Patient-Reported Outcomes–New Opportunities and Challenges in Chinese Clinical Research (Postprint)

Authors: Chen Tingjia, Liu Mingrui, Zhou Hui, Li Hongmin, Yuan Gang, Yao Mi

Date: 2022-08-23T00:00:00+00:00

Abstract

Patient-Reported Outcomes (PROs), as a form of clinical outcome, can intuitively and comprehensively reflect patients' true experiences. A newly published study reviewed clinical trial registration information from 2010 to 2020 in China to understand the utilization of PROs, calling for increased emphasis on PROs application in Chinese clinical research. This article describes the current status of PROs application in China and provides future perspectives, aiming to offer insights and inspiration for the development of PROs in domestic clinical research.

Full Text

Patient-Reported Outcomes: New Opportunities and Challenges in Chinese Clinical Research

Tingjia Chen[1]#, Mingrui Liu[2]#, Hui Zhou[1], Hongmin Li[3], Gang Yuan[1], *Mi Yao*[4]

[1]The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China
[2]School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China
[3]Cangzhou Central Hospital, Cangzhou 061011, China
[4]Institute of Applied Health Research, University of Birmingham, Birmingham B15 2TT, UK

# These authors contributed equally to this work.
Corresponding authors:

Gang Yuan, Associate Chief Physician; E-mail: yuangang@mail.sysu.edu.cn
Mi Yao; E-mail: 755027954@qq.com

Abstract

Patient-reported outcomes (PROs) can intuitively and comprehensively reflect patients' real experiences and perspectives. A recently published study reviewed registration information for clinical trials conducted in China from 2010 to 2020 to understand PROs usage patterns, calling for greater attention to PROs application in Chinese clinical research. This paper describes the current status of PROs application in China and explores future prospects, aiming to provide insights and guidance for the development of PROs in domestic clinical research.

Key Words: Patient-reported outcomes; Clinical trials; Cross-sectional survey; Future development

1. The Significance of PROs

Patient-reported outcomes (PROs) are direct reports from patients about their disease status and health condition without interpretation by clinicians or other intermediaries [1]. Since the 1990s, China has incorporated patients' treatment experiences and satisfaction into healthcare quality management evaluation. Promoting patient involvement in continuous healthcare quality improvement helps implement patient-centered care, aligning with the "Healthy China 2030" strategic blueprint outlined in China' s 14th Five-Year Plan. Patient-reported outcome measurements (PROMs), developed through scientific and rigorous methods, can generate high-quality evidence-based data. Such high-quality PROs research helps ensure that patient preferences are reflected in clinical efficacy assessments, drug labeling, clinical guidelines, and health policies, thereby further optimizing patient-centered healthcare [2, 3].

The U.S. Food and Drug Administration (FDA) issued industry guidance in 2009 to direct the scientific development and standardized application of PROs, calling for disclosure of PROs data in new drug submissions and eventual inclusion in drug labeling [4]. Subsequently, the FDA published final guidance in June 2020 on "Patient-Focused Drug Development: Collecting Comprehensive and Representative Input" and in February 2022 on "Patient-Focused Drug Development: Identifying What Is Important to Patients," establishing the significance of patient-centered concepts represented by PROs in clinical research [2]. In June 2021, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) released a reflection paper on patient-centered drug development, proposing that PROs and patient preferences collected through robust, systematic methods should carry equal weight to clinical data. An increasing number of randomized controlled trials

(RCTs) now incorporate PROMs as primary or secondary endpoints, demonstrating multidimensional considerations in efficacy assessment from the study design perspective [5-7].

Chinese researchers have shown relatively high acceptance of PROs for disease states that cannot be diagnosed or evaluated through clear objective indicators, such as pain and fatigue [5, 8-9]. However, PROs research remains insufficient for many chronic diseases in China, including diabetes, hypertension, and coronary heart disease. Patient experience data obtained directly through PROs can support clinical decision-making, reduce treatment burden, improve adherence to prescribed therapies, and encourage development of patient-centered treatment measures and more tolerable medications [10]. Therefore, in chronic disease management at primary care institutions, particularly among general practitioners, there is a critical need to value patient perspectives and recognize the potential and value of PROs.

2. Application of PROs in Chinese Clinical Research

A newly published cross-sectional survey [11] reviewed clinical trial registration information in China over the past decade, revealing that approximately 20% of trials specified PROs assessment tools, covering less than 5% of participants. This indicates that current PROs usage in Chinese clinical research remains inadequate.

The study examined 36,487 registered clinical trials retrievable from major Chinese clinical trial registries between 2010 and 2020, ultimately including 34,033 non-pediatric studies conducted in China with determinable registration information. Studies were independently classified based on whether clinical outcome measures used PROs assessment tools, categorizing eligible trials into: (1) those with explicitly defined PROs tools, (2) those with undefined PROs tools, and (3) those without any mention of PROs tools. Statistical results showed that among over 32 million study participants, fewer than 5% came from trials with explicitly defined PROs assessment tools. Additionally, 2.1% of participants were from trials with undefined PROs tools, meaning these subjects participated in studies assessing subjective feelings or quality of life, but the specific assessment instruments could not be identified. Clinical trials on pain, oncology, and bone/joint diseases most frequently used PROs assessment tools, accounting for 45.7% of all PROs trials. Skin-related diseases, rheumatic and immunologic diseases, and chronic infections represented the smallest proportions of PROs trials, with their combined total less than 8%. The most commonly used PROs assessment tools in Chinese clinical research were the Visual Analogue Scale (VAS) and the Short-Form 36 Item Health Survey (SF-36).

The study also found that while the number of registered clinical trials in China has increased annually in recent years, the number adopting PROs has shown a corresponding upward trend. Analyzing 10,093 clinical studies that mentioned PROs, post-marketing Phase IV studies accounted for 12.9%, higher than Phase

I, II, III, and early-phase clinical studies. This suggests Chinese researchers are more inclined to incorporate PROs assessment tools in post-marketing drug studies. However, it is noteworthy that over 40% of studies did not specify trial phase in their registration information, possibly due to non-standardized registration practices. Researchers should address the completeness of clinical trial registration. Interestingly, the number of studies enrolling only female participants exceeded those enrolling only males, with PROs trial numbers following the same pattern, indicating that gender is not a factor in Chinese researchers' decisions to use PROs assessment tools. Geographic distribution of clinical trial registration and PROs application is uneven, with eastern, northern, and southern regions conducting over 75% of clinical studies, represented by Shanghai, Beijing, and Guangdong. PROs research shows a highly similar geographic concentration trend. However, some underdeveloped regions, such as Xinjiang and Tibet, had no clinical studies with explicit PROs usage.

In terms of both sample size and trial numbers, oncology and pain symptoms are the most common disease states using PROs assessment tools. Additionally, bone/joint diseases (13.3%), psychiatric disorders (10.6%), and neurological conditions (7.6%) represent substantial proportions of PROs clinical trial registrations. However, among these PROs-mentioned studies, cardiovascular and digestive disease trials covered significantly more participants than bone/joint, psychiatric, and neurological disease trials. Similar patterns were observed in respiratory diseases and metabolic/endocrine disorders, where participant numbers represented higher proportions of the total. This demonstrates that evaluating PROs application breadth requires consideration not only of trial counts but also sample sizes, which carry significant meaning.

Clinical outcomes are core evidence for evaluating drug treatment benefits and risks [10], and high-quality clinical research should assess treatment efficacy from multiple dimensions. PROs represent one form of clinical outcome increasingly used in drug registration studies. The statistical analysis of Chinese clinical research from 2010-2020 will help healthcare professionals and researchers understand domestic PROs application status and provide objective data support for improving PROs clinical research assessment methods. The study identified issues including imbalanced PROs usage across regions, sponsors, and clinical phases, as well as relatively limited diversity in measurement tools, effectively guiding more extensive, robust, and targeted use of standardized PROMs to promote high-quality development of Chinese clinical research.

3. Future Prospects for PROs Application and Research in China

PROs have not yet become routine assessment endpoints in Chinese clinical trials [11]. Over the past decade, only about 20% of Chinese clinical studies listed PROs tools as endpoint measures with explicitly defined instrument types, while 70.3% of trials did not consider PROs [12]. We believe reasons for non-routine collection include [12-15]: (1) PROMs data are prone to missingness; (2) reliability and validity in specific populations are unknown; (3) high requirements for

protocol writing and ethics review (e.g., selecting optimal assessment timepoints to capture meaningful clinical changes; whether there is a comprehensive and detailed PROs data analysis plan; how to assess participant burden in completing assessments); (4) high demands on researchers (e.g., helping participants understand PROMs; guiding participants to complete PROMs properly); and (5) certain requirements for participant compliance and education level. When conducting clinical trials for drug marketing approval, sponsors hope to obtain ideal study data quickly for review by the National Medical Products Administration (NMPA). Unless confident in overcoming these challenges, most sponsors will not readily adopt PROs as primary or secondary endpoints. International emphasis on PROs remains higher than in China; for example, the U.S. encourages disclosure of PROs results in post-marketing studies or use of PROs as exploratory research indicators [16-17].

Chinese attention to PROs has increased significantly in the past two years. The "Guiding Principles for Statistical Design of Clinical Trials of Antitumor Drugs (Trial)" released in December 2020 recognized PROs as an efficacy endpoint in antitumor clinical trials. In September 2021, the Center for Drug Evaluation of the National Medical Products Administration drafted the "Guiding Principles for Application of Patient-Reported Outcomes in Drug Clinical Research (Draft for Comment)," and the December 2021 release of the "Guiding Principles for Application of Patient-Reported Outcomes in Drug Clinical Research and Development (Trial)" further promoted PROs acceptance. Patient-centered clinical trials have gained widespread international recognition in the medical field, and clinical trial institutions and researchers should value and actively adapt to this paradigm shift [18].

Promoting large-scale PROs application requires refining implementation details according to Chinese national conditions. First, policy-level "robustness standards" should be established to weigh patient preferences and incorporate them into broader decision-making evidence bases, thereby guiding standards and confidence for such evidence among sponsors, clinical researchers, and regulatory agencies. Simultaneously, internet technology should be leveraged to improve PROs data collection processes, using artificial intelligence for instrument visualization to help patients understand and use them, and feeding data back to patients for self-health management. National-level promotion of PROs management systems represents an effective method for high-quality PROs development. This includes increasing policy and financial support for PROs research, particularly focusing on remote regions and small clinics, and promoting health information tracking and sharing platforms initiated by community hospitals beyond large tertiary hospitals to improve patient care and conduct related research. Additionally, currently used instruments are mostly derived from foreign PROs assessment tools, but directly translated tools face issues including small sample sizes, regional limitations, lack of comparative standards, and absence of cultural adaptation measures [19], requiring continuous refinement. Shared platforms can overcome limitations of small populations and geographic constraints.

We do not one-sidedly advocate for PROs inclusion in all clinical research. Not all clinical outcomes require patient perspectives as evaluation indicators, and study design must always follow ethical principles prioritizing participant welfare. When PROs results are meaningless and create completion burden for participants, or when casual collection leads to severe data bias and missingness that prevents meaningful use, such practices are unethical and inappropriate. However, this does not mean patient perspectives are unimportant. For chronic diseases or cancers that severely impact quality of life, measuring patient subjective experiences is essential. Research has confirmed that chronic disease patients with comorbid mood disorders experience worse health status and decreased life expectancy compared to those with chronic disease alone [10]. General practice, following the biopsychosocial model, particularly needs to value patient perspectives to improve satisfaction. It is important to note that PROs application remains challenging for elderly patients with comorbidities and frequent cognitive or communication impairments, or pediatric patients who cannot make accurate independent judgments [20-21]. Additionally, patient experience data may not always align with physician perspectives and physiological or objective efficacy indicators, requiring further exploration of relationships between PROs and other efficacy measures for appropriate application [22].

Chinese clinical research must recognize the potential and value of PROs, and further promotion of PROs application in domestic clinical research requires multi-stakeholder efforts. Accelerating the design and development of PROs assessment tools tailored to Chinese national conditions is essential. PROs data from Chinese clinical trials will provide powerful reference evidence for improving China' s healthcare service system and promoting high-quality development of domestic clinical research.

References

[1] Silver Spring MUFA. US Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims[R]., 2009.

[2] Kotecha D, Bunting K V, Gill S K, et al. Effect of Digoxin vs Bisoprolol for Heart Rate Control in Atrial Fibrillation Patient-Reported Quality of Life: The RATE-AF Randomized Clinical Trial[J]. JAMA, 2020,324(24):2497-2508.DOI: 10.1001/jama.2020.23138.

[3] 周慧，姚弥，陈杰，等. 《临床试验方案纳入患者报告结局的指南-扩展声明》解读 [J]. 中国新药杂志, 2021,30(14):1296-1301.ZHOU Hui, YAO Mi, CHEN Jie,et al.Interpretation of" the guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO extension" [J].Chinese Journal of New Drugs, 2021,30(14):1296-1301.

[4] Guidance for industry: patient-reported outcome measures: use in medical

product development to support labeling claims: draft guidance[J]. Health Qual Life Outcomes, 2006,4:79.DOI: 10.1186/1477-7525-4-79.

[5] Jia Y, Wen J, Qureshi R, et al. Effect of redundant clinical trials from mainland China evaluating statins in patients with coronary artery disease: cross sectional study[J]. BMJ, 2021,372:n48.DOI: 10.1136/bmj.n48.

[6] Kochar B, Martin C F, Kappelman M D, et al. Evaluation of Gastrointestinal Patient Reported Outcomes Measurement Information System (GI-PROMIS) Symptom Scales in Subjects With Inflammatory Bowel Diseases[J]. Am J Gastroenterol, 2018,113(1):72-79.DOI: 10.1038/ajg.2017.240.

[7] Santosa K B, Qi J, Kim H M, et al. Long-term Patient-Reported Outcomes in Postmastectomy Breast Reconstruction[J]. JAMA Surg, 2018,153(10):891-899.DOI: 10.1001/jamasurg.2018.1677.

[8] Sultan P, Sharawi N, Blake L, et al. Use of Patient-Reported Outcome Measures to Assess Outpatient Postpartum Recovery: Systematic Review[J]. JAMA Network Open, 2021,4(5):e2111600.DOI: 10.1001/jamanetworkopen.2021.11600.

[9] Li Y, Jing D, Xiao Y, et al. Patient-Reported Outcomes of Arsenic-Related Skin Lesions in China[J].Biomed Res Int, 2020,2020:6195975.DOI: 10.1155/2020/6195975.

[10] Flannery M A, Mohile S, Culakova E, et al. Completion of Patient-Reported Outcome Questionnaires Among Older Adults With Advanced Cancer[J]. J Pain Symptom Manage, 2022,63(2):301-310.DOI: 10.1016/j.jpainsymman.2021.07.032.

[11] Zhou H, Yao M, Gu X, et al. Application of Patient-Reported Outcome Measurements in Clinical Trials in China[J]. JAMA Netw Open, 2022,5(5):e2211644.DOI:10.1001/jamanetworkopen.2022.11644.

[12] Casey D J. Patient-Reported Outcome Measures-Challenges and Opportunities for China[J]. JAMA Netw Open, 2022,5(5):e2211652.DOI: 10.1001/jamanetworkopen.2022.11652.

[13] Michael M, Wirth A, Ball D L, et al. A phase I trial of high-dose palliative radiotherapy plus concurrent weekly Vinorelbine and Cisplatin in patients with locally advanced and metastatic NSCLC[J]. Br J Cancer, 2005,93(6):652-661.DOI: 10.1038/sj.bjc.6602759.

[14] Hallqvist A, Bergman B, Nyman J. Health related quality of life in locally advanced NSCLC treated with high dose radiotherapy and concurrent chemotherapy or cetuximab–pooled results from two prospective clinical trials[J]. Radiother Oncol, 2012,104(1):39-44.DOI: 10.1016/j.radonc.2012.05.006.

[15] Dilling T J, Extermann M, Kim J, et al. Phase 2 study of concurrent cetuximab plus definitive thoracic radiation therapy followed by consolidation docetaxel plus cetuximab in poor prognosis or elderly patients with locally advanced

non-small cell lung cancer[J]. Int J Radiat Oncol Biol Phys, 2014,90(4):828-833.DOI: 10.1016/j.ijrobp.2014.07.023.

[16] Feldman D, Avorn J, Kesselheim A S. Use of Extrapolation in New Drug Approvals by the US Food and Drug Administration[J]. JAMA Netw Open, 2022,5(4):e227958.DOI: 10.1001/jamanetworkopen.2022.7958.

[17] Gnanasakthy A, Demuro C, Clark M, et al. Patient-Reported Outcomes Labeling for Products Approved by the Office of Hematology and Oncology Products of the US Food and Drug Administration (2010-2014)[J]. J Clin Oncol, 2016,34(16):1928-1934.DOI: 10.1200/JCO.2015.63.6480.

[18] 谢静，王焕玲. 以患者为中心的临床试验：医药研发新模式 [J]. 协和医学杂志,2021,12(06):849-853.DOI:10.12290/xhyxzz.2021-0056.XIE Jing,WANG Huan-ling.Patient-centric Clinical Trials: A New Paradigm for Drug Development[J].Medical Journal of Peking Union Medical College Hospital,2021,12(06):849-853.DOI:10.12290/xhyxzz.2021-0056.

[19] Guo X, Tripp C, Huber N L, et al. Patient reported outcomes and quality of life in Chinese patients with implantable cardioverter defibrillators[J]. Heart Lung, 2021,50(1):153-158.DOI: 10.1016/j.hrtlng.2020.05.003.

[20] Hareendran A, Gnanasakthy A, Winnette R, et al. Capturing patients' perspectives of treatment in clinical trials/drug development[J]. Contemp Clin Trials, 2012,33(1):23-28.DOI: 10.1016/j.cct.2011.09.015.

[21] Pilotto S, Carbognin L, Karachaliou N, et al. Moving towards a customized approach for drug development: lessons from clinical trials with immune checkpoint inhibitors in lung cancer[J]. Transl Lung Cancer Res, 2015,4(6):704-712.DOI: 10.3978/j.issn.2218-6751.2015.10.08.

[22] The L N. Patient-reported outcomes spotlight[J]. Lancet Neurol, 2019,18(11):981.DOI: 10.1016/S1474-4422(19)30357-6.

Author Contributions: Tingjia Chen and Mingrui Liu are co-first authors who primarily participated in manuscript writing; Mi Yao contributed to overall conceptualization; Hui Zhou and Hongmin Li participated in manuscript revision; Mi Yao and Gang Yuan were responsible for quality control and final review, and take overall responsibility for the article.

Conflict of Interest: The authors declare no conflicts of interest.

Note: Figure translations are in progress. See original paper for figures.