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Enhancing real-world studies with artificial intelligence: addressing ethical and quality challenges

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Abstract – Real-world studies have been widely conducted in medical research to generate evidence for improving clinical decision-making. However, several issues arise when conducting prospective real-world studies, including a lack of informed consent, increased patient burden, potential decision bias, and the risk of sales promotion. These challenges can compromise real-world studies' integrity, ethics, and reliability. This editorial explores how integrating artificial intelligence technologies can help address the challenges associated with conducting prospective real-world studies.

Key words: Artificial intelligence, Real-world studies, Real-world data, Anticancer drug, Ethical and Quality Challenges.

The rapid development of anticancer drugs in the last two decades has profoundly impacted global healthcare services, as evidenced by the significant increase in survival rates among patients with common malignancies [1–3]. In China, the number of medical entities involved in clinical studies of anticancer drugs has expanded rapidly in the past decade [4, 5]. Moreover, the need to broaden the clinical indications of certain anticancer drugs has further promoted the application of real-world studies [6].

On October 25, 2020, the Medical Ethics Committee of the China Anti-Cancer Association released an online article entitled: "*Risk Warnings Related to Conducting Real-World Studies*" (available at https://mp.weixin.qq.com/s/eA4-gR5gbz63U54bqkC7jA), which highlights the potential challenges in conducting real-world studies, including lack of informed consent, decision bias, increased costs, and suspicion of promotion. The corresponding English version of this article, which has been approved by Professor Ming-Huang Hong (the former Director of the Committee) and Professor Zhao Yan (the current Director of the Committee), can be found in the Appendix.

Addressing the issues mentioned above is crucial for ensuring the ethical conduct and reliability of real-world studies. The development of Artificial Intelligence (AI) techniques, defined as "the use of complex algorithms and software to emulate human cognition in the analysis of complicated medical data, and analyze the relationships between prevention or treatment techniques and patient outcomes [7], could help to manage the challenges appropriately in real-world studies" [8, 9]. However, it should be emphasized that real-world studies can be retrospective using existing administrative data, such as electronic medical records, medical claims data, birth/death registries, and surveillance databases; or could be prospective involving prospective data collection, such as prospective patients survey, traditional prospective cohort studies, or pragmatic clinical trials [6]. The issues mentioned above generally exist in real-world studies involving prospectively patient recruitment, intervention, and data collection. Retrospective real-world studies mainly involve data governance for quality management, data cleaning, and analysis. The informed consent process in retrospective real-world studies is generally waived by the Institutional Review Boards. Therefore, in this editorial, we explore the potential of AI techniques to tackle the challenges associated with prospective real-world studies.

Protecting patients' rights and interests

The complexities of prospective real-world studies often result in scenarios where patients may be unaware of their participation in a study, thereby violating fundamental ethical principles [6]. In our opinion, the most crucial strategy is to strengthen the ethical oversight for real-world studies, particularly for prospective studies involving off-label medications or interventions beyond clinical guidelines. In these cases,

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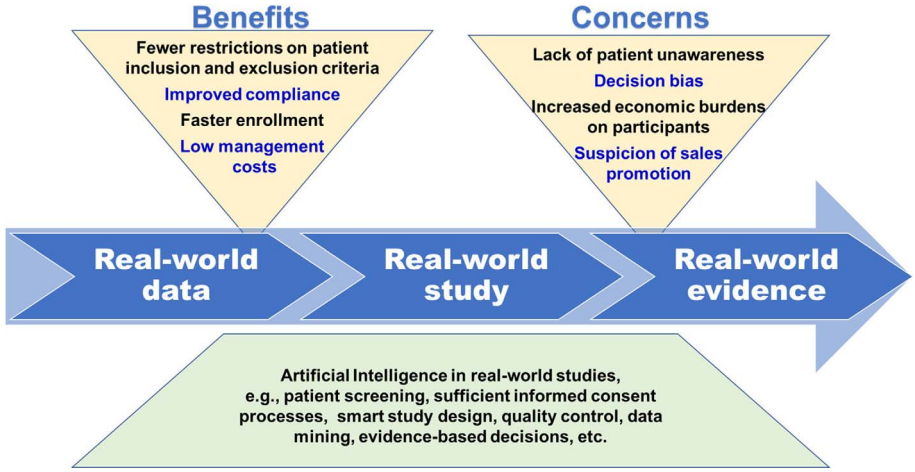

Figure 1. AI in real-world studies. The benefits and concerns in real-world studies have been refined. With the application of AI technology, some concerns can be addressed, and robust real-world evidence is expected.

providing proper financial support or reimbursement to subjects for the drugs, interventions, and clinical tests/examinations that fall outside traditional clinical practices is highly recommended.

To our knowledge, certain policies implemented by medical entities in mainland China (e.g., Sun Yat-sen University Cancer Center) are valuable in protecting subjects' rights and preventing additional financial burdens due to study participation. For instance, off-label medications should be provided free of charge to participating subjects, and the costs of medical tests/examinations outside of traditional clinical practices should not be borne by the subjects. Proper compensation should be provided for subjects when additional human specimens are obtained for study purposes. Additionally, for drugs used within the indications of prospective real-world studies, an "at least buy one, get one free" approach is required to avoid potential sales promotion.

Moreover, oversight and transparency in the informed consent process are crucial aspects of protecting patients' rights and interests. AI-based solutions can play a key role in addressing this issue by streamlining the consent process and ensuring that patients provide fully informed consent [10]. By utilizing AI-driven tools, such as chatbots and virtual assistants, potentially eligible patients can receive comprehensive and easily understandable information about the study and their rights through personalized communication. Natural language processing can be employed to tailor information to the patient's language proficiency and medical literacy level, ensuring comprehension. Patient concerns/queries can be answered in real-time through AI-driven chatbots, providing informed consent before participation.

Additionally, an AI-based digital consent platform could track and manage the consent processes, ensuring compliance with ethical standards and regulatory requirements. AI technology could also provide real-time updates and reminders to subjects to renew their consent preferences, keeping them informed throughout the study. To address concerns about potential promotion, AI-based machine/deep learning analytic methods can mine patients' data from EHR to identify suspicious promotional activities from the prescription that deviated from the standard of care or off-label indications.

Enhancing study design, data quality, and analysis

Real-world studies can be complicated by the potential heterogeneity of enrolled subjects, lower data quality, and various biases [11]. The application of AI-based solutions has the potential to optimize protocol, determine sample size, clean and control data quality, and enhance statistical analysis processes to improve real-world evidence. For instance, AI-powered algorithms could integrate data from various real-world sources (e.g., electronic health records, patient-reported outcomes, claims and billing data, product and disease registries, and data gathered through personal devices and health applications [12]) to generate insights that would be difficult to discern through traditional methods. In addition, AI techniques, such as machine learning and deep learning, can help to identify and correct data errors, ensuring accurate outcome measurements, mitigating/imputing missing values, and harmonizing data formats from various sources, thereby improving the reliability and quality of real-world data in data collection and analysis. This is particularly valuable in retrospective studies where data completeness is often a challenge. Additionally, the use of AI integrated with blockchain technology could create immutable records of all study-related transactions and decisions, and track data privacy and security, ensuring transparency and preventing any manipulation bias [13].

Supporting optimal clinical decision-making

Developing and using AI algorithms that are transparent and explainable can help optimize clinical decision-making processes [14]. For example, intelligent Clinical Decision Support Systems (iCDSS), which analyze patient data in real-time, along

Video 1. Summary of the challenges and solutions for real-world studies in the oncology setting. This video was generated by using a commercially available artificial intelligent platform Invideo AI. https://vcm.edpsciences.org/10.1051/vcm/2024009#V1.

with clinical guidelines and research findings – such as those provided by OpenAI's large language model GPT-4 – can assist healthcare providers in making evidence-based treatment recommendations tailored to individual patient profiles. By integrating the iCDSS into real-world studies, clinicians can make informed treatment decisions that prioritize patient well-being over study requirements.

More flexible study designs (such as adaptive designs, and model-guided designs) guided by AI algorithms offer another approach that can monitor patient outcomes and adapt aspects of study design in a real-time setting. This ensures that the chosen treatments remain optimal as evidence accumulates. This dynamic approach not only reduces decision bias but also enhances the overall effectiveness and safety of the interventions.

In addition, the use of AI in real-world studies can optimize patient recruitment and retention by identifying eligible participants more efficiently [15]. For instance, an intelligent screening system could identify patients who are most likely to benefit from specific treatments. Moreover, AI algorithms can predict treatment outcomes and guide researchers in selecting the most appropriate interventions for each patient in real-world studies.

In conclusion, we believe that integrating AI into real-world studies could offer a transformative and promising approach to addressing the challenges and ethical concerns of prospective real-world studies (Figure 1). By leveraging AI's capabilities in patient screening, informed consent processes, monitoring, financial support for subjects, data management, bias control, predictive analytics, evidence-based decisions, transparency, and ethical integrity, real-world studies can become more efficient and effective, ultimately leading to improved patient-centred healthcare strategies (Video 1).

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Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

No data are associated with this article.

Author contribution statement

Ji-Bin Li and Chao-Nan Qian: Conception and design.

Ji-Bin Li and Chao-Nan Qian: Writing, review, and/or revision of the manuscript.

Ethics approval

Ethical approval was not required.

Appendix

Risk warnings related to conducting real-world studies

The original version of this article was released in Chinese by The Medical Ethics Committee of the China Anti-Cancer Association on October 25, 2020

Real-world studies refer to studies conducted in real-world settings, outside the controlled environment of clinical trials, to collect and analyze data on the effectiveness, safety, and use of medical treatments, interventions, or healthcare practices as they are applied in everyday clinical practice. These studies aim to provide insights that are more generalizable to a broader patient population.

Recently, real-world studies have garnered significant attention, leading to an increase in related study projects. Undoubtedly, real-world studies have their advantages, such as fewer restrictions on inclusion and exclusion criteria for subjects, better compliance,

faster enrollment, and relatively lower study and management costs. However, with the growing number of projects, some issues have emerged during implementation, particularly concerning the rights and safety of subjects. These issues warrant attention from sponsors, researchers, and ethics committees.

1. *Lack of informed consent*: In some institutions, real-world studies do not require obtaining informed consent from patients, potentially leading to patients receiving treatment measures specified by the "study" without their knowledge.
2. *Decision bias*: Under the pressure of enrolling large numbers of participants, researchers may not select the most appropriate treatment plan based on the patient's specific condition and clinical diagnostic and treatment guidelines, instead opting for treatments designated by the "study."
3. *Increased costs*: Subjects receive little to no support, while some additional tests and expenses incurred due to the study are borne by the subjects. The treatment costs recommended by the "study" are generally higher than conventional treatment methods.
4. *Suspicion of promotion*: With the push and exclusivity of the "study" treatments, involving thousands to tens of thousands of cases, and requiring patients to purchase medication at full price, there are concerns about potential promotion and unfair competition.

The design, analysis, and conclusions of real-world studies are complex. Conducting real-world studies should involve clear objectives, protocols, and quality management. For instance, sample size calculations should be carefully justified, avoiding unnecessary enlargement; researchers should select the most appropriate treatment based on the patient's condition and circumstances; and any additional costs incurred due to the study, such as tests, should be covered by the sponsor.

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