CTTI RECOMMENDATIONS:
IMPROVING PEDIATRIC TRIALS IN ANTIBACTERIAL DRUG DEVELOPMENT

BACKGROUND

Children should have access to antibacterial drugs that have undergone appropriate evaluation for safety and efficacy, yet many trial sponsors have challenges enrolling and completing pediatric antibacterial drug trials. Despite legislation enacted to facilitate pediatric drug development, such as the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), many of the antibacterial drugs commonly used in children lack adequate pediatric use information in drug labeling for all age groups, particularly neonates. The time between the approval of a new antibacterial drug for use in adults and pediatric labeling has recently been 5 years or longer, and pediatric studies have yet to be completed for a number of antibacterial drugs more than 5 years after approval in adults.

The goal of the CTTI Pediatric Trials in Antibacterial Drug Development (ABDD) Project was to identify and address barriers in conducting antibacterial drug trials in the pediatric population, with a focus on trial enrollment, design, conduct, and feasibility issues. The multi-stakeholder project team was made up of pediatric investigators, clinicians, and infectious disease specialists, industry scientists, patient advocates and regulators. To develop actionable recommendations for improving pediatric ABDD trials, the project team gathered evidence from interviews with parents and industry representatives, surveys of healthcare providers and clinical investigators, and consensus generated during a multi-stakeholder expert meeting.

Other CTTI resources that may be applicable to improving pediatric antibacterial drug trials, or pediatric trials in other therapeutic areas, include the following:

- Principles and Recommendations for Quality by Design
- Best Practices for Patient Group Engagement Around Clinical Trials
- Recommendations for Informed Consent
- Recommendations for Strategic Recruitment Planning
- Recommendations for IND Safety Assessment and Communication

RECOMMENDATIONS

Global Collaborations

Establish global collaborations, networks and master protocols to expedite the availability of evidence regarding the safety and efficacy of antibacterial drugs in children.

- Leverage pathways to achieve alignment between global regulatory agencies regarding pediatric drug development for new antibacterial drugs.[1]
  - When possible, coordinate submission of pediatric development plans to the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and other regulatory authorities when designing studies.
- Develop pan-global networks and master protocols to conduct pediatric antibacterial drug trials.

Pediatric Drug Development Planning

Sponsors should engage with the FDA with the goal of initiating pediatric studies of their new antibacterial drug as early in drug development as possible.

- Communicate with the FDA early in drug development to ensure a clear understanding of the FDA's recommendations regarding pediatric drug development for the new antibacterial drug.[2]
- Consider discussing the initial pediatric investigative plan (iPSP) with the FDA earlier in drug development than the current practice (for example, while phase 2 adult trials are underway).
- Consider initiating pediatric pharmacokinetic (PK) studies, especially in the older cohort of children, concurrently with adult phase 3 trials when appropriate.

Protocol Design and Development

Minimize the burden of participation for patients, their caregivers and study sites.

- During the design and development of the protocol, obtain the input of stakeholders who will be affected by implementation of the trial (e.g., nurses, study coordinators, parents, patients, clinicians, site investigators).
- Identify barriers that will affect trial efficiency and enrollment, including visit windows, invasive testing, endpoint timing, and length of follow-up.

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[1] See footnote 2 for FDA Guidance. See European Union Guidance for the Pediatric Investigative Plan and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Clinical Investigation of Medical Products in the Pediatric Population.

[2] See FDA Resources for Pediatric Drug Development, specifically sections II and IV (Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans).

- Consider potential logistical problems and solutions such as limiting site visits and the use of mobile or remote technologies.

- Fund studies to the level of the real costs of participation for sites and participants.
  - Develop standard guidelines for participant reimbursement.
- Streamline data collection[3] to include only that which is relevant to the goals of the trial.
  - Focus data collection on pre-specified, relevant outcomes, which should be primarily safety and PK, with efficacy endpoints as appropriate.
  - When efficacy in children can be extrapolated based on the demonstration of efficacy in adults, collection of efficacy data can be streamlined in the safety and PK studies

Improve consistency and standardization of adverse event reporting.

- Follow the FDA guidances provided[4] to help sponsors and investigators comply with requirements for safety reporting.
  - Improve consistency and standardization of adverse event reporting (e.g., address laboratory, clinical events, and expected comorbidities) between protocols and among sites. This is particularly important for trials in hospitalized children and neonatal trials.[5]

Broaden the eligibility criteria to be as inclusive as possible for more efficient enrollment.

- Restrict inclusion/exclusion criteria to those that are ***critical*** to achieving the trial's scientific goals and minimizing the risks to participating children.
- Consider simultaneous enrollment of all age groups above 2 years of age when appropriate (e.g., when there are no safety concerns), with sequential enrollment of children under age 2 years, including neonates.

Special Considerations for Trials in Neonates

Take special care when planning studies with neonates such as limiting additional sampling required while obtaining critical safety and drug exposure information for all stages of neonatal development.

[3] The term "data collection" refers to the recording of study-specific, relevant data in the case report form (CRF), not the comprehensive collection of data captured as part of routine clinical care.

[4] See the following FDA Draft and Final Guidances:
- Safety Assessment for IND Safety Reporting
- Determining the Extent of Safety Data Needed in Late Stage Pre-marked and Postapproval Clinical Investigations
- Safety Reporting Requirements for INDs and BA/BE studies

[5] England A, Wade K, Smith PB, et al. *Contemp Clin Trials*. 2016;47:376-382.

- Conduct studies using minimal, sparse sampling of blood or plasma to achieve an adequate understanding of drug exposure profiles for all stages of neonatal maturity, including extreme prematurity, before starting prospective treatment trials.[6]
- Conduct ***opportunistic*** cerebrospinal fluid (CSF) sampling sub-studies when necessary (e.g., collect samples only when a lumbar puncture is being done for clinical reasons).
  - Knowledge of CSF penetration is important for the treatment of sick neonates, but these data are lacking for many antibacterial drugs used in clinical practice.
  - Appropriate animal and in-vitro models, the anticipated PK-PD profile, and pathogens being targeted by individual antibacterial drugs should be taken into consideration to guide dose selection and planning of CSF assessment in neonates.

Informed Consent

Train research and hospital staff on the challenges typically faced when obtaining consent in the pediatric patient population, with an emphasis on best practices for the informed consent process with the families of seriously ill children.

- The parents of pediatric patients may be overwhelmed with the medical needs of their children, especially if a child is critically ill, leading to challenges in absorbing the information necessary to make an informed decision about their child's participation in a clinical trial.
- Sensitivity training is suggested for all personnel engaged in the informed consent process but should be streamlined, fit-for-purpose, and its frequency sufficiently flexible to accommodate different experience levels.
- When approaching families or caregivers for informed consent, consider the following best practices:
  - **Who:** The choice of who approaches a parent or caregiver to ask them to consider a clinical trial is of critical importance. The approach should be from a trusted source, preferably someone familiar with and involved in the child's care. Use study staff who are most knowledgeable about the child's infection and medical condition and who can best understand and communicate the study's objectives and design, as well as most effectively and confidently address the family's questions and concerns about ethical, risk/benefit, scientific, and other important issues. Consider involving the child's primary care provider in making the initial introduction of the study, or at a minimum, **create an advocate in the child's doctors, nurses, other allied health staff, etc.**, by educating them about the study before approaching the child's family.
  - **When:** Timeliness of the approach is important, especially in situations of critical illness due to infectious diseases or very fragile children or babies. Apply "reasonably available" criteria to obtaining physical consent (i.e., a signature)

[6] See the FDA's Draft Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products.

when one parent or caregiver is physically present while the other is not physically present but is available (e.g., by phone).[7]

- **How:** Those who approach the family or caregivers should be sensitive, compassionate, empathetic, concerned, and familiar with the child's medical care and family situation.

Design the informed consent process and document to empower families to get the information they need to better understand the trial and decide whether their child should participate

- Create a mechanism for parents to engage with other participating parents about clinical trials in general or specific studies.
  - Support the training and development of experienced family or peer navigators to guide inexperienced families and children through the clinical trial process.
  - With the assistance of family or peer navigators and other stakeholders, develop a list of "frequently asked questions" (FAQs) about the study and participation.
- Consider the utility of electronic informed consent,[8] which may reduce pressure and anxiety as information is absorbed by providing supplemental information in tiered formats.[9]
- Always use lay language.
- Clearly convey the following information:
  - That the child's safety and well-being are of primary importance to all involved.
  - How the child may benefit from participation.
  - The study interventions the child may receive, in contrast to the standard of care.

Engaging Healthcare Providers

Provide education and support for healthcare providers to increase their involvement with or referral to pediatric antibacterial clinical trials.

- Determine the best mechanisms for educating general and subspecialty pediatricians (e.g., hospitalists, neonatologists), surgeons, family practitioners, and other referring healthcare providers about the value of new antibacterial drugs and the need for pediatric clinical trials.
  - Emphasize that conducting research *may* provide evidence regarding the safety and efficacy of antibacterial drugs in children.
  - Develop mechanisms for improving awareness of ongoing or planned antibacterial clinical trials.
- Establish trusting relationships with referring healthcare providers.

[7] See the FDA's Informed Consent Information Sheet: Draft Guidance for IRBs, Clinical Investigators and Sponsors.
[8] See the FDA's Draft Guidance, Use of Electronic Informed Consent in Clinical Investigations: Questions and Answers.
[9] See CTTI's Recommendations for Informed Consent for more information about tiered informed consent documents and the consent process.

- Engage pediatric providers by highlighting ***that studies are designed to provide answers they need*** to engage in evidence-based shared decision-making with the families and children they serve.
- Provide support for the extra time needed by clinicians to discuss trial opportunities with families.
- Keep healthcare providers apprised of their patients' progress in clinical trials.

- Provide adequate support for healthcare providers who wish to become investigators.

Pediatric Labeling

Engage all stakeholders in continuing discussion around pediatric labeling for antibacterial drugs to expedite the availability and increase the appropriate use of this important safety and efficacy information.

- Educational efforts are needed to ensure that healthcare providers and parents understand how to read, interpret, and find specific pediatric information in drug labeling.[10]

Reporting Trial Results

Report pediatric trial results so that these data are available to health care providers.

- Report pediatric trial results upon completion to ClinicalTrials.gov.
- Submit manuscripts to journals for publication consideration in a timely fashion.
- Present results at major meetings and conferences to allow for dialogue and discussion.

- *These recommendations are based on results from CTTI's ABDD Peds Trials Project.*
- *CTTI's Executive Committee approved the recommendations.*
- *Released in February 2017*

[10] See the FDA's Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling.