Pediatric Studies in the Retina Space

Pediatric trials present unique challenges during the recruitment and treatment phases.

BY ARON SHAPIRO AND NICOLE KELLEY

Although the adage "A spoonful of sugar helps the medicine go down" may hold true for run-of-the-mill pediatric illnesses, the complex diseases of the retina that affect the understudied pediatric population and the demands of pediatric clinical trial recruitment require stronger solutions than incentivizing kids' cooperation with the promise of a lollipop. Clinical studies are now required to address how new treatments might affect pediatric populations, either by studying neonates and infants (0-1 years), young children (2-7 years), older children (8-12 years), and adolescents (13-17 years) directly; extrapolating data from adult studies to pediatric studies, using detailed explanation and supportive data; or requesting a waiver that specifies limited recruitment potential or the unlikelihood of treatment success in children. When a pediatric patient has a disease that exists exclusively (or almost exclusively) in adults, the clinical study team may request a waiver of pediatric study from the US Food and Drug Administration. Conditions that affect neonates and infants are likely treated in a hospital setting and are unlikely to be studied in the clinic. For retina conditions that affect young children, older children, and adolescents that can be studied in the clinic, study staff can make several meaningful accommodations for these young, vulnerable patients. This article looks at obstacles involved in pediatric retina studies and how specialists might address them.

RECRUITMENT

The most challenging aspect of studying children is perhaps the most obvious: recruitment. Historically, and with good reason, parents have been reluctant to risk their childrens' safety on an unproven treatment. When the benefits outweigh the potential risk, such as palliative treatments for potentially terminal or painful retinal diseases of childhood, recruitment is not difficult. Because many untreated retinal conditions can result in blindness, the balance of a study's risks and potential benefits usually tilts in favor of trying experimental treatments. Clinicians who demonstrate both scientific rigor and the ability to work effectively with children can play a pivotal role in recruitment, inspiring confidence in parents who are considering permitting their children to participate in a study.

Adults seeking treatment naturally gravitate toward the authority of an experienced investigator's credentials. The most successful clinicians, however, will gain an edge in pediatric recruitment by thinking like the parents of their potential subjects. Natural reluctance to place one's child at risk or to cause pain or discomfort through participation in a study, however unfounded that fear may be, is a question the careful clinician addresses during the first encounter with potential particpants and their parents. At the beginning of the process, it is important to demonstrate to the parents that you, as a physician who works well with children, have a high level of care and concern. First, greet the child and demonstrate this important care and concen to the family. Next, turn your attention to the parents and focus on their understanding of the study. For most potential participants and their families, being monitored frequently by highly qualified medical personnel is a strong motivating factor. Discuss parental expectations and ensure that they are realistic and appropriate to the investigation.

Make sure the parents understand every aspect of the study goals and procedures, including randomization. Some parents may be under the impression that participation in the study guarantees access to the active treatment arm. Properly educated parents will act as allies, helping their child comply throughout the duration of the study. Take time to completely review the written informed consent, which makes the rewards and potential risks of treatment clear. Spend extra time on the risks stratified by likelihood, which can help reassure parents that their medical decisions on behalf of their children are made with a thorough understanding.

INFORMED ASSENT

Once the investigator has established comfort and understanding with the parents, it is time to return attention the child. Depending on the age of the potential subject and the nature of the study, consider the informed assent process, which is separate from and in addition to the informed consent process. With informed assent, children themselves consent to participate in a clinical trial and acknowledge the right to withdraw from study at any time. To determine if informed assent and consent are needed, check the Rule of Sevens guidelines, recently recommended by the American Academy of Pediatrics. The Rule of Sevens divides a child's life into 3 sections: birth to 7 years, 7 years to 14 years, and 14 years to 21 years. In brief, before age 7, children are not considered able to perform autonomous decision-making. At age 7, they can distinguish right from wrong. Adolescents 14 years and older are considered completely accountable. Note that if children supply informed assent, parents must still sign an informed consent form, which demonstrates parental responsibility for their minors during the study.

CHILD DEVELOPMENT EXPERTS

The expertise of the investigation staff is reassuring to parents and study staff at all stages of the study, so some sites chose to confer with a child life or child development specialist. These professionals have focused their careers and training on communicating at the level of the child in the most emotionally, cognitively, and linguistically appropriate manner. A child development specialist can support drafting the highest quality informed assent in the early recruitment period and can act as an onsite resource once recruitment begins. For example, child specialists could help regular study staff welcome children and families who may be still be raw from dealing with a difficult diagnosis or who show unanticipated treatment reluctance onsite. In addition, child life specialists are well versed in developmental stage needs that fuel the types of play or behaviors study staff might find puzzling or even challenging and can step in to promote harmonious interactions. Because their professional focus is on children and families and not on medical treatment or compliance, child specialists offer another potential avenue for engaging children and parents in willing, confident study participation. Their experience supporting families throughout a variety of potential medical interventions can ensure an optimal study experience at all stages, including exit and follow-up.

COMMUNICATION

Some communication tactics to employ with pediatric subjects are universal. Interaction with the staff must be friendly and positive, with as much direct conversation at the child's eye-level as possible. Greeting children warmly and by name can never hurt. Explaining upcoming procedures, and providing an ongoing narrative of these procedures in real time builds strong levels of empowerment in many children and adolescents. Listen carefully to their concerns, and allow them to ask questions throughout the procedures, if possible. Young children, however, may be overwhelmed by too much verbal information.

A few well-planned visual aids can be the difference that transforms a difficult patient into a cooperative one. Young children lack a concrete conception of time, so use of an hourglass or other kind of visual timer minimizes anxiety and helps them know when procedures will end. A visual schedule of the visit—labeled or numbered pictures of what will happen first, second, and third—can help children cope with abstract concepts beyond their understanding. A visual procedural map, with pictures of each step of the procedure labeled in numerical order, or a cartoon drawing of such, can cue appropriate anticipation in advance instead of on demand, when children may be too overwhelmed to respond quickly.

Although communication between investigators, staff, and families is critical to a successful pediatric trial, it is important that the clinic itself become a friendly physical environment. Tours of the facility may need to be repeated for younger children to provide a sense of security. Supply age-appropriate waiting room materials, such as books, games, and busy boxes. Adolescents may prefer a separate waiting area or nook where they are allowed to bring their personal electronic devices such as iPods, cell phones, or tablets. Study staff will earn points with these study participants when they are recognized as participants who are capable of more autonomy than younger participants.

We often speak to the benefits of conducting clinical trials, including the satisfaction that comes from knowing that you are contributing to the advancement of retina care. Working with children offers an opportunity to expand these contributions while potentially helping individual children improve their health. Ultimately, children are not miniature adults, and their unique, complex needs, along with the needs of their parents, must be considered when initiating clinical trials.

Lastly, don't forget the candy bowl (or at least a sugar-free recognition, such as a sticker) for a job well done. ■

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