Integrative Medicine Research 11 (2022) 100841

Contents lists available at ScienceDirect

Integrative Medicine Research

journal homepage: www.elsevier.com/locate/imr

Review Article

Toward better translation of clinical research evidence into rapid recommendations for traditional Chinese medicine interventions: A methodological framework

Qianrui Li[a,b,c,d], Xiaochao Luo[a,b,c], Ling Li[a,b,c], Bin Ma[e], Minghong Yao[a,b,c], Jiali Liu[a,b,c], Long Ge[f], Xiaofan Chen[g], Xi Wu[h], Hongyong Deng[i], Xu Zhou[g], Zehuai Wen[j], Guowei Li[k], Xin Sun[a,b,c,g,1,*]

[a] Chinese Evidence-Based Medicine Center, Cochrane China Center and MAGIC China Center, West China Hospital, Sichuan University, Chengdu, China
[b] NMPA Key Laboratory for Real World Data Research and Evaluation in Hainan, Chengdu, China
[c] Sichuan Center of Technology Innovation for Real World Data, Chengdu, China
[d] Department of Nuclear Medicine, West China Hospital, Sichuan University, Chengdu, China
[e] Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou, China
[f] Evidence Based Social Science Research Centre, School of Public Health, Lanzhou University, Lanzhou 730000, China
[g] Evidence-based Medicine Research Center, Jiangxi University of Traditional Chinese Medicine, Nanchang, Jiangxi, China
[h] School of Acupuncture-Moxibustion and Tuina, Chengdu University of Traditional Chinese Medicine, Chengdu, China
[i] TCM Health Service Collaborative Innovation Center, Shanghai University of Traditional Chinese Medicine, Shanghai, China
[j] Key Unit of Methodology in Clinical Research, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China
[k] Centre of Clinical Epidemiology and Methodology, Guangdong Second Provincial General Hospital, Guangzhou, China

ARTICLE INFO

Article history:
Received 6 January 2022
Revised 21 February 2022
Accepted 23 February 2022
Available online 5 March 2022

Keywords:
Clinical practice guideline
Traditional Chinese medicine
Evidence-based practice

1. Introduction

In the era of modernization of traditional Chinese medicine (TCM), the generation and translation of clinical research evidence about TCM interventions – both for effectiveness and safety – are among the central topics of TCM development. Clinical practice guidelines represent an effective approach to translate research evidence into practice for TCM interventions. In recent years, increasing efforts have been devoted to the development and implementation of guidelines for TCM interventions, with approximately one-third of guidelines produced by Chinese developers focusing on TCM.[1]

However, the current practice of guideline development may not be optimal in the context of TCM. First, the current development of guidelines is often focused on the use of TCM interventions in a class of disorders (e.g., neurological diseases) or a specific disease (e.g., stroke), which are broad topics containing a variety of questions that required a large volume of research evidence to address. Although this pattern may offer a comprehensive set of recommendations about the use of TCM interventions, many recommendations developed lack strong clinical evidence as the basis, given the limited number of high-quality clinical studies in the field. Moreover, the volume production of evidence for TCM interventions is not yet ready, and as a result, regular updating of guidelines about TCM interventions – usually every two years – may continue to be faced with the lack of evidence for recommendations on certain topics.

On the other hand, when high-quality clinical evidence emerges for TCM interventions, its translation into practice would sometimes be very slow under the current guideline development

* Corresponding author at: Chinese Evidence-Based Medicine Center, Cochrane China Center and MAGIC China Center, West China Hospital, Sichuan University, Chengdu, China

[1] on behalf of the Multi-dimensional Evidence Synthesis, Evaluation and Recommendations for TCM interventions (MESERT) group

https://doi.org/10.1016/j.imr.2022.100841

Fig. 1. Workflow and target times for developing a rapid recommendation.

framework, thus postponing the adoption of best practice. A main reason for this delay is again due to the periodical guideline update mechanism, as a result of which, potentially practice-changing evidence would not change daily practice until the guideline update is due.

Given the special context of TCM, the classical guideline development process might not best utilize clinical research evidence about TCM interventions and efficiently translate it into practice. With an alternative approach, the recommendations for TCM interventions, on a case-wise manner, may be changed immediately upon the availability of emerging practice-changing studies. A practice-changing study is a critical study that dominates the evidence body, and hence its findings, when systematically evaluated with all available evidence, could derive recommendations that change existing practice. The core strength of this approach is a rapid translation of practice-changing evidence to ready-to-use recommendations, which is not only important for evidence-based practice in TCM, but also promotes the use of TCM interventions in daily practice.

A recent global innovation in guideline development methodology is the proposal of a *rapid recommendation* framework, which has the potential to add value to the translation of evidence to practice for TCM interventions. Rapid recommendation was first officially proposed in 2016 as a solution to create and disseminate timely and trustworthy guidelines.[2] Up to now, more than 180 rapid recommendations have been published in the BMJ and other journals,[3,4] but none of them is pertaining to TCM interventions. Hence, we specifically proposed the development of rapid recommendations for TCM interventions, as a useful complement to classical guidelines, to facilitate timely translation of evidence about TCM interventions.

2. Developing rapid recommendations: overview of the general methodological framework

Rapid recommendation is a novel methodological framework for developing clinical practice guidelines, which shares the basic features of classical guidelines – to provide recommendations to a clinical practice question, developed by main stakeholders, and on the basis of a systematic review and evaluation of evidence using a GRADE approach.[5] But rapid recommendations differ from classical clinical practice guidelines in its 'rapid' development process, with an aim of translating practice-changing studies to recommendations typically within 90 days. The clinical question discussed by a rapid recommendation often focuses on a specific practice issue and is enlightened by a potentially practice-changing study (a.k.a., a triggering study). Clinical questions identified solely from clinical knowledge, without a recently published triggering study, are also acceptable as topics for rapid recommendations.

A typical workflow and target times of developing a rapid recommendation is presented as Fig. 1. In this framework, either a clinician or a researcher may first identify the publication of a practice-changing study, and propose a clinical question for recommendation development considering both the triggering study and current clinical needs. The clinician then works with a methodologist to evaluate and finalise the clinical question given its scientific soundness, rigorousness, and applicability. When the clinical question is defined, a multidisciplinary panel meets to create a research plan, with detailed requirements for evidence synthesis. This panel often consists of clinicians, methodologists, and systematic review experts; some studies might also invite patients, caregivers, health economists, and members of other relevant background. With the finalized research plan, an independent evidence synthesis group tailor search strategy, systematically review the literature, and evaluate the quality of evidence using the GRADE approach. On the basis of evidence, all clinicians in the panel meet to create recommendations through a consensus process. Meanwhile, the evidence synthesis group compose one or more systematic reviews to be published as separate articles accompanying the rapid recommendation. Eventually, the recommendations and systematic reviews are disseminated after peer review.

Despite the shared basic features with classical clinical practice guidelines, rapid recommendations are developed more rapidly, with a more focused topic, by a multi-disciplinary development

Table 1
Differences in the development process for rapid recommendations and classical clinical practice guidelines.

	Rapid recommendations	Classical clinical practice guidelines
Time	1-3 months	2-3 years[6]
Topic	A specific clinical practice question, e.g., colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy[3]	A broad topic, e.g., diagnosis and management of colorectal cancer[7]
Timely inclusion of critical evidence	Yes	Often not
Involvement of systematic review	Systematic review(s) of a specific research question is required	May or may not involve systematic reviews
Use of GRADE approach	The GRADE approach is involved	May or may not include the GRADE approach
Guideline development panel	Multidisciplinary, at least clinicians, methodologists, and evidence synthesis researchers	Sometimes multidisciplinary, but are typically dominated by clinicians

panel and requires generally rigorous methodology for evidence grading (Table 1).

3. Developing rapid recommendations for TCM interventions: the MESERT approach

As earlier discussed, high-quality evidence about TCM interventions is often available for specific topics but lacking in a systematic manner, and thus it is less likely that classical broadly-focused guidelines ensure sufficient strong evidence for all recommendations.[8,9] Moreover, due to the periodical update mechanism and tedious development procedure of classical guidelines, emerging high-quality practice-changing evidence for TCM interventions often fails to translate into practice in a timely manner.

Thus, the *rapid recommendation* framework is proposed and appreciated for its efficiency to develop recommendations from practice-changing evidence as soon as the evidence emerges, given its utilization of the triggering study. Meanwhile, this framework also incorporates a systematic review and assessment of all available evidence and expert consensus, guaranteeing the trustworthiness of recommendations.

However, TCM interventions have specific features that render the evidence synthesis process in recommendation development different from western medicine interventions. Firstly, clear differences exist in the theoretical basis and underlying philosophies between TCM and western medicine. The basic theoretical system of TCM includes the holistic conception, Yin-Yang and five elements theory, and Zang-Fu and meridian theory, which focuses on the pathological changes of body functions. In comparison, western medicine is based on reductionism and focuses on histopathological changes of a disease, which is centered on the changes of body materials. Secondly, TCM interventions form a highly complex system and the use of them is often more individualized than western medicine. A universal principle of TCM practice in the routine clinical setting is syndrome differentiation and treatment, which requires differentiation of disease severity and body resistance for an individual patient when providing treatment. Consequently, for patients with a same disease from the western medicine's perspective, the prescription of Chinese herbs might be different, as well as the selection of acupoints and intensity of electroacupuncture. Even for the same patient at a different time in the disease course, the prescription of TCM interventions would change dynamically according to the change of syndromes. In addition, TCM interventions are often used in combination with western medicine, and this integrative approach would make the assessment of clinical effects of TCM interventions more challenging.[10]

These specific features of TCM interventions strongly warrant appropriate modification to the rapid recommendation framework. In developing rapid recommendations for western medicine interventions, randomized controlled trials (RCTs) are the primary source of evidence about effects of interventions. For TCM interventions, however, the practice-changing study may not always be a classical RCT (i.e., explanatory RCTs), since the complex features of TCM interventions might not be fully reflected by explanatory RCTs. In addition, rare but serious adverse drug reactions (ADRs) pose another important issue in assessing effects of TCM interventions, for example, the Chinese herbal injections.[11] As such, real-world evidence (RWE), including pragmatic trials or observational studies using real-world data, is another important evidence pillar for TCM interventions.[10]

Consequently, the nature of multi-dimensional evidence sources for TCM interventions – including classical RCTs and RWE – would require a more sophisticated methodological approach to synthesize and evaluate the totality of evidence about effects of TCM interventions. In the efforts to respond to these needs, we have proposed a specific approach to developing rapid recommendations for TCM interventions – the Multi-dimensional Evidence Synthesis, Evaluation and Recommendations for TCM interventions (MESERT), as presented in Fig. 2.

This approach is built upon an established methodological framework for generating multi-dimensional evidence about TCM interventions (i.e., the 4R approach,[10]) including RCTs, regardless of explanatory or pragmatic nature, and observational studies, using patient registry data or routinely collected data. Compared with the established rapid recommendation framework, the unique features of MESERT approach are the inclusion of multi-dimensional evidence appropriate for TCM interventions, systematic synthesis of multi-dimensional evidence, assessment of the strength of causal effects in the synthesized evidence. Novel techniques, such as natural language processing,[12] could help evidence identification and screening and accelerate evidence translation.

However, two methodological challenges warrant future efforts. First, since multi-dimensional evidence – trials and RWE – is synthesized to generate summary evidence for TCM interventions, sophisticated statistical models would usually be involved depending on the nature and diversity of evidence. One special need, which is methodologically sophisticated, is the quantitative summarization of evidence across trials and RWE. This is particularly warranted when trial evidence may not fully address the effects of TCM interventions or when the event rate is low. In such cases, Bayesian models may help solve this issue.[13]

Second, the assessment of quality of synthesized evidence would be more sophisticated than the usual GRADE approach, since the synthesized evidence may encompass trials and observational RWE. On the ground of the established GRADE method, one would carefully assess the strengths of causal inference derived from the synthesized evidence and the magnitude of effects. Standardized criteria are warranted to facilitate this work.

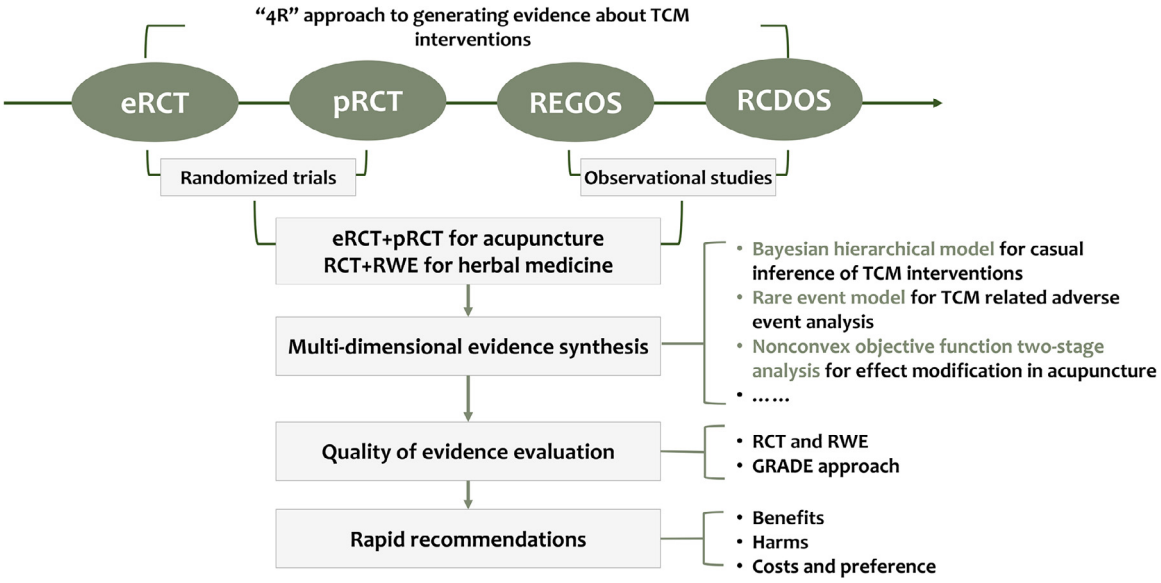

Fig. 2. Multi-dimensional Evidence Synthesis, Evaluation and Recommendations for TCM interventions (MESERT).
Notes: 4R: eRCT-pRCT-REGOS-RCDOS; TCM: Traditional Chinese medicine; eRCTs: explanatory randomized controlled trials; pRCTs: pragmatic randomized controlled trials; REGOS: observational studies using patient registry data; RCDOS: observational studies using routinely collected data; RCT: randomized controlled trial; RWE: real world evidence; GRADE: Grading of Recommendations, Assessment, Development and Evaluations

4. Applying the MESERT approach to acupuncture and Chinese patent medicines

Using the MESERT approach, certain TCM interventions with adequate evidence, such as acupuncture and Chinese patent medicines,[14,15] may be the desirable candidates for developing rapid recommendations. Although no established examples have been readily available, we illustrated two examples as potentially appropriate topics for generating rapid recommendations.

4.1. Example 1. The use of acupuncture for treating knee osteoarthritis

Acupuncture has been frequently studied for treating knee osteoarthritis (KOA), but given the lack of high-quality evidence, recommendations in current clinical practice guidelines were constantly of a low strength.[16] Recently, a multicenter RCT was published to assess the efficacy of acupuncture for KOA treatment,[17] in which 480 patients were randomized to receive electro-acupuncture, manual acupuncture or sham acupuncture 3 times weekly for 8 weeks. The efficacy was measured as the response rate, which was the proportion of participants who simultaneously achieved at least 2-point improvement on the numeric rating scale (NRS) and at least 6-point improved on the 68-point Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function subscale. This trial found that intensive electro-acupuncture significantly reduced pain and improved function at week 8 (between-group differences in response rate: 13.0% [97.5%CI, 0.2% to 25.9%; P=0.0234]), and these effects persisted though week 26. Although no benefit was found for intensive manual acupuncture at week 8 (11.3% [97.5%CI, -1.6% to 24.4%; P=0.0507]), significant benefits were observed during follow-up.

Findings of this trial have the potential to dominate the evidence body and to formulate valuable recommendations for acupuncture practice. However, due to the periodical guideline updating mechanism, it might take years for this piece of evidence to be used for guideline development. Moreover, although this trial provides high quality evidence to support acupuncture use in KOA treatment, evidence remains lacking for many other aspects of acupuncture practice, and hence, the evidence-base for a full-length guideline might still be suboptimal. In this case, the development of a rapid recommendation would help efficient translation of high-quality evidence.

In fact, using this trial as a triggering study, our team has launched the development of a rapid recommendation. In practice, this trial was first noticed by the clinical chair, and after evaluation from both the clinical and methodological aspect, a final recommendation topic was defined to be the use of acupuncture (including both electro-acupuncture and manual acupuncture) for KOA. Then a panel meeting was held to discuss the research plan, during which, a consensus process was used to select the clinical outcomes to measure acupuncture efficacy and safety in KOA patients and to finalize the subgroup analyses. Later, a systematic review and evaluation of the evidence was performed, based on which, recommendations were formulated.

4.2. Example 2. Danhong injection use in angina management

In another example, a recently published RCT found that 14 days of Danhong injection (i.e., a type of Chinese patent medicine) in combination with standard western medicine treatment was more effective than western medicine alone for relieving angina in patients with coronary artery disease, with an increased proportion of patients with clinically significant changes on the angina-frequency, as assessed by the Seattle Angina Questionnaire (difference in proportion: 12.78% [95% CI, 5.86%-19.71%] at day 30 since treatment initiation, 13.82% [95% CI, 6.82%-20.82%] at day 60, and 8.95% [95% CI, 2.06%-15.85%] at day 90).[18] Moreover, a post-market surveillance study showed good tolerance of Danhong injection in a real-world setting, with an incidence rate of adverse drug events (ADEs) being 0.35%, among which 92.6% events were mild to moderate (e.g., pruritus, dizziness, headache, superficial phlebitis, flushing).[19] These studies may not make up sufficient evidence ground for a guideline about the overall clinical application of Danhong injection. But the RCT[18] exploring Danhong injection's improvement of angina may serve as a triggering study, and would be analyzed in combination with the RWE evidence, using the MESERT approach, to develop a rapid recommendation for Danhong injection use in angina management.

In the future, a complete system is needed to support the application of the MESERT approach for TCM interventions. This includes at least an established set of methodological standards, a network of multidisciplinary experts, and a lively updating pool of established recommendations. In the early efforts, priorities may be given to TCM interventions with high quality evidence, and then for interventions with moderate and low-quality evidence.

5. Conclusion

In this paper, we discussed rapid recommendations as a useful framework to develop clinical practice guidelines for TCM interventions. We specifically proposed the MESERT approach, an enhanced rapid recommendation framework for TCM interventions. This approach fully embraces the special features of TCM interventions and captures all the merits of the original rapid recommendation framework, by which clinical evidence about TCM interventions would be efficiently translated into practice. We anticipate that the MESERT approach would well complement classical guideline development, both of which would serve as tools for promoting evidence-based practice of TCM.

Author contributions

Conceptualization: XS. Methodology: XS and QL. Writing – Original Draft: XS, QL, XL, and LL. Writing – Review & Editing: all authors. Visualization: QL and LL. Supervision: XS. Funding acquisition: XS.

Conflict of interest

None to declare.

Funding

This study was supported by National Key R&D Program of China (Grant nos 2017YFC1700400 and 2017YFC1700406), Sichuan Youth Science and Technology Innovation Research Team (Grant no. 2020JDTD0015), China Center for Evidence Based Traditional Chinese Medicine (Grant no. 2020YJSZX-3), and 1•3•5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (Grant no. ZYYC08003).

Ethical statement

Not applicable.

Data availability

Not applicable.

References

1. Chen Y, Wang C, Shang H, Yang K, Norris SL. Clinical practice guidelines in China. *BMJ*. 2018;360:j5158 Clinical research ed.
2. Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ (Clinical research ed)*. 2016;354:i5191.
3. Helsingen LM, Vandvik PO, Jodal HC, Agoritsas T, Lytvyn L, Anderson JC, et al. Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a clinical practice guideline. *BMJ*. 2019;367:l5515 Clinical research ed.
4. Sultan S, Lim JK, Altayar O, Davitkov P, Feuerstein JD, Siddique SM, et al. AGA rapid recommendations for gastrointestinal procedures during the COVID-19 pandemic. *Gastroenterology*. 2020;159(2):739–758 .e4..
5. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924–926 Clinical research ed.
6. World Health Organization (WHO). WHO Handbook for Guideline Development (2012). https://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf [Accessed March 7, 2022].
7. Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of colorectal cancer (2016). https://www.sign.ac.uk/media/1064/sign126.pdf [Accessed March 7, 2022].
8. Yao L, Chen Y, Wang X, Shi X, Wang Y, Guo T, et al. Appraising the quality of clinical practice guidelines in traditional Chinese medicine using AGREE II instrument: A systematic review. *Int J Clin Pract*. 2017;71(5).
9. Yu WY, Xu JL, Shi NN, Wang LY, Han XJ, Wang YY, et al. Assessing the quality of the first batch of evidence-based clinical practice guidelines in traditional Chinese medicine. *J Tradition Chin Med*. 2011;31(4):376–381.
10. Sun X, Li L, Liu Y, Wang W, Yao M, Tan J, et al. Assessing clinical effects of traditional Chinese medicine interventions: moving beyond randomized controlled trials. *Front Pharmacol*. 2021;12:713071.
11. Li H, Deng J, Deng L, Ren X, Xia J. Safety profile of traditional Chinese herbal injection: An analysis of a spontaneous reporting system in China. *Pharmacoepidemiol Drug Saf*. 2019;28(7):1002–1013.
12. Qin X, Liu J, Wang Y, Liu Y, Deng K, Ma Y, et al. Natural language processing was effective in assisting rapid title and abstract screening when updating systematic reviews. *J Clin Epidemiol*. 2021;133:121–129.
13. Jenkins DA, Hussein H, Martina R, Dequen-O'Byrne P, Abrams KR, Bujkiewicz S. Methods for the inclusion of real-world evidence in network meta-analysis. *BMC Med Res Methodol*. 2021;21(1):207.
14. Chen W, Liu B, Wang LQ, Ren J, Liu JP. Chinese patent medicines for the treatment of the common cold: a systematic review of randomized clinical trials. *MC Complement Alternat Med*. 2014;14:273.
15. Hammerschlag R, Milley R, Colbert A, Weih J, Yohalem-Ilsley B, Mist S, et al. Randomized Controlled Trials of Acupuncture (1997-2007): An Assessment of Reporting Quality with a CONSORT- and STRICTA-Based Instrument. *Evid-based Complement Alternat Med*. 2011 2011.
16. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthrit Rheumatol*. 2020;72(2):220–233 (Hoboken, NJ).
17. Tu JF, Yang JW, Shi GX, Yu ZS, Li JL, Lin LL, et al. Efficacy of intensive acupuncture versus sham acupuncture in knee osteoarthritis: a randomized controlled trial. *Arthrit Rheumatol*. 2021;73(3):448–458 (Hoboken, NJ).
18. Liu J, Li DD, Dong W, Liu YQ, Wu Y, Tang DX, et al. Detection of an anti-angina therapeutic module in the effective population treated by a multi–target drug Danhong injection: a randomized trial. *Signal Transduct Target Ther*. 2021;6(1):329.
19. Li XL, Tang JF, Li WX, Li CX, Zhao T, Zhao BC, et al. Postmarketing safety surveillance and reevaluation of danhong injection: clinical study of 30888 cases. *Evid-based Complement Alternat Med*. 2015;2015:610846.