utilized in clinical trials is particularly challenging. Due to the different expression of pattern names (e.g. “insufficiency of the spleen and kidney” comparing with “deficiency of both qi and yang in spleen and kidney”) and/or the lack of specific diagnostic criteria provided in the trials, the results from different research could not be compared, even when the same pattern and/or same disease was studied. The issue of how to standardize the diagnostic procedure for TCM pattern differentiation research studies has been going

on for many years [43-44], and a variety of methods have been introduced and adopted by researchers [45-47]. The value of a standard diagnostic criteria ultimately depends on its use, which could be achieved by concerted efforts from registries, journal editors, and researchers and other interested parties.

4.2. CHM interventions based on pattern differentiation

In this study, TCM pattern differentiation was primarily used in CHM interventional trials (n=296), of which the largest percentage was fixed CHM formulas (71.3%, 211/296), followed by individualized CHM formulas (10.5%,31/296). It is generally considered that the usage of pattern differentiation with CPM is limited due to most being a non-prescription drug. Similarly, few trials (6.3%, 25/296) have used CPM based on pattern differentiation design. Some scholars have emphasized that the reasonable application of CPM must based on TCM pattern differentiation [48]. By contrast, some scholars have randomly investigated 7,233 CPM prescriptions in one hospital (Guangzhou) in 2012, and have found that 25.8% of CPM usage was not according to TCM pattern differentiation. The authors have explored the underlying reasons why this was the case such as: 1) the clinical medical staff, especially Western physicians had a lack of understanding of TCM theory; 2) the safety awareness of CPM application was poor; 3) the clinical application guiding some CPM instructions were ambiguous; and 4) there was no valid evaluation system for the clinical application of the CPM [49].

In terms of the reporting of the TCM pattern, the number of pattern differentiation reported in the title, study objective and study background of CHM trials were 100 (33.8%), 165 (55.7%) and 38 (12.8%), respectively. The major problem in CHM treatment trials has been the focus on the inadequate reporting of information related to formula-pattern correspondences, including what is the applicable pattern scope of the CHM intervention treated in the trial? Other questions such as whether there is

consistency with the diagnostic criteria of pattern in participants inclusion, what is the principle of formula modified according to pattern, whether the application of CPM prescription must be based on TCM pattern differentiation and be consistent with publicly available references, etc., are also need to be addressed and reported if utilized within the study design. More than 90% of the included trials failed to provide these details in the registration records, so it is difficult to judge whether pattern differentiation is provided and appropriately used in clinical trials.

4.3. Non-herbal TCM interventions based on pattern differentiation

For non-herbal TCM treatment trials, only 80 trials were identified which incorporated pattern differentiation design, including: acupuncture (31 trials), acupoint therapy (11 trials), moxibustion (9 trials), tuina/massage (6 trials), qigong (1 trial), TCM five element music therapy (1 trial), and multiple interventions of TCM (21 trials). Previous studies found that non-herbal TCM treatment trials, such as acupuncture trials, opted to choose a disease-oriented design and not include pattern differentiation [50-51]. So, whether pattern differentiation in non-herbal TCM treatments is necessary, and whether pattern differentiation can actually improve the efficacy of these kinds of interventions is still an unsolved but important question.

Compared to CHM trials, the percentage of reporting descriptions of TCM pattern were less evident in the title (18.8%, 15), study objective (31.3%, 25) and study background (11.3%, 9) of non-herbal TCM trials, especially in terms of the study objective compared to CHM trials. The problems apparent in CHM trials, such as the correspondence or alignment between treatment and pattern, were also more obvious in non-herbal TCM trials. In addition, more non-herbal TCM intervention trials did not report the specific name of the pattern (33.8%, 27) or intervention (16.3%, 13). For example, a description of “moxibustion for pattern differentiation” did not present the specific types of moxibustion and TCM pattern used in the trial. These numbers

indicated that little attention is paid to pattern differentiation in non-herbal TCM interventional trials. However, some studies have emphasized the importance and characteristics of non-herbal TCM treatment based on pattern differentiation [52-53]. For example, some scholars have pointed out that pattern differentiation of channels (e.g., *Jing Luo Bian Zheng*) is an important component in the acupuncture-moxibustion pattern differentiation, especially when used for different kinds of jing-jin (e.g. channel sinews belonging to the jing-luo system) diseases and zang-fu diseases [54]. Therefore, high quality clinical trials that aim to investigate the relationship between efficacy and safety of non-herbal TCM treatments with and without pattern differentiation could be able to answer the above questions objectively. This study identified some trial registrations, and it is necessary to keep tracking and analyzing their results once published.

4.4. Control Group design in TCM trials with pattern differentiation

Of 376 included trials with pattern differentiation design groups, this study also identified 97.6% (367 trials) of them which included control group design. Regarding a control arm, 108 trials (29.4%) used a placebo, 80 trials (21.8%) chose conventional drugs, 65 trials (17.7%) adopted an add-on design, and 46 trials (12.5%) assigned other TCM interventions as a control (e.g. treatment with and without pattern differentiation, different dose or dosage form of the intervention, single TCM intervention and multiple TCM interventions, etc.). In addition, several trials selected more than one type of control group, e.g. combining conventional drug, placebo, and/or no treatment, etc. Among these different kinds of control groups, the use of a placebo control is increasing. A proper placebo should be identical to the real CHM intervention in physical form, sensory perception (visual, odor and taste), packaging, and labeling, and it should have no specific pharmaceutical activity [55-56].

The appropriate use and design of a control group is important for evaluating the

efficacy of a particular intervention based on pattern differentiation in a clinical trial. This is especially so when, the results of efficacy and safety of TCM treatment(s), with and without pattern differentiation, are important evidence for the value of pattern differentiation. Thus, researchers should select the appropriate type of control group according to the study objectives of TCM clinical trials with pattern differentiation [57]. Unfortunately, the reporting of pattern differentiation groups and the controls design was poor. For example, (1) 50% trials did not report pattern differentiation related information in the study objectives; (2) there was inadequate reporting of rationale and/or explanation for control design and; (3) no details of control groups were provided. Therefore, an adequate reporting of the control group is necessary for readers to understand the study design of pattern differentiation in the trial.

4.5. Pattern-related outcome evaluation

In this study, 164 trials (43.6%) adopted TCM pattern-related outcomes, of which 134 were CHM intervention trials and 30 were non-herbal TCM intervention trials. Of the 164 trials, 43.9% chose TCM pattern-related outcomes as the primary outcome for efficacy evaluation. Previous studies have shown that RCTs with pattern differentiation had a higher percentage of adopting pattern-related outcomes than those without pattern differentiation ($P<0.01$) [58]. The evaluation of pattern-related outcomes is the key indicator in the efficacy assessment of clinical trials using pattern differentiation design [59]. In general, pattern-related outcomes included TCM pattern scores, TCM symptom scale, tongue and pulse indicators, etc. However, in this study, most trials did not report the measurement methods and/or time points for administering the pattern-related outcomes, which indicated that there was a lack of consensus and standardization for TCM pattern scores for use in clinical trials. Some scholars have suggested that several statistical methods could be used to standardize the TCM pattern related outcome indicators, which aimed to include pattern outcomes

as a primary outcome in efficacy evaluation of a TCM clinical trial [60-61]. By contrast, some scholars have argued that TCM patterns cannot be used as outcome assessment in the clinical trial, for example, patients reported outcomes including TCM-related symptoms are better as outcomes assessments [62]. Further research into TCM pattern outcome evaluation is required to answer these questions.

4.6. Designing an RCT using pattern differentiation

Of the 376 included trials, 97.9% were RCTs, which indicated the wide use of TCM patterns in high quality evidence-based research. Recently, increasing numbers of TCM registered trials applying pattern differentiation occurred during 2016-2017 (52.1%, 196/376). However, an argument against the use of pattern differentiation in an RCT is whether its own dynamic characteristic is applicable if stability requirements for disease and/or interventions is required [63]. Several questions relevant to this argument have not been well investigated, such as “How do the patterns and the nature of the disease change within individuals and among groups?”; “Are they synchronous?”; and “How do these changes affect the outcome assessment?”. Previous studies have suggested that the incorporation of pattern differentiation for further stratification of the patients could improve the efficacy of TCM interventions in clinical trials [64-65]. In contrast, other studies have pointed out that higher quality RCTs with pattern differentiation design are needed, which requires multidisciplinary collaborations amongst different professionals, researchers and scientists of both conventional medical and TCM practices with further input from experts from biomedical, bioinformatics, medical, pharmaceutical and TCM disciplines [66]. In summary, the design and application of pattern differentiation should depend on the research question.

5. Limitations

This study has some limitations. Firstly, this review identified TCM intervention studies registered up to 31 December 2017. Any TCM clinical trials registered in regions which had not yet been included in WHO ICTRP by that cut-off period have not been included in this study. Secondly, this study mainly focused on collecting registration information from different registries rather than acquiring study protocols and publications for the specific details. Thirdly, some eligible TCM trials may well have been conducted without being registered. These limitations mean that the results of the study may not necessarily be comprehensive. We do however believe that the general trends indicated by the analysis of the information we did use, even if incomplete, are valid.

6. Recommendations

To improve the quality of pattern differentiation design in TCM clinical trials, we make the following recommendations:

(1) The design and application of pattern differentiation should depend on the research question. Researchers who include pattern differentiation in the design of their clinical trials should understand the rationale for the key factors related to the correspondence/alignment between the formula and the pattern, as discussed briefly in this review.

(2) Commencing at trial registration, if the TCM interventions target a pattern-oriented or a combination of disease-pattern orientation, it is recommended to report pattern differentiation in the title and study objective of a trial. If applicable, the rationale of the pattern differentiation design should be clearly enunciated.

(3) Specific criteria of the pattern studied in the trial should be described adequately, including diagnostic criteria, inclusion and exclusion criteria. It is

recommended to choose the pattern with well-recognized criteria, especially for specific diseases.

(4) Details of the TCM treatment, based on pattern differentiation, should be provided. For example, details regarding the intervention's specific name, operational details and applicable treating pattern; the pattern's specific name and diagnosis criteria should be reported.

(5) Researchers should select the appropriate type of control group according to the study objective, study design and/or study phase.

(6) The adoption of standardized pattern-related outcomes is suggested as primary outcome indicators for efficacy evaluation of TCM trials using a pattern differentiation design.

7. **Conclusion**

A total of 376 TCM interventional trial registrations were identified that included pattern differentiation in their design. Standards for pattern differentiation used in these included trials, especially in terms of specific criteria for participants, interventions, comparisons and outcomes, are lacking. The reporting quality of key information related to pattern differentiation, such as criteria of the pattern, needs to be improved in the future. It is recommended that if pattern differentiation is used, a trial should be appropriately designed according to the theories of correspondence/alignment between the formula (treatment) and the pattern.

Abbreviations

PD: Pattern differentiation; CHM: Chinese herbal medicines; TCM: Traditional Chinese medicine; WM: Western Medicine; WHO: World Health Organization; ICTRP: International Clinical Trials Registry Platform; CPM: Chinese proprietary medicine;

RCT: Randomized controlled trial; WM: Western Medicine; CPT: Conventional Physical Therapy; CAM: Complementary Alternative Medicine; OTC: Over-the-counter; ChiCTR: Chinese Clinical Trial Registry; ANZCTR: Australian New Zealand Clinical Trials Registry; ISRCTN: International Standard Randomized Controlled Trial Number Register; EU-CTR: EU Clinical Trials Register; NTR: Netherlands National Trial Register; ReBec: Brazilian Clinical Trials Registry; CTRI: Clinical Trials Registry-India; CRiS: Clinical Research Information Service-Republic of Korea; RPCEC: Cuban Public Registry of Clinical Trials; DRKS: German Clinical Trials Register; IRCT: Iranian Registry of Clinical Trials; JPRN: Japan Primary Registries Network; PACTR: Pan African Clinical Trial Registry; SLCTR: Sri Lanka Clinical Trials Registry; TCTR: Thai Clinical Trials Register; REPEC: Peruvian Clinical Trials Registry; TRDS: Trial Registration Data Set.

Supplementary Files

S_1. Main ID of all included 376 trial registrations. (DOC)

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Figure legends

Figure 1. Flow chart of trials identified, included and excluded.
Figure 2. Number of included TCM trial registrations with pattern differentiation design from 2003 to 2017.
Figure 3. Distribution of TCM registered trials with pattern differentiation design in 3 registries from 2003 to 2017.

Word count (main text except figure, tables, reference, etc.): 4,885

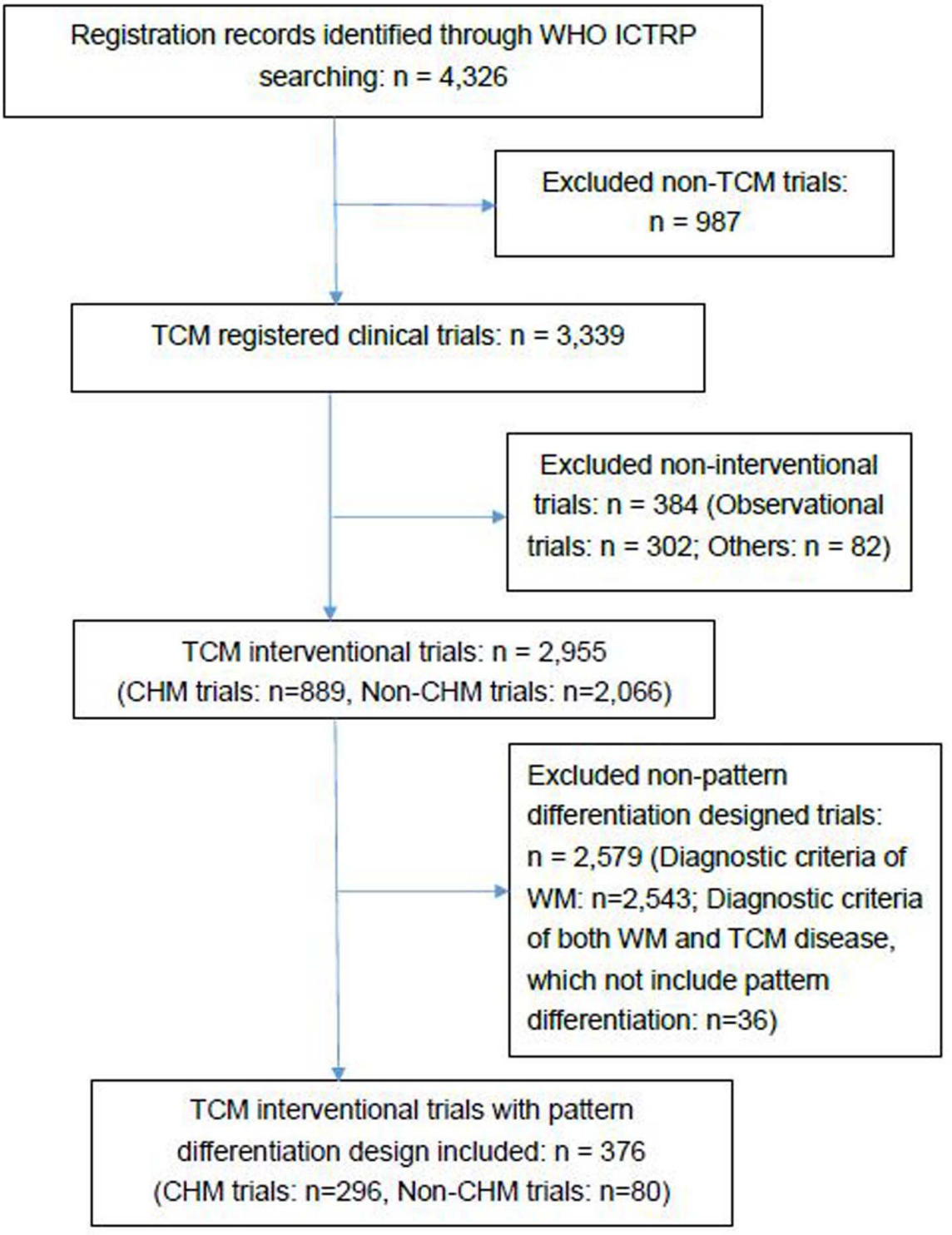

Figure 1. Flow chart of trials identified, included and excluded

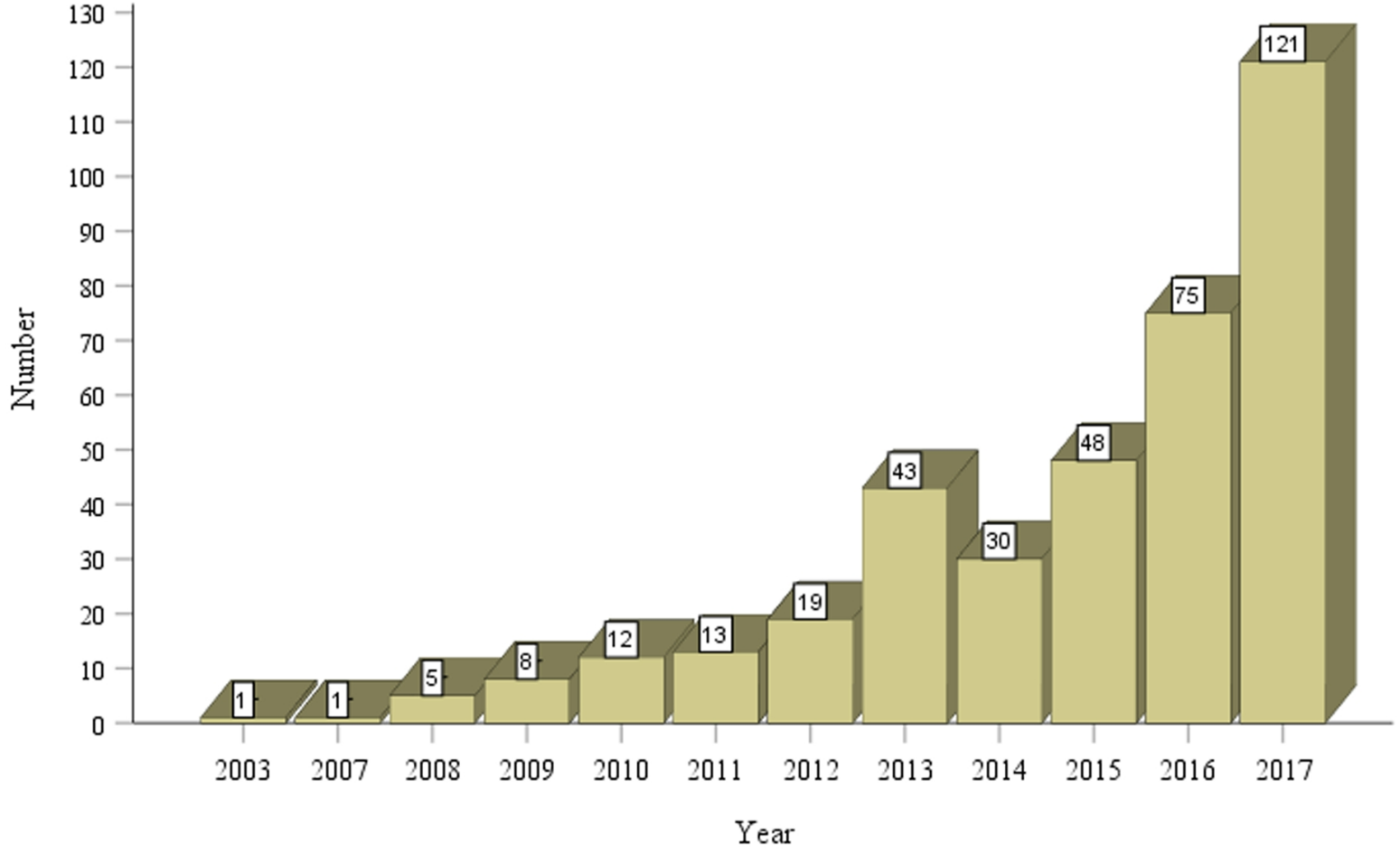

Figure 2. Number of included TCM trial registrations with pattern differentiation design from 2003 to 2017

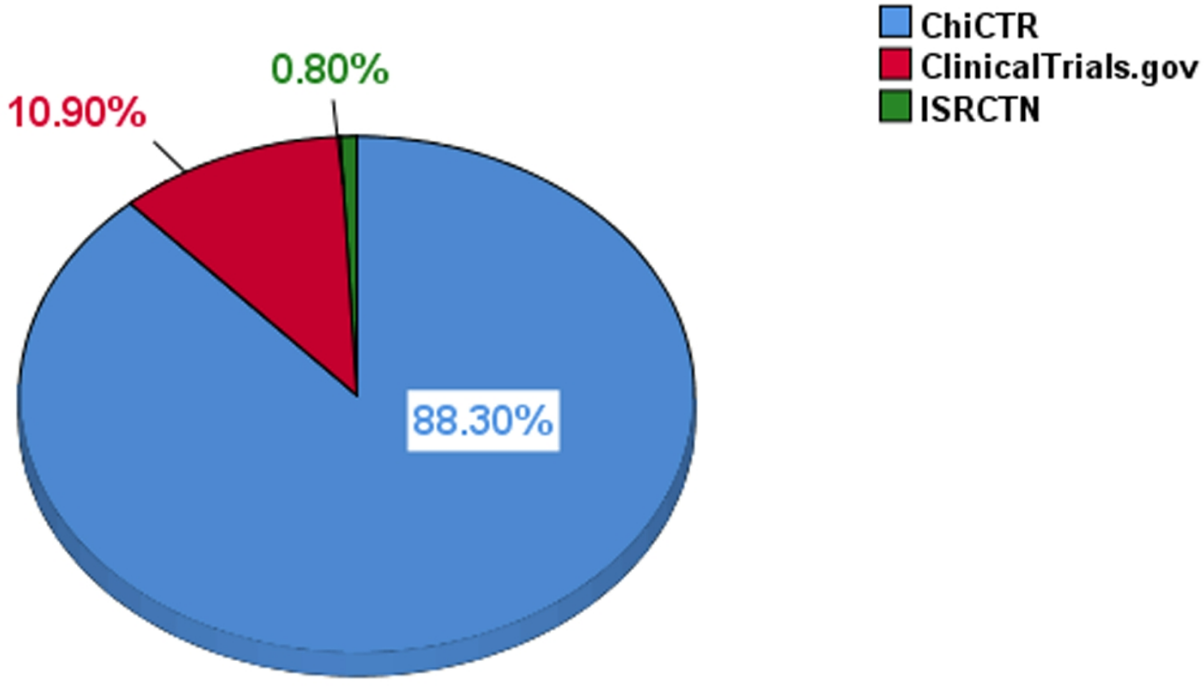

Figure 3. Distribution of TCM registered trials with pattern differentiation design in 3 registries from 2003 to 2017

Tables:

Table 1. Baseline characteristics of the included trials

Category	Descriptive Characteristics	N=376 (%)
Diagnostic criteria [1]	Disease and pattern diagnosis	373 (99.2)
	Single TCM pattern diagnosis	3 (0.8)
Diseases	Diseases of the circulatory system	54 (14.4)
(ICD-11 codes) [2]	Diseases of the genitourinary system	49 (13.0)
	Diseases of the respiratory system	47 (12.5)
	Diseases of the musculoskeletal system or connective tissue	41 (10.9)
	Diseases of the digestive system	38 (10.1)
	Certain infectious or parasitic diseases	28 (7.5)
	Mental, behavioural or neurodevelopmental disorders	19 (5.1)
	Neoplasms	18 (4.8)
	Endocrine, nutritional or metabolic diseases	17 (4.5)
	Diseases of the nervous system	14 (3.7)
	Sleep-wake disorders	13 (3.5)
	Diseases of the skin	8 (2.1)
	Symptoms, signs or clinical findings, not elsewhere classified	7 (1.9)
	Diseases of the immune system	6 (1.6)
	Diseases of the blood or blood-forming organs	5 (1.3)
	Certain conditions originating in the perinatal period	4 (1.1)
	Pregnancy, childbirth or the puerperium	3 (0.8)
	Traditional Medicine conditions - Module I	3 (0.8)
	Diseases of the visual system	2 (0.5)
Types of interventions	Chinese herbal medicine (CHM)	296 (78.7)
	Acupuncture	31 (8.2)
	Acupoint therapy [3]	11 (2.9)
	Moxibustion	9 (2.4)
	Tuina (massage)	6 (1.6)
	Qigong	1 (0.3)
	TCM Five element music therapy	1 (0.3)
	Multiple interventions [4]	21 (5.6)
Types of CHM intervention[5]	Fixed CHM formulas	211 (71.3)
	Individual CHM formulas	31 (10.5)
	Chinese proprietary medicine (CPM)	25 (8.4)
	Not reported	29 (9.8)
CHM dosage form [6]	Granule	104 (35.1)
(The top three)	Capsule	39 (13.2)
	Decoction	22 (7.4)
Study design	RCT	368 (97.9)
	Others [7]	8 (2.1)
Assignment	Single arm	9 (2.4)
	Treatment group vs control group	367 (97.6)
Study arms [8]	TCM intervention vs placebo group	108 (29.4)
	TCM interventions vs conventional drug	80 (21.8)
	TCM intervention+conventional drug vs placebo/other TCM	65 (17.7)

	intervention+conventional drug	
	TCM intervention vs other TCM intervention	46 (12.5)
	TCM intervention+conventional drug vs conventional drug	22 (6.0)
	TCM intervention vs conventional drug vs TCM intervention+conventional drug	12 (3.3)
	TCM intervention vs placebo vs other TCM intervention/no treatment	11 (3.0)
	TCM intervention vs conventional drug vs placebo	10 (2.7)
	TCM intervention vs no treatment	5 (1.4)
	TCM vs conventional drug vs other TCM intervention	4 (1.1)
	TCM intervention +placebo vs other TCM intervention+placebo	2 (0.5)
	TCM intervention+conventional drug vs other TCM intervention+conventional drug vs conventional drug	1 (0.3)
	TCM intervention vs other TCM intervention+placebo vs placebo	1 (0.3)
Sample size of PD group [9]	1-100	255 (67.8)
	101-300	100 (26.6)
	301-500	17 (4.5)
	> 500	3 (0.8)

[1] This column is according to the inclusion criteria of participants in each trial registration record. The disease and pattern diagnosis included WM disease and/or TCM disease (e.g., *Bing*) diagnosis plus TCM pattern (e.g., *Zheng*) diagnosis. The single TCM pattern diagnosis means there was no WM and/or TCM disease diagnosis.

[2] According to International Statistical Classification of Diseases and Related Health Problems ICD-11 for Mortality and Morbidity Statistics (2018).

[3] Acupoint therapy included acupressure, acupoint injection, catgut embedment in acupoint, and acupoint application.

[4] Multiple interventions refer to the combination of TCM therapies. For example, acupuncture and moxibustion, acupuncture and cupping, massage and cupping, CHM plus any TCM external treatment, etc.

[5] [6]The percentage of these two columns (e.g. CHM types and dosage form) were based on the total number of CHM trials of 296, respectively.

[7] Others refers to non-RCT trials, including cross-sectional, case-control study, case series, etc.

[8] The trials included two groups assignment (n = 367) were used for the category of control group design. We calculated the percentage of each control group was based on the total number of 367.

[9] PD group refers to treatment group that used the TCM pattern differentiation.

Table 2. Characteristics of pattern differentiation application in the included trials [1]

Item	CHM trials (n=296)	Non-CHM trials (n=80) [2]	Total (n=376)
Title included PD	100 (33.8)	15 (18.8)	115 (30.6)
Study objective included PD	165 (55.7)	25 (31.3)	190 (50.5)
Study background included PD	38 (12.8)	9 (11.3)	47 (12.5)
Diagnostic criteria included PD	296 (100)	80 (100)	376 (100)
PD diagnosis with a clearly criteria basis or reference	21 (7.1)	6 (7.5)	27 (7.2)
Outcomes included PD-related indicator [3]	134 (45.3)	30 (37.5)	164 (43.6)
PD-related outcome as primary outcome [4]	56 (41.8)	16 (53.3)	72 (43.9)

[1] To calculate the percentage of the term regarding “pattern differentiation (PD)” that reported in the following items of a trial: title,

study objective, background, diagnosis and outcomes. For PD diagnosis, we added to calculate the percentage of those had a clearly reporting of diagnostic criteria basis or reference.

[2] Trials with multiple interventions (n=21) were also calculated to the category of non-CHM trials, although some of them included a CHM intervention (n=12).

[3] PD-related outcome(s) including TCM pattern score, TCM symptom score, Patterns (including clinical symptoms, signs, tongue, pulse), and the efficacy of TCM pattern, etc.

[4] The percentage of this item was based on the number of PD-related outcomes, respectively. For example, 41.8%=56/134.

Table 3. Assessment on pattern differentiation design in the included trials

Answer of the seven questions	CHM trials (n=296)	Non-CHM trials (n=80)	Total (n=376)
Q1 Gave no specific name of the intervention[1]	42 (14.2)	13 (16.3)	55 (14.6)
Q2 Fail to provide the applicable pattern scope of the intervention[2]	265 (89.5)	71 (88.8)	336 (89.4)
Q3 Gave no Specific name for the pattern	34 (11.5)	27 (33.8)	61 (16.2)
Q4 Fail to report the diagnostic criteria for the pattern (e.g. related standards or references)	275 (92.9)	74 (92.5)	349 (92.8)
Q5 Same intervention was used for different patterns in the same category	13 (4.4)	4 (5.0)	17 (4.5)
Q6 Same intervention was used for different patterns in the different categories	15 (5.1)	4 (5.0)	19 (5.1)
Q7 The concept of correspondence between formula (intervention) and pattern was unclarified in the trial design [3]	291 (98.3)	76 (95.0)	367 (97.6)

[1] For example, a specific name of the intervention included Ruan-Jian-San-Jie Capsule (a CHM Formula), Acupuncture of the five heart acupoints, etc. By contrast, a generalized name was classified to the answer that without a specific name, such as CHM granule, TCM treatments based on pattern differentiation, Chinese herbs, etc. These kinds of names are difficult to figure out what specific technologies and/or what specific compositions of CHM were adopted in a trial.

[2] For example, a CHM intervention (Er-Zhi Wan that included herbs nourishing the Kidney-yin) adopted in a trial had reported its applicable pattern scope was the pattern of Kidney-yin deficiency. This kind of reporting was classified as “provide the applicable pattern scope of the intervention”. By contrast, a tuina intervention (Shanghai pediatric massage) adopted in a trial did not report its associated treating scope of the pattern, it was not possible to judge whether the intervention was applicable for excessive pattern or deficiency pattern. This kind of reporting was classified as “failed to provide the applicable pattern scope of the intervention”.

[3] The assessment on Q7 was based on the answers of the previous Q1-Q6, especially in Q1-Q4. If the intervention and the pattern had reported their specific names, and they had correspondence between the treating scope of the intervention and the pattern studied with a related criterion. This kind of treatment based on pattern differentiation was classified as “clarified”. By contrast, if some of the reporting in Q1-Q6 were incomplete, the Q7 was classified as “unclarified”.

S $_1$: Included trials ID

ChiCTR(n=332)			
ChiCTR-IOR-17014195	ChiCTR-IOC-17013954	ChiCTR-IOC-17013974	ChiCTR-IOR-17013931
ChiCTR-IIR-17013983	ChiCTR-IOR-17013829	ChiCTR-IOR-17013791	ChiCTR-IOR-17013779
ChiCTR-IPR-17013758	ChiCTR-IOR-17013699	ChiCTR-INR-17013653	ChiCTR-IIR-17013609
ChiCTR-IOR-17013577	ChiCTR-IIR-17013532	ChiCTR-INR-17013495	ChiCTR-INR-17013467
ChiCTR-IOR-17013390	ChiCTR-IOR-17013387	ChiCTR-IOR-17013378	ChiCTR-IID-17013318
ChiCTR-IIR-17013275	ChiCTR-INR-17013222	ChiCTR-IOR-17013189	ChiCTR-INR-17013157
ChiCTR-INR-17013155	ChiCTR-IIR-17013018	ChiCTR-INR-17013012	ChiCTR-IPR-17012999
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ClinicalTrials.gov (n=41)

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6-7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page /line#
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 (Add Fig.1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

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Conflict of Interest Policy

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Declarations

European Journal of Integrative Medicine requires that all authors sign a declaration of conflicting interests. If you have nothing to declare in any of these categories then this should be stated.

Conflict of Interest

A conflicting interest exists when professional judgement concerning a primary interest (such as patient's welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry). It may arise for the authors when they have financial interest that may influence their interpretation of their results or those of others. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

Please state any competing interests

None

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Signature (a scanned signature is acceptable, but each author must sign)

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Author Agreement

Authors

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

Corresponding Author

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Ethical and Legal Requirements

We also declare that the study was performed according to the international, national and instutional rules considering animal experiments, clinical studies and biodiversity rights.

Financial Disclosure

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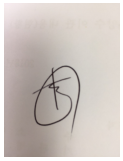

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