

Clinical trials in children with Friedreich Ataxia
July 2023

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We thank members of the FARA Board of Directors and Scientific Advisory Board for their review of and suggestions for the document.

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I. Executive Summary

Clinical development of treatments for Friedreich Ataxia (FA) should include pediatric trials at the earliest possible stages so that an approval for early use in children is not delayed. FA symptoms most often present between the ages of 5-15 years and earlier treatment will have the most significant impact for improving clinical outcomes.

- The FA community has demonstrated feasibility and success in conducting multi-national trials in children with FA.
- Natural history studies, clinical outcome assessment, biomarker studies and other clinical trial design resources pertinent to pediatric trial participants are available and continue to be developed with great urgency.

Regulatory agencies provide guidance on and are increasingly supportive of pediatric trials early in clinical development, especially in rare conditions like FA.

- *“If the product is being developed for an indication that occurs in both children and adults, the goal should be concurrent licensure unless there are safety concerns that would delay or even preclude pediatric studies...”*
Robert “Skip” Nelson, M.D., PhD., Deputy Director and Senior Pediatric Ethicist, OPT, FDA, September 15-16, 2016, joint meeting of the Pediatric Advisory Committee, the Anesthetic and Analgesic Drug Products Advisory Committee, and the Drug Safety and Risk Management Advisory Committee.

- There is precedent in other rare neurological diseases that affect children and adults that registration trials in children, teens and young adults are often sufficient to support extrapolation to adults of all ages.
- EMA is encouraging sponsors developing FA therapies to conduct trials in pediatrics and to include enrollment or supplemental studies of very young children.

Enabling early pediatric trials requires early, collaborative discussions between sponsors, investigators, FARA, and regulators.

- As treatments for FA are approved there will be more children diagnosed with FA, including those who are pre-symptomatic, which presents a crucial opportunity to treat FA at the earliest possible time and prevent or delay the onset of symptoms.

II. Introduction

The Friedreich's Ataxia Research Alliance (FARA) believes it is imperative that FA patients be treated as young as possible, when the greatest therapeutic benefit is anticipated. Consequently, FARA wants to ensure that children with FA are included early in clinical trials and, as a result, quickly gain access to safe, effective treatments. Enabling pediatric trials requires early, collaborative discussions between sponsors, investigators, the FA community, and regulators. FARA has developed this document to provide critical information on the disease course in children, the regulatory views and requirements for pediatric trials, biomarker and clinical assessment approaches, and clinical trial designs, as well as FA parent views on participation of children in clinical trials. FARA is eager to support industry partners as they develop plans for pediatric trials, including participation in discussions with the regulators from very early in the development process, because FARA is convinced that, together, we can enable earlier inclusion of children with FA in clinical trials, significantly increase the likelihood of successful outcomes of those trials, and provide earlier access by children to safe and effective treatments.

FA is a debilitating, life-shortening, progressively degenerative, multisystem disorder. It is an autosomal recessive disease caused by mutations in the frataxin

(FXN) gene [1]. In most cases, it is caused by biallelic expanded GAA triplet repeats in intron 1 of the FXN gene. In about 4% of cases, patients have a triplet repeat expansion on one allele and a loss of function mutation on the other allele [2, 3].

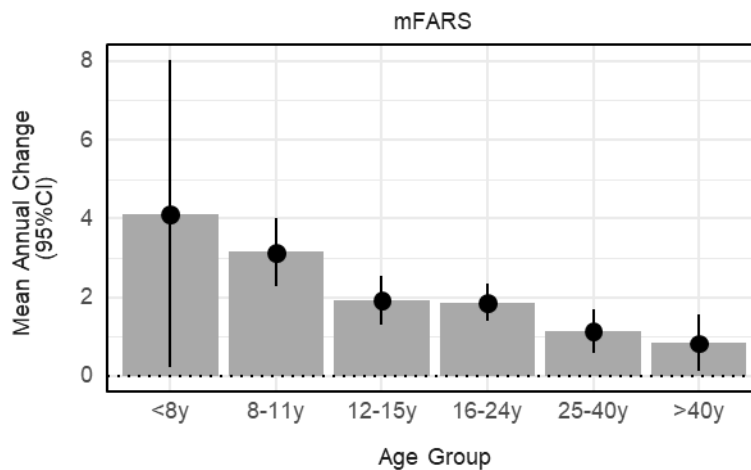
About 65% of patients are diagnosed before adulthood, while about 35% are diagnosed after 18 years of age [4]. Therefore, children represent a substantial portion of the FA population. Typically, beginning between the ages of 5 and 15 years, loss of balance and coordination are the most common presenting symptoms, with progression of symptoms leading to loss of ambulation, dysarthria, swallowing difficulties, and progressive loss of independence of all activities of daily living [5]. FA also affects the heart, skeletal muscles, skeleton (scoliosis, pes cavus), and endocrine system (diabetes, bones). While neurological features of the disease are fully penetrant, affecting 100% of those with FA, other systems are not affected in all patients. In children, a small group presents with cardiomyopathy or scoliosis prior to the onset of neurological disease [6, 7]. Overall, two thirds of patients develop cardiomyopathy, and more than half develop severe scoliosis, requiring corrective surgery in teen years [8]. Between 10 to 40% develop diabetes [9]. Symptoms such as vision impairment, hearing loss, swallowing difficulties and urinary disturbances are generally more prominent in late-stage disease. However, on careful examination, signs of these problems are often detectable in patients early in disease course (e.g., loss of retinal nerve fiber layer measured by ocular coherence tomography). Thus, we believe as treatments for FA are approved, more children, including those that are presymptomatic, will be diagnosed with FA. Treatment prior to clinical manifestation of FA may be the only opportunity to prevent or delay the onset of some symptoms.

Most young people diagnosed with FA require mobility aids such as a cane, walker, or wheelchair by their teens or early 20s. The progressive loss of coordination and motor control leads to motor incapacitation and the full-time use of a wheelchair, typically within 10-15 years of diagnosis. In addition, children with early onset may have difficulty speaking, which can negatively impact development. Finally, fatigue has a profoundly negative impact on quality of life, including social and emotional well-being. As one parent explained:

The fatigue is hard to quantify but plays out in every moment of every day. With a child who is too tired to play, or they lie on the floor while life happens around them, when coloring books and snacks are delivered on trays to a child who is still in bed because they are too tired to get up, you feel a sense of loss as a parent that is unexplainable. Childhood is the time of curiosity, joy, and wonder; but, much of my child's life has been lost to fatigue.

The mean GAA1 repeat length is longer in those that show neurological symptoms in early childhood [5], indicating a relationship between GAA repeat length, disease onset, and rate of progression. Mean annual change in neurological assessment by the modified Friedreich Ataxia Rating Scale (mFARS) depends on age and is more rapid in younger patients (Figure 1).

Figure 1: Mean Annual change in mFARS, by Age-Group (data from FACOMS).



In younger children ages 8 years and younger, the application of the mFARS scores is complicated by high variability in the results (see later section on Challenges for Pediatric Trials in FA). One possible reason is the interaction of neurological development in early childhood with the progression of the disease. However, the data both from previous clinical trials and natural history studies indicate that

measurable neurological deficits are present and the rate of decline in children makes pediatric trials feasible in general.

Data from large, well run natural history studies aid in the design of pediatric clinical trials. FARA established a large longitudinal natural history study in 2003 -- the Friedreich Ataxia Clinical Outcome Measures Study (FA-COMS). Today, more than 1350 participants are enrolled at 15 participating CCRN in FA clinical sites in the United States, Canada, Australia, New Zealand, India, and Brazil and those sites are fully collaborative with additional FA clinical sites in Europe. In FA-COMS, 41% of patients enrolled as children. The data are available to qualified investigators and sponsors through the Friedreich's Ataxia Integrated Clinical Database (FA-ICD) curated and standardized in Clinical Data Interchange Standards Consortium (CDISC) format. Sponsors and researchers can access and analyze data in aggregate, or filter and view individual de-identified patient-level data. In addition, the database also includes de-identified patient-level data from placebo arms of six clinical trials, three of which included children. The full database is accessible on the FDA-funded Rare Disease Cures Accelerator – Data and Analytics Platform that is managed by the Critical Path Institute in collaboration with the National Organization for Rare Disorders (NORD). Link to databased here <https://c-path.org/programs/rdca-dap/working-group/fa-icd/>.

In addition to FA-COMS, a second natural history study is focused solely on children. The FA-CHILD study is a non-interventional natural history study of 108 participants under the age of 18 years, enrolled at a mean age of 13.9 years. Each participant was followed for three years, with visits at baseline, 6 months, 12 months, 18 months, 24 months, and 36 months (ClinicalTrials.gov Identifier: NCT03418740). These data provide a reference for modeling clinical trial designs focused on younger individuals with FA.

Starting clinical trials in children provides the most promising opportunity to slow or block the progressive changes and the underlying neurodegeneration of FA. Studies in early stages of the disease also allow full evaluation of the clinical benefit of a therapeutic approach, as changes in gait and balance, as well as upper limb function, are most rapidly progressing in earlier-stage, ambulatory individuals. Thus, while starting populations for Phase I trials might include non-

ambulatory or later stage adults, we strongly believe that transition to earlier stage young adult and pediatric ambulatory patients early in development is needed for a more complete evaluation of efficacy potential. In sum, because of the rate of decline and the presence of detectable, measurable functional impairments, including pediatric subjects early in clinical trials provides the best opportunity to demonstrate the efficacy of an experimental FA therapeutics well as providing an opportunity for children to gain early access to safe, effective therapies.

III. Regulatory Views, Guidance, and Statutes Regarding Pediatric Trials

Evolving FDA View

Recent FDA public statements and draft guidance packages indicate a shift in regulatory thinking from protecting children FROM clinical trials to protecting children WITH clinical trials that are more thoughtfully designed with the goal of more timely access to effective treatments.

This shift, however, is in its early stages and not yet well defined in text or practice. Consequently, it is important that we take advantage of the fact that the FDA is strongly encouraging sponsors to come into the Agency very early to discuss this matter and present all the data the sponsor might have to determine the best time to include pediatric subjects in the clinical plan.

FDA Speakers during the February 27, 2023, FDA Rare Disease Day virtual event emphasized both the shift in regulatory thinking and the encouragement that sponsors come in very early for discussions. For example, Dr. Martha Donoghue, MD, Associate Director for Pediatric Oncology and Rare Cancers, Oncology Center of Excellence, Office of the Commissioner, stated, 'We can best protect children through more timely and thoughtful conduct of clinical trials that give them the opportunity to benefit from participating in those trials and with the goal of increased, more timely access to effective treatments. ... So, study the right drugs at the right time in children.' (Video recording at <https://www.youtube.com/watch?v=yIk7eYTgUMM>)

Speaking on the same panel, Dr. Michelle Campbell, Office of Neuroscience, CDER, said, 'In the Office of Neuroscience, we see a lot of rare diseases, including neurodegenerative diseases in which there is early progression, so on the

pediatric side, we understand that the opportunity to intervene may be in a limited window depending on when the diagnosis happens and what we understand about the condition. So, when we are reviewing protocols that come in, we are constantly thinking about what is the broadest population we can study in the timeframe that will give us the best answers to interpret the data, and a lot of that information can be based upon good, high quality, rigorously collected natural history data – that can help us consider the best trial design ... In a more typical setting, we would often begin with an adult population. But that is not necessarily true in rare diseases, especially when the disease starts in pediatrics and is identified when the child is young. In SMA, we actually supported the trial design and gave the advice to begin in the most severely affected and extrapolate the positive findings into the later-stage population. So, we really encourage you to come in and talk with us early and present to us all the data you might have – e.g., natural history, observational data, any first-in-human data, so we can help determine what trial design will enable us to obtain the interpretable data.’ (Video recording at <https://www.youtube.com/watch?v=yIk7eYTgUMM>)

In the FDA Briefing Document prepared for the September 15-16, 2016 joint meeting of the Pediatric Advisory Committee, the Anesthetic and Analgesic Drug Products Advisory Committee, and the Drug Safety and Risk Management Advisory Committee, Robert “Skip” Nelson, M.D., PhD., Deputy Director and Senior Pediatric Ethicist, OPT, stated, “If the product is being developed for an indication that occurs in both children and adults, the goal should be concurrent licensure unless there are safety concerns that would delay or even preclude pediatric studies. Adult and pediatric development may proceed either sequentially or concurrently, depending on the product and factors such as the severity of the disease, anticipated risks to children and availability of alternate treatments. ... In other words, when appropriate, adults should be enrolled prior to adolescents and younger children only to establish the data needed in support of the judgment that the risks of introducing the intervention in children are justified by the prospect of direct benefit (21 CFR 50.52). Once this threshold has been reached, pediatric product development should proceed, even if an appropriate adult disease population exists.”

<https://fda.report/media/100035/FDA-Briefing-Information-for-the-September-15-16--2016-Joint-Meeting-of-the-Anesthetic-and-Analgesic-Drug-Products->

[Advisory-Committee--the-Dr.pdf](https://fda.report/media/100035/FDA-Briefing-Information-for-the-September-15-16--2016-Joint-Meeting-of-the-Anesthetic-and-Analgesic-Drug-Products-Advisory-Committee--the-Dr.pdf)
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In his briefing during the same joint Advisory Committee meeting and in his presentation the following month, Dr. Nelson stated, “Thus, we need ‘proof of concept’ data from human adults and/or animal disease models establishing a sufficient prospect of direct benefit to justify exposing children to the known (and unknown) risks of the intervention. This requirement does not imply that adult studies must be completed before beginning pediatric studies. Rather, once sufficient adult and/or animal data exist to make this judgment, pediatric development should proceed without further delay.”

https://bioethics.nih.gov/sites/nihbioethics/files/bioethics-files/courses/pdf/2016/session3_nelson.pdf)

In an April 2022 interview, Dr. Susan McCune, a pediatrician and neonatologist, who was at the FDA for 18 years, the final four of which (2017-2021) were as Director, Office of Pediatric Therapeutics in the Office of the Commissioner, stated, “Early planning for pediatric studies, even during the planning for adult trials, may facilitate pediatric programs in the long term. Early meeting with the agency at the pre-IND phase is encouraged, as this can help prevent any clinical hold issues and identify (and avoid) unnecessary studies. The earlier the conversation begins with the regulatory agencies, the better.” (Regulatory Rapporteur, vol. 19, No 4, April 2022).

See the [Appendix](#) for a summary of pertinent FDA guidance and statutes regarding pediatric studies.

The Paediatric Committee (PDCO) of the European Medicines Agency's (EMA). The PDCO is the scientific committee responsible for oversight of medicines for children. Their role includes supporting development of medicines for children in the European Union by providing scientific expertise and defining pediatric needs. The PDCO published a 2023 workplan which includes several initiatives to expedite pediatric trials, including determining how real-world evidence (RWE)

can support pediatric medicine development and promote its use and the Step-wise Pediatric Investigation Plans (PIP) pilot program, intended to allow greater flexibility for sponsors of innovative medicines in developing such plans. A PIP is a development plan aimed at ensuring that the necessary data are obtained through studies in children, to support the authorization of a medicine for children. (https://www.ema.europa.eu/en/documents/work-programme/pdco-work-plan-2023_en.pdf)

Health Canada

The Pediatric Drug Action Plan was developed in 2020 with the goals of helping to ensure that children in Canada have access to medicines they need in age-appropriate formulations. There are three specific goals of the action plan:

- improve access to pediatric medicines and formulations;
- increase the development of pediatric medicines and formulations, and
- provide more information to people in Canada on pediatric activities and data.

Health Canada intends to modernize regulations to require meaningful information about the safety and effectiveness of drugs in children, develop a National Priority List of Pediatric Drugs that are available elsewhere and needed in Canada, and to identify regulatory pathways and flexibilities that can be implemented to encourage industry to bring these pediatric products to Canada.

IV. FA Parents' views on pediatric trials

For children with FA, any positive change in outcomes has significant impact on development and well-being. The symptoms of FA go beyond the medical implications and have social, emotional, and psychological consequences. In addition, when children present at an early age, there is an accelerated disease progression.

Children with FA have already lost significant segments of their childhood to mobility decline, frustration, fatigue, and medical appointments. While some parents fill up their children's schedules with sporting events, FA parents fill theirs

with occupational and physical therapy, and appointments for speech, behavioral health, cardiology, neuromuscular dysfunction, etc.

Therefore, parents are highly motivated to act -- hope is a powerful thing. In addition, parents believe that children can understand and support the purpose of a clinical trial, and the sense of and commitment to a shared purpose helps build a stronger sense of community and identity. It will also lead children with FA to be more willing participants in future trials when they are older.

Parents view the option to participate in a trial as potentially buying the child time to continue to engage in activities and, most importantly, it provides a sense of action when so much seems outside of their control. The ability to choose, to contribute to the science and move the community closer to treatments and potentially a cure, not only provides empowerment, but it can also provide the child and the family with a sense of meaning, hope, and community.

V. Challenges for Pediatric Trials in FA

The natural history of FA has been well documented in children over 10 years of age. Although the symptoms of FA frequently start occurring between 5 and 10 years of age, those younger than ten are not well represented in FA-COMS and have not been as intensively studied. In addition, the yearly assessments in FA-COMS may not capture the velocity of change in younger FA patients. Finally, the application of outcome measures derived from FA-COMS present specific challenges in very young children.

The FA-CHILD study, funded by FDA and FARA, started in 2017 and was designed to address some of these limitations of FA-COMS (ClinicalTrials.gov Identifier: NCT03418740). During twice-a-year visits, children with FA were given a core set of tests and procedures, including the collection of medical history, a detailed neurological exam, ataxia scales, and health questionnaires. At each visit, blood and cheek-swab samples were obtained to monitor frataxin levels. Study sites included the Children's Hospital of Philadelphia, the University of California Los Angeles, and the University of Florida. The goal was to enroll 103 subjects and collect 3 years of data per subject. All subjects were under the age of 18. Visits included baseline and 6, 12, 18, 24, 36 months. A select number of Children's Hospital of Philadelphia (CHOP) participants underwent Magnetic Resonance Imaging (MRI) scans and a Motor Evoked Potentials (MEP) procedure.

While the study population in FA-CHILD was severely affected, (median age at disease onset of 7 years), the results demonstrate that the mFARS can capture change over time in those participants greater than 8 years of age. Other measures, including the upright stability subscale of the mFARS, the Activities of Daily Living (ADL) scale, timed-walking tests (25 ft and 1 minute), and the Berg Balance Scale function well in both early and late ambulatory children and are appropriate for pediatric clinical trials.

VI. Overcoming Challenges

The ability to enroll pediatric subjects and assess disease state and the potential for therapeutic impact in that population has been demonstrated in previous clinical trials. A Phase III trial of idebenone in FA enrolled seventy ambulatory pediatric patients between the ages of 8 and 18 years [10]. Interferon gamma-1 β (Actimmune) was also studied in a Phase III trial of safety, tolerability, and efficacy in individuals with FA, ages 10 to 25 years [11]. Finally, a large phase 3 study of vatiquinone enrolled more than 140 participants with FA, with more than 85% being children (MOVE-FA <https://ir.ptcbio.com/news-releases/news-release-details/ptc-therapeutics-announces-topline-results-vatiquinone-move-fa>). There is also an open-label study to evaluate pharmacokinetics, safety, and efficacy of vatiquinone in children with FA under age 7. This study was encouraged by EMA to gather additional safety data in the youngest individuals with FA.

In younger children, biomarkers may be essential to supplement clinical assessments that may be confounded by developmental changes. TRACK-FA is a natural history study to investigate brain and spinal cord changes in FA. It includes children as young as 5 years of age. As of May 31, 2023 - 161 individuals with FA, including 20 under 10 years of age and 55 between 11 and 17 years of age were enrolled in the study.

At three study visits, each approximately 12 months apart, neurologic, and functional data, a blood draw and brain and spinal cord MRI scans are conducted. Controls are healthy volunteers who are age- and gender-matched to the FA cohort. The data from this study may support the use of imaging endpoints to follow disease progression in younger people with FA. In addition, imaging data may provide additional evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations.

Previous trials have demonstrated the feasibility of assessing safety and tolerability in children with FA. PK studies can provide evidence of common drug metabolism and similar concentration-response relationships in adults and children. In concert with biomarker and natural history data that demonstrate the common pathophysiology and natural history of the disease in the adult and pediatric populations, it may be possible that efficacy in the pediatric population can be extrapolated from data obtained in the older child and adult studies.

FARA believes that pediatric trials are warranted as soon as safety information is available in adults, and that sufficient safety data can be collected in the early stages of a clinical trial. If sufficient adult and/or animal data exist to evaluate the prospect for direct benefit for children, pediatric development should proceed without further delay. The goal should be concurrent access to new, effective treatments for both children and adults. Enrollment of adults prior to adolescents and younger children should serve to provide the data needed to evaluate risks and potentially prospect of direct benefit to children, enabling enrollment of children as quickly as possible.

While clinical trials in very young children require sensitive and age-appropriate clinical assessments, natural history data supports the use of current clinical assessment tools in children aged 8-10 and older. Early planning for pediatric studies, even during the planning for adult trials, will facilitate pediatric programs in the long term. Thus, FARA encourages sponsors to include FARA in discussions with regulators very early and to present all the available data including the natural history studies, supportive data in juvenile animals, biomarker data and any available safety data to get input on trial design that will enable interpretable data and the earliest possible safe inclusion of pediatric subjects. Again, FARA believes it is imperative that FA patients be treated as young as possible, when the greatest therapeutic benefit is anticipated. Consequently, FARA wants to ensure that children with FA are included early in clinical trials and, as a result, quickly gain access to safe, effective treatments.

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VIII. Appendix

FDA Draft Guidance - Ethical Considerations for Clinical Investigations of Medical Products Involving Children - Guidance for Industry, Sponsors, and IRBs - September 2022 (<https://www.fda.gov/media/161740/download>)

The following excerpts from this draft guidance, and FARA's comments on those excerpts, are not intended as a substitute for careful review of the document. Rather, they are intended to highlight the possible regulatory pathways to inclusion of pediatric subjects in FA clinical trials at the earliest possible stages.

This draft guidance begins with the statement that "Clinical investigations in children are essential for obtaining data on the safety and effectiveness ... in children and to protect children from the risks associated with exposure to medical products that may be unsafe or ineffective" and adds that "Children are a vulnerable population who cannot consent for themselves and who therefore are afforded additional safeguards." (p.1)

Ethical Framework

IRBs are required to "find that no greater than minimal risk to children is presented ... and adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians. For "clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects" IRBs are required to "find that the risk is justified by the anticipated benefit to subjects" and that the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches." For clinical investigations

involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition" IRBs are required to find that "the risk represents a minor increase over minimal risk; the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, physiological, social, or educational situations; the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians. (pp. 2,3)

Principle of Scientific Necessity

"Children should not be enrolled into a clinical investigation unless their participation is necessary to answer an important scientific and/or public health question directly relevant to the health and welfare of children. For example, for products that are being developed for use in adults and children, if effectiveness in adults can be extrapolated to children, then effectiveness studies in adults should be conducted to minimize the need to collect effectiveness data in children." Key elements of well-designed clinical investigations include the selection of appropriate control groups and study endpoints relevant in the pediatric population. (pp. 3,4)

Risk Categories

FDA regulations include two categories of risk for procedures or interventions in a clinical investigation that do not offer a prospect of direct benefit:

"Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests ... Given that investigational drugs generally are considered to have the potential to cause harm, the use of an investigational drug in a clinical investigation that includes children is unlikely to be considered minimal risk."

"Minor increase over minimal risk should be understood to mean a slight increase over minimal risk that poses no significant threat to the child's overall health or

well-being. Any potential harms with the intervention or procedure should be expected to be transient and reversible and the probability for severe pain, discomfort, or harm should be extremely small or nonexistent.” (pp. 4,5)

Prospect of Direct Benefit

“The Prospect of Direct Benefit refers to the potential benefit to the individual child from exposure to the research intervention.” For clinical trials “considered to offer prospect of direct benefit, the IRB must find not only that the risk is justified by the anticipated benefit to the child, but the relation of the anticipated benefit to the risk is at least as favorable as any available alternatives”. The IRB must also consider whether the proposed dose and duration of exposure are adequate to offer the individual child potential clinical benefit. In conditions such as FA, that exist in both adults and children, the prospect of direct benefit to children can be supported by clinical benefit data from adults. In addition, however, animal data may also provide evidence of the prospect of direct benefit to children and “may preclude or mitigate the need to preliminarily collect relevant adult data.” Also in such conditions, “demonstration of a drug’s favorable effect on a biomarker(s) or surrogate endpoint(s) linked to the causal pathway of the disease in adults may also support prospect of direct benefit in children.”

(pp. 5,6)

Application of Subpart D to Pediatric Clinical Investigations

“Multiple sources of information may be used to inform the design of an acceptable pediatric clinical investigation. Information from nonclinical studies ... and literature may be used to assess the potential risks and benefits of initiating the investigation in children. Depending on the quality and applicability of these data, collection of relevant adult data prior to initiation of a trial in pediatric subjects may not always be necessary. ... Early inclusion of children in medical product development or initiation of clinical trials directly in children may be appropriate.” (pp. 10-14)

Statutes and Additional Incentives for Sponsors to Conduct Pediatric Studies

In addition to the Draft Guidance above, there are statutes that pertain directly to the conduct of pediatric clinical trials include the Best Pharmaceuticals for

Children Act (BPCA) and the Pediatric Research Equity Act (PREA). An important additional incentive for sponsors to commit to and conduct pediatric studies as early as possible is the Rare Pediatric Disease Priority Review Voucher program.

BPCA (Section 505A of the Federal Food, Drug, and Cosmetic Act) became law in 2002 and was most recently reauthorized in 2022. It provides a financial incentive to companies to voluntarily conduct pediatric studies. It enables FDA to issue written requests for pediatric studies prior to approval of a new drug application if FDA has determined that information related to the use of the drugs in the pediatric population may produce health benefits. The sponsor company can also ask the FDA to issue a written request for a pediatric study. As an incentive to industry to conduct such studies requested by the Agency, the BPCA also provides for an additional 6-month period of marketing exclusivity (pediatric exclusivity).

(PUBLIC LAW 107–109—JAN. 4, 2002)

PREA (Section 505B of the Federal Food, Drug, and Cosmetic Act) – Requires companies to assess safety and effectiveness of certain products in pediatric patients. It requires pediatric assessments of new drugs and biological products for all new active ingredients, indications, dosage forms, dosing regimens, and routes of administration to assess the safety and effectiveness of a drug/biologic for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug or biological product is safe and effective. Pediatric studies must be conducted using age-appropriate formulations. PREA authorizes FDA to require pediatric studies of approved drug/biologic indications and provides criteria for FDA to waive or defer pediatric studies.

Waivers may be granted when there is evidence strongly suggesting that necessary studies are impossible or highly impracticable (e.g., number of patients in that age group is so small), the drug or biological product would be ineffective or unsafe in that age group, the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and is not likely to be used by a substantial number of pediatric patients in that age group, or reasonable attempts to produce a pediatric formulation necessary for that age group have failed. Deferral of submission of pediatric assessment can be granted if the drug or biological product is ready for

approval for use in adults before pediatric studies are complete, pediatric studies should be delayed until additional safety or effectiveness data have been collected, or there is another appropriate reason for deferral.

FDA review divisions and sponsors should discuss PREA requirements early in the drug development process. Pediatric Study Plans, including outlines of the pediatric study or studies the applicant plans to conduct, are required to be submitted for all products subject to PREA. If the applicant plans to request a deferral or waiver, the application must include plans to make such a request along with supporting data. Final deferral and waiver decisions are made at the time of NDA/BLA approval. (PUBLIC LAW 108–155—DEC. 3, 2003)

Rare Pediatric Disease Priority Review Voucher (RDPRV) program: A company that holds an RDPRV can use it to obtain an expedited, priority review for a future marketing application. Because marketing applications for rare diseases are quite likely to receive priority reviews anyway, companies that plan to continue developing orphan products often sell their RDPRVs, for large dollar amounts, to companies developing products for common disorders. The purchasing companies can then use the vouchers to obtain priority reviews for their common disease marketing applications. The first step in the process of obtaining a RDPRV is securing the FDA's Rare Pediatric Disease Designation. That requires the company to establish with the FDA that the targeted disease is a rare pediatric disease, provide data suggesting that the experimental therapeutic may be effective in that disease, and demonstrate the commitment to develop the product for pediatric subjects with that disease. While each applicant must establish with the FDA that the targeted disease is a rare pediatric disease, it is important to note that multiple companies, after close consultation with FARA, have been successful in doing so. (Section 529, Federal Food, Drug, and Cosmetic Act)