Not Just Tiny Humans: Considerations for Conducting Pediatric Clinical Trials

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When it comes to the conduct of pediatric clinical trials, there are number of things you need to consider in order to ensure the successful conduct of a study. While we can't predict the outcome, planning ahead for appropriate site and subject selection will take you one step closer. From study design to logistics to recruitment, there are real differences between studies conducted in pediatric populations and studies conducted in adult populations.

PATIENT RECRUITMENT

While patient recruitment can be challenging in any study, there are additional challenges to recruiting pediatric patients. Parents may be more risk averse to giving an unproven therapy to their child than they would towards receiving it themselves. To improve the chances of successfully enrolling a study, it is important to consider potential motivators for participation:

- **Therapeutic benefit:** If you are working on a therapy for a rare disease or for an indication where there is no approved or effective product, parents may be motivated by the opportunity to receive treatment that could improve their child's condition even if it isn't proven and if there is a chance they will receive placebo. When there is an approved effective treatment available parents are likely to be reluctant to sign their child up when they may receive placebo, receive a treatment whose effectiveness is unknown, or receive a treatment with unknown side effects and safety issues.
- **Financial incentives:** Many studies offer financial incentives to participants, and this can be a motivating factor for some parents. Additionally, patients may receive study related medications, assessments, or more routine care that could be cost prohibitive otherwise.
- **Research benefit:** Particularly for studies in rare disease or orphan indications, parents may see the benefit in research that provides a better understanding of the disease or the prospect of better treatment options in the future even if their child does not receive a direct benefit in participation.

Understanding what motivates parents to allow their child to participate in a clinical research study will help you to determine how to advertise and recruit for your study. Some recruitment tactics (with appropriate ethics committee approval) to consider include:

- Directly reaching out to parents by calling or through email.
- Advertising at family events or locations where children and parents are likely to attend.
- Reaching out to healthcare providers who may be the patients' first point of contact even if they are not the location where the study will be conducted. For example, if you conduct a study where the sites and investigators are typically at specialty practices, you may still want to recruit through primary care providers.
- Consider referral processes for these types of sites to ensure patients are considered in a timely manner, based on their indication/treatment needs.

PATIENT RETENTION

Getting pediatric patients enrolled in a study is great, but it is just as important to make sure most patients are completing the study. There are a number of factors that make this more difficult in a pediatric study:

- **Multiple schedules to coordinate:** Each study visit requires both the parent and child to be available. Studies with numerous visits can become a significant hassle for parents, which can lead to discontinuations. Making sure that every visit is necessary and being as accommodating as possible with scheduling, such as including flexible visit windows can mitigate this risk. (Remember: Most of the parents still have to work and kids attend school).
- **Parents don't see the therapeutic benefit:** If parents come to believe that their child is receiving placebo or that the treatment is ineffective, they may withdraw their child from the study. Providing clear information about what the trial is evaluating and encouraging frequent communication will help facilitate the parent voicing any concerns.

- **Discomfort of participation:** No one likes long doctor visits or being stuck repeatedly with a needle, but these discomforts are even harder on pediatric patients and their parents. Evaluate each assessment carefully during protocol development (even ones like blood pressure and temperature monitoring) to reduce the overall burden to the patient.

What can be done to improve retention? Encourage investigators to talk with parents about the importance of completing the study. Consider what incentives may be appropriate to improve retention and work within the limitations of what the IRB will allow based on your study. Cash incentives may be effective with older patients and with parents. In some cases, we've seen where study information or assessments are loaded on a device like a tablet that the patient may get to keep at the end of the study. Treats or fun activities such as coloring books or video games to play at study visits can be good incentives for younger patients. Keep in mind that there may belimitations on what you can provide as incentives. All incentives will require IRB approval. Finally, keep visits as short as possible, limit blood draws and invasive procedures, that every procedure and assessment is truly necessary to determine the safety or efficacy of the investigational product.

INFORMED CONSENT

Pediatric studies introduce several challenges when it comes to informed consent:

- Typically, if patients are at least 7 years old, in addition to parental consent you will need assent from the patient. Assent documents will need to be written at an appropriate reading level.
- In pediatric studies, parents are likely to want to know which treatment their child received and the outcome of the study after the study is complete. Information on whether this will be made available needs to be included in the consent document.
- You will need to decide whether consent is required from both parents. If not, and the parents are divorced, can either parent make the decision? If you do need consent from both parents, this can be an additional hurdle to enrollment.

OTHER CONSIDERATIONS

In our experience there are a number of other considerations that require proper planning to ensure study success:

- **Pregnancy tests:** In many cases, pregnancy tests will be needed for female patients. Depending on the age of the child and the view of the parents, this may be a hurdle. In many cases, these tests are required at an earlier age than parents anticipate—typically as young as 9 years old. Parents and patients do need to be informed if the test is being done.
- **Objective outcomes:** For studies with young patients, objective outcomes are highly preferable to outcomes that rely on the reporting of the patient or parent. If patient-reported scales are used, staff will need to be trained to get answers from the patient rather than the parent.
- **Sibling bias:** The protocol will need to specify whether siblings can participate in the study. Allowing siblings to participate may be helpful for enrollment, but it can also introduce bias into the results and potentially create a risk if home treatment is required. There is a risk that if siblings are in different treatment arms, the treatments could be mixed up, while at home, resulting in subjects receiving the incorrect treatment.
- **Dosing during school hours:** If the protocol requires dosing during school hours, this may require extra paperwork/legwork on the part of the parent to gather supportive information allowing the school staff to give this investigational product (IP). Many schools will not give IP to students and may not allow students to retain IP even if it is self-administered.
- **Missed school:** Frequent visits during the school day or overnight visits may cause absenteeism issues for school-aged children.
- **Continuation:** Consider whether participants will be able to continue receiving the product after the study, for example, through an open label extension of the study. Even for a Phase III study, it may be several years before a product receives marketing approval.

Conducting clinical research in pediatric populations does introduce a unique set of challenges. With proper planning, however, many of these challenges can be avoided or mitigated.

ABOUT THE AUTHORS

Project Director Jamie Arnott, RN, BSN and Clinical Team Lead Caitlin Hirschman, RN, BSN have extensive experience in pediatric clinical research including recent studies in rare diseases and diseases with a seasonal component.