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From the Formation of Conceptual Framework to Regulatory Decision-Making: Considerations for the Developments of Patient-Reported Outcome Instruments

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Abstract: In recent years, patient-focused drug development (PFDD) has received widespread attention as a new paradigm in clinical trials. The PFDD emphasizes patients are partners in research projects, where patients can participate in research design, implementation, and outcome measurement, rather than just providing data. PFDD has shown great value in the research and development of pharmaceutical products, such as in accelerating the process of patient enrollment and improving the success rate of drug approval. Many countries and regions, including the United States, China, and Europe, have issued relevant regulatory policies and guidelines related to PFDD, covering study design, implementation, and risk–benefit assessment. The core of PFDD implementation is clinical outcome assessment (COA), of which patient-reported outcome (PRO) is most common. As far as the US Food and Drug Administration is concerned, there are numerous COA tools waiting for qualification, but currently all qualified are PROs. This review focuses on PRO and explores the key elements of PRO instruments' development, application, and inclusion in regulatory decision-making.

Keywords: patient-reported outcome, patient-focused, drug, development, clinical trial

Background

The concept of "patient-focused drug development (PFDD)" was formally proposed by the US Food and Drug Administration (FDA) in 2012,[1] and a PFDD team was established in the same year to encourage patients to participate in the research and development (R&D) decision-making process.[2] By the end of 2023, the US FDA held 195 special meetings for various diseases,[3] all of which invited patients to participate and solicit their opinions. PFDD is increasingly valued by global drug R&D. From 2018 to 2023, the US FDA,[4–7] China Center for Drug Evaluation (CDE),[8] and European Medicines Agency (EMA),[9] all promulgated regulations, guidelines, or workshops on PFDD, covering many aspects such as method design, implementation and risk-benefit assessment.

To ensure the developed drugs better meet the needs of patients,[10] PFDD conceptualizes patient experience and use clinical outcome assessment (COA) tools to measure patient experience data (PED) quantitatively or qualitatively. The COA qualification is a regulatory conclusion.[11] According to FDA, COA authentication needs to go through the drug development tool (DDT) authentication procedure,[12] which includes three stages: submission of the letter of intent (LOI),[13] certification plan qualification program (QP), and submission of the full qualification package (FQP).[14] However, without qualification by US FDA, COA can still be used to support labeling claims.[15] According to EMA, the qualification process is an optional, scientific pathway, which leads to either a Committee for Medicinal Products for Human Use (CHMP) Qualification Opinion or a CHMP Qualification Advice.[16] CHMP Qualification Opinion means COA is accepted for qualification, but in the claimed use in a defined context of drug development.

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There are four types of COA: patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO), and performance outcome (PerfO).[17] Which COA to use depends on the specific situation, and the influencing factors usually include the endpoints, patients' age and mental status. For example, when measuring the functional status like walking ability after hip replacement, the best way is to carry out quantitative tests using PerfO. However, when measuring the mental status or life quality, the direct report from patients themselves would be more accurate, thus PRO would be a better choice. The US FDA has issued a Roadmap explaining how to perform COA measurement.[18] Among the four kinds of COA, PRO is particularly worthy of attention. PRO refers to any report directly from the patient about the patient's health without the need for clinicians or anyone else to explain the patient's reaction.[19] PROs are increasingly utilized across a variety of disease areas, and the US FDA has approved them as clinical endpoints for oncology like lung cancer, infectious diseases[20] like human immunodeficiency virus, chronic diseases like chronic obstructive pulmonary disease, and biologics.[21–23] It was worth noting that if PROs were used in Children clinical trials or in psychiatric conditions when patients have not insight or disease awareness, they may need a proxy. However, researchers should be aware that the information collected in this way is actually different from the narrow sense of PRO. Researchers should also be aware proxy reporting is acceptable in some contexts and not in others.[24] If any proxy reporting is used, it should be documented clearly in the study protocol. For the time being, both FDA and EMA discourage the use of proxy-reported outcomes for drugs labeling due to bias.[24]

In general, PFDD and PRO are still relatively new concepts, and many researchers have limited understanding of them. This review discusses the considerations of the whole process of PRO instrument development, from the formation of conceptual framework to the inclusion of PROs into regulatory decisions.

Current Status of PRO Application in Global Drug R&D and Regulation

PROs are now being more and more widely used in clinical trials. Taking tumor drugs for example, between 2007 and 2013, 26% of industry-sponsored oncology trials included assessment of PROs.[25] This proportion increased to 75% in between 2014 and 2018.[26] In addition to tumors, PRO is also widely used in other diseases area, such as glomerular disease,[27] alopecia areata,[28] retinal degeneration,[29] lupus,[30] heart failure,[31] uveitis,[32] and so on.

With the increasing application of PROs, the importance of supervision has become increasingly prominent. In 2020, the International standards for the analysis of quality-of-life and PRO endpoints in cancer randomized controlled trials: recommendations of the SISAQOL Consortium,[33] was published with effort of regulators or research organizations from all around the world, including European Organization for Research and Treatment of Cancer, Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK), Institute for Quality and Efficiency in Health Care of Germany, Health Canada, and others.

A variety of countries have also issued their own regulations or guidelines to guide the use of PROs. The MHRA of UK released a series of guidelines on PROs, including "how to carry out PRO and experiences study",[34] "how to perform PRO measurement",[35] etc. The US FDA released a guidance document called "Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making",[36] describing how stakeholders (patients, caregivers, researchers, medical product developers, and others) can collect and submit PED and other relevant information from patients or caregivers to be used for drug R&D and regulatory decision-making. Besides, China,[8] Japan,[37] Canada[38] and many other countries have issued or are developing PRO-related guidelines.

Among supervision agencies all around the world, the US FDA is at the forefront of the research and application of COA tools including PRO. Currently, the US FDA has approved seven COA tools and they are all PROs (Table 1). Another 72 COA tools are in the US FDA review process, of which 41 are PROs and five are combined tools containing PROs. It was worth mentioning that letters of intent of 54 submitted COA tools were accepted but not yet qualified (See eTable 1 in the Appendix). The qualification statement of COAs by FDA usually contains four sections: Section I: Concept of Interest. Section II: Context of Use. Section III: COA Interpretation. Section IV: Contact Information for Access to the Qualified COA. The qualification statements of these approved COA tools are of great reference significance for understanding the decision-making priorities of regulatory authorities.

Table 1 The Details of Seven COA Tools Approved by FDA

ID	Disease/Condition	DDT COA Number and Instrument Name	Concept of Interest	Context of Use	COA Type
1	Chronic Heart Failure (CHF)	DDT COA #000084: Kansas City Cardiomyopathy Questionnaire (KCCQ)	CHF symptoms and their impact on physical limitations	Patients with CHF	PRO
2	Major Depressive Disorder (MDD)	DDT COA #000008: Symptoms of Major Depressive Disorder Scale (SMDDS)	Overall symptoms of MDD	Adults (>18 years) with a clinical diagnosis of MDD and: treated in an ambulatory setting experienced a major depressive episode within the last 6 months a HAM-D score > 18 meets the DSM-IV or DSM-V criteria for MDD	PRO
3	Irritable Bowel Syndrome (IBS)	DDT COA #000005: Diary for Irritable Bowel Syndrome Symptoms- Constipation (DIBSS-C)	Aspects of symptom experience associated with irritable bowel syndrome with constipation	Patients 18 years and older with a diagnosis of IBS-C as defined by the Rome Criteria and the final FDA IBS Guidance	PRO
4	Asthma	DDT COA #000006: Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD)	Asthma symptoms	Adolescent (12 −17 years) and adult patients	PRO
5	Chronic Obstructive Pulmonary Disease (COPD)	DDT COA #000017: Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease (E-RS: COPD)	Respiratory symptoms of stable COPD	Adult outpatients with stable COPD	PRO
6	Acute Bacterial Exacerbation of Chronic Bronchitis in patients with Chronic Obstructive Pulmonary Disease (ABECB-COPD)	DDT COA #000003: Exacerbations of Chronic Pulmonary Disease Tool (EXACT)	Symptoms of ABECB-COPD	Outpatients with ABECB-COPD who meet the clinical trial entry criteria as described in the FDA Guidance:Acute Bacterial Exacerbations of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment.	PRO
7	Non-Small Cell Lung Cancer (NSCLC)	DDT COA #000009: Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)	Symptom severity (cough, pain, dyspnea, fatigue, and appetite)	Adult patients (> 18 years) with Stage IIIB or IV NSCLC that are: Treatment naïve (ie, treatment naïve to current chemotherapy and not having received chemotherapy for the past 6 months from study enrollment) Treated (ie, received chemotherapy in the last 6 months and recovered from any prior treatment related toxicities/ adverse events to CTCAE v4.03 grade 1 or better)	PRO

Notes: As shown above, seven approved COA tools are all PRO instruments.

Why is PRO Important for Regulatory Decision Making?

PRO is an important complement to traditional clinical endpoints and helps to understand the patient's experience. PRO has been used as secondary or even primary endpoints in a growing number of trials, providing supportive evidence of clinical significance that is critical for regulatory decision-making.[39]

When the US FDA held its first special public meeting in 2013, 24 diseases were selected, including chronic fatigue, HIV, lung cancer, breast cancer and so on[40] (Table 2). Choosing these 24 diseases has its specific considerations. Taking breast cancer as an example, patients and doctors have encountered two dilemmas: one was that some patients had prolonged survival, but the quality of life was poor. Another is that some patients have to remove their breasts for survival, but at the same time losing female body characteristics makes them very painful. In this case, when making regulatory decisions should be particularly careful, and the patients' experience and PRO measurements should be fully considered.

Specifically, when two or more drugs show similar treatment effects, PRO is crucial to understand which side the balance hangs.[41,42] The classic case is the comparison of carboplatin and cisplatin combined with paclitaxel in the treatment of ovarian cancer. Cisplatin plus paclitaxel achieved equal efficacy compared with Carboplatin plus paclitaxel, as the proportion of patients without progression at two years was not statistically significantly different between two treatments. However, a higher frequency of gastrointestinal and neurologic toxicity, as well as a lower global quality-of-life scores at the end of treatment was observed in the cisplatin regimen group, thus cisplatin was not recommended as the first-line chemotherapy.[43]

Not All PRO Measurements Can Be Used for Regulatory Decisions

When PRO is used to support the review of drug efficacy, it should be more rigorous than evaluating drug safety.[21] This is evident from the five PRO tools vetoed by the US FDA (Table 3).

Table 2 The First Batch of 24 Diseases Selected by FDA to Hold PFDD Public Meeting

ID	Diseases
1	Chronic fatigue syndrome/ myalgic encephalomyelitis
2	HIV
3	Lung cancer
4	Narcolepsy
5	Sickle cell disease
6	Fibromyalgia
7	Pulmonary arterial hypertension
8	Inborn errors of metabolism
9	Hemophilia A,B, and other heritable bleeding disorders
10	Idiopathic pulmonary fibrosis
11	Female sexual dysfunction
12	Breast cancer
13	Chagas disease
14	Functional gastrointestinal disorders
15	Parkinson's disease and Huntington's disease
16	Alpha-1 antitrypsin deficiency
17	Non-tuberculous mycobacterial lung infections
18	Psoriasis
19	Neuropathic pain associated with peripheral neuropathy
20	Alopecia areata
21	Autism
22	Hereditary angioedema
23	Patients who have received an organ transplant
24	Sarcopenia

Table 3 Five PRO or PRO-Containing Tools Rejected by FDA and the Reasons

ID	DDT Number	Disease/Condition	COA Type	Reason
1	DDT COA #2019-01	Recovery from surgery and anesthesia	PRO, PerfO, and ClinRO	The demand for this instrument is insufficient for drug development and regulatory decision making. At present, there are several evaluation tools available for the postoperative evaluation of surgery and anesthesia, such as pain scales and anesthesia satisfaction surveys. In addition, this instrument combines multiple COAs to provide patients with an overall score that regulators think is unclear for use.
2	DDT COA #000093	Crohn's Disease (CD)	PRO	This symptom is atypical and not unique to patients with CD (some patients with chronic obstructive pulmonary disease also show this symptom)
3	DDT COA #000116	Itch	PRO and ObsRO	This PRO instrument evaluates the "effects caused by itching" and uses them as a secondary outcome, whereas the FDA believes that a secondary endpoint is not needed in clinical trials for pediatric itching. Instead, a primary endpoint for evaluating the severity of itching is required. In addition, the recall period of "7 days" set by this PRO is too long for children, and the FDA has suggested changing it to 24 hours
4	DDT COA #000140	Itch	PRO and ObsRO	
5	DDT COA #000121	Cancer	PRO	It tries to assess the physical function and use as the primary outcome. FDA suggested it as a secondary endpoint. Besides, the developers aim to use this PRO for evaluation of "tumor of all types and stages", which the FDA disagree with. The FDA suggests narrowing the scope, as this endpoint may be particularly insensitive to early stage cancer

Abbreviations: COA, clinical outcome assessment; DDT, Drug Development Tool; PRO, Patient-reported outcome.

Five PRO applications have been explicitly rejected and the reason varies: DDT COA #2019-01, DDT COA #000093, DDT COA #000140, DDT COA #000116, and DDT COA #000121.

The DDT COA #2019-01 is a scale developed to assess recovery from Surgery and Anesthesia. The US FDA believes that the demand for this instrument is insufficient for drug development and regulatory decision making. At present, there has been several tools available for the postoperative evaluation of surgery and anesthesia, such as pain scales and anesthesia satisfaction surveys. In addition, this instrument combines multiple types of COAs to provide patients with an overall score that regulators think its' clinical meaning is unclear for use.

The DDT COA #000093 instrument evaluates the symptoms of "parenteral pain" in Crohn's disease (CD). The US FDA believes that this symptom is atypical and not unique to patients with CD (some patients with chronic obstructive pulmonary disease also show this symptom).

DDT COA #000140 and DDT COA #000116 were submissions of one same PRO instrument, which was designed to evaluate the "effects caused by itching" and use them as a secondary outcome, whereas The US FDA believes that a secondary endpoint is not needed in clinical trials for pediatric itching. Instead, a primary endpoint for evaluating the severity of itching is required. In addition, the recall period of "7 days" set by this PRO is too long for children, and The US FDA has suggested changing it to 24 hours.

DDT COA #000121 is an instrument developed for patients with cancer, which attempts to take the evaluation of physical function as the primary outcome, this is not recognized at present, FDA suggested it as a secondary endpoint. Besides, the developers aim to use this PRO for evaluation of "tumor of all types and stages", which was not recommended by the US FDA. The measurement scope was suggested to be narrowed, as this endpoint may be particularly insensitive to early stage cancer.

In order to support regulatory decision-making, PRO must have sufficient content validity, which is determined by a series of factors. Taking the DDT COA #000009 for example, which is qualified by FDA for Non-Small Cell Lung Cancer (NSCLC) symptom assessment. To ensure the content validity, researchers followed the scientific best practices put forth by the International Society for Pharmacoeconomics and Outcomes Research,[44] and individual qualitative interviews were conducted with NSCLC patients, including concept-elicitation (CE) and cognitive interviews. In the process of item generation, the data of CE interviews were considered together with the existing literature and clinical

expert opinions, thus forming a preliminary version of the NSCLC symptom assessment questionnaire. Then, to make improvement, three waves of cognitive interviews were further conducted.[45]

The Application Scenarios of PRO

There are similarities and differences between PROs and traditional clinical endpoints. On one hand, PROs can be used for label claiming, or as secondary outcomes, or even primary outcomes. On the other hand, PROs are different from traditional endpoints, PROs focus on symptoms rather than signs. In other words, PROs care more about subjective indicators, measured directly from the patients.

Among the four types of COA, PRO is the most frequently used one, but it does not mean that PRO is the best one. Each COA has its application scenarios. For example, the indicator "pain intensity" can only be felt and reported by patients themselves, and cannot be accurately assessed by doctors, nurses or functional measurement tools. In this case, PRO is the best choice. ClinRO should be used if clinicians are need to explain the observed results. If the benefits of treatment can only be fully captured through observation in daily life (outside the medical environment) and patients cannot report for themselves, ObsRO would be a better choice. When patients need to complete specific tasks to evaluate the physical function, PerfO is more suitable.

Taking NSCLC symptom assessment questionnaire for example. This PRO instruments contains items such as "pain" and "fatigue" (which also involves the judgment of the degree, such as fatigue). This information can only be experienced and fed back by the patients themselves, and cannot be objectively measured from the outside. Obviously, other types of COAs are not suitable, and even have ethical risk. The ethical risk should not be neglected when using COA tools including PRO, as the PRO content of clinical trial protocols and the reporting of PRO results are not always adequate. An evaluation of 160 cancer trials in 2019 showed that nearly 50,000 participants were included in studies that failed to publish their PRO data.[24,46] To help address the ethical issues, Cruz Rivera S[24] and coworkers proposed the PRO Ethics Guidelines in 2022.

General Considerations of PRO Instrument Development

The development of PRO instruments should focus on the evaluation of clinical value, including the efficacy of treatment, interpretability of clinical significance, guidance for treatment decisions, and the safety of drugs. The general process of developing a PRO instrument includes eight steps:[45,47,48] building a conceptual framework (consulting literature, consulting experts, and interviewing patients); establishing an item pool (designing dimensions and levels of the scale); determining the measurement method of items; conducting expert interviews to make necessary revisions to items; conducting pre-investigation and formal investigation to verify the availability of PRO instruments (involving reliability and validity analysis); and finally translating, debugging, and improving. The OMERACT[49] Vasculitis Working Group proposed a 5-step tool to facilitate the development and assessment of the PRO instruments. The five steps[50] covers including (1) good match with domain (face and content validity), (2) feasibility (practicability, length, burden, cost, access, and translations), (3) do numeric scores make sense (construct validity)?, (4) overall ratings of discrimination, and (5) can individual thresholds of meaning be defined. Besides, the EMPRO (Evaluating the Measurement of Patient-Reported Outcomes) condensed eight key attributes[51] to help researchers selection PRO instruments: conceptual and measurement model, reliability, validity, responsiveness, interpretability, burden, alternative modes of administration, and cross-cultural and linguistic adaptations. It is worth noting that patient interviews are necessary to ensure content validity.[52]

In addition to the OMERACT and EMPRO guidance, researchers should also check the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN)[53] reporting guidelines when using PRO instruments. The COSMIN working group developed a set of consensus and empirically based reporting recommendations for studies using patient-reported outcome measures, covering how to choose PRO, how to assess related bias, how to assess the content validity,[54] and so on.

Special Considerations for PRO Development in Scenario of Traditional Medicine

There are many medical systems in the world, not just western medicine, such as traditional Chinese medicine (TCM), which has existed for more than 5000 years and is still being widely used.[55,56] One typical case is the Chinese herb Artemisia annua, which has a history of more than 2000 years in clinic use.[57] The Chinese medical scientist You-you Tu purified its components to treat malaria and won the Nobel Prize in 2015.[58] Indian also has a system of traditional medicine that characterized by Ayurveda, Yoga, Unani, Siddha, and Homeopathy.[59] In addition, there are Tibetan medicine, etc.[60]

Each medical system has its own unique characteristics. When we develop PRO instruments within the framework of these medical systems, there are special considerations. For example, within the TCM framework, doctors believe that human beings and nature are as a whole, patients' physical, spiritual and social attributes are inseparable. In this scenario, a PRO instrument not only needs to measure the treatment of the lesion, but also needs to pay attention to the overall rehabilitation and mental changes of the patient.

In addition, the development of PRO instruments of TCM requires special attention to the expression of items, which determines whether the target information could be accurately transmitted to the patient, and whether the information could be accurately collected. TCM has some unique expression that are difficult for patients to understand, such as "Na Cha", which means "loss of appetite" in western medicine.[61] Many patients could not understand these expressions and their responses could not accurately reflect their real situation, causing bias or even mistakes during measurement. In this case, it is recommended that patients participate in the design of the PRO scale at an early stage to ensure that the items are well expressed.

Challenges in PRO Instrument Development for Rare Diseases

The development process of PRO instruments follows the US FDA COA R&D Roadmap, where the initial step is to understand the natural history of diseases. Usually, the natural history of diseases can be understood by reviewing the literature, interviewing expert clinicians, or qualitatively interviewing patients and their caregivers.

However, for rare diseases, it is difficult to fully understand the natural history of the disease. A disease is defined as rare when it affects less than 1 in 2,000 people,[62] such as frozen disease.[63] Firstly, the etiology of rare diseases can be extremely unclear. Secondly, the variation in disease genotype and/or phenotype makes the disease more diverse and complicated. Data show that approximately 80% of rare diseases have genetic causes and are accompanied by multiple phenotypes.[64] For rare diseases, it usually take an average of 15 years from the initial symptoms to diagnosis. Misdiagnosis and missed diagnosis are very common in patients with rare diseases. There is usually no sufficient information about the disease or condition, and it is difficult to conceptualize the benefits of treatment.[65]

Advances and Considerations in Data Collection During the Development or Use of PRO Instruments

Electronic PRO (ePRO)

ePROs are being more and more widely used in drugs R&D nowadays. With ePROs, paper documents is no longer necessary, the process of transcribing paper data to electronic data is omitted, the risk of data recording error is thus reduced, and the efficiency is improved at the same time. ePROs further promote the application of PRO in drug R&D.[66]

Wearable devices could be important carrier and convenient way to implement ePRO. Taking glycemic control in diabetic patients for example, hypoglycemia is a very common complication of diabetic patients, which can lead to death, prolonged hospitalization and increased readmission rate.[67] Maintaining blood glucose at the target parameter can significantly reduce the risk of diabetic complications, which can be achieved through a variety of self-management behavior such as medication, diet, exercise, and health monitoring. However, self-management behavior is easily affected by many factors,[68] such as psychological problems or lack of motivation. In such case, we can embed ePRO into electronic devices, so that in addition to monitoring the patient's blood glucose in real time remotely,[69–71] we can also measure the patient's mental status or other self-management behaviors in a timely manner.

Although wearable devices have the above advantages, it does not mean that wearable devices can be used for data collection at will. When using ePRO, its consistency with PRO of paper version must be validated. To ensure content validity, Patrick DL et al[72] recommended using Tourangeau model to conduct cognitive interviews and to track the revision process. In addition, if ePRO measurement is to be adopted by regulatory decision-making, the electronic equipment used must meet the requirements of the guidelines in terms of safety, suitability, etc.[73,74]

Crowdsourcing

Crowdsourcing refers to the use of the internet to outsource work to a large number of unspecified individuals voluntarily and freely. Previous studies have shown that it is feasible to obtain patient feedback on a clinical research plan through crowdsourcing or crowdsourcing competition, modify the plan according to patient feedback, and increase patient participation, which shows the potential to accelerate research progress and reduce costs.[75] Studies in psychological and other health science have supported the reliability and validity of data gathered using crowdsourced samples.[76] At present, there have been successful cases of researchers using crowdsourcing platform to develop PRO instruments.[77]

Social Media Based Data Source

Karmalkar P and coworkers believed that social media is an important way to understand patients' needs and experiences, and much information could be mined from patient' posts, messages, and conversations on social media without additional interviews. They used AI and natural language processing technology to extract the opinions of patients and caregivers from social media data and built a PED database. This method can effectively take use of a large number of underutilized data and provide valuable insights for R&D design.[78]

Patient-Related Outcome-Common Terminology Criteria for Adverse Events (PRO-CTCAE)

PRO-CTCAE collects adverse events in the form of patient reports that are gradually accepted and used.[79] Compared with symptomatic AE reported by clinicians, PRO-CTCAE improves the precision and reliability of symptomatic AE detection in trials,[80] and its validity and reliability has been verified.[80] When PRO-CTCAE is applied, a subset is usually selected according to the purpose. For example, Sandler KA[81] and coworkers selected items endorsed by ≥20% of participants from PRO-CTCAE to assess the symptomatic toxicities in patients undergoing radiation therapy. Meanwhile, it is necessary to evaluate the content validity, which often requires interviews with patients. In addition, before clinical use, it is better to evaluate its consistency with AE reported by clinicians, so as to clarify its clinical application value. For example, in Children aged 7–18 years who were first diagnosed with cancer, Freyer DR[82] and coworkers used weighted kappa statistics to test the concordance between PRO-CTCAE reported directly from Children with AE reported by clinicians or caregivers. Results showed low consistency between children and clinicians, low-moderate agreement between children and caregivers, suggesting the necessity of routine PRO-CTCAE measurement from Children.

Discussion and Conclusion

PRO is an important complement to other clinical endpoints and may be a key factor in understanding overall treatment benefit. For example, they can provide important evidence in addition to survival benefits and drug toxicity in oncology clinical trials. PROs help researchers further understand patients' experiences. When two or more drugs are comparable in terms of survival outcomes, PRO may be decisive in assessing the risk-benefit of drugs. Besides, if a drug has a limited therapeutic effect and does not show an advantage in PRO, its clinical value is debatable and should be used cautiously in clinical practice.[79]

PROs are being more and more widely used in drugs R&D. Taking FDA-approved new drugs for example, between 2006 and 2015 there were 46.5% approved drugs and (46/99) with PRO labeling.[39] This proportion increased to 50% (47/94) between 2016 and 2020.[83] Similarly, in China, PROs also play an important role in drugs R&D. There were 34,033 registered clinical trials from 2010 to 2020 in China, of which 29.6% (10,093/34,033) used PRO endpoints.[84] For now,

most trials used mature scales for PRO measurement, such as the Visual Analog Scale, Short-Form 36, and Hamilton Depression Scale. There are also disease-specific PRO instruments, like coronary heart disease[85] and gastric cancer.[86] It is worth mentioning that PROs are also being increasingly used as endpoints in non-western medicine scenario, there has been PRO instruments developed within TCM framework for hypertension,[87] rheumatoid arthritis,[88] and recurrent oral ulcers.[89] Similarly, in Japan, PROs have been used for outcome assessment of gynecological diseases,[90] tumors,[91] and so on. However, special attention should be paid when developing PRO instruments in a traditional medicine scenario. Taking TCM as an example, there are a large number of TCM-specific, incomprehensible terms that describe symptoms, these expressions must be carefully and accurately paraphrased into the vocabulary of western medicine to minimize the measurement bias. Sometimes, limited by the patients' education level, researchers may need to train them before measurement.

PRO is not always ready-made, developing disease-specific PRO instrument is inevitable sometimes. The most important thing for PRO instrument development is to ensure the effectiveness and clinical relevance,[92] especially the content validity, which is highly valued by the regulatory authorities including FDA, China CDE, and EMA.[72] Similar to the development process of the conventional scale, appropriate statistical methods are needed to test reliability and validity according to the type of outcomes.[93] The development process must follow regulatory requirements and avoid endpoints with unclear meaning. For example, when a comprehensive score is used as the endpoint, each score should have a clear clinical significance.

Use of ePROs is another trend in clinical trials nowadays, and devices are usually needed for performing ePROs measurement. If patients need to operate devices daily on their own, communication is required when signing the informed consent form to confirm whether the patient is acceptable and can complete the operation independently. We suggest researchers to make it clear that if patients encounter difficulties in operating ePROs systems, they should first use the paper version of PRO to collect information, and then enter the data into an electronic database.

Despite the value of PROs in clinical trials, excessive use should be avoided. The transitional use of PROs places an additional burden on patients and increases the implementation time of trials. In fact, PROs do not apply to every disease. At present, diseases using PRO endpoints are mainly concentrated in the nervous and respiratory systems. PROs on these diseases are usually characterized with measuring patients' feelings, symptoms, and health-related quality of life. In a word, PROs care more about "subjective" information rather than "objective" indicator.

Finally, on the regulatory side, there is still a lot of work to be done despite more and more countries have promulgated or are developing regulations or guidelines. From this point of view, it is urgent to issue guidelines for the development of PRO instruments for rare diseases. Due to the very low incidence of rare diseases, natural history information is often unclear, and it is difficult to conceptualize treatment benefits. In addition, it is difficult to observe a sufficient survival endpoints. It should be considered to develop alternative endpoints based on PRO. In this regard, Fuhlbrigge Anne L and collaborators have made a good attempt. They proposed a novel PRO endpoint "CompEx" to replace severe asthma exacerbations, which is the cornerstone of assessing asthma management, but the incidence is low and requires long observation time. CompEx has been proved to help reduce trial cycles and sample size, while preserving the ability to show a treatment effect compared with severe exacerbations.[94] PRO endpoints for rare diseases are of great significance to doctors, patients, and sponsors.

Abbreviations

PFDD, Patient-focused drug development; COA, Clinical outcome assessment; PRO, Patient-reported outcome; FDA, US Food and Drug Administration; R&D, Research and development; CDE, China Center for drug evaluation; EMA, European Medicines Agency; DDT, Drug development tool; LOI, Letter of intent; QP, Qualification Program; FQP, Full qualification package; ClinRO, Clinician-reported outcome; ObsRO, Observer-reported outcome; PerfO, Performance outcome; NSCLC-SAQ, Symptom Assessment Questionnaire for Non-small Cell Lung Cancer; PED, Patient experience data; PRO-CTCAE, Patient-Reported Outcome-Common Terminology Criteria for Adverse Events; CHF, Chronic Heart Failure; MDD, Major Depressive Disorder; IBS, Irritable Bowel Syndrome; COPD, Chronic Obstructive Pulmonary Disease; FSHD, facioscapulohumeral muscular dystrophy; HD, Huntington's Disease; PD, Parkinson's Disease; CD, Crohn's Disease.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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