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Application Status and Practical Analysis of Surrogate Endpoints in Clinical Trial Design for Orphan Drugs

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ABSTRACT

Rare diseases are characterized by high heterogeneity, small patient populations and wide geographic dispersion. Clinical trials of orphan drugs generally face problems such as recruitment difficulties, long follow-up, and difficulty in evaluating traditional endpoints. Surrogate endpoints can indirectly predict clinical benefits and have become an important research tool for the design of clinical trials for rare disease drugs. This article refers to the accelerated approval rules of the US FDA, the conditional marketing authorization system of the EU EMA, and the relevant guidelines for clinical research and development of rare disease drugs in China. It systematically sorts out the regulatory norms and application system of surrogate endpoints, analyzes their implementation points, practical shortcomings, and potential safety risks in clinical trial design. Research has found that surrogate endpoints can effectively break through the experimental bottleneck of orphan drug development, but there are still many problems in indicator validation standards, practical application, and risk management. Based on the current situation of domestic research and development, this paper proposes targeted optimization strategies to provide practical references for the design of orphan drug trials, regulatory review, and clinical research in China. These strategies can not only accelerate the market entry of orphan drugs, but also keep clinical medication safety as a top priority.

KEYWORDS

Orphan Drugs; Rare Diseases; Clinical Trials; Surrogate Endpoints; Conditional Approval; Biomarkers

1. INTRODUCTION

Rare diseases have both genetic and clinical heterogeneity. The international Orphanet database has included over 6500 related diseases, and the academic community generally estimates a global total of over 7,000 [1]. Rare diseases affect a large population, with approximately 20 million rare disease patients in China and an average of over 200000 new confirmed cases per year. From the perspective of the global diagnosis and treatment pattern, only about 5% of rare diseases have standardized treatment plans, and the vast majority of diseases still lack effective intervention methods, leaving a long-standing unmet clinical need.

In recent years, with the gradual implementation of China's orphan drug special support policies, the pace of rare disease drug research and development has continued to accelerate. However, the clinical trial process is still constrained by the characteristics of the disease itself, presenting numerous inherent challenges. Conventional clinical trials often use hard clinical endpoints such as overall survival and long-term functional prognosis as the core of efficacy evaluation. These indicators not only have a long observation and follow-up period, but also rely on a large sample of subjects to

support them, making it difficult to adapt to the reality of scarce rare disease populations and complex disease subtype lineages [2].

Given this backdrop, surrogate endpoints rely on intermediate observation indicators such as pathological and physiological indications, specific biomarkers, and clinical functional scores, which can effectively compress the trial period, alleviate the problem of small sample inclusion, and highly adapt to the development scenarios of orphan drugs. The current US FDA accelerated approval, EU EMA conditional marketing authorization, and domestic NMPA conditional review system have all included surrogate endpoints as compliance evaluation criteria for new drug launches. However, in practical applications, surrogate endpoints still face challenges such as inconsistent validation criteria, insufficient matching between indicators and real clinical benefits, and slow progress in post-market confirmation research. Therefore, this article focuses on clinical trials of orphan drugs, systematically analyzes the application status, design points, and practical pain points of surrogate endpoints, proposes optimization directions, and provides academic reference and practical support for the standardized construction of rare disease clinical trials in China.

2. REGULATORY FRAMEWORK AND CURRENT APPLICATION STATUS OF SURROGATE ENDPOINTS IN CLINICAL TRIALS OF ORPHAN DRUGS

Regulatory bodies worldwide have built tailored review systems for surrogate endpoints in orphan drug trials based on the unique characteristics of orphan drug research and development. The policy design always adheres to the same core idea: while expanding access to therapies for rare disease patients, ensuring stringent full-cycle drug safety risk control [3].

The US FDA relies on the Orphan Drug Act and accelerated approval mechanism, and provided that a surrogate endpoint is supported by robust pathological and clinical evidence, it can be used as the core evaluation basis for new drug marketing. To avoid bias in evaluation results, regulatory authorities have explicitly imposed hard constraints, requiring that after new drugs are approved for market, confirmatory clinical trials must be conducted to effectively verify the intrinsic relationship between surrogate endpoints and actual treatment benefits for patients.

The EU EMA adopts a more flexible conditional marketing authorization model, which appropriately relaxes the stringent thresholds for pre-approval validation of surrogate endpoints for rare diseases for which there is currently no effective treatment plan in clinical practice, and allows for evaluation based on mid-term clinical data. Subsequently, a complete clinical evidence chain will be supplemented through long-term safety monitoring and secondary evaluation of efficacy after listing.

The guidelines for the development of rare disease drugs issued by the National Medical Products Administration of China clearly define the applicable boundaries of conditional approval, recognize surrogate endpoints with clear pathological mechanisms and stable and controllable detection methods for clinical trial design, and provide detailed regulations for conducting real-world research and confirmatory trials after market launch.

From the perspective of actual research and development scenarios, surrogate endpoints are mostly applied in the three major fields of genetic metabolic diseases, rare neuromuscular diseases, and rare tumors, effectively alleviating the practical problems of small sample sizes and long cycles in clinical trials of orphan drugs. Throughout the global market achievements, multiple classic orphan drugs have been approved using functional scale scores and changes in core biomarkers as surrogate endpoints. The therapeutic drugs for diseases such as spinal muscular atrophy and phenylketonuria rely on metabolic indicators and motor function scores in the body to complete clinical evaluation, and subsequent clinical practice has fully confirmed the practical value of such indicators [4]. Compared to generic drugs and chronic disease drugs, orphan drug development is more dependent on surrogate endpoints due to the clinical characteristics of rare diseases. This is a universal consensus

in global orphan drug development and regulation. Although regulatory models vary among countries, the core principles are highly consistent.

3. VERIFICATION METHODS AND EVIDENCE STANDARDS FOR SURROGATE ENDPOINTS

According to FDA regulations and internationally recognized standards, surrogate endpoints are divided into two categories: validated and reasonably possible, with significant differences in evidence requirements and evaluation rules between the two. Verified surrogate endpoints require multiple layers of evidence support, not only to maintain stable associations with core clinical indicators such as overall survival and quality of life scores, but also to clearly reflect the drug's pathway of action. The improvement effect of indicators can be directly translated into long-term clinical benefits for patients, and can serve as a direct basis for routine drug marketing approval. Reasonably likely surrogate endpoints are often used in the development of rare diseases for which there is currently no mature validation system. They rely on disease pathogenesis and small sample clinical observation data as support, and are also the most commonly used indicator types in orphan drug development, often used to accelerate approval pathways. After the drug is launched, it needs to continue to complete confirmatory trials.

Surrogate endpoint validation focuses on three core dimensions. Combining the pathogenesis of rare diseases, clarifying the role of biomarkers and functional indicators in disease progression, and determining the direct correlation between indicator changes and disease improvement, is the most fundamental pathological mechanism verification [5]. By analyzing the correlation between surrogate indicators and patients' quality of life and organ dysfunction using real data from previous clinical cohorts and rare disease registration databases, the clinical relevance is verified. Based on randomized controlled trials or single-arm trial data, verify whether the improvement of surrogate indicators under drug intervention can be translated into actual clinical benefits. The FDA's rare disease evidence principle also allows for the approval of single group high-quality studies with supporting evidence in special circumstances.

Global drug regulatory agencies have adopted differentiated evaluation methods for surrogate endpoints of orphan drugs. Compared with the strict long-term validation requirements for large samples of ordinary drugs, orphan drugs can build an evidence chain through pathological mechanism research, small sample clinical trials, and rare disease registration data, without the need to apply the validation mode of conventional drugs. The differential evaluation of orphan drugs is not about relaxing the safety bottom line, but about balancing the difficulty of research and development with the scientificity of evaluation through multidimensional evidence cross validation [6]. EMA requires the completion of the evidence chain through post-market monitoring, and the relevant guidelines issued by China's NMPA also provide clear regulations for post-market real-world research and confirmatory testing.

4. DESIGN POINTS OF SURROGATE ENDPOINTS IN CLINICAL TRIALS OF ORPHAN DRUGS

The selection of surrogate endpoints for orphan drug clinical trials must meet four basic conditions. The indicators should be related to the actual clinical needs, the test results should be stable, the inter-group data differentiation effect should be obvious, and the research mode of small-sample rare disease should be adapted. The screening criteria should closely focus on the clinical benefits of patients and avoid biochemical indicators that have no practical diagnostic and therapeutic significance; The detection method should be standardized, have good repeatability, and reduce cross-center errors. The selected surrogate endpoints should have sufficient sensitivity to distinguish between drug intervention effects, natural disease development trends, and fluctuations in indicators

caused by placebo, and be suitable for the basic characteristics of small sample studies in rare disease clinical trials [7].

When designing the overall clinical trial plan for orphan drugs, the characteristics of surrogate endpoints can be combined to optimize the core aspects of the trial. The limited population of rare disease patients makes it difficult to conduct large-scale randomized controlled trials. In clinical practice, small sample randomized trials or single-arm trials are mostly designed. Relying on surrogate endpoints can effectively shorten the observation duration of the trial and reduce the probability of participants dropping out midway during long-term follow-up [8]. The control group setting can be flexibly adjusted according to actual conditions, and placebo control should be given priority when it meets ethical standards. Some diseases cannot achieve placebo blinding. Researchers can refer to historical clinical data or use external real-world studies as reference standards. The follow-up duration can be flexibly set according to the effective law of surrogate endpoints, without following the traditional clinical endpoint observation cycle of several years, effectively reducing the overall development time of new drugs.

Clinical trials of orphan drugs commonly suffer from problems such as small sample sizes and uneven data distribution. Conventional statistical models adapted to large sample studies are difficult to adapt to such experimental scenarios. In the actual research process, adaptive experimental design and rank sum class analysis methods are often used to improve the statistical power of small-sample data. Integrating multiple related surrogate indicators to build a composite endpoint can compensate for the shortcomings of single endpoint evaluation, more comprehensively reflect the overall therapeutic effect of drugs, and is also a commonly used optimization method in the clinical trial design of orphan drugs.

5. CHALLENGES AND RISKS IN SURROGATE ENDPOINT APPLICATIONS

There are still many practical issues and potential risks associated with using surrogate endpoints in orphan drug clinical trials. Some biochemical surrogate endpoints only reflect localized pathological changes caused by drug intervention, making it difficult to connect with core clinical benefits such as long-term survival and quality of life for patients. Drugs approved for market based on such indicators often fail to meet clinical treatment expectations and may face revisions and adjustments in subsequent review conclusions [9].

Rare disease genetic heterogeneity can also skew evaluation results. Most rare diseases exhibit significant genetic heterogeneity and give rise to multiple clinical subtypes. When the same set of surrogate endpoint evaluation criteria is applied to patient populations with different gene mutation subtypes and different age groups of onset, the actual evaluation effectiveness varies greatly, which can easily lead to systematic bias in clinical trial results.

The regulatory loop after listing also has obvious shortcomings. Orphan drugs that obtain conditional marketing qualifications based on surrogate endpoints are generally required by the industry to undergo confirmatory trials or real-world research after being marketed. The geographical distribution of rare disease patients is scattered, and the recruitment of subjects is difficult. The overall research cycle is lengthy, and many drugs are difficult to complete subsequent verification within the prescribed time limit, making it difficult for the review and supervision to form a complete closed loop.

Relaxing the evaluation criteria for surrogate endpoints can enable rare disease patients to use new drugs more quickly and effectively improve patient access to medication. Short term detection indicators are difficult to cover long-term adverse reactions of drugs, and cannot accurately predict the long-term prognosis of patients, which also poses safety risks to clinical medication.

The global mainstream drug regulatory agencies have not unified the validation standards and evidence grading standards for surrogate endpoints, and the differences in evaluation scales across regions have invisibly increased the time and economic costs for pharmaceutical companies to conduct cross-border research and development and cross-border applications. There is still a lack of a unified national rare disease registry in China, and there is insufficient accumulation of surrogate endpoint historical data [10]. Small sample experiments have inherent statistical randomness, and favorable Phase II results often fail to be replicated in subsequent trials, introducing substantial uncertainty into development and regulatory review.

6. STRATEGIES AND FUTURE PROSPECTS FOR OPTIMIZING SURROGATE ENDPOINT APPLICATIONS

We can first refine the validation system from a scientific standpoint to address surrogate endpoint challenges. Referring to the relevant regulations on rare disease research and development issued by mainstream global drug regulatory agencies, and combining with the characteristics of rare diseases in China, develop a surrogate endpoint assessment framework tailored to domestic rare disease profiles. Unified criteria for indicator screening, mechanism validation, and clinical association analysis, relying on multi-omics technologies such as genomics and metabolomics, combined with existing data from the national rare disease registration system, to develop more specific composite surrogate endpoints. Replacing traditional single biochemical and functional testing indicators with such comprehensive indicators can significantly improve evaluation accuracy and adapt to the evaluation needs of different rare disease subtypes. It can also refer to the FDA official list to distinguish between available and discontinued indicators.

At the regulatory and industry implementation levels, it is necessary to strengthen cross-institutional collaboration and establish channels for sharing various research data [11]. Domestic drug regulatory authorities can refer to the mature model of FDA accelerated approval and EMA conditional marketing to establish a publicly available rare disease surrogate endpoint reference database. Integrate endpoint indicators that have been reviewed and verified in the past, providing ready-made references for the design of clinical trial plans for pharmaceutical companies. Fully utilizing domestic rare disease registration platforms and real hospital diagnosis and treatment data, incorporating real-world evidence into surrogate endpoint validation and post-market research processes, effectively addressing industry pain points such as insufficient evidence from small sample trials and recruitment difficulties after market launch. FDA related research and development principles also recognize the value of real-world data in rare disease drug development [12].

With the continuous accumulation of clinical research data and iterative analysis techniques, the application of surrogate endpoints will gradually move towards standardization and refinement. The concept of focusing on the actual benefits of patients will gradually be integrated into the entire process of endpoint screening. As long as the experimental design is standardized, industry validation standards are unified, and real-world data is fully utilized in the future, the application risks of surrogate endpoints can be effectively reduced. Let this type of evaluation method serve the clinical research and development of orphan drugs stably, while accelerating the launch of new drugs, firmly uphold the standards of clinical efficacy and patient safety.

7. CONCLUSION

Surrogate endpoints fit the small-sample, short-cycle nature of orphan drug development and are fully integrated into the entire process of clinical trial design and evaluation, serving as a core approach to overcome recruitment barriers and challenges with long-term follow-up in rare disease research. At present, relevant policies and regulations have been introduced in both international and domestic drug regulatory fields, providing institutional support for the implementation of surrogate endpoints.

This evaluation method has also accumulated mature practical experience in the research and development of common diseases such as genetic metabolic diseases, neuromuscular diseases, and rare tumors.

In the actual clinical application process, surrogate endpoints still face many practical obstacles. Some evaluation indicators are difficult to effectively correspond with the true clinical benefits of patients, and the subtype differentiation and genetic heterogeneity of rare diseases themselves can also easily lead to deviations in clinical trial evaluation results. The slow progress of the verification work after the conditional listing of drugs and the differences in the evaluation criteria for surrogate endpoints around the world have invisibly increased the pressure on pharmaceutical companies to apply for research and development. The statistical bias inherent in small sample studies, as well as the long-term medication safety hazards that are difficult to predict in short-term assessments, are key issues we cannot overlook in real-world use.

To fix these problems, standardizing the application of surrogate endpoints can be promoted from three aspects. Develop unified validation standards and evaluation processes based on the characteristics of domestic diseases, improve the evidence system with the help of rare disease registration platforms and real clinical data, improve clinical trial design schemes and statistical analysis methods, and adapt to the actual conditions of small sample studies. The development of the industry needs to adhere to the two core values of clinical value and patient safety, balance the flexibility and scientificity of evaluation work, and better support orphan drug development using surrogate endpoints, in order to promote the standardized application of surrogate endpoints and effectively improve patient access to therapies and the quality of clinical care for rare disease patients in China.

REFERENCES

[1] Nguengang Wakap, S., Lambert, D. M., Olry, A., Rodwell, C., Gueydan, C., Lanneau, V., ... & Rath, A. (2020). Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. European Journal of Human Genetics, 28(2), 165–173. https://doi.org/10.1038/s41431-019-0508-0

[2] Pizzamiglio, C., Vernon, H. J., Hanna, M. G., & Pitceathly, R. D. (2022). Designing clinical trials for rare diseases: unique challenges and opportunities. Nature Reviews Methods Primers, 2(1), 13. https://doi.org/10.1038/s43586-022-00013-9

[3] Ciani, O., Manyara, A. M., Davies, P., Stewart, D., Weir, C. J., Young, A. E., ... & Taylor, R. S. (2023). A framework for the definition and interpretation of the use of surrogate endpoints in interventional trials. EClinicalMedicine, 65. https://doi.org/10.1016/j.eclinm.2023.102292

[4] Waisbren, S. E., Noel, K., Fahrbach, K., Cella, C., Frame, D., Dorenbaum, A., & Levy, H. (2007). Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. Molecular Genetics and Metabolism, 92(1–2), 63–70. https://doi.org/10.1016/j.ymgme.2007.05.002

[5] Burzykowski, T., Molenberghs, G., & Buyse, M. (Eds.). (2005). The evaluation of surrogate endpoints. Springer Science & Business Media. https://doi.org/10.1007/0-387-25145-2

[6] Pease, A. M., Krumholz, H. M., Downing, N. S., Aminawung, J. A., Shah, N. D., & Ross, J. S. (2017). Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review. BMJ, 357. https://doi.org/10.1136/bmj.j2780

[7] Manyara, A. M., Davies, P., Stewart, D., Weir, C. J., Young, A. E., Blazeby, J., ... & Ciani, O. (2024). Reporting of surrogate endpoints in randomised controlled trial protocols (SPIRIT-Surrogate): extension checklist with explanation and elaboration. BMJ, 386. https://doi.org/10.1136/bmj-2023-077335

[8] Gagne, J. J., Thompson, L., O'Keefe, K., & Kesselheim, A. S. (2014). Innovative research methods for studying treatments for rare diseases: methodological review. BMJ, 349. https://doi.org/10.1136/bmj.g6802

[9] Gyawali, B., Rome, B. N., & Kesselheim, A. S. (2021). Regulatory and clinical consequences of negative confirmatory trials of accelerated approval cancer drugs: retrospective observational study. BMJ, 374. https://doi.org/10.1136/bmj.n1659

[10] Ioannidis, J. P. (2005). Why most published research findings are false. PLOS Medicine, 2(8), e124. https://doi.org/10.1371/journal.pmed.0020124

[11] Sun, W., Zheng, W., & Simeonov, A. (2017). Drug discovery and development for rare genetic disorders. American Journal of Medical Genetics Part A, 173(9), 2307–2322. https://doi.org/10.1002/ajmg.a.38325

[12] Rupp, T., & Zuckerman, D. (2017). Quality of life, overall survival, and costs of cancer drugs approved based on surrogate endpoints. JAMA Internal Medicine, 177(2), 276–277. https://doi.org/10.1001/jamainternmed.2016.7627