

Methodological and Ethical Challenges for the Implementation of Complementary and Alternative Medicine-Related Clinical Trials: Review of Reviews

Nazila Javadi-Pashaki ^{1,2}, Hamidreza Mehrabi ³, Iman Asdaghihromi ⁴, Seyedeh Mahjabin Taheri Otahsara ⁵, Mohammad Javad Ghazanfari ⁶, Pooyan Ghorbani Vajargah ⁷, Amirabbas Mollaei ⁷, Atefeh Falakdami ⁷, Poorya Takasi ⁷, Aghil Mollaei ⁸, Hatf Mashhadi ⁹, Samad Karkhah ^{7*}

1. Social Determinants of Health Research Center (SDHRC), Guilan University of Medical Sciences, Rasht, Iran
2. Department of Nursing, Cardiovascular Diseases Research Center, School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran
3. Student Research Committee, School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran
4. Department of Anesthesiology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
5. Student Research Committee, Nasibeh School of Nursing and Midwifery, Mazandaran University of Medical Sciences, Sari, Iran
6. Department of Medical-Surgical Nursing, School of Nursing and Midwifery, Kashan University of Medical Sciences, Kashan, Iran
7. Department of Medical-Surgical Nursing, School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran
8. Department of Biostatistics, School of Health, Mazandaran University of Medical Sciences, Sari, Iran
9. Department of Geriatrics, School of Nursing and Midwifery, Kashan University of Medical Sciences, Kashan, Iran

Article Type:

Review Article

Article History:

Received: 24 Jan 2022

Revised: 5 Sep 2022

Accepted: 10 Sep 2022

Published: 10 Jun 2022

*Correspondence:

Samad Karkhah

Department of Medical-Surgical Nursing, School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran

samad.karkhah@gums.ac.ir



DOI: [10.29252/jorjanibiomedj.10.3.61](https://doi.org/10.29252/jorjanibiomedj.10.3.61)

Abstract

Background and Objectives: The implementation of complementary and alternative medicine (CAM) has increased in recent decades. Due to the positive effects of CAM interventions, 5 to 74.8% of people use these treatments worldwide. However, implementing CAM-related clinical trials is associated with challenging issues. Failure to address these challenges can lead to poor quality of studies, publication of non-scientific findings, and ultimately disregard for human rights and ethics. This review aims to comprehensively review the literature focusing on methodological and ethical challenges for implementing CAM-related clinical trials.

Material and Methods: This review of reviews was conducted via international databases, including PubMed/MEDLINE, Web of Science, and Scopus using keywords extracted from medical subject headings such as “Methods”, “Methodological Study”, “Methodological Studies”, “Ethics”, “Complementary Therapies”, “Complementary Medicine”, “Alternative Medicine”, “Clinical Trial”, and “review” from the earliest to May 1, 2022.

Results: In general, challenging issues for the implementation of CAM-related clinical trials can be divided into two categories: 1) methodological and 2) ethical. Methodological challenges included: Risk of bias, Lack of knowledge of researchers, and Blinding. On the other hand, ethical challenges in clinical trial studies are divided into two categories: patients' rights and placebo use.

Conclusion: Overall, the present study emphasizes the need for special attention to the quality of CAM-related clinical trials. Also, this study can pioneer the introduction of critical challenging issues in CAM-related clinical trials and provide appropriate suggestions for researchers to solve these issues in future studies.

Keywords: Methods [[MeSH](#)]; Complementary Therapies [[MeSH](#)]; Ethics [[MeSH](#)]; Clinical Trial [[MeSH](#)]

Highlights

- Challenging issues for implementing complementary and alternative medicine (CAM)-related clinical trials can be divided into 1) methodological and 2) ethical.
- This study can pioneer the introduction of critical challenging issues in CAM-related clinical trials and provide appropriate suggestions for researchers to solve these issues in future studies.

Introduction

Implementation of Complementary and Alternative Medicine (CAM) has increased in recent decades (1-7). CAM consists of two components, including 1) complementary medicine and 2) alternative medicine. "Complementary medicine" is defined as non-mainstream practices that are not part of standard medical care but are used in conjunction with conventional medical methods. On the other hand, "alternative medicine" includes non-mainstream practices that are used instead of standard medical care (8-10). In general, CAM interventions can be divided into four main groups, including 1) mind-body-spirit therapies (such as imagery, yoga, and music therapy), 2) manipulative and body-based therapies (massage, tai chi, and relaxation therapies), 3) natural products (aromatherapy, and herbal medicines), and 4) energy therapies (light therapy, reflexology, acupressure) (11-14). Due to the positive effects of CAM interventions, 5 to 74.8% of people use these treatments worldwide (15-19). Nearly half of patients in the USA use CAM therapies to treat medical conditions and improve well-being (1). CAM is widely used to improve disease-related outcomes and patients' quality of life (20-25). Complaints of chronic diseases, physical disabilities, and mental stress play an essential role in the implementation of these treatments (15, 26, 27). However, the implementation of CAM-related clinical trials is associated with critical challenging issues (28, 29). Failure to address challenging issues can lead to poor quality of studies, publication of non-scientific findings, and ultimately disregard for

human rights and ethics. Therefore, these challenging issues can be divided into two categories: 1) methodological and 2) ethical (30).

In relation to methodological challenges, one of the critical issues in clinical trial studies is the existence of biases. There are different types of biases in Randomized Controlled Trials (RCTs) (31). One of the most common is selection and implementation bias, and the best way to minimize selection bias is randomization, which means randomly assigning participants to study groups. Blinding can minimize implementation bias and produce more reliable results (32). Also, blinding the adverse effects of researchers' and participants' awareness of the intended intervention reduces the results. However, there are criticisms of blindness (33-35). Ethical challenges have always been discussed, including issues such as using placebos, guaranteeing the rights and interests of participants, and attention to treatments' effectiveness or side effects (36).

It is evident that in the implementation of RCT studies, it is necessary to pay attention to ethical and methodological challenges, and since the results of RCT studies play an important role in therapeutic decisions and are presented as part of the body of knowledge; It is essential to observe the considerations that pay attention to the quality of studies. Dissemination of scientific and reliable findings can play an essential role in improving the quality of clinical care and complying with ethical principles, given the importance of ethical and methodological issues in the implementation of CAM-related clinical trials and the role of these issues in the publication of scientific and reliable findings, this review of reviews aimed to summarize the evidence regarding the methodological and ethical challenges for the implementation of CAM-related clinical trials.

Materials and Methods

This review of reviews was conducted via international databases, including PubMed/MEDLINE, Web of Science, and Scopus using keywords extracted from medical subject headings such as "Methods", "Methodological

Study”, “Methodological Studies”, “Ethics”, “Complementary Therapies”, “Complementary Medicine”, “Alternative Medicine”, “Clinical Trial”, and “review” from the earliest to May 1, 2022. For example, the search strategy was in PubMed/MEDLINE database including (“Methods”) OR (“Methodological Study”) OR (“Methodological Studies”)) AND (“Ethics”) OR (“Bioethical Issues”) OR (“Morals”) OR (“Ethical Issues”)) AND (“Complementary Therapies”) OR (“Complementary Medicine”) OR (“Alternative Medicine”) OR (“Alternative Therapies”)) AND (“Clinical Trial”) OR (“Review”). Keywords were combined via Boolean operators (AND/OR). English-language published reviews related to the purpose of the present review were included. The search was performed by two authors independently. This

review does not include gray literature such as expert opinions, conference presentations, dissertations, research and committee reports, and ongoing research. Gray literature includes articles produced in print and electronic formats but not evaluated by a commercial publisher (37). Lists of references from eligible studies were assessed manually to achieve maximum search comprehensiveness. Data management were conducted using the EndNote X8 software. A total of 974 articles were obtained initially using database searches. After removing the duplicates, two researchers independently evaluated the title, abstract, and full text of the articles based on inclusion/exclusion criteria. Finally, full texts of selected articles were reviewed, and six studies were included in this review (Figure 1).

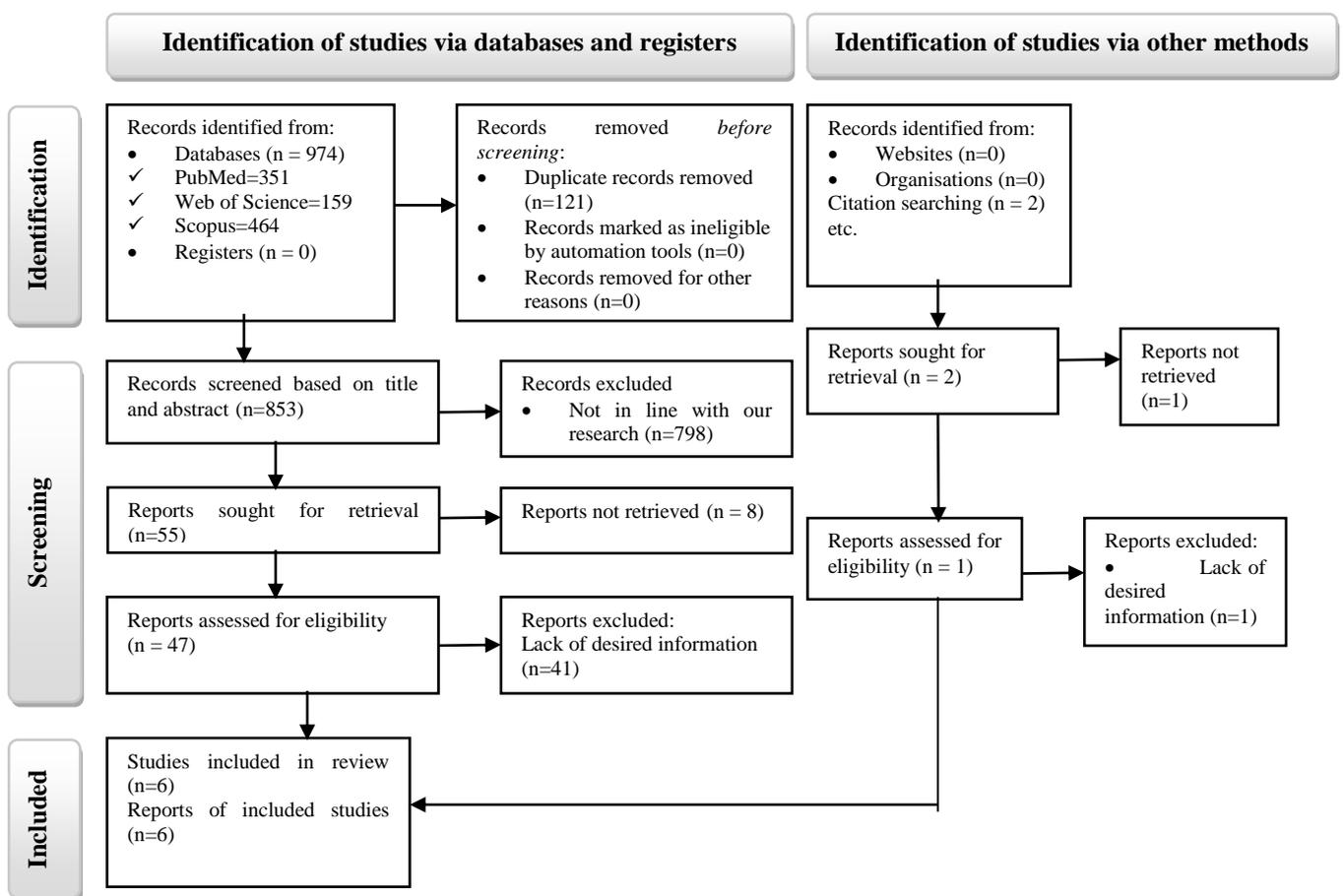


Figure 1. Flow diagram of the study selection process

Results

The basic characteristics of the included studies in this review are presented in [Table 1](#).

Methodological and ethical challenges for the implementation of CAM-related clinical trials

Overall, challenging issues for the implementation of CAM-related clinical trials can be divided into two categories: 1) methodological and 2) ethical.

1. Methodological

1.1. Risk of bias

Although the best and most accurate clinical trials to measure causal relationships, RCTs are always prone to various errors. Hence, one type of error in RCTs is called bias. This type of error is generally defined as any systematic error in the design, implementation, data collection, analysis, and interpretation of data that can distort the validity of the findings and conclusions. Bias can lead to underestimation or overestimation of the effects of RCT interventions. Based on a systematic review, half of the RCT studies on CAM implementation in hemodialysis patients had low bias [\(38\)](#).

1.2. Lack of knowledge of researchers

Some researcher-related challenging issues include lack of knowledge of researchers in the implementation of RCTs, lack of proper communication between the researcher and the statistical expert for randomization and sampling, weakness of researchers in correct randomization, non-use of blinding, failure to the management of sample erosion and report all relevant variables, small sample size, incomplete information regarding the validity and reliability of data collection tools, failure to consult with statisticians during the study, which require special attention by policy-makers in research fields and universities [\(38, 39\)](#).

1.3. Blinding or not?

In retrospect, the call for new methodologies appears to have been a reaction against the perceived dominance of the Randomized Controlled Trial (RCT). This reaction stemmed

first from misconceptions regarding the nature of the RCT and second from a desire to ask what were thought to be new questions about medicine, the answers that cannot be determined by an RCT. Concerning the first point, it is interesting how often CAM practitioners and other commentators use the terms RCT and double-blind trial interchangeably [\(40\)](#).

This is an excellent example of how certain incidental or additional features of particular trials have been mistakenly perceived to be an integral part of the RCT. RCTs do not have to be double-blind. An RCT can still be conducted even if the therapy cannot be given in a double-blind fashion [\(38, 39\)](#).

In addition to double-blinding, several other features of clinical trial methodology have been said, by critics, to be a necessary component of any RCT. It has often been argued that RCTs should not be conducted because research on a CAM therapy should not involve a particular methodological technique and because such a technique is an inherent part of an RCT. Some examples of this kind of argument are given below. This is to show that rigorous RCTs can be conducted to solve real-world problems and which do not conform to the caricature of the "double-blind trial" [\(40\)](#).

One problem with focusing on paradigms, the problem with much of the early methodological debate was that, this approach is of limited use to prospective researchers. One of our primary roles at the Research Council for Complementary Medicine is to advise individuals who wish to get involved in research. An obvious first step would have been to refer an inquirer to the relevant methodological literature. Unfortunately, this is often of little benefit. Esoteric comparisons of "the reductionist causal" paradigm, said to characterize "orthodox" biomedical science, and the "integrative holistic" paradigm, said to be characteristic of CAM, were no doubt theoretically attractive, but they were of limited practical value [\(38, 39\)](#).

Table 1. Essential characteristics of the studies included in this review

Author/Year	Title	Design	Number of included studies	Main Findings
Huanhua n et al., 2021	Challenges for ethics committees in biomedical research governance: illustrations from China and Australia	Narrative Review	45 Clinical trials	To maximize the benefits and minimize the risks to participants, the following aspects should be considered in the ethical review of clinical trials: (1) Calculate and minimize sample content in such a way as to prevent an overdose of treatment participants (2) Guaranteeing the rights and interests of the participants (3) Pay close attention to the occurrence of adverse events, including serious cases (4) An add-on design scheme can be adopted in which the experimental group and the control group can adopt standard treatment
Katz et al., 2021	Research design considerations for randomized controlled trials of spinal cord stimulation for pain: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials/Institute of Neuromodulation/International Neuromodulation Society recommendations	Narrative Review	43 Clinical trials	Clinical trials have been criticized as double-blind.
Zhang et al., 2021	The Challenges of Ethical Review in Clinical Research of Traditional Chinese Medicine	Narrative Review	18 RCTs	Three recommendations for using a placebo in clinical trials: (1) the disease under investigation is limited and can be treated even without treatment (2) there is currently no specific treatment for the research disease, which means that new treatments should be considered (3) chronic illness and short-term absence of treatment will have no significant effect on the prognosis
Adib-Hajbageri et al., 2019	Bias in clinical trials into the effects of complementary and alternative medicine therapies on hemodialysis patients	Narrative Review	114 RCTs	Half of the RCT studies related to CAM implementation in hemodialysis patients had low bias.
Mohammadi et al., 2014	Risk of Bias in Randomized Controlled Trials Published in Iranian Nursing and Midwifery Journals in 2010	Narrative Review	68 RCTs	The majority of studies had an unclear or high risk of bias. Random sequence generation in 22%, concealment allocation in 4.5%, blinding in 22%, incomplete outcome data in 35.3%, selective outcome reporting in 51.5%, and other bias in 36.7% of the studies was in low risk of bias.
Louis et al., 1983	Critical issues in the conduct and interpretation of clinical trials	Narrative Review	12 RCTs	Patients should be aware of the potential advantages and disadvantages of interventions and have the right to withdraw from the study at any stage of the study.

2. Ethical

2.1. Patient rights

Quality assurance to ensure the protection of patient rights is essential to research ethics in the implementation of CAM-related clinical trials. Also, one of the most important aspects of patient rights is informed consent, a primary concern in clinical trials. However, its proper implementation has been controversial in many cases. Patients should be aware of the potential advantages and disadvantages of interventions and have the right to withdraw from the study at any stage (41). It is suggested that researchers adhere to the Nuremberg Code and the Helsinki Declaration and institutional review boards, to resolve this challenging issue and promote ethical behaviors. Also, monitoring clinical trials and research ethics-related workshops is necessary to promote the ethical behaviors of researchers in clinical trials.

2.2. Use of placebo

In addition, the use of a placebo in RCTs is one of the main concerns in ethical studies in clinical trials. Especially when it is clear that effective treatment is available to prevent the progression of the disease, treating patients is not the only ethical placebo. However, there are three recommendations for the use of a placebo, including (1) the disease under investigation is limited and can be treated even without treatment, (2) there is currently no specific treatment for the research disease, which means that New treatment should be considered, and (3) chronic illness and short-term absence of treatment will have no significant effect on the prognosis (42).

However, to maximize the benefits and minimize the risks to participants, the following aspects should be considered in the ethical review of clinical trials: (1) Calculate and minimize sample content in such a way as to prevent overdose of treatment participants with poor efficacy or adverse reactions. (2) Guaranteeing the rights and interests of the participants; Ensuring the safety and reliability of pharmacological excipients or raw materials; in the placebo production process,

the relevant materials must be in accordance with the relevant international standards to ensure the quality and safety of the placebo.

(3) Pay close attention to the occurrence of adverse events, including serious cases. (4) An add-on design scheme can be adopted in which the experimental and control groups can adopt standard treatment as the primary intervention to minimize the possibility of harm (43).

Conclusion

The present study emphasizes the need for special attention to the quality of CAM-related clinical trials. Also, this study can play an important role in introducing important challenging issues in clinical trials related to CAM and provide appropriate suggestions to researchers to solve these issues in future studies. While the importance of addressing barriers to conducting and applying research In CAM, it is recognized that, to date, addressing the barriers and challenges has been limited. Numerous barriers remain, requiring coordinated efforts and collaboration among various CAM stakeholders and across multiple sectors. Further research can contribute to the evidence base on how best to overcome these barriers to promote the conduct and application of research in CAM.

Funding

This research did not receive any specific grant from public, commercial, or not-for-profit funding agencies.

Declaration of Conflicting Interests

The Author(s) declare(s) that there is no conflict of interest

References

1. Patel SJ, Kemper KJ, Kitzmiller JP. Physician perspectives on education, training, and implementation of complementary and alternative medicine. *Advances in medical education and practice*. 2017;8:499. [DOI] [PMID] [PMCID] [Google Scholar]

2. Ghazanfari MJ, Karkhah S, Emami Zeydi A, Mortazavi H, Tabatabaee A, Adib-Hajbaghery M. A Systematic Review of Potentially Effective Nonpharmacological Interventions for Reducing Fatigue among Iranian Patients Who Receive Hemodialysis. *Complementary medicine research*. 2021;1-11. [[view at publisher](#)] [[DOI](#)] [[PMID](#)] [[Google Scholar](#)]
3. de Moraes Mello Boccolini P, Siqueira Boccolini C. Prevalence of complementary and alternative medicine (CAM) use in Brazil. *BMC complementary medicine and therapies*. 2020;20(1):1-10. [[DOI](#)] [[PMID](#)] [[PMCID](#)] [[Google Scholar](#)]
4. Firkins R, Einfeld H, Keinki C, Buentzel J, Hochhaus A, Schmidt T, et al. The use of complementary and alternative medicine by patients in routine care and the risk of interactions. *Journal of cancer research and clinical oncology*. 2018;144(3):551-7. [[DOI](#)] [[PMID](#)] [[Google Scholar](#)]
5. James PB, Wardle J, Steel A, Adams J. Traditional, complementary and alternative medicine use in Sub-Saharan Africa: a systematic review. *BMJ global health*. 2018;3(5):e000895. [[DOI](#)] [[PMID](#)] [[PMCID](#)] [[Google Scholar](#)]
6. Buckner C, Lafrenie R, Dénomée J, Caswell J, Want D. Complementary and alternative medicine use in patients before and after a cancer diagnosis. *Current Oncology*. 2018;25(4):275-81. [[DOI](#)] [[PMID](#)] [[PMCID](#)] [[Google Scholar](#)]
7. Hon KL, Bao YM, Chan KC, Chau KW, Chen R-S, Cheok KTG, et al. Determinants for asthma control, quality of life and use of complementary and alternative medicine in asthmatic pediatric patients in four cities. *World Journal of Pediatrics*. 2018;14(5):482-91. [[DOI](#)] [[PMID](#)] [[Google Scholar](#)]
8. Ng JY, Parakh ND. A systematic review and quality assessment of complementary and alternative medicine recommendations in insomnia clinical practice guidelines. *BMC complementary medicine and therapies*. 2021;21(1):1-11. [[DOI](#)] [[PMID](#)] [[PMCID](#)] [[Google Scholar](#)]
9. Ng JY, Dhawan T, Dogadova E, Taghi-Zada Z, Vacca A, Wieland LS, et al. Operational definition of complementary, alternative, and integrative medicine derived from a systematic search. *BMC complementary medicine and therapies*. 2022;22(1):1-39. [[DOI](#)] [[PMID](#)] [[PMCID](#)] [[Google Scholar](#)]
10. Odegard BR, Ferguson MR, Naja F, Ayoub J, Banna J. A qualitative investigation of the perceptions of complementary and alternative medicine among adults in Hawai'i. *BMC complementary medicine and therapies*. 2022;22(1):1-9. [[DOI](#)] [[PMID](#)] [[PMCID](#)] [[Google Scholar](#)]
11. Lindquist R, Tracy MF, Snyder M. *Complementary & alternative therapies in nursing*: Springer Publishing Company; 2018. [[DOI](#)] [[Google Scholar](#)]
12. Wang C, Preisser J, Chung Y, Li K. Complementary and alternative medicine use among children with mental health issues: Results from the National Health Interview Survey. *BMC complementary and alternative medicine*. 2018;18(1):1-17. [[DOI](#)] [[PMID](#)] [[PMCID](#)] [[Google Scholar](#)]
13. Barcan R. *Complementary and alternative medicine: bodies, therapies, senses*: Routledge; 2020. [[DOI](#)] [[Google Scholar](#)]
14. Lindquist R, Tracy MF, Snyder M. *Complementary and alternative therapies in nursing*: Springer Publishing Company; 2018. [[DOI](#)] [[Google Scholar](#)]
15. Ghaedi F, Dehghan M, Salari M, Sheikhrabari A. Complementary and alternative medicines: usage and its determinant factors among outpatients in Southeast of Iran. *Journal of evidence-based complementary & alternative medicine*. 2017;22(2):210-5. [[DOI](#)] [[PMID](#)] [[PMCID](#)] [[Google Scholar](#)]
16. Lee JA, Sasaki Y, Arai I, Go H-Y, Park S, Yukawa K, et al. An assessment of the use of complementary and alternative medicine by Korean people using an adapted version of the standardized international questionnaire (I-CAM-QK): a cross-sectional study of an internet survey.

- BMC complementary and alternative medicine. 2018;18(1):1-11. [DOI] [PMID] [PMCID] [Google Scholar]
17. Kiran C, Akdeniz M, Kavukcu E. Evaluation of Attitudes and Using About Complementary and Alternative Medicine of People Aged 18 and Older In Antalya. [Google Scholar]
18. Kalantar Motamedi MH, Abouie A, Hafezi-Nejad N, Saadat S, Rahimi-Movaghar A, Motevalian A, et al. Prevalence and Costs of Complementary and Alternative Medicine among Traumatic Patients in Iran: A Nationwide Population-based Study. Iranian journal of public health. 2018;47(10):1558-66. [Google Scholar]
19. Motamedi MHK, Abouie A, Hafezi-Nejad N, Saadat S, Rahimi-Movaghar A, Motevalian A, et al. Prevalence and costs of complementary and alternative medicine among traumatic patients in Iran: a nationwide population-based study. Iranian Journal of Public Health. 2018;47(10):1558. [Google Scholar]
20. Hlubocky FJ, Ratain MJ, Wen M, Daugherty CK. Complementary and alternative medicine among advanced cancer patients enrolled on phase I trials: a study of prognosis, quality of life, and preferences for decision making. Journal of Clinical Oncology. 2007;25(5):548-54. [view at publisher] [DOI] [PMID] [Google Scholar]
21. Albabtain H, Alwhaibi M, Alburaikan K, Asiri Y. Quality of life and complementary and alternative medicine use among women with breast cancer. Saudi pharmaceutical journal. 2018;26(3):416-21. [DOI] [PMID] [PMCID] [Google Scholar]
22. Dikmen HA, Terzioglu F. Effects of reflexology and progressive muscle relaxation on pain, fatigue, and quality of life during chemotherapy in gynecologic cancer patients. Pain Management Nursing. 2019;20(1):47-53. [DOI] [PMID] [Google Scholar]
23. Xu G, Lei H, Zhou Y, Huang L, Tian H, Zhou Z, et al. Acupuncture for Quality of Life of Patients with Defecation Dysfunction after Sphincter Preserving Surgery for Rectal Cancer: A Systematic Review. Evidence-Based Complementary and Alternative Medicine. 2021;2021. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]
24. Hack CC, Hackl J, Hüttner NB, Langemann H, Schwitulla J, Dietzel-Drentwett S, et al. Self-reported improvement in side effects and quality of life with integrative medicine in breast cancer patients. Integrative cancer therapies. 2018;17(3):941-51. [DOI] [PMID] [PMCID] [Google Scholar]
25. Sajadi M, Davodabady F, Ebrahimi-Monfared M. The effect of foot reflexology on fatigue, sleep quality and anxiety in patients with multiple sclerosis: a randomized controlled trial. Archives of Neuroscience. 2020;7(3). [DOI] [Google Scholar]
26. Dilekçi E, Özkuk K, Kaki B. Effect of balneotherapy on pain and fatigue in elderly with knee osteoarthritis receiving physical therapy: a randomized trial. International Journal of Biometeorology. 2019;63(12):1555-68. [DOI] [PMID] [Google Scholar]
27. Takahashi N, Kasahara S, Yabuki S. Development and implementation of an inpatient multidisciplinary pain management program for patients with intractable chronic musculoskeletal pain in Japan: preliminary report. Journal of pain research. 2018;11:201. [DOI] [PMID] [PMCID] [Google Scholar]
28. Ayati MH, Pourabbasi A, Namazi N, Zargaran A, Kheiry Z, Kazemi AH, et al. The necessity for integrating traditional, complementary, and alternative medicine into medical education curricula in Iran. Journal of integrative medicine. 2019;17(4):296-301. [DOI] [PMID] [Google Scholar]
29. Jung S-Y, Kang JW, Kim T-H. Monitoring in clinical trials of complementary and alternative medicine. Integrative medicine research. 2021;10(2):100666. [DOI] [PMID] [PMCID] [Google Scholar]
30. Jung S-Y, Kang JW, Kim T-H. Monitoring in clinical trials of complementary and alternative medicine. Integrative medicine research.

- 2020;100666. [DOI] [PMID] [PMCID] [Google Scholar]
31. Brantingham PJ, Valasik M, Mohler GO. Does predictive policing lead to biased arrests? Results from a randomized controlled trial. *Statistics and public policy*. 2018;5(1):1-6. [DOI] [Google Scholar]
32. Krauss A. Why all randomised controlled trials produce biased results. *Annals of medicine*. 2018;50(4):312-22. [DOI] [PMID] [Google Scholar]
33. du V. Florey C, Yule B, Fogg A, Napier A, Orbell S, Cuschieri A. A randomized trial of immediate discharge of surgical patients to general practice. *Journal of Public Health*. 1994;16(4):455-64. [DOI] [PMID] [Google Scholar]
34. Vickers A. Methodological issues in complementary and alternative medicine research: a personal reflection on 10 years of debate in the United Kingdom. *The Journal of Alternative and Complementary Medicine*. 1996;2(4):515-24. [DOI] [PMID] [Google Scholar]
35. Probst P, Zschke S, Heger P, Harnoss JC, Hüttner FJ, Mihaljevic AL, et al. Evidence-based recommendations for blinding in surgical trials. *Langenbeck's Archives of Surgery*. 2019;404(3):273-84. [DOI] [PMID] [Google Scholar]
36. Goldstein CE, Weijer C, Brehaut JC, Fergusson DA, Grimshaw JM, Horn AR, et al. Ethical issues in pragmatic randomized controlled trials: a review of the recent literature identifies gaps in ethical argumentation. *BMC medical ethics*. 2018;19(1):1-10. [DOI] [PMID] [PMCID] [Google Scholar]
37. Corlett RT. Trouble with the gray literature. *Biotropica*. 2011;43(1):3-5. [DOI] [Google Scholar]
38. Adib-Hajbaghery M, Nabizadeh-Gharghozar Z, Nasirpour P. Bias in clinical trials into the effects of complementary and alternative medicine therapies on hemodialysis patients. *Journal of family medicine and primary care*. 2019;8(7):2179. [DOI] [PMID] [PMCID] [Google Scholar]
39. Mohammady M, Toghian Chaharsougi N, Abdoli S. Risk of bias in randomized controlled trials published in Iranian nursing and midwifery journals in 2010. *Iranian Journal of Epidemiology*. 2014;9(3):24-36. [view at publisher] [Google Scholar]
40. Katz N, Dworkin RH, North R, Thomson S, Eldabe S, Hayek SM, et al. Research design considerations for randomized controlled trials of spinal cord stimulation for pain: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials/Institute of Neuromodulation/International Neuromodulation Society recommendations. *Pain*. 2021;162(7):1935. [DOI] [PMID] [PMCID] [Google Scholar]
41. Louis TA, Shapiro SH. Critical issues in the conduct and interpretation of clinical trials. *Annual review of public health*. 1983;4(1):25-46. [DOI] [PMID] [Google Scholar]
42. Zhang J, Zhang Z-M. The Challenges of Ethical Review in Clinical Research of Traditional Chinese Medicine. *Evidence-Based Complementary and Alternative Medicine*. 2021;2021. [DOI] [PMID] [PMCID] [Google Scholar]
43. Huanhuan C, Li M, Wang M, Roder D, Olver I. Challenges for ethics committees in biomedical research governance: illustrations from China and Australia. *Journal of Medical Ethics and History of Medicine*. 2021;14. [DOI] [PMID] [PMCID] [Google Scholar]

How to cite:

Javadi-Pashaki N, Mehrabi H, Asdaghihahromi I, Taheri Otaghsara S.M, Ghazanfari M.J, Ghorbani Vajargah P, Mollaei A, Falakdami A, Takasi P, Mollaei A, Mashhadi H, Karkhah S. Methodological and Ethical Challenges for the Implementation of Complementary and Alternative Medicine-Related Clinical Trials: Review of Reviews. *Jorjani Biomedicine Journal*. 2022; 10(3):61-69.