以患者为中心的药物获益-风险评估

技术指导原则（试行）

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I. Overview

(1) Background

"Patient-centered" drug development refers to drug development based on the patient's perspective.

The process of drug development, design, implementation and decision-making, aiming to efficiently develop more suitable for patients

Drugs with clinical value that patients need.

Patients are the direct feelers and experiencers of disease states and drug treatments.

In the entire process of drug development and decision-making, patients should be regarded as active participants.

The patient's experience, opinions, needs and preferences regarding the disease and related treatments

experimental data as a key consideration in drug R&D design and implementation, and included

Benefit-risk assessment system to develop and develop valuable drugs that meet patient needs

Listed with scientific evidence.

The entire process of drug research and development should fully consider patient needs and be patient-centered

Three technical guidelines for drug clinical trial design, trial implementation and benefit-risk assessment

The guiding principle is to systematically conduct

Explain how to fully consider patient needs in the early stages of research and development and incorporate patient experience data

Conduct clinical trial design based on data; how to ensure scientific reliability, subject safety and

Under the premise of privacy and other conditions, optimize the patient experience of participating in clinical trials; and how to

Fully weigh the clinical benefits and risks of drugs from the patient's perspective and make scientific decisions

Plan.

Patient-centered drug benefit-risk assessment, focusing on patients' clinical needs

request that patient experience data collected in clinical trials be

data, PED) into the benefit-risk assessment framework, in treatment context analysis, drug

Patients can be considered in terms of benefits, risks and risk management, uncertainty analysis, etc.
perspectives, and combine patient experience data with a complete clinical evidence chain to jointly support
Maintain a dynamic assessment of benefits and risks throughout the life cycle and fully evaluate drugs from the patient's perspective
benefit-risk ratio.

(2) Purpose and scope of application

This guideline is intended to clarify patient-centered benefit-risk assessments of medications.
The overall principles of assessment and the science of benefit-risk assessment based on patient experience data
considerations and communication with review agencies, etc., to provide sponsors with a
Use patient experience data to conduct benefit-risk assessments to provide a reference after marketing.

This guidance represents only the current views and understanding of this drug regulatory agency.
Not legally binding. As scientific research progresses, this guidance
The relevant content in the principles will be continuously improved and updated. When applying these guidelines,
Please also refer to the International Conference on Harmonization of Technical Harmonization of Medicinal Products for Human Use (ICH) and other
He has published relevant guidelines.

2. General principles

Benefit-risk assessment of a drug should be based on systematic clinical effectiveness of the drug and
Evaluate safety trial evidence. Robust patient experience data helps discover
Unmet clinical needs, identification of target patient populations, validation of clinical trial designs
key elements, determine the clinical significance of endpoint assessments, and assess patient benefit bias.
and acceptance of risks, etc.

The applicability and scope of patient experience data in benefit-risk assessment,
Depends on the type of patient experience data, purpose of collection, study design, collection site

context, data quality, interpretability of results, etc. Generally speaking, how to use

Patient experience data obtained through reasonable and fit-for-purpose collection tools can

Provide direct evidence for benefit-risk assessment. Methodological rationality means that it should ensure the use of

The methods and processes for collecting and analyzing patient experience data are rigorous and reliable,

and adhere to scientifically established principles and best practices; fitness for purpose refers to research

There should be a match between the study design and the intended use of the data. When patients experience

When the data is used as key evidence or one of the key evidence to support the benefit-risk assessment,

It is necessary to communicate with the review agency in advance to ensure that the data are collected through pre-designed studies.

Set, the study has a pre-set research protocol and analysis plan, and ensures inclusion

The representativeness of the sample, the standardization of data collection, and the reliability and completeness of the data

integrity and authenticity.

The process of collecting patient experience data is dynamic and progressive. in medicine

During the project establishment and early clinical stages, patient experience data are mostly qualitative, and the collection content

Focus more on the patient's perspective on the disease and available treatments. Along with product development

Going deeper, quantitative methods can be added to the collection of patient experience data, gradually focusing on

The patient's perspective on the expected benefits of a particular drug, including rights to benefits and risks

balance. Once the drug is on the market, real-world drug users can continue to collect data as needed.

Use patient experience data to maximize patient benefits and minimize risks

the ultimate goal.

3. Classification of patient experience data

There are many ways to classify patient experience data. Patient experience data is available from Sponsored

Collected by parties or non-sponsors. According to the method of collecting patient experience data, it can be divided into

Pre-designed clinical trials, patient preference studies, natural history studies, interviews,

Questionnaires, expert consultations, patient communication meeting summaries, etc. The nature of patient experience data

Qualitative includes qualitative, quantitative or semi-quantitative. Patient experience data can be used to support clinical

clinical outcome assessment (COA), which provides an assessment of benefits and

Risky patient preference information (PPI)

and other insights, needs or priorities regarding diseases and treatments, etc., and then

Support adequate benefit-risk assessment. The following describes clinical outcome assessment and patient

Preference information related content.

(1) Clinical Outcome Assessment (COA)

Clinical outcome assessments are derived from patients, their caregivers, physicians, or other assessors

Person, an assessment tool used to evaluate an individual patient's feelings, functioning, or survival status

or means, often requiring subjective assessment rather than direct presentation of facts. clinical outcome

Dimensions of assessment include symptoms, signs, daily functioning, overall health status,

Quality of life and satisfaction, etc. Depending on the reporter, clinical outcome assessments were divided into

Clinician-reported outcome (ClinRO), patient-reported

Patient-reported outcome (PRO), observer-reported outcome

(observer-reported outcome, ObsRO), also includes test-based assessment

Patient performance-based outcome (PerfO).

PROs are symptoms, signs, functions, or other symptoms reported directly by the patient themselves

Measurements of aspects without external correction and interpretation by a physician or others. Measurement

PRO tools are usually scales, questionnaires, numerical scores, or patient diaries.

For example, patient global assessment (PGA), digital

Numeric rating scale (NRS), SF-36 health survey scale

(the 36-item short from health survey) etc. ClinRO is a professional medical

based on examination or observation of the patient's disease and health status.

results, which mostly involve the patient's signs, symptoms, behaviors or other phenomena related to the disease.

Clinical judgment based on images or clinical judgment based on laboratory indicators. For example, Glass

Glasgow Coma Scale (GCS), psoriasis area

and Severity Index (Psoriasis Area and Severity Index, PASI), etc.

ObsRO is a measure of patient health outcomes reported by daily caregivers.

quantity. For example, caregiver-recorded frequency of seizures in children with Dravet syndrome

Diary etc. PerfO is a process in which a patient performs a standardized functional task.

Measurements assessed independently by appropriately trained personnel or patients. For example, walking speed

measurement (such as 6-minute walk test, 6MWT), memory recall test (such as single

Word Recall Test) or other cognitive tests (such as Digit Symbol Substitution Test), etc.

In addition, composite clinical outcome assessment tools may include multiple types of clinical

Outcome assessment, such as the combination of ClinRO and PRO, etc.

Tools based on clinical outcome assessment can be used to evaluate clinical benefit. Clinical gains

Benefit is defined as the impact of a treatment or intervention on an individual patient's feelings, functioning or survival.

Beneficial impact can be measured as improvement or delay in deterioration. clinical outcome assessment endpoints

It can be used as the primary endpoint (single endpoint or composite endpoint) or predictive endpoint to evaluate clinical benefit.

Define the secondary endpoint first. For example, a pivotal clinical trial in idiopathic constipation

Average number of spontaneous complete bowel movements per week

movement, SCBM) greater than or equal to 3 times as the primary endpoint; in bone marrow fibrosis

In the pivotal clinical trial for vitreous indications, imaging results (reduced spleen volume)
As the primary endpoint, modified myelofibrosis symptom assessment collected from patient diaries
In the sub-form (Myelofibrosis Symptom Assessment Form, MFSAF)
Symptom improvement served as a key secondary PRO endpoint. In addition, security can also be achieved through
Evaluation of clinical outcome assessment tools. For example, clinical trials in non-small cell lung cancer
, using the Visual Symptom Assessment Questionnaire
Questionnaire, VSAQ-ALK) to assess the ophthalmic safety of therapeutic drugs.

(2) Patient preference information (PPI)

Patient preference information refers to the different clinical outcomes of patients for specific treatments
A qualitative or quantitative assessment of the willingness and acceptance of other features. exist
In benefit-risk assessment, patient preference information can provide patients with a preference for benefits.
Good and tolerance for risk. For example, ask the patient about different uses (such as external
medication, oral, or injected), or ask the patient whether for
be willing to accept the potential risks for the possible benefits.

At different stages of drug development, patient preference information may be relevant to the treatment.
There is certain guidance on scenarios, endpoint selection and dynamic benefit-risk assessment.
effect. For example, patient preference information can help clarify the clinical significance of trial endpoint measurements.
The importance of benefits to the patient, understanding the patient's benefits and risks of a particular drug
weigh the risks and understand the patient population’s preferences and differences in various treatment options
Qualitative.

The application of patient preference information in benefit-risk assessment needs to fully consider appropriate
Background of symptoms, application value of patient preference information, collection of patient preference information

Representativeness of methods and patient perspectives. The following situations need to be carefully considered

Whether patient preference information has value: ÿ The drug has clear efficacy but serious or

Uncertain safety risks, and patients are willing to accept higher risks for a safe

possible benefits; ÿ There are differences in opinions among patients regarding the most important benefits and/or risks.

There is a big difference; ÿThe patient's point of view is inconsistent with the medical professional's point of view. Generally

In other words, for drugs with poor efficacy or serious safety problems, we cannot rely solely on

Benefit-risk assessment based on patient preference information.

4. Patient experience data supports benefit-risk assessment

(1) Benefit-risk assessment framework based on patient experience data

Patient experience data can provide key considerations in drug benefit-risk assessments

white. Within the overall framework of drug benefit-risk assessment, patient experience data can be included

improve it, pay attention to patients' clinical needs and patient perspectives, and ensure that patients

Patient-centered benefit-risk assessment.

Benefit-risk assessment framework and focus based on patient experience data include

The following aspects (see Table 1): "Treatment background analysis" (the incidence of the disease,

severity and prognosis, characteristics of currently available therapies, unmet clinical needs, etc.),

Specific drug "benefits" and "risks and risk management"; each of these aspects needs to be

To assess relevant evidence (including data quality and credibility) and reasons for uncertainty

factors and their potential effects. Finally, combining the severity of the disease and the current unmet

clinical needs and synthesize the evidence and uncertainties regarding the benefits and risks of the drug

nature, and draw specific conclusions from the benefit-risk assessment.

Table 1. Patient-centered benefit-risk assessment framework

Assessment Dimensions	Application scenarios of patient experience data
treatment background analyze	Identify and measure the patient's primary clinical symptoms, signs, and disease burden bear Understand the natural history of disease, including its occurrence, progression, and severity sex, prognosis, etc. Determine the important risks and possible benefits of existing treatments for patients, and evaluate Estimated unmet clinical needs Understand the treatment features that patients care about most and identify their needs for new treatments degree
benefit	Integrate assessment results from clinical outcome assessments, patient preference information and their It incorporates patient experience data information into assessments of benefit • Evaluate the clinical benefit of a drug based on clinical outcome assessment endpoints • Determine the clinical relevance of study endpoints and measurements • Evaluate whether the change value (threshold) of the measurement index has clinical significance Significance, including the smallest clinically meaningful difference between groups and individual-level change thresholds, etc. • Patient preference information indicates patient preferences for benefit
risks and risks risk management	Integrate assessment results from clinical outcome assessments, patient preference information and their It incorporates patient experience data into risk assessments • Evaluate the safety and efficacy of drugs based on clinical outcome assessment endpoints Tolerance • Assess the severity and frequency of safety incidents

	bed meaning • Understand patient knowledge of risks and patient perceptions of risks Impact on quality of life • If adverse events occur and corresponding management measures are taken, Understand the burden of this risk management measure on patients • Patient preference information provides patient acceptance of risk
Uncertainty Benefit-Wind risk assessment Influence	For uncertainty, patient preference information may prompt patients to Overall tendency of benefit-risk assessment
Benefit-Risk Conclusion	

(2) Key considerations in using patient experience data for benefit-risk assessment

In a benefit-risk assessment, patient experience data can be a series of:

Metrics provide useful information. For example, the natural history of a disease, its main

The impact of symptoms, signs and disease on the patient's quality of life, the patient's response to treatment

experience or perspectives on unmet needs, patient-reported effectiveness or safety results

situation, patients' preferences for treatment options or outcome indicators, etc. (see Table 1 for details). according to

Purpose of data collection, data type and data quality, appropriateness of patient experience data

The scope and functions are different.

1. Treatment background

Patient experience data can provide insights into the impact of disease and available treatments

experiential perspective. For example, patient experience data can help provide a clearer understanding of disease Impact on patients, which symptoms and signs patients are most concerned about and troubled by, most affect the quality of life. Patient experience data can also help understand currently available treatments how well the treatment meets the medical needs of the patient population, as well as the patient's response to the new Level of demand for the therapy, including effectiveness, safety, tolerability, convenience, Accessibility etc.

There are no evaluation indicators of pathogenesis, clinical symptoms and/or clinical benefit. A well-understood disease, patient experience data can also help to gain a deeper understanding of the disease natural history. For example, some rare diseases have low incidence rates, complex phenotypes, and lack of Effective therapeutic drugs, clinical trial design for drug development and drug effectiveness and Safety assessment poses significant challenges. Patients' experiences and perspectives can inform disease development development, disease severity, effectiveness and safety of treatment, prognosis, etc. Assessment provides important reference.

2.Clinical benefits

Clinical benefit requires attention to the clinical relevance and compliance of its effectiveness indicators. Patient needs, whether the degree of benefit is clinically significant, etc., patient physical examination data can To provide information on patient perspectives and preferences for assessment of clinical benefit.

2.1 Degree of clinical relevance of effectiveness results

Descriptions of clinical benefit often include effectiveness (e.g., survival, clinically important Changes in outcomes, reduction in symptoms and signs, improvement in function, improvement in quality of life goodness), effect strength and uncertainty, distribution of treatment effects in the population, Duration of efficacy, etc. For the selection of effectiveness indicators, it is recommended to base on the current

Based on the understanding of the disease and the patient experience data obtained, determine the trial endpoints and
The clinical relevance of the measurement, i.e. whether it is of most concern to patients or has an impact on patients
The largest clinical measure, or whether the measure predicts clinical benefit.

For those with direct or relatively direct measures of clinical benefit (e.g., symptoms and signs)
clinical trials with the research endpoints of alleviation, improvement of function, and improvement of quality of life).
For testing, clinical outcome assessment endpoints can be selected. If the endpoint is a primary or critical
For secondary endpoints, the basis for selection should be fully explained and clinical outcome assessment data should be provided.
Data collection methods, measurement performance (such as reliability, validity), detailed data analysis
and interpretation of results.

In addition to clinical benefits, other benefits (such as medication convenience, compliance
gender, etc.) may also affect patient preferences and should play an appropriate role in the benefit-risk assessment.
The right weight.

2.2 Clinical significance of benefit

It is necessary to assess whether the degree of clinical benefit is clinically significant, which is why
Patient-centered benefit-risk assessment is one of the important considerations.

Based on minimally clinically significant differences
important difference (MCID) or minimum meaningful difference (MCID)
important difference (MID) to set a clinically valuable benefit threshold,
Represents the minimal improvement that the patient considers valuable. When determining the MCID, one should
Set based on patient experience data, and refer to relevant guidelines and expert consensus.
and other recognized standards, and communicate with review agencies in a timely manner to reach consensus.

When groups show meaningful differences, it does not mean that individuals gain meaningful

clinical benefit. A clinically meaningful preset can be considered based on MCID/MID
The indicator change threshold within the patient (clinically meaningful within-patient change) is used to judge whether
the patient has achieved the treatment goal.
This value can be used as supporting evidence of evaluation benefit.

3. Acceptability of security risks

It is necessary to pay attention to patients' feelings and experiences when evaluating drug safety, such as
For example, some patients may experience mild adverse reactions during medication.
However, long-term medication may also have a significant impact on their quality of life.

When judging drug risks, the severity and occurrence of adverse reactions should be considered
Characteristics such as frequency and reversibility, and patient compliance with medications following adverse reactions
The impact and potential consequences of sex. Patient experience data can be the safety outcomes themselves
(i.e., safety endpoints based on clinical outcome assessment) and may also serve as additional support
evidence, such as risk awareness (does the patient understand each type of risk and
the severity and likelihood of the risk occurring), clinical importance (the patient's perception
Which risk has the greatest impact on quality of life), tolerance of adverse effects,
Acceptability of risk management measures and their impact on patients
The burden of success, etc.

Patient preference data provide information on patient risk acceptance based on
The likelihood of clinical benefit, and whether patients are willing to accept both predictable and unknown risks
risk. For example, whether patients are willing to accept potential risks for possible benefits;
For some patients with chronic diseases, the patients have adapted to the disease and its impact on daily life.
impact on survival, existing treatments can stabilize the condition, while new treatments can, in contrast,

They may expect greater benefits but are unwilling to take higher risks.

4. Benefit-Risk Assessment

When a drug has clear clinical benefit, a good safety profile, and has not yet been discovered

When there are serious safety risks, it can be judged that the benefits outweigh the risks.

When a drug has clear clinical benefits but has safety risks, it needs to be authorized

Balance the benefit-risk ratio and consider whether risks can be controlled through reasonable risk management measures.

risk.

When the drug has potential serious safety risks (such as life-threatening, etc.) and/

or when the possible benefits are limited, or when there is uncertainty, the benefit-risk assessment will

Challenging. In this case, a fit-for-purpose and reliable patient experience

Data will be helpful in assessing drug benefits-risks.

The benefit-risk assessment for the entire population is based on the totality of clinical trial subjects

evaluation; and subgroup evaluation is an evaluation of some patient subgroups. when the whole benefits

- Inconsistencies between risk assessment and subgroup assessment need to be carefully weighed from

Supporting data in both parts may also incorporate the patient's perspective. For example, after evaluating

When the expected risks of a drug outweigh the benefits for the overall indication population, if the patient

Experimental data can help identify subgroups with good benefit-risk ratios, then

In subsequent research and development, studies will be carried out using this population as test subjects to prove that the drug is

Does it have a favorable benefit-risk ratio in this population?

(3) Consideration of the entire drug life cycle

1. Pre-market R&D stage

The collection and application of patient experience data is a cumulative process. clinical prescription

During the development process, patient experience data is continuously accumulated to guide broader acquisition
Benefit-risk assessment to support drug development continuation/termination decisions.

The patient experience data collected in the early stages are mostly qualitative data, which can benefit
-Information provided for risk assessment and drug development decisions including identification of unmet risks
bed needs, identifying target patient groups, determining key elements of trial design, etc.
For example, patient experience data collected early in clinical development can be
methods or analyze patient health data to understand the natural history of diseases,
clinical practice preferences, differences in patient subgroups, etc., to identify unmet patient needs.
identify target patient groups based on patient needs.

With the continuous accumulation of patient experience data, the later use of patient experience
The scope of data is gradually focused and the methods are gradually quantitative. For example, developing quantitative
Clinical outcome assessment tools to more directly measure the clinical outcomes of greatest concern to patients
bureau, and validate the clinical relevance of the tool and determine clinically meaningful change thresholds
value; quantitative patient preference information can be collected to determine patients' use of medications
willingness, quantifying risk acceptance and basing drug decisions on clinical and patient preference evidence
Conduct a benefit-risk assessment. This later collection of quantitative patient experience data information can
Serve as direct evidence or supplementary information for clinical efficacy and safety data to support
Dynamically assess benefits-risks. When faced with major development decisions, it is necessary to communicate with the review agency
During discussions, the collection and application of patient experience data can also be used as a basis for communication with review agencies.
One of the important contents of communication.

2. Post-marketing use stage

During the period of post-marketing use of drugs, new information (including

patient experience data), and continuously assess the benefit-risk status of medicines, such as the discovery of new risks, decide whether to take corresponding regulatory measures, including modifying the risk management plan plans, increase post-marketing research requirements, change instructions or withdraw from the market, etc., in order to treat the disease maximize the benefits and minimize the risks. Encourage post-market collection of more patients Experience data, which may be used by a sponsor in response to specific post-marketing requests Collected for a purpose or on a voluntary basis by sponsors, investigators or patient organizations Various studies initiated (such as interviews, questionnaire surveys, patient preference studies, etc.) And collect. These patient experience data can truly inform patients, doctors and nurses personnel and relevant personnel to communicate and reflect patients' experiences and feelings regarding drug use, It may also provide new evidence for the dynamic assessment of benefit-risk.

5. Communication

When sponsors plan to collect and utilize patient experience data as a benefit-risk As part of the evaluation, early consultation with the review body at the design stage of such studies is encouraged. Communicate regularly to obtain information on whether the research design, data collection and supervision meet the requirements. Ask for timely feedback.

When a sponsor plans to use a PRO or other COA for a confirmatory study When determining the primary or key secondary endpoints, timely communication should be made with the review agency. In addition, in During the clinical trial, if changes to the PRO or other COA result in clinical If any major adjustments are made to the test plan, timely communication should be communicated with the review agency. For details, see "Measures for Communication and Exchange of Drug Research and Development and Technical Review" "Patient Reported Outcomes in Drug Development" Guiding Principles for Application in Clinical Research of Drugs (Trial)" "Patient-centered Clinical Trial Design Guidelines" and other related guiding principles.

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