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Commentary

Neurocognitive clinical outcome assessments for inborn errors of metabolism and other rare conditions

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ABSTRACT

Well-defined and reliable clinical outcome assessments are essential for determining whether a drug provides clinically meaningful treatment benefit for patients. In 2015, FDA convened a workshop, "Assessing Neurocognitive Outcomes in Inborn Errors of Metabolism." Topics covered included special challenges of clinical studies of inborn errors of metabolism (IEMs) and other rare diseases; complexities of identifying treatment effects in the context of the dynamic processes of child development and disease progression; and the importance of natural history studies. Clinicians, parents/caregivers, and participants from industry, academia, and government discussed factors to consider when developing measures to assess treatment outcomes, as well as tools and methods that may contribute to standardizing measures. Many issues examined are relevant to the broader field of rare diseases in addition to specifics of IEMs.

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1. Introduction

This article summarizes key points discussed among participants at a workshop convened by the U.S. Food and Drug Administration (FDA) in April 2015 entitled, "Assessing Neurocognitive Outcomes in Inborn Errors of Metabolism." The workshop brought together clinicians, parents/caregivers, and representatives from industry, academia, and government (FDA and National Institutes of Health). Participants presented their perspectives on factors to consider when developing measures to assess clinical outcomes of candidate and approved treatments for diseases resulting from inborn errors of metabolism (IEMs). [Points raised are meant as considerations and should not be interpreted as

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guidance for drug development. Similarly, discussion of particular scales does not constitute FDA endorsement of these scales for trial endpoints.] Full proceedings of the meeting are available online at http://www.fda.gov/downloads/Drugs/NewsEvents/UCM493766.pdf.

2. Challenges of clinical studies of rare diseases

Clinical studies of rare diseases that affect the brain and neurological systems are challenging by their nature. Developing reliable and valid study endpoints can be difficult due to many factors, including small numbers of patients who are often geographically dispersed; heterogeneity of deficits between patients and within individual patients over time; limited clinical data describing signs and symptoms of disease and its progression; and lack of knowledge about the natural history of many rare diseases, especially in regard to neurocognitive outcomes [1]. The FDA convened the workshop to provide a forum for discussing challenges of and methods for measuring such clinical outcomes in individuals affected by IEMs. While the workshop focused on IEMs, the cases and approaches presented may also be relevant to the assessment of cognitive function in other diseases. This article summarizes meeting presentations and discussions about opportunities for working with FDA to establish well-defined and reliable clinical outcome assessments (COAs); the role of natural history studies in identifying disease and treatment effects; the value of stakeholder collaboration in using and improving neurocognitive assessment tools; lessons learned from clinical studies of rare diseases; and best practices for assessing cognition and behavior to obtain the most useful and comparable data.

3. Establishing clinical neurocognitive outcome assessments for IEMs and other rare diseases

Recent advances in diagnostics and enhanced newborn screening programs have made it possible to identify diseases earlier in life and begin treatment sooner, if treatments are available. Such is the case for many IEMs as well as other rare diseases. Increased understanding of the mechanisms of IEMs has led to development of a substantial number of new treatments. Evaluating outcomes of these treatments, however, requires that researchers distinguish brain changes resulting from treatment effects from those resulting from child development or disease progression (Fig. 1).

3.1. Clinical outcome assessments and drug development: a collaborative process

Clinical outcome assessments are an essential part of drug development – they aid in determining whether a drug provides clinically meaningful treatment benefit(s) to patients. FDA's regulatory standard includes a statement that methods of assessment of subjects' response should be 'well defined and reliable' (21CFR314.126) [2]. In 2009, FDA released Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims [3] to aid instrument developers in meeting this regulatory standard. The Guidance provides details on how to establish a COA instrument's content validity, i.e., the extent to which a COA measures what it purports to measure in a specific context of use. In addition, FDA offers the Clinical Outcome Assessment Qualification Program, which provides specifics on evidence needed and steps to take to qualify COAs for drug development [4]. Stakeholders can work with FDA to evaluate existing measurement tools or develop novel COAs in two ways (described in detail in the full meeting proceedings, http://www.fda.gov/downloads/Drugs/NewsEvents/UCM493766.pdf):

1. Through an individual drug development program (the traditional method); or
2. Through FDA's Center for Drug Evaluation and Research Drug Development Tool Qualification Program, which are designed to produce qualified measures for use across multiple drug development programs.

Although COAs used in clinical trials are not required to be qualified through the COA Drug Development Tool Qualification Program, developing COAs in consultation with FDA can increase the likelihood that the Agency will agree with the content and measurement properties of the COA. In addition, in 2015, FDA issued Guidance for Industry – Critical Path Innovation Meetings [5]. Such meetings, known as CPIMs, are means by which CDER and investigators from industry, academia, patient advocacy groups, and government can communicate to improve efficiency and success in drug development. The goals of CPIMs are to discuss a methodology or technology proposed by the meeting requester and for CDER to provide general advice on how this methodology or technology might enhance drug development.

In many patients with IEMs, measures of cognition, behavior, and activities of daily living may be the factors most relevant to improving symptoms of a disease and thereby have the greatest impact on patients and their families. In addition to direct measurement, parent/caregiver and patient-reported outcomes are essential when developing COAs for diseases resulting from inborn errors of metabolism, and instruments should be developed and validated with these populations. Impact on the functioning of the individual and the family are also important factors to consider when developing COAs for other rare diseases. Reliable and valid measures that are developed through interdisciplinary collaboration and with stakeholder input can lead to better understanding of disease progression and more reliable assessments of treatment efficacy.

4. Natural history studies of rare diseases

Ideally, natural history studies investigate the natural course of a disease from or before inception, through pre-symptomatic, symptomatic, and clinical stages to the point of cure, chronic disease, or death [6]. They are valuable tools for improving understanding of a disease, establishing clinical outcome assessments that aid in identifying treatment effects, and enhancing and accelerating drug development. Natural history studies may: (1) provide a clinical baseline; (2) quantify rate and variability of disease progression; (3) aid in detecting safety concerns; (4) provide context for efficacy evaluation; (5) help identify biomarkers or other surrogate measures and determine correlations with disease; (6) guide dose selection; and (7) help establish the optimal window of intervention. Results of natural history studies are important for designing clinical trials as well as informing benefit-risk analyses and regulatory decision-making, especially for rare and poorly understood conditions. More information about the role of natural history studies in drug development for rare diseases may be found in FDA's Draft

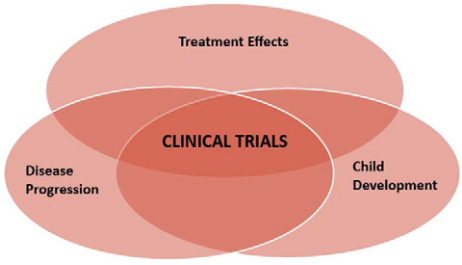

Fig. 1. Clinical trials designed to measure treatment outcomes must also take into account child development and disease progression. The dynamic factors of child development and disease progression are likely to have opposing effects. Standardized, well-defined, and reliable measures of neurocognitive outcomes are essential to enable researchers to assess treatment results reliably. Natural history studies aid in identifying factors associated with disease progression in the context of child development.