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PECULIARITIES OF CLINICAL TRIALS IN COMPLEMENTARY AND ALTERNATIVE MEDICINE

Actuality. *Complementary and alternative medicine (CAM) refers to a wide range of healthcare practices, products, and therapies that are not generally considered as a part of conventional medicine. The use of CAM is widespread and growing because patients seek more holistic approaches to health care and their well-being. Clinical trials play a key role in the evidence-based medicine system to prove the effectiveness and safety of various treatments.*

Materials and methods. *Analysis of literature data.*

Research results. *Evidence from clinical trials can facilitate the integration of effective CAM therapies into mainstream healthcare. CAM is associated with unique challenges in clinical trial conduct due to its inherent diversity and holistic approach, which often defies conventional standardisation. These challenges include establishing consistent dosing, selection of appropriate control groups, and ensuring the reproducibility of personalised treatments. For consistently of CAM therapy across all study participants, it is necessary for practitioners (investigators) to be trained in CAM treatment deliver. Moreover, correctness of the treatment delivery throughout the trial should be monitored throughout the study. Pragmatic clinical trials (PCTs) offer a valuable approach for testing the efficacy and safety of CAM therapies. PCTs are designed to evaluate the effectiveness of interventions in real-world clinical settings, which can provide advantages for CAM research. PCTs can help in revealing how CAM therapies perform when used by a diverse patient population.*

Conclusion. *Evidence from CAM clinical research can ultimately help patients and healthcare providers make informed decisions about the use of CAM in clinical care with necessary recognition and approval by regulatory bodies.*

Key words: *complementary medicine, alternative medicine, clinical research, pragmatic clinical trials, real-world settings.*

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ОСОБЛИВОСТІ КЛІНІЧНИХ ДОСЛІДЖЕНЬ У КОМПЛЕМЕНТАРНІЙ ТА АЛЬТЕРНАТИВНІЙ МЕДИЦИНІ

Актуальність. *Комплементарна та альтернативна медицина (КАМ) включає у себе широкий спектр медичних практик, препаратів та методів лікування, які зазвичай не розглядаються як частина традиційної медицини. Використання КАМ широко розповсюджене і зростає, оскільки пацієнти шукають більш цілісні підходи до покращення здоров'я та благополуччя. Клінічні випробування відіграють ключову роль у системі доказової медицини для доведення ефективності та безпеки різних методів лікування.*

Матеріал і методи. *Огляд даних наукової літератури.*

Результати дослідження. *Дані клінічних випробувань можуть сприяти інтеграції ефективних методів лікування КАМ у систему охорони здоров'я. Із методами КАМ асоційована низка складнощів під час проведення клінічних випробувань через притаманну їй варіабельність і холістичний підхід, які часто не піддаються традиційній стандартизації. Ці складнощі включають у себе встановлення однакової дози, вибір відповідних контрольних груп і забезпечення відтворюваності персоналізованих методів лікування. Для забезпечення аналогічності проведення лікування методами КАМ серед усіх учасників дослідження необхідно, щоб практикуючі лікарі (дослідники) пройшли відповідні тренінги. Окрім того, правильність проведення лікування повинна бути об'єктом моніторингу протягом усього дослідження. Прагматичні клінічні випробування (ПКВ) пропонують цінний підхід для дослідження ефективності та безпеки методів КАМ. ПКВ призначені для оцінки ефективності втручань у реальних клінічних умовах, що може забезпечити переваги для досліджень у сфері КАМ. ПКВ можуть допомогти встановити результативність використання підходів КАМ за застосування в різних популяціях пацієнтів.*

Висновок. *Доказова база за результатами клінічних досліджень у КАМ може сприяти прийняттю обґрунтованих рішень пацієнтами та медичними працівниками щодо використання КАМ у клінічній практиці з необхідним визнанням і схваленням регуляторними органами.*

Ключові слова: *комплементарна медицина, альтернативна медицина, клінічні дослідження, прагматичні клінічні випробування, умови реального застосування.*

Relevance. Complementary and alternative medicine (CAM) refers to a wide range of healthcare practices, products, and therapies that are not generally considered as a part of conventional medicine. CAM is characterized by its holistic approach to patient care, focusing on all aspects of human being. CAM encompasses a diverse group of medical and healthcare systems, practices, and products, such as (Chugh-Gupta et al., 2013; NCI, 2024):

– mind–body therapies (e.g., meditation, yoga, tai chi);

– biologically based practices (e.g., vitamins, botanicals, dietary supplements);

– manipulative and body-based practices (e.g., massage, chiropractic);

– energy healing (e.g., reiki, therapeutic touch);

– whole medical systems (e.g., ayurvedic medicine, traditional Chinese medicine).

The use of CAM is widespread and growing because patients seek more holistic approaches to health care and their well-being. The effectiveness and safety of CAM therapies are becoming increasingly researched in clinical trials to provide evidence for their use (WHO, 2013; Sayligil, 2021).

Clinical trials play a key role in the evidence-based medicine system to prove the effectiveness and safety of various treatments (NCCIH, 2010). While many common principles can be applied to the conduct of clinical trials for CAM therapies, the planning and conduct of such clinical trials require additional efforts and attention due to the nature of CAM practices, including but not limited to peculiarities with their standardisation, complexity of their application, often personalised or individualised approach for each patient (Sikorskii et al., 2009; Rzepiński & Tabaczewski, 2016; Zhang & Zhang, 2021).

Purpose of the work. The purpose of this literature review is to discuss the peculiarities of planning and conducting clinical trials for CAM products, to look at the regulatory field in this area, as well as to highlight the role of pragmatic clinical trials in CAM research.

Materials and methods of the study. Review of literature data is provided.

Research results and discussion. The need to conduct clinical trials in CAM is based on the same principles that underlie the necessity for clinical trials in conventional medicine: to provide evidence of safety,

efficacy, and effectiveness. For example, the fact that a treatment is natural does not guarantee that it is safe and effective by default. Clinical trials can help in identifying potential side effects and interactions between CAM interventions and in providing scientific data for dose-selection and proof for efficacy and effectiveness of CAM therapies (Sikorskii et al., 2009; NCCIH, 2010; Rzepiński & Tabaczewski, 2016; DeBar et al., 2023; Cancer Research UK, 2019).

Evidence from clinical trials can facilitate the integration of effective CAM therapies into mainstream healthcare, providing more options for patient care, and will help patients and healthcare providers in making their informed decisions about using CAM therapies. Moreover, rigorous clinical trial evidence is often required for CAM therapies to be recognised and approved by regulatory bodies (NCCIH, 2010; WHO, 2013; Cancer Research UK, 2019).

Therefore, clinical trials should be considered as an important component of evidence-based practice in all areas of medicine, including CAM (NCCIH, 2010, Rzepiński & Tabaczewski, 2016; Cancer Research UK, 2019). It should be taken into account that conducting clinical trials for CAM can have a number of peculiarities (Sikorskii et al., 2009; NCCIH, 2010).

General peculiarities of clinical research in CAM. Clinical trials in CAM represent unique challenges and peculiarities compared to conventional medical research and often require collaboration between traditional researchers and CAM practitioners to ensure that the study design is both scientifically rigorous and applicable to the CAM therapy being tested (Zhang & Zhang, 2021).

The process of participant recruitment for CAM clinical trials may be easier in some cases due to public interest in CAM. Since CAM therapies often aim to improve overall well-being and quality of life, which can be subjective, well-defined and validated outcome measures are required (WHO, 2000).

CAM treatments often involve complex interventions that may include multiple components, such as the combination of diet, lifestyle advice, and herbal supplements, making it difficult to isolate the effect of a single component. Due to this fact, interpretation of study results can be complicated (Macpherson, 2004; Zhang & Zhang, 2021).

It can be challenging also to create an appropriate placebo for CAM therapies particularly for practices like acupuncture or chiropractic where physical interventions are apparent (NCCIH, 2010) or traditional Chinese herbal therapy (Zhang & Zhang, 2021). Similarly, blinding participants and practitioners can be challenging in these interventions (Caspi et al., 2000).

Cultural considerations play a critical role in the design, conduct, and interpretation of CAM clinical trials due to the diverse origins and cultural significance of many CAM practices (Zhang & Zhang, 2021). Moreover, CAM practices are often deeply rooted in specific cultural or traditional beliefs, which can affect participants' expectations, engagement, and response to treatment. Special training of the research staff in the field of cultural competence can be helpful in better interactions with participants and can increase the quality of data collected. It can also help in recognising and respecting cultural differences in healthcare (WHO, 2000).

Standardisation in CAM clinical research. In clinical trials, it is essential to achieve a certain level of standardisation to ensure that the results of a clinical trial are reliable, valid, and replicable. However, standardisation in CAM clinical trials can be particularly challenging due to the inherent personalised nature of many CAM therapies (WHO, 2000; Shamabadi, 2021).

Standardisation in CAM clinical trials can be supported by predefined patient selection process with clearly specified inclusion and exclusion criteria to ensure a homogeneous study population. When study population is selected, randomisation can help in evenly distribution of patient characteristics that could affect the outcome across different intervention groups (Sikorskii et al., 2009).

Standardisation in CAM clinical trials can be also achieved with clear protocols prespecifying administration of the CAM therapy, including dosage, frequency, duration, and the method of delivery. Moreover, practitioners (investigators) should be trained to deliver the CAM therapy consistently across all study participants and the fidelity of the treatment delivery throughout the trial should be monitored. This helps ensure that all participants receive the intervention in the same manner (WHO, 2000; Sikorskii et al., 2009).

When testing herbal medicines or supplements, standardised extracts with known concentrations of active constituents should be used to ensure consistency (WHO, 2000; WHO, 2018; Shamabadi, 2021).

Considering that placebo-control is a golden standard in clinical development, the use of placebo should be encouraged in CAM clinical trials, although development and use of a placebo can be often a complex task, especially for modalities like acupuncture, massage or herbal therapy (WHO, 2000; Sikorskii et al., 2009; Ang et al., 2012; Zhang & Zhang, 2021).

Implementation of blinding wherever possible and feasible, for both practitioners and participants, can help in bias reduction (Caspi et al., 2000; Sikorskii et al., 2009). Alternatively, evaluator should be blinded to reduce bias (DeBar et al., 2023).

In order to ensure reproducibility and generalisability of results, it is advisable to use widely accepted outcome measures that can be consistently applied across all trial sites and participants and to document the specifics of the CAM intervention in such a way that the trial can be reproduced by other researchers (WHO, 2000; Cabo & Browne, 2023).

To support necessary level of standardisation in planning, conduct and reporting of clinical trials in CAM, specific guidelines have been developed. While the fundamental principles of conducting clinical trials are similar across all types of medicine, these guidelines address the unique challenges and considerations inherent in CAM research (WHO, 2000; Jung et al., 2021; NCCIH, 2024).

Guidance on conducting research on CAM therapies, including best practices for designing and conducting clinical trials, are provided by the National Center for Complementary and Integrative Health, which is the part of the U.S. National Institutes of Health (NCCIH, 2024). The Consolidated Standards of Reporting Trials (CONSORT) Group has developed an extension for trials of herbal medicine interventions, which can be applicable to some types of CAM therapies (Sikorskii et al., 2009). World Health Organization has published guidelines on how to conduct research and evaluate the safety and efficacy of traditional medicine, which is often considered under the CAM umbrella (WHO, 2000). While not specific to CAM, the International Council for Harmonisation's Good Clinical Practice (GCP) guidelines are the international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with GCP ensures that the data and reported results generated in a clinical trial, including those conducted for CAM therapies, are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected (Jung et al., 2021; Sayligil, 2021). Moreover, some academic journals that publish CAM research may have specific guidelines for authors on how to conduct and report CAM trials (springer.com, 2024).

While these measures can standardise the intervention to a degree necessary for rigorous clinical trials, it's also important to balance standardisation with the personalised nature of CAM. Researchers often use pragmatic clinical trial designs to study the effectiveness of CAM therapies in real-world settings, which allows for some variation in how the therapy is administered. This approach can provide evidence that is more applicable to everyday practice, where CAM therapies are often personalised to individual patient needs.

The role of pragmatic clinical trials in CAM. The concept of pragmatic clinical trials (PCTs) was first formally introduced by Schwartz and Lellouch in 1967. In their fundamental paper, they distinguished between "explanatory" trials, which aim to understand the underlying mechanisms of interventions, and "pragmatic" trials, which aim to inform decisions about practice (Schwartz & Lellouch, 1967).

Schwartz and Lellouch proposed that the choice between these two types of trials should be based on the objective of the trial: whether it is to test a scientific hypothesis with understanding causal relationship or to decide about which treatment to choose between options (Schwartz & Lellouch, 1967; Macpherson, 2004; Arvidsdotter et al., 2013).

PCTs offer a valuable approach for testing the efficacy and safety of CAM therapies. PCTs are designed to evaluate the effectiveness of interventions in real-world clinical settings, which can provide advantages for CAM research (Macpherson, 2004; Chan et al., 2021; DeBar et al., 2023).

Since PCTs test treatments under conditions that are much closer to everyday practice compared to the more controlled environment of explanatory trials, this can reveal how CAM therapies perform when used by a diverse patient population in routine clinical care. Consistently, PCTs typically have fewer exclusion criteria, allowing for the inclusion of patients with comorbidities and varying demographics. The use of broader patient populations and less restrictive protocols in PCTs can lead to a more complete understanding of the safety profiles of CAM therapies, including the identification of rare or long-term adverse events (Macpherson, 2004; Chan et al., 2021; DeBar et al., 2023).

Since CAM therapies often require a degree of individualisation which challenges their standardisation, PCTs can accommodate the variations in treatment delivery that are characteristic of many CAM practices, such as adjustments in acupuncture points, herbal formulations, or dietary interventions (Macpherson, 2004; Sundberg et al., 2009; Lim et al., 2024).

In some level of contrast to conventional clinical trials with more common use of objective study endpoints, PCTs often focus on outcomes that are meaningful to patients, such as quality of life, symptom relief, and functional status. These outcomes align well with the holistic approach of many CAM therapies, which emphasize overall well-being (WHO, 2000; Macpherson, 2004; Zhang & Zhang, 2021).

Moreover, PCTs can measure adherence to CAM therapies and acceptability to patients, which are critical factors for the successful implementation of these treatments in practice. The evidence generated from PCTs can support the integration of effective CAM therapies into mainstream healthcare systems, as they demonstrate

how these therapies work in typical clinical settings (Macpherson, 2004; Chan et al., 2021).

Therefore, PCTs can provide evidence that is more generalisable to routine practice, which is particularly useful for evaluating the real-world efficacy and safety of CAM therapies. This evidence can ultimately help patients and healthcare providers make informed decisions about the use of CAM in clinical care (Macpherson, 2004; Sundberg et al., 2009).

Conclusions

In comparison to conventional healthcare, CAM has unique characteristics that represent challenges in the conduct of clinical trials. Particularly, individualised and holistic nature of many CAM therapies can complicate standardisation and outcome measurement. PCTs are an important option in this context because they are designed to evaluate the effectiveness and safety of interventions in real-world settings with primary focus on outcomes that are meaningful to patients. Evidence from CAM clinical research can ultimately help patients and healthcare providers make informed decisions about the use of CAM in clinical care with necessary recognition and approval by regulatory bodies.

Prospects for further research. Development and refinement of methodologies that can accommodate the personalised and holistic nature of CAM therapies within the framework of clinical research is a perspective task for further research.

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