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From concept to practice: evolution and implementation of data monitoring committees in traditional Chinese medicine clinical research

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ABSTRACT

Establishing a Data Monitoring Committee (DMC) is crucial for safeguarding participant safety and ensuring data integrity in clinical research. Originating in the United States and subsequently adopted worldwide, the DMC concept has been progressively integrated into China's clinical research system. Through a series of clinical studies and the introduction of regulations tailored to traditional Chinese medicine (TCM) research, the Chinese Medicine Data Monitoring Committee (CMDMC) framework has been progressively defined, encompassing its formation, operational mechanisms, responsibilities, and standard operating procedures. Nevertheless, as DMC development in China remains at an early stage, CMDMCs continue to face numerous pressing challenges. This article provides an in-depth analysis of the evolution of CMDMCs and the current issues surrounding their implementation within the context of TCM clinical research in China. Further advancement and optimization of CMDMCs will require coordinated efforts among sponsors, committee members, regulatory agencies, and other relevant stakeholders.

KEYWORDS

Data Monitoring Committee, Chinese Medicine Data Monitoring Committee, clinical research, traditional Chinese medicine

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1. Introduction

The Data Monitoring Committee (DMC), also known as the Data and Safety Monitoring Board, is an independent group of experts that operates separately from clinical trial organizers, sponsors, and investigators.[1,2] Its primary responsibility is the continuous oversight of trial-related risks, especially those affecting participant safety, alongside the systematic review and evaluation of accumulated safety and efficacy data. As a key governance mechanism, DMCs play a critical role in safeguarding study participants and upholding the scientific integrity of clinical research.

The formalization of the DMC concept can be traced back to the 1967 "Greenberg Report" submitted to the American Heart Association.[3] Subsequently, the U.S. National Institutes of Health championed its adoption in large-scale clinical trials, formally establishing the DMC's role in interim data review and in monitoring safety, efficacy, and overall trial conduct. Over time, global regulatory agencies increasingly recognized the critical importance of DMCs. The European Medicines Agency issued its "Guideline on Data Monitoring Committees" in 2005,[4] followed by an updated question-and-answer document in 2020.[5] The U.S. Food and Drug Administration (FDA) published comprehensive guidance in 2006,[6] with a draft update issued in 2024 that expands on key areas such as integration with innovative trial designs and the enhancement of DMC functions.[7] Japan's Pharmaceuticals and Medical Devices Agency released its own guideline in 2013,[8] reflecting the broader international adoption and standardization of DMC practices.

Parallel to these global developments, the scale of clinical trials in China has expanded significantly, driven by the rapid progress in new drug research and development (Figure 1).[9] The National Medical Products Administration has progressively strengthened clinical trial oversight by incorporating the DMC into national regulatory and technical guidance, thereby enhancing participant protection and scientific validity. Key milestones include the 2015 "General Principles for Clinical Research of New Traditional Chinese Medicines",[10] which recommended the establishment of independent DMCs for group sequential designs; the 2016 "Guidelines for Biostatistics in Drug Clinical Trials",[11] which detailed DMC concepts and responsibilities; and the landmark 2020 "Guideline for Data Monitoring Committee of Drug Clinical Trials (trial implementation)",[12] which provides comprehensive operational specifications. Collectively, these guidelines underscore the necessity of DMCs and herald a new era of clinical trial monitoring in China.

However, the application of this modern clinical trial oversight mechanism in traditional Chinese medicine (TCM) presents unique challenges. As TCM clinical research has gradually transitioned from experience-based approaches towards evidence-based medicine, there is an urgent need for standardized procedures to strengthen methodological rigor. The inherent complexity of TCM—characterized by multicomponent therapies, holistic interventions, and pattern-based diagnoses—necessitates a tailored approach to data monitoring. Therefore, this study aimed to analyze the development and localization of Chinese Medicine DMC (CMDMC), examine its current challenges, and discuss its future trajectory within the evolving landscape of TCM clinical research.

2. The evolving landscape of the CMDMC

Although the core principles of DMCs are broadly consistent globally, their operational implementation must be adapted to regional contexts and specific clinical study characteristics. In recent years, clinical research on TCM has advanced substantially and gained increasing international recognition. Several high-quality randomized controlled trials (RCTs) have generated robust evidence supporting the efficacy of TCM interventions.[13-17]

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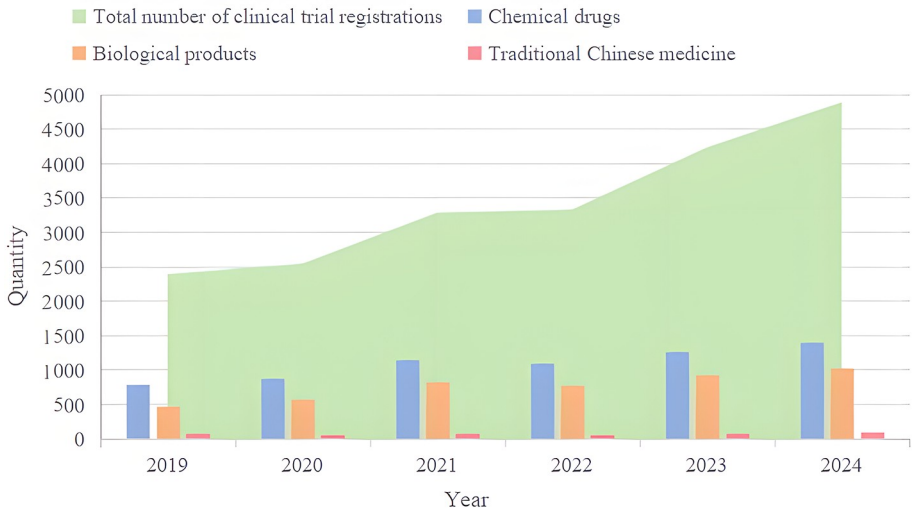

Figure 1 Overview of clinical trials in China (2019–2024): total registrations and drug-type composition of new drug trials

Notes: Data source: National Medical Products Administration annual report on the progress of clinical trials for new drug registration in China (2019–2024).

Nonetheless, such high-quality studies represent only a small fraction of the overall body of TCM research. The complexity of herbal compositions often results in multi-target effects and relatively low effect intensities, thereby contributing to measurement bias and increased data variability. Therefore, ensuring data accuracy, integrity, and reliability is paramount for enhancing the quality and methodological rigor of TCM clinical research. The adoption of comprehensive, dynamic, and internationally recognized data monitoring approaches throughout the trial process is essential for establishing a robust quality control system and improving the scientific credibility of TCM studies.

Since 2006, TCM experts have progressively incorporated DMC mechanisms into several key clinical trials, thereby exploring the feasibility and development of DMCs within TCM clinical research. The initial integration of DMCs into TCM research began in 2009, with an RCT of Di'ao Xin Xue Kang capsules for the treatment of chronic stable angina pectoris.[18] This pioneering study employed an adaptive design in which the DMC recommended an increase in sample size based on interim analysis, thereby ensuring the trial's robustness and reliability. This trial represents one of the earliest successful applications of a DMC in TCM clinical research and serves as an exemplary model for the subsequent development of DMC practices in China.

A significant milestone was reached in 2012 with a phase IV clinical trial of Danhong injection, which established a specialized CMDMC.[19-21] This initiative marked a critical step towards localizing the DMC framework by incorporating TCM-specific characteristics into its organizational structure and operational processes (Figure 2). The CMDMC established for the Danhong injection trial was designed to address the unique demands of TCM clinical research. The chairperson of the CMDMC was a senior expert in TCM internal medicine and clinical research. The committee comprised specialists with integrated expertise in Chinese and Western medicine, as well as professionals in clinical trial management, cardiovascular medicine, biostatistics, epidemiology, ethics, and pharmacology. Crucially, CMDMC members were required to possess a solid foundation in TCM theory and clinical practice, enabling a more nuanced understanding of the complexity of TCM interventions. During the trial design, the CMDMC ensured that the study protocol was grounded in TCM theory and diagnostic principles. Data collection included TCM-specific indicators, such as tongue appearance, pulse characteristics, and pattern differentiation, while statistical analyses applied methods appropriate for capturing TCM-related features.

A distinctive feature of the CMDMC was the implementation of risk-based on-site monitoring and data verification triggered by serious events with potential implications for trial safety or efficacy. This proactive measure

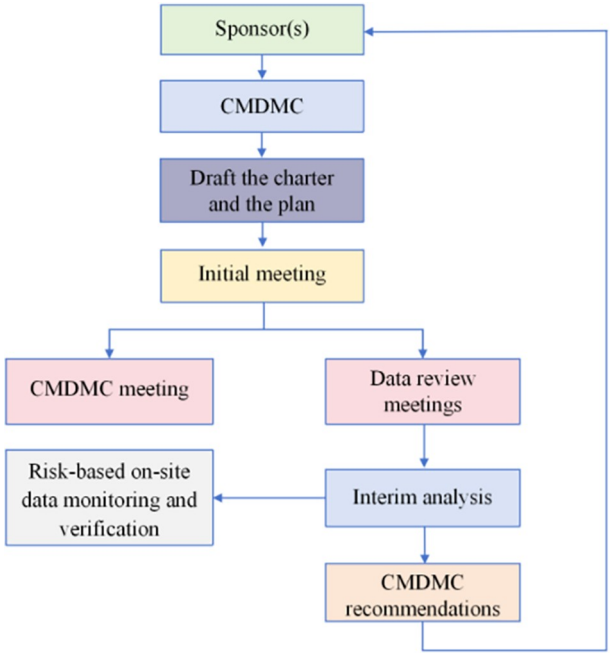

Figure 2 Operational process of the CMDMC in the phase IV clinical trial of Danhong injection

Notes: CMDMC: Chinese Medicine Data Monitoring Committee.

exceeded the typical scope of conventional DMC practices at the time.[22] According to statistics from the U.S. FDA Office of Scientific Investigations and the Office of Research Integrity and Oversight, in 2021, among 399 inspections conducted by investigators, 82% involved data verification, whereas only 18% were cause-based inspections.[23] The CMDMC explicitly defined the conditions that would trigger such cause-based inspections, recognizing them as crucial mechanisms for ensuring the accuracy, integrity, and safety of clinical trial data.

This approach was subsequently extended to other TCM clinical studies, including a safety study of Compound Kushen injection[24] and a multi-center, drug-induced, non-controlled clinical study. In these studies, the CMDMC consisted of experts proficient in both Chinese and Western medicine, who conducted evaluations incorporating TCM pattern assessment alongside risk-based on-site data monitoring and verification as integral components of the

monitoring framework.

3. CMDMC-SOP: championing the creation of a DMC framework specifically tailored to the unique characteristics of TCM

Through these practical experiences,[18,19,24,25] a unique Chinese model of data monitoring has emerged. This model is aligned with international DMC frameworks while remaining distinct in its integration of TCM-specific principles and practices. Building on this foundation, a national expert committee issued China's first group standard for CMDMCs in 2019, entitled the "Standard Operating Procedures for CMDMC" (CMDMC-SOP), followed by the publication of its English version.[22,26] The release of these documents bridged a critical gap in the quality control and quality assurance system for TCM clinical research, marking the advent of formalized data monitoring standardization within China's TCM clinical research landscape.

Based on CMDMC-SOP, the frequency of CMDMC meetings should remain flexible. This determination is guided by the projected accrual rate, the anticipated incidence of key events defined during trial design, and the identified risks associated with the experimental and/or control interventions. Depending on study progress and specific operational requirements, meetings may be scheduled on a monthly, quarterly, or annual basis. In addition, ad-hoc meetings may be convened when necessary, such as in response to emerging safety concerns or when pertinent external evidence arises that could affect trial conduct. CMDMC meetings consist of both closed and open sessions. Closed sessions are attended exclusively by CMDMC members and an unblinded independent statistician, allowing the committee to maintain the confidentiality of interim data. Open sessions involve representatives of sponsor, steering committee, study investigators, regulatory authorities, or other individuals with clinical study responsibilities, thereby facilitating direct interaction between DMC and the study team regarding the trial conduct.

Beyond general clinical trial contexts—such as large-sample multi-center studies, adaptive designs, or research involving toxic drugs or vulnerable populations—the establishment of a CMDMC is specifically emphasized in the following distinct TCM-focused scenarios: (1) TCM interventions with potential risks: trials involving TCM-specific treatments with safety concerns, such as TCM injections or other innovative diagnostic and therapeutic techniques; (2) Complex TCM pattern evaluation: studies focused on the diagnosis and assessment of complex TCM patterns, including pattern stratification, drugs targeting specific patterns, or the use of complex TCM pattern assessment scales; (3) Innovative TCM-derived drugs: research on novel TCM-based products—including injections, active ingredients, and effective components—with limited prior human use experience; (4) CMDMC-specific justifications: any other TCM-related studies in which clearly defined reasons warrant the establishment of a CMDMC.

The CMDMC-SOP emphasizes that expert panel members should possess both profound knowledge of TCM and extensive experience in clinical trials. Notably, the CMDMC-SOP introduces a novel element absent from earlier DMC guidance documents: a "risk-based on-site data monitoring and verification" procedure. This protocol empowers the CMDMC to initiate on-site data validation following endorsement by the sponsor or an expert steering committee. Such validation may be prompted by significant enrollment deviations, substantial data discrepancies, or an abnormal incidence of adverse events, all with the aim of ensuring clinical data quality and protecting participant safety. Building on this foundation, the safety monitoring responsibilities of a CMDMC encompass additional considerations unique to TCM. Specifically, the CMDMC should evaluate whether trial formulations include highly toxic or severely toxic herbal ingredients and whether specific herbal combinations may provoke toxic reactions. In addition, potential associated with the clinical interventions or therapeutic procedures employed—such as safety concerns related to herbal injections or characteristic TCM diagnostic and therapeutic techniques—should be systematically assessed.

This pioneering document represents the first set of SOPs for DMCs with a specific focus on CMDMCs. It addresses critical gaps by explicitly delineating the scope of CMDMC decision-making authority, regulatory prerequisites, the justification for adopting a risk-based on-site monitoring approach, and an explicit emphasis on risk-benefit evaluation within the context of Chinese Medicine.

4. Advances and challenges in clinical data monitoring for TCM research

The Special Committee on Data Monitoring in Clinical Research of TCM has established clear guidelines governing the establishment, composition, and operation of CMDMCs. However, the practical application and development of DMC systems in China remain at an early stage, and these mechanisms have not yet been widely implemented across domestic clinical studies, including those involving TCM.

Challenges persist in both the conceptual understanding and standardized implementation of DMCs in China. This is evidenced by the relatively low overall utilization rates—19.14% in oncology, 23.04% in pediatrics, and 10.01% in cardiovascular clinical trials (Figure 3)—which are even lower in TCM clinical research, at 8.16%, 3.28%, and 6.83%, respectively.[27-29] Moreover, publicly accessible case studies and references documenting domestic DMC applications remain scarce, limiting deeper insight into their real-world operational practices and challenges.

The current CMDMC framework faces several critical and interrelated challenges that must be addressed to fully realize its intended function and potential.

(Ⅰ) Insufficient expertise among CMDMC members. Although the use of DMCs in clinical trials is growing,[27-29] systematic training opportunities and hands-on practical experience remain limited among many committee members.[30,31] An unpublished survey indicated that only 8% of DMC members had received formal procedural training.[32] Given the essential role that DMCs play in safeguarding participant welfare and trial integrity, members are expected to possess substantial prior monitoring experience. This expectation is even more critical for CMDMCs, where integrated expertise in both TCM theory and clinical trial methodology is indispensable. Therefore, the enhancement of specialized training programs, including structured mentorship models,[31] is urgently required. Furthermore, because current Good Clinical Practice regulations do not mandate the establishment of DMCs, strengthening the legal and regulatory frameworks is necessary to improve data oversight and accountability.

(Ⅱ) Threats to DMC independence. In a clinical trial of the renin inhibitor aliskiren for acute heart failure,[33] concerns were raised that excessive regulatory involvement could undermine DMC autonomy. Joint data analyses conducted by regulatory authorities and DMCs increase the risk of premature unblinding, thereby potentially compromising trial integrity. Financial relationships between DMC members and sponsors represent another potential threat to independence,[32] although complete financial separation is often difficult to achieve. Accordingly, flexible procedural safeguards have been proposed to mitigate these risks. These include maintaining clear role delineation among sponsors, independent statisticians, and DMC members; ensuring strict confidentiality of interim data; and upholding objectivity in decisions regarding protocol amendments or trial continuation.

(Ⅲ) Lack of DMC guidelines for social or behavioral intervention trials. Most existing safety monitoring and adverse event reporting guidelines focus primarily on pharmacological or medical interventions and offer little methodological guidance for social or behavioral intervention studies. This gap has resulted in the absence of standardized frameworks for DMC oversight in nonpharmacological clinical research.

(Ⅳ) Integration of artificial intelligence (AI). AI is increasingly being applied across TCM domains, including education, diagnosis, drug development, and translational research.[34] Incorporating AI into data monitoring is expected to transform oversight practices in TCM clinical studies. Researchers are encouraged to explore the effective integration of AI-driven tools into clinical monitoring workflows to address TCM-specific challenges, thereby improving the efficiency, accuracy, and analytical depth of data oversight in this evolving research field.

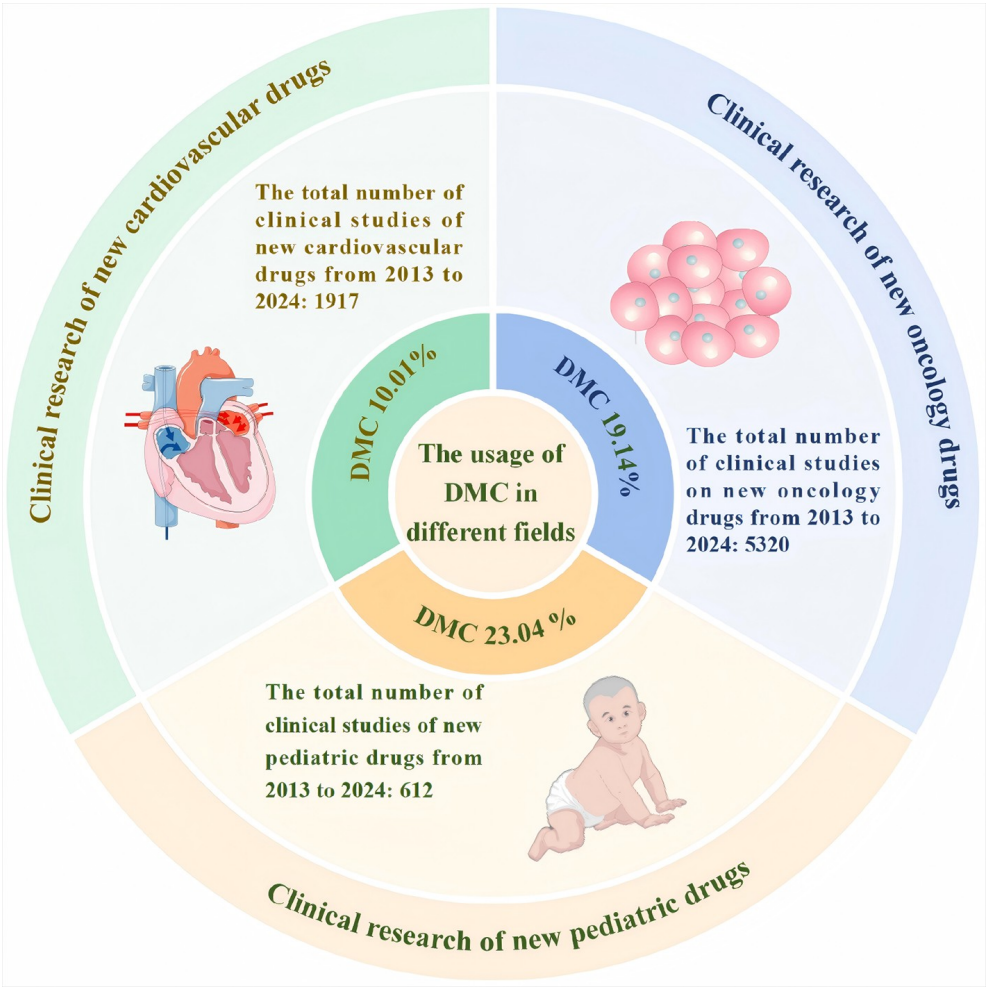

Figure 3 Utilization rates of DMCs across oncology, pediatrics, and cardiovascular clinical trials

Notes: DMC: Data Monitoring Committee.

5. Summary

The anticipated increase in large-scale, multi-center clinical trials in China presents substantial opportunities for the maturation and broader application of DMCs. Against the backdrop of an increasingly globalized research landscape, the establishment and continuous refinement of the DMC mechanism within TCM clinical research constitute a strategic imperative. This evolution serves as a methodological cornerstone, not only by strengthening the scientific rigor and credibility of TCM-derived evidence but also by facilitating closer alignment with international research standards. Consequently, the continued localization and optimization of CMDMCs are pivotal for advancing the overall quality and transparency of the TCM industry, thereby accelerating its integration into mainstream healthcare systems worldwide.

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Author Contribution Statement

Ya-nan Yu: Investigation, visualization, writing – original draft, and writing – review & editing. **Yu Zheng:** Investigation, visualization, and writing – original draft. **Hai-xia Dang:** Writing – review & editing. **Zhong Wang:** Conceptualization, project administration, funding acquisition, supervision, and writing – review & editing.

Declaration of Competing Interest

All authors have no conflict of interest to disclose.

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