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Review Article

# Patient-Focused Drug Development and Real World Study

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ABSTRACT

*Background:* Patient-focused drug development (PFDD) is an important direction in the field of medical research and is of great significance to the development of medicine. In recent years, PFDD and real-world study (RWS) have gained much interest, of which both have their advantages. This study aims to promote research methods innovation and optimize clinical research design and implementation.

*Methods:* After a brief introduction of PFDD and RWS, this review focused on the comparison of clinical trials of PFDD and RWS in terms of objectives, Population, Intervention, Comparator, Outcome (PICO) elements, research team members, data acquisition, and research key points, and clarified the feasibility and significance of "patient-focused RWS" research model.

*Results:* PFDD emphasized that patients' needs as well as the willingness and satisfaction of patients should be considered throughout the whole research process and the patient experience data should be collected during the study development and drug use. RWS emphasized the facticity of research implementation environment and the breadth of patient sources, which concerned the problem of the extrapolation of study results, the clinical localization, and patient applicability of the target drug. However, there is a connection between both of the above. Both clinical trials of PFDD and RWS bring benefits to patients.

*Conclusions:* Combining PFDD idea and RWS research method to carry out new research will maximize the benefits for patients. The study model combining the PFDD concept with RWS can facilitate drug development and dissemination, which can be popularized and applied in various research areas. This study can innovate research methods and provide new ideas for future research.

## 1. Introduction

Patient-focused drug development (PFDD) is an approach established by the US Food and Drug Administration to systematically incorporate patient experiences into drug development and evaluation.[1] PFDD emphasizing the importance of patients' experiences, values, needs, and preferences, has some common points with traditional Chinese medicine (TCM) people-oriented concept.[2,3] Real-world study is a trial methodology that takes the best parts of traditional RCT and observational study designs to produce evidence, avoiding evidence quality compromising by confused indication or a general lack of rigorous collection standards, which can provide adequate scientific evidence for regulatory decision-making.[4] The field of TCM was the first to introduce and carry out the practice of RWS, especially in the field of TCM safety evaluation, which has achieved remarkable results.[5]

*The Guidelines for the Application of Patient-Reported Outcomes in Clinical Drug Development (Trial)* and four Patient-focused drug development-related guidelines issued by the Center for Drug Evaluation, National Medical Products Administration (CED-NMPA) encourage patient participating in new drug development, which reveals that PFDD is the future trend of drug development. If RWS follows this trend, the value and feasibility of study will be greatly improved.[6] After a brief description of PFDD and RWS, we will focus on the comparison of clinical trials of PFDD and RWS in terms of objectives, Population, Intervention,

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Comparator, Outcome (PICO) elements, research team members, data acquisition and research key points, and clarify the feasibility and significance of patient-focused RWS research model, aiming to innovate research methods and provide new ideas for future research.

## 2. Patient-focused drug development

The PFDD clinical trial pays full attention to the clinical benefits of patients and their feelings about participating in a trial. The main reasons are as follows: in medical practice, there is a difference in the perception of disease recovery between patients and clinicians. The disease recovery from the clinician's perspective is based on conventional biochemical outcomes, while the disease recovery from the patient's perspective is reflected in the improvement of quality of life, which is also the clinical demand of patients. Therefore, it is important to pay attention to patients' clinical needs in the process of medical practice and incorporate that into the key elements of clinical trial design and drug benefit-risk assessment system.[7] Especially, in the real clinical environment, it is difficult to achieve the ideal state of "high benefit-low risk", and when "low benefit-low risk" or "high benefit-high risk" situations occur, it is more difficult to balance the benefits and risks of drug, which making medicine decision more difficult. At this time, attention to the patients' needs and understanding the patients' tolerance for risk can be an aid to medical decision-making.[8]

Many policy documents have been issued in China and other countries to promote the patient-focused concept in drug development. In 2012, the *US Food and Drug Administration Safety and Innovation Act (FDASIA)* was released, mentioning "patient participation in medical product discussions".[9] The *Prescription Drug User Fee Act (PDUFA)* also suggested that the FDA needs to enhance patient engagement in benefit-risk assessment, patient-reported outcome, product development supervision, advisory committees, endpoint development and risk communication, and called for the FDA to develop a plan to formally incorporate patient's needs and perspectives into FDA decision-making.[10] In May of the same year, the concept of PFDD was formally introduced in a public presentation by FDA staff,[11] to comprehensively collect patient requests and suggestions through multiple channels and standardize the information collected into the entire drug development process to help ensure that patient's experience, perspectives, needs, and priorities are incorporated into drug development and evaluation.[12]

In June 2012, the PFDD panel was established. In December 2016, the US Congress enacted the *21st Century Cures Act*, which required FDA to develop one or more guidelines within five years on the collection of patient experience data and how to use such data and related information.[13] From June 2020 to April 2023, the PFDD panel issued four guidelines one after another[14-17] to provide methodological guidance on data collection, use, and the role of PFDD in drug development.

The CED-NMPA of China has issued several patient-focused guidelines, including the *Guidelines for Benefit Risk Assessment Techniques in Patient-Focused Clinical Trials (Draft for Soliciting Opinions)*,[18] the *Guidelines for Patient-Focused Clinical Trial Design Techniques (Draft for Soliciting Opinions)*,[19] and the *Guidelines for Patient-Focused Clinical Trial Implementation Techniques (Draft for Soliciting Opinions)*,[20] which created a new pattern for clinical study design and scientific assessment.[6]

The diagnosis and treatment process of TCM is very consistent with the concept of PFDD.[21] Many researchers have proposed the patient-focused selection methods of TCM clinical diagnosis and treatment plans, and patient-focused pharmaceutical research ideas of new TCM drugs.[21,22]

## 3. Real world study

RWS is a research aiming at a clinical question, that collects data related to the health of subjects (real-world data) or aggregates existing data derived from the real-world environment to analyze them using methods and techniques such as epidemiology, health statistics, and information science, obtaining clinical evidence of drug use and potential benefit-risk (real-world evidence).[23-25]

Randomized controlled trials (RCTs) have been regarded as the gold standard in clinical guidelines and drug review decisions, but are detached from the real-world environment due to their stringent criteria for exclusion, poor extrapolation of results, and high study costs. Hence, RWS conducted in a real clinical research environment emerged. RWS breaks the limitations of RCT, expands sample size by establishing broader inclusion and exclusion criteria, and meanwhile, its research approaches are not limited by prospective study or retrospective study, which can make full use of data with many advantages of high external validity and large sample size. Many countries' regulatory agencies have begun to encourage researchers to conduct RWS and issued a series of guidance documents related to RWS.

In 2016, the *21st Century Cures Act* in US have encouraged using real world evidence to support regulatory decision making for medical products and drugs. In China, National Medical Products Administration have released the *Notice on Publicly Soliciting Opinions on the Guiding Principles of Real World Data for Clinical Evaluation of Medical Devices (Draft for Soliciting Opinions)*[26] and the *Notice of the National Medical Products Administration on the Guiding Principles for Releasing Real World Evidence to Support Drug Research and Evaluation (Trial)* in December 2019 and January 2020, respectively,[27] which proposed conducting RWS to support the research, development, evaluation and supervision of drugs and medical devices.

The number of RWS on TCM has been steadily increasing.[28] The first RWS on TCM was published in 2008, and since then, 373 RWS-TCMs have been published in 10 years.[29]

## 4. Patient-focused drug development clinical trial versus real world study

### 4.1. Objective

Both PFDD clinical trial and RWS can be conducted to evaluate the efficacy and safety of interventions. However, the PFDD clinical trial pays more attention to patients' satisfaction and demands during the treatment and trial implementation process, which focuses on assessing the clinical value of intervention from patients' perspective. A study *Integration of Patient Reported Outcomes in Drug Development in Genitourinary Cancers* indicated that patient-reported outcomes (PRO), a form of attention to patient needs, is critically important in assessing the subjective experience of patients and the effects of both disease and treatment, as the mode of administration, cost, etc. may all contribute to patients' overall experience and preferred choice between drugs.[30]

RWS, on the other hand, focuses more on the effectiveness and safety of treatment and trial implementation process under real-world conditions. RWS usually includes a larger group of patients and collects a variety of data types to obtain more clinically useful evidence, which can better understand the appropriate population of an intervention, and aid clinicians to make better decisions.[31]

In general, the former focuses more on "patient", emphasizing whether the study results meet patients' needs and values and whether patients' willingness can be improved in the drug use process. The latter focuses more on "intervention", pointing out whether the study results can be applied in a larger clinical scope and to a larger number of patients (Table 1).

### 4.2. PICO elements

Patient (P): Both PFDD clinical trial and RWS need to formulate inclusion and exclusion criteria based on the study objective and design. In PFDD clinical trial, participants with the best benefit-risk ratio are included, after weighing disease characteristics, drug action mechanisms,

**Table 1**
Comparison of objectives between PFDD clinical trial and RWS.

| | Patient-Focused Drug Development Clinical Trial | Real World Study |
|---|---|---|
| **Objectives** | Evaluate the efficacy/effectiveness and safety of an intervention | |
| | • Bring more clinical benefits to patients according to their clinical needs<br>• Identify the type of intervention that patients are satisfied | • Conduct in a real environment to meet the decision-making needs of clinicians<br>• Identify the type of intervention that doctors consider as most appropriate |

known safety characteristics, and positive treatment options. The representativeness of participants should be emphasized, while respecting the wishes of participants to protect the rights and interests of participants. The RWS usually loosens inclusion and exclusion criteria as much as possible, such as including ethnic minority patients, patients with underlying diseases, the elderly, pregnant women, children, or other special heterogeneous groups, as well as participants who are unwilling to participate in or underrepresented participants.[25,32]

Intervention/Control (I/C): In PFDD clinical trials, patients' views on current treatment plan are fully collected, including expected benefit, tolerance of hazards or risks, an acceptable balance of benefits and risks, and attitude towards the unknown things that may happen. Clinicians and investigators develop intervention/control protocols with full reference to patients' willingness and they also invite patients to participate in the selection and decision-making of intervention/control, making clinical decisions in full compliance with the three core elements (clinical expertise, patient values and preferences, and best evidence) of evidence-based medicine. In contrast, the intervention/control of RWS is consistent with clinical practice,[33] without too many strict limitations in general and mainly rely on clinicians' decisions.[34]

Outcomes: PFDD clinical trials focus more on collecting patient experience data (PED) and use PED to generate appropriate outcomes (such as quality of life, happiness, and other subjective qualitative outcomes). PED provides evidences on treatment effect and safety from the perspective of patients and is mainly used to judge clinical efficacy and report adverse reactions, etc., which has been widely realized by domestic and foreign medical communities.[35,36] In addition, PFDD clinical trials focus on patient preference information, such as assessing patients' willingness to choose and acceptance of different outcomes. In PFDD clinical trials, outcomes usually are clinical outcome assessment (COA) which is developed to evaluate patients' illness experience, physiological function, or survival status by collecting PED, the experience, needs, opinions, preferences, and other aspects of disease and treatment provided by patient themselves. COA is a carrier for patients to express their subjective feelings. In recent years, the development, evaluation, and promotion of COA have received great attention, includes patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO), and performance outcome (PerfO).[37] However, RWS usually chooses outcomes that doctors more prefer to measure, which are usually recommended by the guide or core outcome set.[33] Most of them are end-points[5] (Table 2).

### 4.3. Research team member

The team member of PFDD clinical trials mainly includes patient, family members, community managers, clinicians, and researchers. They complement each other to facilitate the completion of the trial. Patients can actively participate in medical decision-making, understand the advantages and disadvantages of treatment plans and possible prognosis, and then fully express their feelings, follow their willingness to the greatest extent to decide whether to accept treatment, which improve the patients' sense of self-sufficiency in the trial. In addition, patients can also take this opportunity to establish contact with doctors, have mutual understanding and support, thus promoting the harmonious development of the doctor-patient relationship.[38] In this process, clinicians can accumulate experience in how to achieve patient-centered treatment,[39] and improve their communication skills with patients to understand the real needs of patients. Community managers act as assistants, who build partnerships with doctors to help them manage patients in their area. In this process, researchers can find more meaningful research questions

**Table 2**
Comparison of PICO between PFDD clinical trial and RWS.

| | Patient-Focused Drug Development Clinical Trial | Real World Study |
|---|---|---|
| **P** | Formulate inclusion and exclusion criteria based on study objective and design | |
| | • Inclusion of participants with the best benefit-risk ratio<br>• Strong patient representation<br>• Respect the wishes of participants<br>• Inclusion criteria are relatively strict<br>• Patients assist the researchers in identifying the target population and participate in recruitment | • Wide source of patients, including clinical, community, or family, etc.<br>• Consider special populations<br>• May include patients who are unwilling to participate or underrepresented patients<br>• Inclusion criteria are lenient, and the results can be promoted easily |
| **I** | • Respect patients' choices and consider the benefit of patient from the perspective of individual wishes<br>• Collect patients' opinions on current treatment options<br>• Patient participates in protocol formulation and decision-making<br>• The target intervention is selected based on the patient's expected benefit, tolerance for harm or risk, and the acceptable ratio of benefit to risk. | • Give more play to the role of clinicians, and consider the benefits of patients from the perspective of disease diagnosis and treatment<br>• The interventions are the same as the clinical practice. Do not impose too many strict restrictions.<br>• Decisions made by clinicians |
| **C** | • Patient participates in protocol formulation and decision-making<br>• Treatments that patients prefer and that are in line with their values<br>• The control is selected according to the control principle of clinical trials, and the patient's willingness also need to be respected. | • Decisions made by clinicians according to clinical practice<br>• Conventional control or no control |
| **O** | • Collect patient experience data<br>• Collect information on patient preferences for different outcomes<br>• Patients participate in the process of outcome selection, outcome monitor and outcome report.<br>• Clinical outcome assessment (COA): patient-reported outcome, (PRO), observer-reported outcome, (ObsRO), clinician-reported outcome (ClinRO), performance outcome (PerfO) | • Outcomes recommended by the guidelines or core outcome set<br>• Outcomes that doctors focus on<br>• Usually are end-points |

**Table 3**
Comparison of team member between PFDD clinical trial and RWS.

| | Patient-Focused Drug Development Clinical trial | Real World Study |
|---|---|---|
| **Team member** | • Patients<br>• Family members<br>• Community managers<br>• Clinicians<br>• Researchers (Sponsor, investigator, clinical coordinator, monitor, data manager, etc) | • Clinicians<br>• Researchers(Sponsor, investigator, clinical coordinator, monitor, data manager, etc) |

and research evidence that meet the needs of patients to make research results more applicable to the daily management of patients' conditions and to rapidly transform and apply research results[40,41]; hence, producing high-quality evidence and promoting academic progress.[42]

In RWS, clinicians, researchers, and patients are both involved in research, but only clinicians and researchers participate in the execution and management of research. Patients participate in research as subjects but do not participate in decision-making as research stakeholders (Table 3).

### 4.4. Data acquisition

Data source: PED stems from patients themselves or family members who care for them. When PED is not available directly, valuable and diverse information can also be obtained from caregivers, patient advocates, clinicians, and others. RWS data usually comes from a wide range of sources, including electronic medical records, healthcare databases, devices and apps, patient enrollment programs, and even social media.[32,43]

Data type: in PFDD clinical trials, PED can be presented in many forms, including qualitative, semi-quantitative, or quantitative data, which are the experience, needs, opinions, preferences, and other aspects of disease and treatment provided by patients themselves, thus may be most data are qualitative. Therefore, researchers need to standardize it. Researchers can design a unified data collection form before data collecting, or summarize patients' data by a specialized personnel after data collecting, to ensure the normalization of PED.[16] In contrast, RWS data are usually quantitative data measured by instruments, which are documented by clinicians. However, it is also necessary to be standardized before data analysis.

Data collection methods: In addition to routine trial data, PED is usually obtained through in-depth communication between stakeholders (clinical doctors, researchers, etc.) and patients or patient representatives with the assistance of community managers, such as interviews, focus groups, patient meeting discussions, etc. Stakeholders view individual patients as the primary unit of original analysis and interpretation to achieve the aim of focusing on patient dynamics and patients' values. In contrast, data collection of RWS is based on clinical routine data collection methods to obtain preset index data, such as case report forms and hospital information systems, etc.[44]

Statistical analysis: The statistical analysis methods of PFDD clinical trial are similar to those of traditional clinical trials, and the methods can be intention-to-treat (ITT) analysis and per-protocol effect (PP effect) analysis. PFDD clinical trial focuses on patients' willingness and have higher patient compliance; therefore, ITT analysis is more suitable.[45,46] Different statistical analysis methods are used in RWS according to different designs of studies. For experimental RWS, both ITT analysis and PP analysis can be used. However, in the real medical environment, individual patient differences may be large, the standardization of received interventions may be reduced, patient compliance may be poor, the medical technology of clinical professionals may be different, and the loss of follow-up may increase. In this case, it is more appropriate to use PP analysis.[46-48] The differences of baseline and prognostic between observational RWS groups are always more or less inadequate, resulting in a large amount of known and unknown confounder that ultimately results in bias. When RWS is conducted as an observational study, the key to statistical analysis is to control the bias caused by confounders to the maximum extent, thus, hierarchical analysis, multivariate regression model, propensity score analysis, and other methods should be used to control confounders before subsequent analysis.[49] At the beginning of observational RWS, data may have already been collected and recorded, and there may be unclear or missing. Therefore, it belongs to post hoc analysis and needs to formulate research hypotheses for statistical analysis based on the characteristics of the data itself, which is prone to be influenced by multiple verifications, resulting in false positive results[49] (Table 4).

### 4.5. Research key points

PFDD Clinical trial: (1) Emphasize the patient as the center of information exchange and maintain effective communication between patients and stakeholders at all stages of study, including identification of study topic, hypothesis development, data analysis, and dissemination

**Table 4**
Comparison of data acquisition between PFDD clinical trial and RWS.

| | Patient-Focused Drug Development Clinical trial | Real World Study |
|---|---|---|
| **Data source** | • Patients themselves<br>• Family members who care for patient<br>• Caregivers, patient advocates, clinicians, and others.<br>• Other clinical trial data | • Electronic medical records<br>• Healthcare databases<br>• Devices and apps<br>• Patient enrollment programs<br>• Social media |
| **Data type** | • Qualitative, semi-quantitative, or quantitative data<br>• Most are qualitative | • Qualitative, semi-quantitative, or quantitative data<br>• Most are quantitative |
| **Collection process** | • Active reporting by patients<br>• Others indirect reporting of PED<br>• Trained researchers collect data through interviews, focus groups, patient meeting discussions, etc<br>• Not limited to the data specified in protocol | • Researchers collect the data specified in protocol<br>• Collect by case report form<br>• Extract from case records or databases |
| **Statistical analysis** | • Intention-to-treat analysis (more applicable)<br>• Per-protocol effect analysis | • Intention-to-treat analysis<br>• Per-protocol effect analysis (more applicable)<br>• Hierarchical analysis<br>• Multivariate regression model<br>• Propensity score analysis |

of findings.[50] Stakeholders include clinicians, researchers, caregivers, payers, representatives of policy makers, principal investigators, and members from societies/associations.[51] Trials are conducted to meet ethical requirements and respect patients' right to informed consent. (2) Emphasize providing sufficient time for the research team to engage in meaningful communication with patients. When patients' time is difficult to manage, investigators can reduce the frequency of meetings, select patient representatives to communicate, or consider providing more allowance to patients who participate in communication to ensure that the research team has sufficient time to understand patients' needs. (3) Emphasize the training of researchers to understand the study context and implementation standards, help researchers integrate into the community as much as possible, and gain community participation and support for the study, of which the power of community is used to better communicate with patients. (4) Emphasize further expanding patient recruitment through the social network of patient representatives already enrolled in the study. (5) Emphasize maintaining relatively stable cooperative relationships between the research team and patients, developing a perfect communication scheme to accommodate their actual needs.[52] (6) Emphasize the selection of PED collected methods. Appropriate methods should be selected according to the specific characteristics of diseases, satisfying the principle of applicability, scientificity, confidentiality, and convenience.[15] (7) Emphasize the design and evaluation of COA. COA applicable to collect PED should adapt to research objectives, survey population, and usage scenarios, etc., and also should be evaluated to ensure its convenience and practicality.[15]

Real World Study: (1) Identify research questions related to actual clinical care and health maintenance, and essential elements of PICOTS (Population, Intervention, Comparator, Outcome, Timing, Settings) or PECOS (Population, Exposure, Comparator, Outcome, Study design). The research questions should be clinically and scientifically significant, which have not been addressed by previous studies, being proposed for the first time, or have controversial research conclusions.[53] (2) Ethical review and informed patient consent are key elements, that should be adjusted according to different study designs.[54] (3) Predict the final evidence strength: in RWS model, around specific issues (such as effectiveness, safety evaluation), identify appropriate research design (such as observation, effectiveness), and select reasonable statistical analysis methods. According to the actual situation of the data to be included, the requirements for the strength of evidence and the matching degree of resources should be considered. In addition, the selected data resources and research design should be comprehensively evaluated in advance to avoid waste of research resources.[34] (4) Ensure data accessibility and ensure data quality to meet the needs of research purposes. The collected data include: routinely collected medical data (hospital electronic medical record data, medical insurance data, health records, death registration data, etc.); additional collected data around disease, product, or service patterns based on preset research purposes[55]; other real-world data from different sources which can be used to build specialized research databases. (5) Identify team composition: a high-quality RWS team should at least includes multidisciplinary experts in clinical and methodological such as clinical/drug epidemiology, statistics, informatics, evidence-based medicine, etc. The clinical team should include clinical experts in traditional Chinese medicine, Western medicine, or integration of traditional and Western medicine, as well as technical personnel with daily practical experience.[34]

## 5. Patient-focused RWS

PFDD is a research concept, which must be combined with research methods before it can be compared with other research methods. Therefore, this paper adopts the research method of PFDD clinical trial to compare its similarities and differences with RWS. On this basis, further explores the combination of PFDD concept and RWS.

The concept of "patient-centered" is in line with the people's pursuit of a healthy life, and also has the potential value of improving the success rate of research, speeding up the process of clinical trials, and reducing research costs. The changing role of patient is enable patients to better understand their disease condition and research objective, which improving treatment compliance, and improving the effectiveness and credibility of clinical trials.[56] Patient-focused RWS, on the basis of respecting the experience, views and needs of patients, pays more attention to clinical practice under real conditions, reduces the difficulty of research to a greater extent, improves the clinical value of research, and has higher external validity. The patient-focused RWS model is shown in Fig. 1.

Although patient-focused RWS makes sense, there are limited examples of engaging patients in RWS.[57-59] At present, only a few examples that patients participated in RWS have been published, which can provide a reference. The Crohn's and Colitis Foundation of America Partners Patient-Powered Research Network (PPRN) created a portal website to recruit and attract patients and encourage patients building partnership with researchers. PPRN hears from patients by qualitative research (focus groups and one-on-one interviews) and forms a patient governance committee with 5 patients to assist website constructing, and conducts research using health data shared by inflammatory bowel diseases (IBD) patients. IBD patients can propose their own research ideas and research questions that are most important to them in the website, and also can vote on research topics proposed by peers. Currently, PPRN has recruited 14,200 patients from the United States and collected 67 research questions from patients, of which 12 research ideas are under study.[60] The Pfizer–Bristol Myers Squibb Alliance partnering with the National Health Council and the Arrhythmia Alliance contacted with patients diagnosed with atrial fibrillation (AF) through advisory committee, to understand patients' perspectives, obtaining PED for their future AF RWS. Before face-to-face interviews with patients, they set interview goals, namely the patients' data they want to obtain. In addition, they conducted introductory webinars that provide patients with the opportunity to meet prior to face-to-face meetings, introduced examples of RWS to patients in advance, and provided an easy-to-understand RWS vocabulary. They also pointed out that communicating in a health literacy way can improve patient acceptance and diversity advertising board are an effective way to engage patients to participate in RWS.[57]

However, these studies are at the beginning stage, and patient participation is limited to the problem construction stage. The specific implementation process of RWS. as well as the whole process in which patients participated, has not been fully completed and published yet. In addition, patients have a variety of ways to participate in the study (not limited to RWS): participating in medical care directly (patients can express their preferences and wishes for a treatment plan); participating in organizational work (assessing patient experience and organizing discussions around patient concerns); participating in clinical research, including consultation (listening to patients' needs) and participation (expressing preferences and wishes for interventions); participating in the development of assessment tools; as well as discussing on research design and implementation.[61]

## 6. Discussion

At present, the European Union, Canada, the United States, and other developed countries have issued official guidance documents for PFDD clinical trials.[62] CDE- NMPA has also issued relevant guidelines, indicating that PFDD clinical and research work is one of the directions of China's healthcare reform and is of great significance. However, there is still a gap between research evidence and treatment received by patients in real situations, and traditional research has not fully integrated PFDD concept but is carried out with the opinions of clinicians or researchers.[63,64] Therefore, it is necessary to strengthen promotion and training to accelerate the integration of PFDD concept into clinical research.

PFDD concept encourages investigators to listen to and accept patients' opinions in the whole drug development phase and collect PED

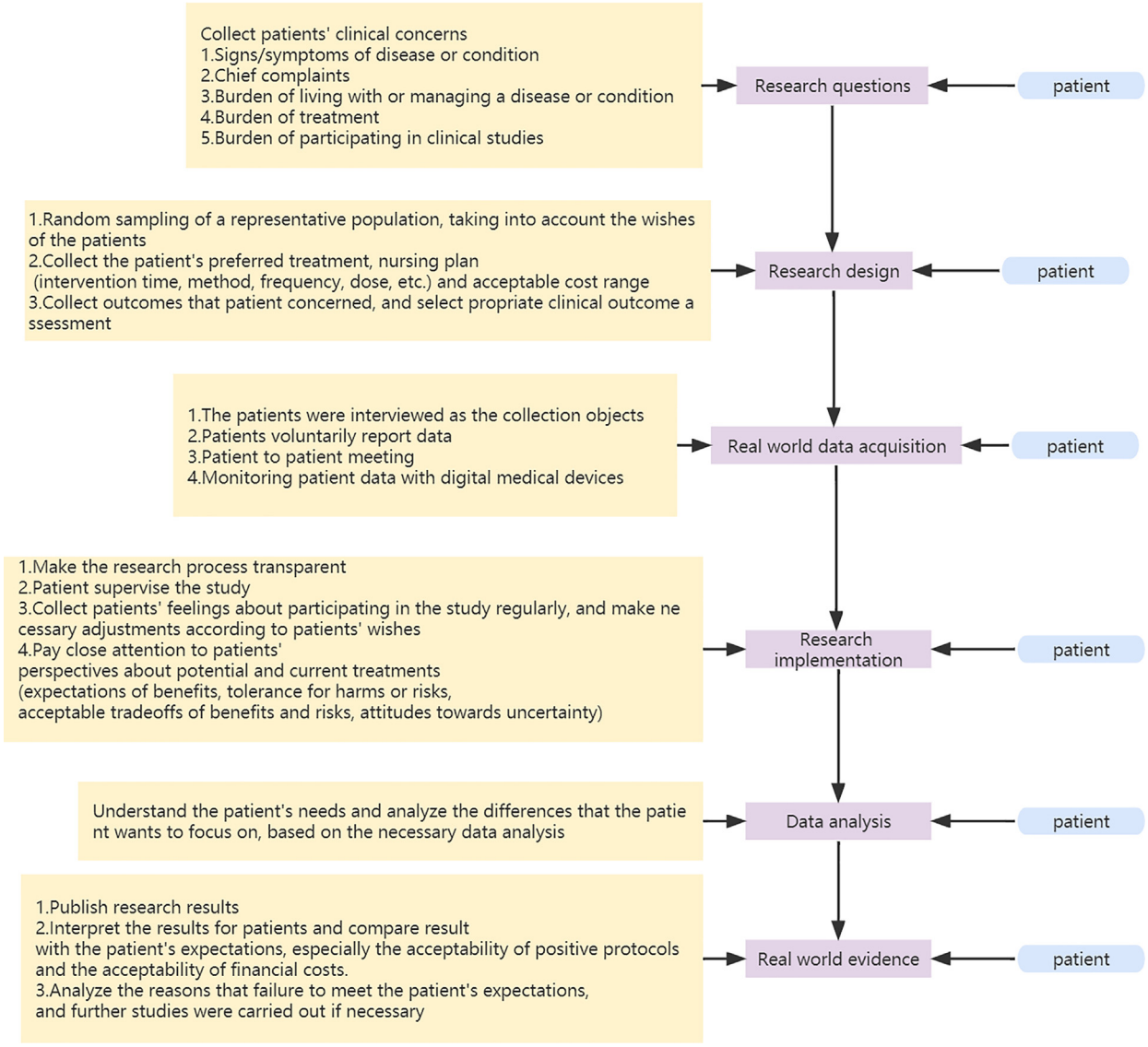


**Fig. 1.** patient focused RWS model.

based on actual needs to understand unmet clinical needs and important clinical outcomes. This concept is important in any stage of drug development, but the trial design should not ignore the characteristics of disease, existing treatments, characteristics of target population, and other factors while paying attention to patients' needs.[65] The concept of PFDD can guide the optimization of clinical trial design. Clinical trials can adopt a fit-for-purpose study design, define study purpose, target population, intervention control, and outcomes from the perspective of patients, and incorporate PED into the consideration of key elements of clinical trial design. In study design, fully reflecting the clinical benefits of patients in terms of physical and mental feeling, function, and living state, can improve the convenience of clinical trials, reduce the burden of patients, reduce the rate of patient shedding, improve patient representation and compliance, and provide a basis for further drug development and regulatory decision-making. Therefore, PFDD clinical trials are suitable for premarket drug development and post-market drug clinical application, which can not only identify unmet clinical needs, identify target patient population, clarify the key elements of clinical trial design, determine the clinical significance of endpoint evaluation, but also assess patients' benefit preferences and risk acceptance, providing direct evidence for benefit-risk assessment.[66]

*Key Considerations in Using Real-World Evidence to Support Drug Development*[67] published by CDE-NMPA in China proposed that RWS is a strategy and path for drug development. RWS is a process of obtaining real-world evidence from real-world data, which emphasizes the routine and normalization of data sources, and obtaining data in daily life or clinic to research is better operability and economy.[5] The value orientation of RWS follows Outcomes Research, placing more emphasis on the actual clinical situation and paying more attention to the extrapolation of research results, with the characteristics of attaching importance to individualized treatment, pursuing actual clinical effects, and assisting patients in making medical decisions to ultimately benefit them.[68,69]

The risks of some therapies outweigh their benefits in real situations, so more researchers began to treat "how patients feel better or live longer" as a key issue to be solved while focusing on the effectiveness, safety, and economy of treatment.[70] Patients' quality of life, body function, and satisfaction when receiving medical treatment have become one of the important contents in medical decision-making.[70] In 2010, the US Patient-Centered Outcomes Research Institute (PCORI) stated that patient-focused outcomes research (including real-world research), ensures that patients and their families communicate effectively with researchers and that patients can participate in the value assess-

ment of medical decisions as they wish, making medical decisions more reliable.[71] Outcomes research such as RWS should have the key attribute of being patient-centered, always taking patients as the main body, and giving more consideration to "how patients feel and what patients want to do", that is one of the preconditions to build a high-quality medical system.[71] *Guidelines for Real-world Evidence Supporting Drug Development and Review (Trial)* released by CDE-NMPA of China in 2020, also pointed out that RWS should focus on patient's needs and advocate patients to report outcomes.

By including patients with a variety of complex conditions, RWS makes up for the limitation that the conclusions of traditional clinical trials cannot fully represent the target population, making the research results more clinically practical.[8] If research is conducted combining with PFDD idea and RWS research method, making real-world data fully reflect patients' needs, the results will be more clinically valuable. Patient-focused RWS should consider patients' characteristics, illness, and preferences, and pay attention to patients' views on their conditions; focus on what the patient's choice is and its acceptable potential risk-benefit ratio; realize that what is the most important clinical outcome for the patient; understand how clinicians make the best decisions for patients' health and health care.[69]

However, there are limitations to patient-focused clinical trials. Whether the trial successfully implemented depends on patients' initiative and motivation, and the data provided by patients may be incomplete and untrue. When patients are involved in the design, implementation, and decision-making processes of clinical trials, the results may be influenced by implementation bias and reporting bias. Patients' cognitive level, physical function, mental state, language skills, numeracy, health literacy, and health status affect the difficulty of data collection.[72] When collecting patients' data, some new technologies may be adopted to obtain more comprehensive data, such as wearable digital devices, then, patients' privacy may be exposed.[73] Towards RWS, big data, as the foundation of RWS, has strong heterogeneity and many confounders. RWS design and data management are more demanding, and are difficult to implement, which cost more money. Inconsistencies in baseline between samples, due to non-randomization, may distort the true association between exposure and outcome.[74,75] Above questions are also considered in patient-focused RWS. In addition, there is a lack of applicable guidelines and model cases to guide patient-focused RWS. Patient participation and respecting patient wishes during RWS increase the complexity of research and the workload of researchers.[73] The full involvement of patients increases the difficulty of blinding in RWS.

Over the past 10 years, the number of RWS-TCM has shown an overall upward trend, with observational studies as the most, while experimental studies are less, including effective randomized controlled trials, non-randomized controlled trials, and single-arm clinical trials.[23,44] The integration of RWS-TCM and PFDD idea is not yet deep, and patients have not truly participated in the full process of medical decision-making and research involving their own interests. In the future, patient-focused RWS still has great prospects to develop in the field of TCM. TCM diagnosis and treatment are characterized by holistic concepts and syndrome differentiation.[76] The diagnosis and treatment process of TCM is very consistent with the concept of patient-centered.[21] TCM doctors pay more attention to the "sick person" rather than the "patients' disease", take the whole person as observed object, and collect individual information comprehensively as well, so as to obtain rich clinical case data. There are generally two method to evaluate treatment effect, one is to ask about the patient's personal feelings and experiences after taking medicine, and the other is to assess the progression of the illness according to the patient's clinical symptoms, signs, and mental activity.[77] In addition, TCM doctors treat according to symptoms, based on understanding the patients' TCM constitution. The characteristic treatment of TCM based on pattern identification, including warming Yang, nourishing Yin, clearing heat, fortifying spleen, etc. For patients with Yang deficiency and heartache, it is necessary to give drugs regulating qi and relieving pain on the basis of supporting Yang.[78] Thus, the patient-focused RWS method can highlight the advantages of TCM characteristic diagnosis and treatment scheme, especially the patient-side clinical value, and is more conducive to the clinical promotion of TCM unique treatment. To carry out patient-focused RWS on TCM, full consideration should be given to the clinical characteristics and research needs of TCM,[79] and it should be clear whether the TCM research mode is "disease", "syndrome" or "combination of disease and syndrome" at the same time.[80] Then, under the guidance of PFDD concept, evaluating and optimizing the rationality and rigor of study design, paying attention to PED collection, especially the PED with TCM characteristics.

In general, the patient-focused RWS research model is worth promoting, which can better balance the interests of patients and other stakeholders by sharing decision-making rights with patients,[81] ensuring that research priorities are consistent with patients' demands, which is conducive to drug development and promotion and to increase the clinical value of study results.

## Author contributions

Hui Wang and Haiyin Hu conceived, designed, and drafted this article. Zhaochen Ji and Junhua Zhang conceived the study and revised the manuscript. Menglong Shi, Xiaolei Wu and Chenyao Zhang collected the literatures. Kai Li drew and modified statements. Lin Ang, Mei Han and Shigang Liu gave suggestions and revised the manuscript.

## Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Ethical statement

Not applicable.

## Data availability

Not applicable as this article is a literature review article.

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