



Clinical Outcomes Assessments

Unique Considerations in Pediatric Rare Diseases

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Researchers are often asked to make recommendations for strategic protocol development for clinical trials for rare diseases, to create evidence dossiers to support regulatory filings, and to design studies to assess validity or reliability for clinical outcome assessments (COAs). What makes pediatric rare disease research unique and challenging? How do the challenges impact COA selection and align with the U.S. Food and Drug Administration (FDA) Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims?¹

The FDA recognizes that there are many challenges in rare disease drug development and that certain aspects that are feasible for common diseases may not be feasible for rare diseases. In 1983, the Orphan Drug Act was established to provide financial incentives associated with orphan drug development designation and to make developing drugs for small numbers of patients financially feasible. Rare diseases without approved treatments may be given fast-track designation to facilitate development and to expedite the regulatory review process. In addition to fast-track designation, a pediatric voucher program is available for expedited review based on surrogate breakthrough designation.² Selecting or developing COAs in consultation with the FDA can increase the likelihood of agreement on the content and measurement properties.³ The FDA has a meeting structure called Critical Path Innovation Meetings that provides a means for patient groups, industry, clinicians, and academics to communicate on key drug development issues, and to improve the efficiency of development and approval. The

regulatory approach seems to be having an impact on the volume of emerging studies in rare diseases. Rare disease research is one of the fastest areas of drug development with an average per patient cost of \$137,000/year.⁴ The percent of pharmaceutical sales is anticipated to increase to 16% of all drug development by 2018, and in 2014, orphan drug approvals represented 37% of all drug approvals. Furthermore, 50% of rare diseases affect children, with 30% affecting before the child's fifth birthday.⁴ It is clear that sponsors are reacting to the unmet needs of rare disease interventions. With such an emphasis and the fact that so many rare diseases affect the pediatric population, there is a very clear need for strategic consideration when designing trial endpoints.

The Roadmap to Patient-Focused Outcome Measurement in clinical trials⁵ provides guidance on the steps to COA selection or development, but each pediatric rare disease study has unique challenges that need consideration. With this article, we propose using Hypophosphatasia (HPP), to illustrate COA selection in a pediatric rare disease. HPP, a rare genetic metabolic musculoskeletal disorder, is an inborn error of metabolism caused by mutations in the tissue-nonspecific alkaline phosphatase gene, which can manifest in a broad range of symptoms and vary in its severity.⁶ Heterogeneous manifestations can include rickets, fractures, muscle weakness, limb deformities, pain, and respiratory compromise, which result in delayed acquisition of age-appropriate

developmental skills, gait impairments, and decreased functional independence in activities of daily living.⁶ The disease has a particularly high burden in children and is associated with high mortality rates in infants.⁸

Application to Hypophosphatasia (HPP)

The U.S. Food and Drug Administration approved Strensiq® (asfotase alfa) in 2015 as the first approved drug for perinatal, infantile, and juvenile onset HPP, following development with orphan drug and breakthrough therapy designation. HPP is a rare disease with multi-system impairments, a wide heterogeneity in disease presentation, a small sample size with international site distribution, and natural history literature that had limited functional characterization. The asfotase alfa clinical development plan included multiple studies to evaluate

safety tolerability, pharmacokinetics, pharmacodynamics, and efficacy. Targeted clinical trial populations were created by age and functional presentation. The primary efficacy endpoint in all studies was HPP-related rickets as measured by skeletal radiographs. The study endpoint models included secondary and exploratory variables with a combination of patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO), and performance outcome (PerfO) instruments to provide a comprehensive picture of function, disability, pain, and health-related quality of life (HRQoL). Heterogeneity in functional presentation and a wide range of ages necessitated use of COAs that characterize function relative to normative values. The results highlighted below focus on use of normative values in the infants and children in the clinical trials.

Roadmap to Patient Focused Outcome Measurement in Clinical Trials- Application to Pediatric Rare Disease Research and Hypophosphatasia

Understanding the Disease or Condition	Conceptualizing Treatment Benefit	Selecting/Developing the Outcome Measure
Challenges specific to pediatric rare disease research		
<ul style="list-style-type: none"> • Literature void of natural history data, especially related to function • Heterogeneity in disease presentation by phenotypes with variable age and functional presentations • A broad inclusion of disease phenotypes allows better characterization for which therapy may be feasible, but adds increased design and analysis complexity • Multi-system impairments • International site distribution with variable standards of care • Developing children have dynamic health states and impacts so static measures are not sufficient to benchmark or assess the target population • Infantile or severe disease presentations may include progressive loss of developmental skills and high mortality with no available treatment 	<ul style="list-style-type: none"> • Concept of interest for infantile presentation is often survival with an open label single arm study design • Conceptualizing benefit by how a child feels and functions is complicated because typical developmental function varies by age and involves a complex interaction between cognitive, communication, and motor skills • Consideration must not only be given to the concepts of interest but also to the interactions between the concepts. Cognition, communication, or attentional capacity may limit ability to measure primary treatment benefit • May be difficult to distinguish between treatment affect and change due to developmental maturation. Identical function may be age appropriate for a younger child and considered atypical or delayed in an older child. In the juvenile form of a rare disease, function may exceed the infantile presentation but the children have multiple co-morbidities and the impact of the impairments need to be measured by comparison to age appropriate task execution, social and peer interaction, and function within the home, school and community environment. • Difficult to develop responder definition with heterogeneity in age and function • Open label clinical trials where patients and investigators are aware of assigned therapy are rarely adequate to support labeling claims based on PRO instruments alone. COAs that support improvement in specific symptoms would not support a general claim related to improvement and multi-domain claims cannot be substantiated by instruments that do not adequately measure the individual disease concepts. Clinical designs often require complicated endpoint models with multiple COA types to capture the constructs • Targeted clinical trial populations are desirable for optimal design and ability to demonstrate treatment benefit, but often are limited by recruitment in rare disease and less desirable to have a narrow disease categorization for labeling 	<ul style="list-style-type: none"> • Existing standardized developmental instruments can provide a measure of the impact of multisystem impairment and classify function relative to normative values but; <ul style="list-style-type: none"> ○ Require extension training for administration often within an international site distribution ○ Challenging to establish disease-specific validation and that conceptual framework is appropriate for study population and endpoint ○ Instrument manuals do not include guidelines for accommodations for special populations, such as strategies to obtain reliable neurocognitive assessments in children that are low functioning, have non-cooperative behavior, or physical disabilities⁹ ○ Longitudinal data collection over years may require transitioning between developmental assessments with different psychometric properties ○ Standard scores can be used to discriminate function relative to standard deviations from the normative mean or percentile rank <ul style="list-style-type: none"> • May not show a treatment benefit (stable or increasing standard score) if new skills are acquired but at a slower rate than the normative sample. Age-equivalent scores may be more useful than standard scores to demonstrate skill acquisition in a child with severe motor impairment⁹ • Development of disease-specific validated PROs is challenging due to feasibility, time, and associated costs. <ul style="list-style-type: none"> ○ In the preschool child, motor skills and level of independence in activities of daily living (ADL) vary greatly by age and require validation of many items and multiple age versions

Understanding the Disease or Condition	Conceptualizing Treatment Benefit	Selecting/Developing the Outcome Measure
Potential strategies		
<ul style="list-style-type: none"> Utilize comprehensive prospective, observational, natural history studies with multiple COAs to gain insight into the multi-system impacts on age appropriate markers (symptoms/impacts) Use these natural history studies to gain insights to the COA performance (sensitivity and specificity) and to look to the relationships between outcome measures (consider language, motor ability, behavioral and cultural aspects) Characterize disease by distinct age and functional groups using natural history data, KOLs, patient, and caregiver perspectives 	<ul style="list-style-type: none"> Treatment benefit in the infant population may be defined by global development and the pediatric/ juvenile group may require performance-based or patient-reported assessments that are focused on a specific functional skill that is age specific or disease specific Treatment benefit may be defined by a responder definition based on acquiring a developmental skill that exceeds function observed in natural history study Treatment benefit may also be defined by Developmental Quotients (Age Equivalent Scores/Chronological Age x 100) and compared to decline in DQ in the natural history.⁹ Use KOL, focus group, caregiver, and patient perspective to define treatment benefit 	<ul style="list-style-type: none"> Utilize assessment batteries with normative data for the age and culture being targeted Utilize disease relevant domains of content within a developmental test Supplement the batteries with COAs specific to the anticipated treatment benefits Develop standardized order for all COAs, evaluate areas of overlap between multiple performance instruments to reduce redundancy and subject fatigue Content validity-establishing evidence that an existing developmental instrument measures concepts of interests in rare disease <ul style="list-style-type: none"> Highlight validation data used to develop instrument from diseases with similar impairments Complete literature searches to support use in interventional studies with similar impairments Use KOL perspective and consensus meetings to establish disease-specific recommendations for COAs Examine relationship between performance assessments and HRQoL in prospective observation study PRO instrument development - Use the Patient Reported Outcomes Measurement Information System (PROMIS) item banks to derive items and to expedite the development process. The item banks have already had extensive field testing and are consistent with the International Classification of Function for Children and Youth.¹⁰ Develop responder definition based on distribution analysis of groups in prospective observation study and expert, patient, and caregiver perspective
HPP example		
<ul style="list-style-type: none"> Systematic literature searches and KOLs used to characterize distinct groups by age and function Retrospective natural history studies completed Sub-study of larger retrospective natural history study was conducted that assessed gait impairments from clinical gait videos 	<ul style="list-style-type: none"> Open label, multinational, multicenter, single arm design due to unmet medical need, serious mortality and morbidity risk, and absence of disease-modifying treatment Multiple studies to measure treatment benefit in infantile, pediatric, and adult onset HPP Multiple inter-related endpoints in each study that included PROs, ObsROs, ClinROs, and PerfOs 	<p>COAs used in Infantile and Pediatric Studies</p> <p>Biochemical parameters</p> <ul style="list-style-type: none"> Tissue nonspecific alkaline phosphatase enzyme substrates <p>Skeletal system measures</p> <ul style="list-style-type: none"> Bone mineralization- Biopsy and DEXA Rickets Severity <ul style="list-style-type: none"> Rickets Severity Scale Radiographic Impression of Change Growth <p>Developmental Function and Strength- Infantile</p> <ul style="list-style-type: none"> Bayley Scales of Infant Development - third edition¹³ Survival – Respiratory Status <p>Physical Function, Strength and Ambulation –Pediatric</p> <ul style="list-style-type: none"> Bruininks-Oseretsky Test of Motor Proficiency –second edition: Running Speed and Agility and Strength substests Hand Held Dynamometry 6MWT Modified Performance Orientated Mobility Assessment-Gait (MPOMA-G)¹⁰ <p>Disability and HRQoL- Pediatric</p> <ul style="list-style-type: none"> Childhood Health Assessment Questionnaire (CHAQ) Pediatric Outcomes Date Collection Instrument (PODCI)

The Childhood Health Assessment Questionnaire (CHAQ) does not produce normative data but was also included in the summary as a measure of disability and pain. The modified performance-oriented mobility assessment (MPOMA-G) illustrates inclusion of a supplemental instrument to target an age and disease specific area of anticipated treatment benefit.

Bayley-3

The five Bayley-3 developmental domains: cognitive, language, motor, social-emotional, and adaptive behavior were developed (normed and validated) for use in impaired and healthy children between 1 and 42 months of age, and reflect current federal, state, and professional standards for early childhood assessment.¹³ The scales have clinical and research utility as a diagnostic assessment for young children with varied disorders and disabilities, and the manual includes strategies to accommodate patients with physical or cognitive limitations. Eleven patients with infantile HPP and an age of 3 years or less were assessed using the Bayley-3 at baseline and at 24 and 48 weeks after initiation of asfotase alfa for treatment of HPP.^{6,8} All patients had fine motor, gross motor, and cognitive delays at baseline and 87.5% of patients for whom data were available showed improvements in these components.⁶ Bayley-3 use supported measurement of global development and highlighted that the largest degree of impairment was present in the gross motor subtest. Age-equivalent scores were used to illustrate linear skill acquisition, and scaled scores (mean 10, standard deviation [SD] 3) illustrated rate and level of skill acquisition relative to a normative sample, with median (min, max) Gross Motor scaled scores increasing from 1 (1, 8) at baseline to 2 (1, 5) at Week 48.¹⁴

Bruininks-Oseretsky Test of Motor Proficiency (BOT-2)

In Pediatric HPP, only the BOT-2 Running Speed and Agility and Strength subtests¹⁵ were utilized because they were the most relevant to the HPP disease-specific impairments and mobility restrictions, and involved a reasonable amount of administrative time when paired with additional outcomes. The BOT-2 provided an opportunity to illustrate that HPP ambulatory function was well below expected values of healthy peers, thus limiting possible patients' participation in the community and school activities. The BOT-2 was used in children 5–12 years of age (N=13) treated with asfotase alfa. At baseline, the median scaled scores for both the BOT-2 Strength and Running Speed and Agility subtests were >2 SDs below the normative mean.¹² Asfotase alfa treatment resulted in significant and clinically meaningful improvements in strength and function, demonstrated by improvements in BOT-2 mean scores to ± 1 SD of normal.

Hand-Held Dynamometry (HHD)

HHD is a reliable and easy method to measure muscle strength. In children and adolescents, force values in Newtons are multiplied by limb length to calculate torque, which can be compared with gender-specific norms.¹⁶ In 5 to 12 year-old children with HPP, bilateral hip and knee extension and flexion, hip abduction, and grip strength were assessed by HHD.¹¹ Across muscle groups tested, baseline strength ranged from median 32% (9.4, 52.7) predicted in the hip extensor, to 60% (20.8, 149.2) predicted for grip (reported in torque for the right side as percent predicted for age- and weight-matched healthy peers). With asfotase alfa treatment, strength in all tested muscle groups except grip improved and continued to improve to last assessment ($P < .05$); e.g., a median 83% (45.7, 118.7) predicted was achieved for hip abductor at last assessment.¹¹

6-Minute Walk Test (6MWT)

The 6MWT is used to assess the distance a patient can walk on a level course in 6 minutes. The 6MWT reflects an integrated exercise response of multiple systems including the cardiorespiratory, neurological, and musculoskeletal systems and does not isolate the specific system of change. Normative data are available for children and the distance walked can be compared as a percent of the predicted values by age, gender, and weight. In 5 to 12 year-old children with HPP, a rapid improvement with asfotase alfa treatment was demonstrated using 6MWT: the median score increased from 61% predicted at baseline to within the normal range (80–100% of predicted) after 3 months, and remained within the normal range through 5 years of treatment.¹⁷

Childhood Health Assessment Questionnaire (CHAQ) and Pediatric Outcomes Data Collection Instrument (PODCI)

The PODCI questionnaires include self-report and parent/caregiver reports, with raw scores converted to a standardized scale from 0 to 100, with higher scores corresponding to less disability.¹⁸ Normative scores can also be calculated based on a mean of 50 and an SD of 10. In 5 to 12 year-old children (N=13) with HPP receiving asfotase alfa, physical function, ADL, and pain were assessed using the CHAQ¹⁹ and PODCI.²⁰ At baseline, children had difficulty with upper extremity tasks (e.g., lifting heavy items and pouring a gallon of milk), functional mobility items (e.g., walking, running, climbing stairs, and getting on or off a bus), and participation in community recreation and sports.²⁰ Decreases in disability and pain were consistent across both measures. Median parent-reported normative PODCI scores for global function (baseline: 27 [-2, 55], ≥ 2 SD below the normative mean of 50 (SD 10), sports/physical function (baseline: 20 [-13, 53]), and transfer/basic mobility (baseline: 37 [-7, 53])

all improved, reaching normal values (≥ 44) at 6 months ($P < .05$). The median (min, max) CHAQ disability score decreased from 1.0 (0.0, 2.3) at baseline to 0.0 (0.0, 1.8) at 24 months ($P = .002$). Median PODCI discomfort/pain normative scores improved from below normal (39 [18, 55]) at baseline to a median score of 55 (23, 57; $P = .055$). CHAQ median pain scores decreased from 20.0 (0.0, 72.0) at baseline to 0.0 (0.0, 42.0) at 3 months ($P = .04$).

Modified POMA-G (Performance-Orientated Mobility Assessment- Gait)

The POMA-G is a validated tool for evaluating gait and balance in elderly and community dwelling adults¹⁹ that was modified to capture musculoskeletal impairments that are most relevant to children with HPP.¹⁰ Retrospective clinical gait videos were used to compare the non-interventional natural history group to the interventional group. Children in both groups had gait impairments at baseline and the patients treated with asfotase alfa (8) showed significantly greater improvements (+3.0 [+0.0, +7.0]) compared with controls (6) at last assessment (+1.5 [0.0, 2.0]; $P = .03$; time from baseline to last assessment, 1.7 [0.2, 3.3] and 4.1 [2.0, 5.9] years, respectively).

Conclusion

Pediatric rare diseases present unique challenges in clinical trial design and in selection of COAs that can support claims in medical product labeling. Guidance is not available on best practices to deal with the

developing child with cognitive, motor, language, and level of independence in activities of daily living that vary greatly by age. This article illustrates use of multiple COAs with normative data in the HPP clinical trials for asfotase alfa (Strensiq®). Multiple endpoints were required to capture multi-system impacts and to tell the complicated story from biochemical parameters to age-appropriate recreational and community participation. Infants and children on asfotase alfa treatment demonstrated improved bone density, increased strength, and reduced pain; improved functional mobility in age appropriate developmental motor skills and ambulation; reduced disability and increased independence in activities of daily living; improved ability to navigate in the community and school environment; and, increased ability to participate in age-appropriate recreational and community sports. Similar to HPP, many rare diseases present with multi-system impairments and a wide distribution of age and functional levels that are desirable to be included within labeling claims for medical product approval. It is imperative to consider multiple COAs early in the development process to design comprehensive prospective, observational, natural history studies to gain insight into the multi-system impacts on age-appropriate markers. It is also important to consider use of COAs that provide normative data and reflect current standards for early childhood assessment in order to support payer approval and reimbursement for the approved drug intervention and for early intervention services. ■

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