Utilizing Innovative Statistical Methods and Trial Designs in Rare Disease Settings

Discussion Guide

Background

Rare diseases are a complex and diverse set of conditions which, when taken together, affect an estimated 30 million Americans, or 10% of the population. A disease is defined as rare when fewer than 200,000 people in the U.S. are living with the diagnosis at any given time, and it is estimated that 7,000 such diseases exist. Over 80% of rare diseases are genetic, clinically progressive, and life-limiting or life-threatening.

The history of drug development for these diseases has been a story of steadily increasing, if not widespread, success. Relatively few medical products to treat rare diseases were developed and approved in the middle decades of the 20th century, owing largely to the inherent challenges related to incomplete scientific knowledge, difficult clinical studies given small population sizes, and few economic incentives for pharmaceutical companies to enter limited rare disease markets.

Pressure from patient and advocacy groups led Congress to address a number of these challenges in 1983’s Orphan Drug Act. The legislation initially provided three potential incentives for drug companies to develop products for rare diseases: 1) federal funding through a grant program to perform clinical trials of orphan products; 2) a tax credit for 50% of clinical testing costs; and 3) eligibility for marketing exclusivity of seven years from the date of approval; and later 4) waiver of marketing application user fee.

Orphan drug submissions and approvals began to climb steadily, resulting in over 500 orphan drugs and biologics approved to date by the U.S. Food and Drug Administration (FDA). A recent analysis of new molecular entity (NME) orphan drugs has shown that more than 50% of these treatments are first-in-class (Figure 1), with a growing focus on rare cancers and metabolic disorders.

![Figure 1: Number of orphan new molecular entities (NMEs) approved, by year and innovation category (Source: Health Affairs)]
Moreover, orphan NMEs appear to be more innovative than non-orphan products, as they account for 40% of first-in-class approvals between 1983 and 2014 but only 25% of all NMEs approved during the same period. In 2015, nearly half (47%) of all novel new approved drugs received an orphan designation. Many of the drugs approved over this time period, such as Adcetris for a rare type of Non-Hodgkin’s lymphoma or Kalydeco in cystic fibrosis, have been transformational products that improve the length and quality of life for patients who until recently had few options.

Despite this progress, only five percent of rare diseases have an approved treatment, and continued advocacy from patient and research organizations has encouraged industry, regulators, and policy-makers to identify new opportunities for improving the science and process of drug development for rare disease populations. Congress, for example, has put forward a number of proposals that could enable more nimble drug development: the 21st Century Cures Act, passed by the House of Representatives in June 2015, would promote use of modern trial designs, real-world evidence, and innovative analysis techniques such as Bayesian statistics.

At the same time, industry and FDA have advanced user fee commitment goals that would allow for greater flexibility in studying and reviewing drugs by leveraging innovative biomarkers and considering non-traditional clinical development programs. The draft commitments for reauthorizing the Prescription Drug User Fee Act (PDUFA) specifically create pilot programs to foster the development and use of innovative clinical trial designs and model-informed drug development (MIDD) approaches. These proposals could have meaningful impact on the development of rare disease treatments at a time of increasing public attention on patient populations with severe unmet need.

In order to support the goal of expediting the development and review of novel drugs intended to address unmet medical needs, the Duke-Margolis Center for Health Policy, under a cooperative agreement with the FDA, is convening an expert workshop to advance the discussion around innovative trial designs, methods, and statistical tools for rare disease drug development. Specifically, the objectives for this workshop are to: 1) identify promising statistical methods and trial designs for rare disease drug development, 2) discuss challenges in the use of these approaches in small patient populations, 3) tackle issues related to regulatory acceptability, and 4) lay out practical next steps for advancing the development and use of these tools. Workshop discussion will be used to inform potential papers and additional convening on this topic.

**Challenges in Rare Disease Drug Development**

While rare disease drug development presents common challenges that occur with more prevalent conditions, the most prominent statistical challenge is that small (less than a prevalence of 200,000 in the United States) and very small (prevalence of fewer than 1,000 in the United States) affected populations may restrict trial design and preclude replication and use of traditional statistical approaches. Historically, the median disease prevalence for orphan designated drugs in the US is around 39,000 patients.
Other unique challenges in this space include:

- Geographically dispersed disease-affected populations and limited numbers of clinical research centers, which hinder clinical trial participation by patients and caretakers

- Phenotypic diversity within such small populations due to inter-patient variability and intra-patient diurnal/weekly variability, which must be addressed through carefully developed trial endpoints and study designs

- A lack of well-developed and validated trial endpoints, outcome measures, and biomarkers or surrogate endpoints

- Limited availability of contemporaneous, disease-specific, natural history information that could serve as a source for external control data

- No precedent for drug development for a specific disease

- Unanticipated or unaddressed ethical considerations for children participating in pediatric clinical trials, which are governed by additional regulatory requirements (21CFR50 Subpart D) and may only proceed if they do not involve greater than minimal risk or, if there is greater than minimal risk, there is the prospect of direct benefit to individual research subjects.

The most expeditious approach to these challenges is to identify them as early as possible in the drug development process. With this knowledge, scientifically based plans for data acquisition can be formulated; discussed with regulators, academic investigators, corporate sponsors, patients, and caretakers; and implemented. This approach may have a favorable effect on both the drug development process and time to approval.

**Regulatory Perspectives on Novel Development Approaches**

The level of evidence presented in rare disease submissions varies significantly. Based on the submission data collected in the Center for Drug Evaluation and Research (CDER) from late 2007 to early 2016, while more than 60% contain one adequate and well controlled clinical study and about 25% have two, many of these studies are either under-powered or tested against a lowered threshold. Furthermore, the quality of control information used for comparison has varied between studies that used a parallel control group, a historical control group, or simply a derived threshold based on historical information. This is demonstrated by the fact that approximately two-thirds of the submissions have at least one randomized and parallel-group trial and the others have only a single-arm. Half of the submissions have at least one double-blinded trial while the other half consisted of open-label trials only.

The regulatory acceptability of these types of designs is largely established through a draft guidance document that currently outlines the agency’s views on drug and biological products intended to treat or prevent rare diseases. This draft guidance, *Rare Diseases: Common Issues in Drug Development*, addresses important aspects including:*xv*
• Adequate description and understanding of the disease’s natural history: This may include outcome measures selection and biomarker development or refinement.

• Adequate understanding of the pathophysiology of the disease and the drug’s proposed mechanism of action: This understanding may be useful in the design of study endpoints, timing of dosing, and identification or refinement of biomarkers.

• Nonclinical pharmacotoxicology considerations to support the proposed clinical investigation or investigations: Prior to initiating human studies, FDA requires toxicology information from both in vitro and animal studies. For drugs to treat serious and life-threatening disorders, FDA may apply flexibility in the evaluation of nonclinical development programs.

• Reliable endpoints and outcome assessment: Well-characterized efficacy endpoints appropriate for a rare disease may not be available. The characteristics of selected assessment tools should be evaluated for validity, reliability, feasibility, resistance to bias, ability to detect change, relationship to meaningful symptoms or function and clinical interpretability.xvi

• Standard of evidence to establish safety and effectiveness: The substantial evidence required for approval is based on adequate and well-controlled trials (21 CFR 314.126). The number of study subjects to be enrolled in a clinical trial is determined on a case-by-case basis. The prevalence of the disorder is one factor used to make this determination. In addressing the benefit and risk of a candidate drug, FDA recognizes that greater risks may be acceptable to study participants for a treatment that may offer advantage(s) over available therapy, especially when patients have unmet medical needs.

• Drug manufacturing considerations during drug development: Developmental plans for drug manufacturing and associated product quality issues should be discussed with FDA early and throughout the drug development process.

**Promising Tools for Improving Rare Disease Drug Development**

Challenges in rare disease clinical development provide an opportunity to discuss innovative trial designs and data analysis methods. For trial design, careful attention should be paid to endpoint selection, which can be especially difficult for rare diseases about which there is a lack of knowledge of disease progression. The endpoints for the clinical trial should be both feasible and clinically meaningful, and trial designs should be suitable for the endpoints selected.

The limited patient numbers in rare diseases make the size of most trials necessarily small, and that in turn restricts the usage of some forms of inferential statistics (i.e., methods that rely on large sample approximations for their performance). With the usual requirements for significance level and study power, small population trials employing a conventional design may only be able to detect very large treatment effects. It is therefore often required to practice flexibility in establishing evidence of
effectiveness in rare diseases, and there are many ways to accomplish this. In the past, FDA has considered the following as providing substantial evidence of effectiveness in rare disease settings: 1) a single pivotal trial in conjunction with supporting evidence; 2) a single-arm, non-randomized, open-label trial design; and 3) relaxing the significance level for hypothesis testing (e.g., from a two-sided to a one-sided α of 0.05). These approaches have been shown to be feasible in some settings, but there are consequences to their use, and other options for providing substantial evidence are very much of interest.

Trial designs that incorporate external data from other sources may offer advantages in the rare disease setting, and for many rare diseases, patient or disease registries are available. Whether the data from such a registry are of sufficient quality and completeness, however, may be a challenge. Patient-level data with sufficient detail on the variables of interest may not be available on the registry or the data may not be of the quality FDA usually requires. The coverage of the registry may be lacking, the group of patients included may have a different disease status, or their diagnoses may not be able to be verified. The standards of care represented on a registry may vary significantly for a rare disease, especially if the registry spans a long time period. And when these various challenges in the data source itself can be overcome, we are often lacking agreement on how or with what statistical approaches the external data can be best utilized to demonstrate efficacy or safety.

Two good examples of challenging but successful rare disease development programs are provided by the programs for Myozyme and Fabrazyme, enzyme replacement therapies for Pompe and Fabry disease, respectively. For Pompe disease, a natural history database was used as a control group in evaluating the long-term efficacy of Myozyme for the infantile patient population. For Fabry disease, data analysis of a clinical outcome trial conducted under a post-marketing commitment for Fabrazyme supported a conclusion of efficacy.

For trials with small sample sizes, standard statistical methods that rely on large-sample approximations to establish their operating characteristics (e.g., Type I error probabilities) do not necessarily apply, thus making the results and conclusions of the analysis difficult to interpret. Also, modern trials of rare diseases often involve multiple patient subgroups, such as gene-mutation subgroups, with subgroup sample sizes even smaller. In situations like this, Bayesian analysis methods may be appropriate, as they allow for borrowing of information from homogeneous subgroups while discounting the information from heterogeneous subgroups, regardless of subgroup sample sizes. In addition, when there is historical information available (e.g., through historical control groups, early phase trials, or some observational studies), Bayesian methods naturally lend themselves to incorporating the historical information through the Bayes Theorem, in a way that some of the historical data that are obsolete or less useful can be down-weighted.

Recently, FDA has received several promising trial proposals for rare disease programs. They include platform trials and master protocols in which control patients are shared among trials; various Bayesian analysis models; and sophisticated trial designs, such as n-of-1 designs. The acceptance of these proposals may be specific for the disease and treatment; however, one should note that the traditional statistical paradigm is being challenged by these designs. For example, under a Bayesian framework, Type I error probabilities are difficult to define given that the null hypothesis space is multi-dimensional and not just a single null value. Consequently, computer simulations are usually
required to determine the operating characteristics (Type I error probability and power) of the design analysis approach. The general acceptance of this paradigm shift from both the regulatory agency and the public is slowly progressing, albeit promising.

It is important to gain general understanding of the use of Bayesian models, simulation results, and adaptive designs in the rare disease setting. The goal of adopting these or other innovative approaches is to provide accurate analysis results in small samples that are interpretable and can inform regulatory decisions.

Workshop Discussion and Next Steps

In order to further the multi-stakeholder dialogue around innovative approaches to developing rare disease medical products, this expert workshop has been designed as a set of connected open discussions.

First, speakers from FDA will provide an overview of the Agency’s approach to reviewing rare disease drug applications, highlight areas in which they are hopeful that collaborative progress can be made, and outline questions for consideration during the rest of the day-long roundtable. Experts from FDA and industry will provide framing presentations covering recent experiences with rare disease drug development and regulatory review, recurrent challenges within and across development programs, and potential models for success. The morning’s opening session will be capped by an open conversation in which all participants can share additional challenges and questions that need to be tackled within this space.

The day’s second main session will cover challenges specific to designing studies that utilize registry or historical data. An introductory presentation will outline a number of topics for group discussion. Among these will be variability and potential confusion surrounding types of historical controls, ambiguity or inconsistency in regulatory guidance related to controls, and the utility and pitfalls of harnessing registries in order to make maximum use of patients and their data.

A third session will be dedicated to the use of Bayesian statistical methods in designing a rare disease clinical trial. The primary presentation will highlight a platform study for rare subsets of Alzheimer’s disease as a case study for further discussion. The final session will allow for wide-ranging synthesis of the workshop’s key takeaways and a chance for participants to help outline next steps.

Throughout, participants should consider a number of key questions that may help refine continued work on innovative approaches to rare disease drug development:

- What are the current gaps in methods, infrastructure, data collection, and statistical capabilities that need to be addressed?
- Are there priority areas where – due to disease burden, emerging knowledge of underlying disease pathways, or mobilized patient populations – momentum can be built and maintained for exploring promising approaches?
• How might FDA be able to collaborate with sponsors and other stakeholders to increase clarity around rare disease regulatory review? How might sponsors engage FDA at earlier points in a drug development program to discuss design and methods?

• What opportunities exist under the outlined PDUFA VI commitment goals to advance novel designs and approaches? Are there targeted research opportunities or specific therapeutic areas that in which pilots may be immediately feasible under the PDUFA VI rubric?

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3 FAQs About Rare Diseases | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program. (n.d.). Retrieved September 19, 2016, from https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases
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