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COVID-19 Vaccine Clinical Trials in Children: Challenges on the Horizon

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Vaccine clinical trials against COVID-19 in adults are leading the effort before studies begin in children. Although early reports show COVID-19 symptoms tend to be milder in children, some develop severe manifestations of the disease. With an even larger gap in symptomology between adults and children, adult trials will not be easily adaptable to children.

Despite decades of progress in pediatric product development, pediatric clinical research remains challenging. A comment from FDA's Dr. Dianne Murphy in 1999 highlights a relevant keystone during the rapid pace of this pandemic, "*We have a very high bar to pass if we are going to enroll children in clinical trials.*"[1] Adapting the accelerated activities in the adult vaccine programs to children will be inherently difficult as clinical trials will be needed to establish safety and efficacy. However, this goal is achievable with strategic, early planning to ensure ethical trial conduct.

Understanding Pediatric Protocols

Multiple vaccine platforms are currently being evaluated in adults in which some candidates will demonstrate greater efficacy and safety in some subpopulations compared to others. The potential reasons for the differences in response include individual unique biological properties, the need for repeated doses, storage requirements, delivery route, and other characteristics. In addition, some vaccines may be more effective in younger adults versus individuals over 65 years due to age-dependent differences in our immune systems. Similarly, developmental differences in immune responses from infancy through adolescence may warrant age-group specific endpoints in pediatric trials. It's evident, then, that adding pediatric studies into a diverse array of platforms increases the challenges for vaccine developers.

Fortunately, industry experience with requirements for including pediatric use information in FDA product labels as early as 1979 will pave the way to designing pediatric COVID-19 vaccine trials. The collective experience of vaccine developers, pediatric investigators, and advocates will reduce missteps or duplicative efforts. Harmonizing plans for pediatric vaccine programs will best serve the needs of children and their parents. Unknown at this point are specific details on protocol requirements from regulatory authorities.

FDA guidance on COVID-19 vaccines[2] notes the pediatric requirements under the 2003 Pediatric Research Equity Act (PREA). PREA mandates that clinical trials cannot begin until a developer presents their initial Pediatric Study Plan (iPSP) that includes content on design, endpoints, and other product-specific details.[3] The content list is preceded by "to the extent practicable." That is, design studies from a practical perspective to ensure that implementation is feasible in children. The iPSP should be presented after data from Phase 1 and 2 studies are available. The European Medicines Agency (EMA) has a similar process in which sponsors submit a Paediatric Investigation Plan (PSP) at the end of Phase 1. FDA and EMA meet regularly to harmonize plans when applicants seek market authorization in both the U.S. and EU. To streamline the dual FDA/EMA process for pediatric COVID-19 products, the agencies issued a joint statement to remind licensure applicants that although iPSPs and PSPs are similar, each is required for their respective regions.[4]

Harmonization efforts across COVID-19 vaccine developers are underway in the U.S. and globally. The U.S. formed a private/public partnership to prioritize product candidates and harmonize clinical trials under the National Institutes of Health (NIH), *Accelerating COVID-19 Therapeutic Interventions and Vaccines* (ACTIV). A descriptive list of adult vaccine studies under the ACTIV model can be found on the NIH website.[5] Similar collaborative efforts under NIH leadership are expected for vaccine trials in children. In the interim, anticipating areas that may be important to regulators and the pediatric research community will facilitate planning for site operations.

The FDA has emphasized that protocols for pediatric COVID-19 vaccines will need to reflect the unique aspects of the disease process in children.[3] Characteristics in the natural history of COVID-19 in children have yet to be fully elucidated due to small sample sizes and heterogenous study designs. Findings on clinical presentation and outcomes have shown some similarities in children and adults, but not in all cases.[6]

Aspects of the virus in children unrelated to clinical disease are also of concern. One is correlation between the level of virus (viral load) and its ability to spread (transmission). Limited studies, to date, are contradictory about duration of viral shedding, but one study suggests two weeks or more in asymptomatic children.[7] The finding raises the possibility that endpoints related to transmission may be especially important for pediatric vaccine trials. Why? It's no surprise to parents and teachers, that children, especially young ones, easily share viruses among themselves and adults, so understanding viral transmission in children has implications for our communities. A recent study from Mass General Hospital for Children has shown high viral loads in nonhospitalized children compared to hospitalized children,[8] suggesting that children may, indeed, be "silent spreaders." However, FDA's goal for licensure is "protecting humans from SARS-CoV-2 infection and/or clinical disease."[3] In other words, FDA's current objective is focused on prevention of disease and not spread of disease. On the other hand, groups such as the World Health Organization suggest evaluating shedding and transmission.[9] Transmission data will add complexity to pediatric studies, but the risks of viral spreading by children, especially those without symptoms, suggests the effort is worthy of consideration. It's conceivable that FDA could update the vaccine guidance to include transmission data for licensure or in postmarketing studies.

Planning for Pediatric Sites

The path from the Pediatric Study Plan to enrollment has logistical hurdles distinct from adult clinical trials, even in the absence of a pandemic. As mentioned in the first section, protocols must be feasible. Managing roadblocks, therefore, begins with planning protocol roll-out through the lens of pediatric investigators and their clinical trial teams. Equally important is appreciating the perspective of parents and their children to aid in planning for recruitment, compliance, and retention. Protocol feasibility should be thoroughly explored with potential investigators prior to finalizing the protocol.

Vaccine trials, especially for annual influenza vaccines, are generally conducted in settings that can accommodate a rapid flow and high volumes of participants. The pandemic has expectedly changed the routine of pediatric clinics and their clinical research. COVID-19 precautions such as temperature screening, social distancing, and hand sanitizing are now in place and must be integrated into the flow of protocol requirements. Added to the flow for COVID-19 vaccine studies will be safety precautions for handling biospecimens. Timely feedback from sites on their operational plans to run the trial can inform initial drafts of sponsor's operational manuals.

Pediatric sites conduct practice runs for vaccine trials, as a rule, to prepare for study visits once the final protocol and manuals are received. Although enrollment pace will likely be slower during COVID-19, a dry run will still be important to avoid missteps. Sponsors and their partners should be readily available to answer questions as sites work through the logistics of study visits.

Ethical principles on consent for pediatric trials require parental permission. Agreement (assent) from children, typically starting at age 5, is also required once age-appropriate information has been explained to them.[10] During this pandemic, sponsors and sites should prepare answers to foreseeable questions from parents and children related to the public discourse on COVID-19 and vaccine trials. Checklists could be used by sites for important points and consistent messaging across study sites. Ideally, dry runs should also include investigator and staff role-playing for the parental consent and child-assent process to answer questions about procedures and safety.

Pediatric sites typically have waiting areas designated for research participants. Books, toys, and games may be more limited due to COVID-19, or else will require frequent disinfection. Sites may need to adjust those areas, especially for postvaccination observation periods. Sites may also need temporary barriers to separate participants. Sponsors should consider reasonable remuneration to support those efforts.

Sponsors and pediatric sites rely on age-appropriate materials for children and their parents to promote recruitment and compliance through the final study visit. These materials will need to counteract inaccurate information about vaccine research in general and specifically about COVID-19 prevention and spread. Several approaches could be used to identify concerns for designing materials. For example, child and/or parent focus groups and surveys are useful, especially for novel products and complex protocols. Pediatric advocacy groups are also a source for eliciting perspectives of parents and children.

The time expended by pediatric sites to enroll, conduct visits, and monitor safety is inherently greater than in adult trials. The so-called “hidden cost” differences are obvious, but sometimes overlooked in preparing site budgets. Each encounter involves a child participant and their parent. Beginning with the consent process, duration for discussions with a parent and age-appropriate engagement to obtain assent from young children and adolescents can be understandably longer than in adult trials. Time involved in collecting vital signs is also longer, especially when corralling active toddlers. The same applies to nasal swabs, blood collection, injections, and other procedures that will be included in COVID-19 studies. In summary, plan for higher reimbursement to sites.

Bridging Expertise With Implementation

As the ultimate healthcare-enabling research organization, the mission of Elligo Health Research® is to bring clinical research directly to clinical healthcare, solving patient-access challenges by enabling research as a care option. Through their existing capabilities, the company was able to immediately contribute to ongoing, crucial efforts to fight the pandemic. As one of the few companies to project-manage and staff drive-by COVID-19 test sites since mid-March, Elligo has the knowledge and solutions needed to support vaccine trials including:

- A network of practices, including more than 25 sites capable of conducting vaccine trials, enabling enrollment for the entire trial and for many protocols.
- The approved infrastructure, training, and research personnel needed to seamlessly integrate vaccine trials into current physician workflows to support trials.
- Tech-enabled solutions such as the IntElligo® Research Stack proprietary system designed to streamline data collection at the point of care, automating it for regulatory compliance and study-operational management while enabling a real-time view of all trial information in one place.

As clinical trials for COVID-19 vaccines continue to evolve, Elligo understands the need to work efficiently, safely, and inclusively to successfully provide treatments to patients including adults and children. Elligo’s proactive strategies will ensure integrity of the data and safeguard our heroic participants—children and parents.

[1]Dianne Murphy, M.D., is former Director, Office of Pediatric Therapeutics. FDA Pediatric Advisory Meeting, 1999.

[2]FDA Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19 (June 2020).

[3]FDA Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans (July 2020).

[4]FDA/EMA Common Commentary on Submitting an initial Pediatric Study Plan (iPSP) and Paediatric Investigation Plan (PIP) for the Prevention and Treatment of COVID-19 https://www.ema.europa.eu/en/documents/other/fda/ema-common-commentary-submitting-initial-pediatric-study-plan-ipsp-paediatric-investigation-plan-pip_en.pdf (accessed August 30, 2020).

[5]https://www.nih.gov/research-training/medical-research-initiatives/activ/sars-cov-2-vaccine-clinical-trials-using-activ-informed-harmonized-protocols (9/4/2020).

[6]Rajapakse, N. and Dixit, D. (2020): Human and novel coronavirus infections in children: a review, Paediatrics and International Child Health.

[7]Han, MS et al. Clinical characteristics and viral RNA detection in children with Coronavirus Disease 2019 in the Republic of Korea. JAMA Pediatr. (8/28/2020).

[8]"Mass General study finds children have high COVID-19 viral load despite mild or no symptoms," Press Release, (8/20/2020) https://www.massgeneral.org/news/press-release/Massachusetts-general-hospital-researchers-show-children-are-silent-spreaders-of-virus-that-causes-covid-19 (accessed 9/12/2020).

[9]WHO Target Product Profiles for COVID-19 Vaccines (4/29/2020) https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines (accessed 9/8/2020).

[10]Simar, MR, The Consent and Assent Process in Pediatric Clinical Trials in Pediatric Drug Development: Concepts and Applications, Second Edition. Mulberg, AE, Murphy, D, Dunne, J., and Mathis, LL (2013).

About Elligo Health Research®

Elligo Health Research, a healthcare-enabling research organization, uses electronic health records and the trusted patient and physician relationship to ensure all patients have access to clinical research as a care option. Powered by our *Goes Direct*® approach and novel IntElligo® Research Stack clinical technology, our team provides access to the best healthcare experts, patients, and research technologies. We engage physicians and patients who otherwise would not participate in clinical research and accelerate the development of new pharmaceutical, biotechnology, and medical device and diagnostic products. Learn more at elligodirect.com.