Understanding Pediatric Clinical Trials—A Guide for Families

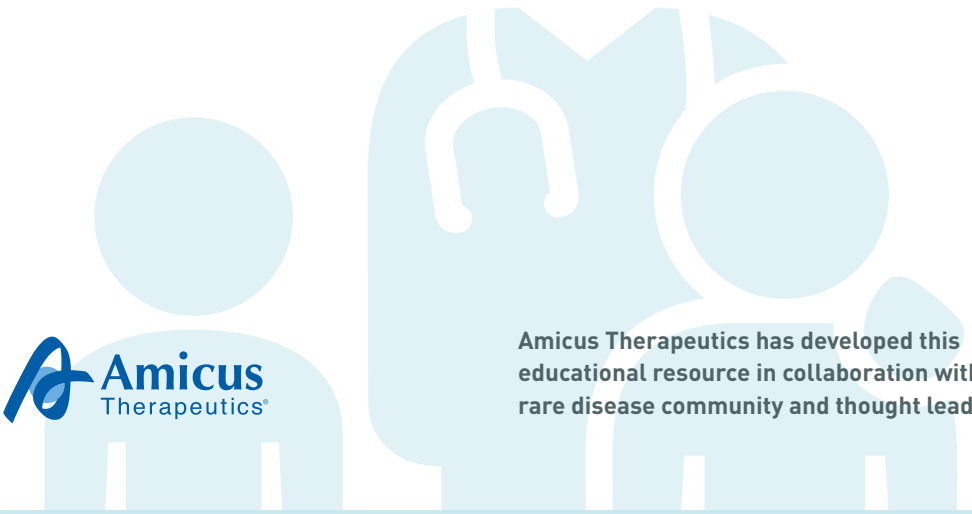
Why clinical research in children is so important—and information to help you to decide if joining a pediatric clinical trial is the right choice for your family

Clinical trials (types of medical research conducted in people, rather than in the laboratory or in animals) are the final and most essential stage of developing a new medicine or other new medical therapy. Their purpose is to evaluate the direct effects of potential new therapies (sometimes called investigational drugs or investigational therapies) in human health.[1]

Results from clinical trials provide the key information required for the approval of any new therapy: they provide information about a new therapy's safety and effectiveness, and help confirm its proper dosing regimen. This means that without clinical trials—and the people who volunteer to participate in them—developing new therapies for any disease or condition would not be possible.

People of all ages take part in clinical trials. This brochure describes why pediatric* clinical trials—clinical trials conducted in children—are so important, and offers information that may help children and their parents or legal guardians decide whether participating in a clinical trial is the right choice for them.

*Note: In clinical trials, a pediatric patient is usually defined as a person who has not yet reached the age when they would legally be considered an adult in their country of residence.



Amicus Therapeutics

Amicus Therapeutics has developed this educational resource in collaboration with the rare disease community and thought leaders.

The importance of pediatric clinical trials in advancing children's health

Why clinical research in children is so important, why too little was done in the past and how laws and regulations are helping increase progress

Children have different medical needs than adults

Children typically receive health care from pediatricians—health-care professionals (HCPs) who specialize in preventing and treating disease in young people, from birth through the beginning of adulthood. Children are cared for by pediatric specialists because their bodies are fundamentally different from adult bodies in several important ways:[2]

- Certain diseases primarily or only affect children, or (in the case of some chronic or rare diseases) are usually first diagnosed during childhood
- Diseases that can affect both children and adults may progress at different rates, or may involve different signs and symptoms,* depending on the person's age
- Children's bodies often process and react to medications differently from adult bodies

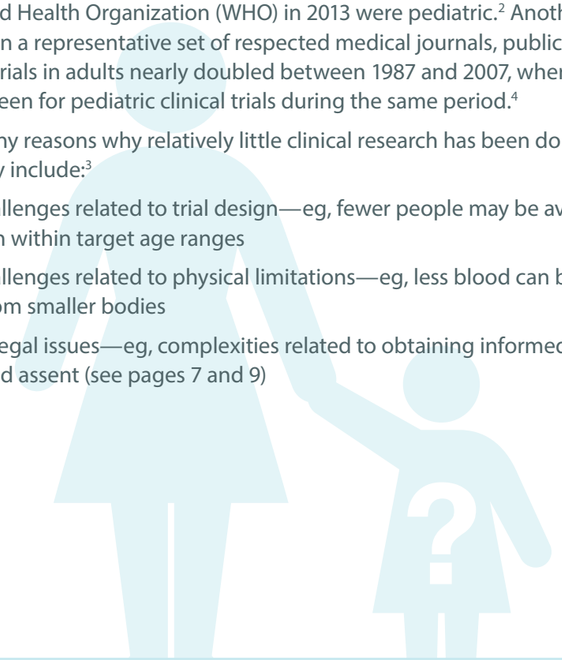
*Signs are evidence of a disease or condition that can be measured or recognized by others (eg, low blood pressure); symptoms are evidence of a disease or condition that can be recognized only by the patient (eg, a headache).

Children are underrepresented in clinical research

Although the medical differences between children and adults are well recognized, limited clinical research has historically been done in children.[2,3] Although children make up more than one quarter of the world's population, only 17% of clinical trials registered with the World Health Organization (WHO) in 2013 were pediatric.[2] Another review showed that in a representative set of respected medical journals, publication of results from clinical trials in adults nearly doubled between 1987 and 2007, whereas almost no change was seen for pediatric clinical trials during the same period.[4]

There are many reasons why relatively little clinical research has been done in children. They include:[3]

- Practical challenges related to trial design—eg, fewer people may be available for participation within target age ranges
- Practical challenges related to physical limitations—eg, less blood can be collected from smaller bodies
- Ethical and legal issues—eg, complexities related to obtaining informed consent and informed assent (see pages 7 and 9)



Although these challenges have limited clinical research in almost every area of children's health, their impact in rare diseases has been especially severe. Many pediatric rare diseases are serious, chronic and sometimes life-threatening conditions, which make the ethical issues involved in clinical research more complicated. And because patient populations in these diseases are (by definition) even smaller, some practical and financial roadblocks may be more difficult to overcome.

Pediatric clinical trials are needed to develop new therapies for diseases affecting children

Pediatric clinical trials are essential to advancing children's health care. In one well-known example, large-scale pediatric clinical trials held in the 1950s and early 1960s made it possible for vaccines to be developed for polio—a disease that had once crippled or killed thousands of children every year—and widespread polio vaccination programs have since resulted in near-complete eradication of the disease worldwide.[5-7] Pediatric clinical trials have also contributed to dramatic progress in the treatment of childhood cancers. With the availability of new and better therapies, more than 80% of pediatric cancer patients can now expect to survive into adulthood.[8]

Unfortunately, similar successes have not yet been seen in many other diseases that affect children—partly because not enough pediatric research is being done. Relevant clinical trials are lacking, resulting in great unmet needs.[2,9]

Pediatric clinical trials provide important information about the safety and effectiveness of existing medications in children

Many medications regularly used to treat children have been clinically studied only in adults. As many as 1 in 3 medications prescribed to children in the non-hospital (outpatient) setting have not been studied in pediatric clinical trials and are not approved by regulatory authorities for use in children.[10] In the hospital setting (inpatient), as many as 79% of children are treated with medications that are not approved for use in children.[10] The lack of pediatric clinical data for existing medications can negatively affect medical care in children in a number of ways.

When HCPs do not have age-specific data about a medication, they generally prescribe it to their young patients according to research done in adults. But data from clinical trials in adults do not always translate well to the treatment of children. Children's bodies are constantly growing and changing, sometimes very rapidly. They often respond to medications differently from the bodies of adults (or even younger or older children). Determining the correct dose of a medication for a child is often more complex than simply adjusting the recommended adult dose for a smaller body. Many other considerations can come into play, such as how and when different organ systems mature, as well as age-related variations in the amount of certain substances produced by the body (such as enzymes) that are involved in processing medications.[2,11]

Because of this, when medication doses are calculated for children based on clinical data from research in adults, the amount of medication may be too high or too low. This may result in increased side effects or reduced treatment efficacy. For example, children's bodies process cyclosporine—a drug used to reduce immune response—more quickly than adult bodies. When a child is prescribed cyclosporine based on the appropriate dosage for adults, the amount of the drug in the child's body may be too low, making the treatment less effective.[2]

Medications that have not been clinically studied in children also may also cause different or unexpected side effects when prescribed to pediatric patients. For example, when the antibiotic tetracycline is given to children in a certain age range, it can cause the enamel (the outside coating of teeth that is usually white) of their developing adult teeth to become permanently darkened or discolored.[2] Phenobarbital, a drug often used to help control seizures, can cause hyperactivity in children, despite having a sedative (calming or sleepiness-inducing) effect in adults.[2]

Also, when data from pediatric trials are lacking, safety concerns or other uncertainties may make HCPs reluctant to prescribe certain medications for children at all, even when they could potentially be beneficial. This may further limit treatment options for children.[10]

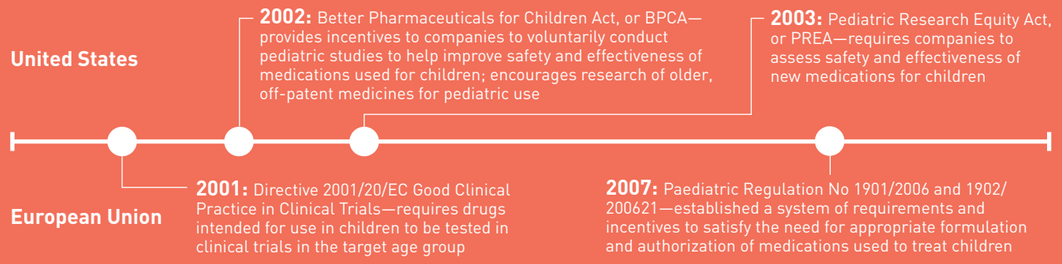
What is being done to encourage more clinical research for children?

The need for more, and better, pediatric clinical research has been recognized for more than half a century. Harry Shirkey, an influential pediatrician and pharmacologist, was one of the first HCPs to help create awareness of the need for more pediatric clinical research. Fearing that medical progress was bypassing children, in 1968 Dr. Shirkey urged scientist to develop strong pediatric research programs to keep children from becoming what he called "therapeutic orphans."[12]

Progress was slow. In 1994—almost 25 years later—nearly 80% of drugs still lacked a pediatric "label" (official data and guidance for HCPs about the safety, effectiveness and dosing of a medication in children).[12] But over the following decades, important new laws and policies were put in place by health authorities around the world (see box below) that successfully increased pediatric clinical research and contributed to the development of new therapies for diseases affecting children.[2,13]

Milestone laws and regulations in pediatric clinical research[2,13]

Key incentives and legislation introduced by regulatory agencies of the United States (US Food and Drug Administration, or FDA) and European Union (European Medicines Agency, or EMA) to encourage and/or require research on the efficacy and safety of new and existing medicines in children are listed below. European Union regulations have a broad impact because the EMA also regulates drug research in much of Australasia and some other regions throughout the world.



Information for families considering enrollment in a pediatric clinical trial

What to expect—and some things to consider—when deciding whether to join a clinical trial

Learning and making decisions as a family

When a family is considering enrolling their child in clinical trial, it can be important that the child participate as much as possible in the decision-making process, according to his or her age and abilities. Even very young children have the right to learn about the trial and to weigh its potential benefits and risks. Many older children are capable of being equal partners in the decision to enroll. This means that all children who are capable of understanding spoken and/or written language and of asking questions could be included in discussions about the trial—both with the trial investigators and within the family—and can have a voice in the decision of whether or not to participate.[14]

The trial investigators (sometimes also called the research team or study site team) will help with the decision-making process by providing important information about the clinical trial in language that each family member can understand. They will explain:[14,15]

- Who can enroll in a trial (ie, eligibility requirements such as age, medical history and current health status)
- The goals of the trial (ie, the specific research questions the trial is designed to answer)
- The treatment(s) being studied
- All medical procedures or tests that may be required during the trial
- The personal health data to be gathered from participants during the trial, and how this data will be used and protected
- Any anticipated risks to participants, as well as the actions or rules put in place to help protect participants from risks
- Any potential benefits to participants
- The time commitment required to participate in the trial (including how long the trial will last, the number of office or hospital visits that will be required and any travel that could be involved)
- The participants' rights and responsibilities

During this process, each family member will be given the opportunity to ask the investigators questions about anything they do not understand or wish to learn more about (see pages 7 and 9 for a list of questions to consider). The family should also be given time to discuss their thoughts and concerns among themselves—as well as with other trusted individuals, such as the family pediatrician—before making the decision to enroll.

Weighing risks and benefits

Potential new therapies must demonstrate acceptable safety profiles in preclinical testing (ie, research done in the laboratory and in animals) before they can be tested in people. However, it is important to understand that clinical trials do not always offer benefits to participants, and that they may involve risks, some of which may not be anticipated by the researchers.[1]

Many clinical trials involve certain general risks and benefits. These may include the following:[16]

Potential benefits

- Gaining access to an investigational therapy before it is widely available
- Receiving close medical attention from an expert team of researchers and HCPs
- Helping other families by contributing to general medical knowledge and/or the development of a new treatment

Potential risks

- Discomfort or problems caused by treatments, tests or other procedures involved in the trial study
- Inconvenience resulting from the required procedures and office or hospital visits

The research team will describe the potential risks and benefits that could be involved in the specific trial being considered. It's especially important to make sure that all family members understand the potential benefits and risks that could be involved in the trial before deciding to participate.[16]

Providing informed consent

After all the family members have been fully informed about the trial and the family decides to move forward, the parent(s)/legal guardian(s) of the child who will be enrolling may be asked to read and sign a document called an Informed Consent Form, or ICF. The ICF provides information about the purpose, design, potential benefits and risks and other important aspects of the clinical trial in written form.[14]

A signed ICF is required to join most clinical trials. It serves as proof that sufficient information has been provided to allow the participant (or, in the case of pediatric trials, the participant's parent(s)/legal guardian(s)) to give informed consent, which is defined as an educated decision to join a trial. However, it is very important to understand that anyone can choose to withdraw from a clinical trial at any time, for any reason.[14]

In pediatric clinical trials, written informed consent is often required from both parents for a child to enroll. However, there are exceptions. These include cases when the child's legal guardian(s) are not his or her parents, cases when only one parent is listed on the child's birth certificate and other specific scenarios. Informed consent requirements also may vary in other ways depending on factors such as the design of the trial and the country in which the trial is to be conducted.[14,17]

Questions to consider in deciding whether to enroll your child in a pediatric clinical trial

Investigational treatments

- What is the treatment being studied? Has this treatment been studied in other clinical trials?
- What other treatments will be given to trial participants? Will any participants receive a placebo (a substance that has no therapeutic effect and no interactions with other medications)?
- How will it be determined which treatment I/my child will receive (for example, by chance)?
- How do the treatments I/my child will receive in this trial compare with other treatment options (if any)?
- How will the treatments provided during the trial affect my/my child's existing treatment plan (if any)?
- If I/my child benefit(s) from the treatment received, will I/my child be able to continue receiving it after the trial ends?

Notes

Trial requirements

- How long will the trial last?
- What tests or other procedures will be involved in the trial?
- By when (ie, what date) must we decide whether to join this trial?
- Who will be available to answer our questions before, during and after the trial?
- How and when will we be told about the trial results?
- Will the trial involve any long-term follow-up?

Notes

Although young people generally must provide informed assent to participate in a clinical trial (see *Understanding the importance of informed assent*, below), they ordinarily cannot provide legal informed consent for their own enrollment until they reach a specific age—usually 18, but sometimes younger—as defined by the laws of their country.[14,17] However, some young people who have not yet reached that age may be able to provide legal informed consent under certain circumstances.* These include:[14,17]

- **Mature minors**—young people who are judged to be mature enough to make certain decisions about their own health care under specific circumstances
- **Self-sufficient minors**—young people who are above a defined minimum age and who live independently and are financially self-sufficient
- **Emancipated minors**—young people who have been released from parental custody or control by events such as marriage, military service or court order

*Whether or not parents or guardians must be informed about (or must give permission for) the participation of mature, self-sufficient or emancipated minors in clinical trials may vary depending on the laws of the country or region, the design of the trial and many other factors.

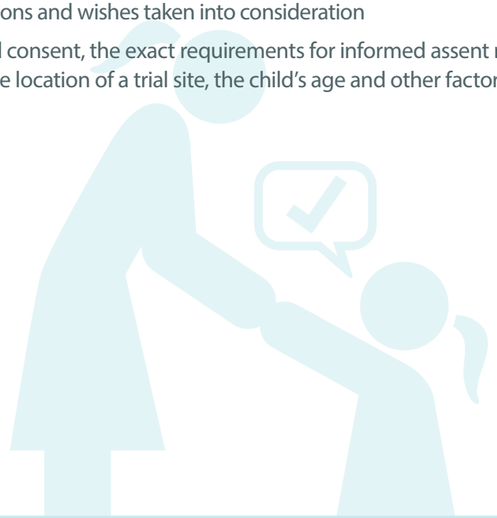
Understanding the importance of informed assent

Informed assent—defined as permission or agreement given by a child to join a clinical trial, after having been fully informed about the trial at an age-appropriate level—is an important ethical requirement in pediatric clinical research.[14] As mentioned above, most pediatric clinical trials require informed assent from the child who will be enrolling, in addition to informed consent from his or her legal guardian(s).

The informed assent process gives all children (regardless of age) who are able to understand basic facts about the trial the right to:[14]

- Have researchers and family members try their best to help them understand what the trial involves, including its goals, design and potential risks and benefits
- Have the opportunity to ask questions
- Consider whether or not to give assent
- Have their opinions and wishes taken into consideration

As with informed consent, the exact requirements for informed assent may vary depending on the location of a trial site, the child's age and other factors.[14,17]



Benefits and risks

- What benefits might the trial offer?
- What are the potential side effects or risks?
- How do the possible risks and benefits of participating in this trial compare with those of continuing my/my child's current treatment (if any)?
- Are other clinical trials being done to evaluate treatments for my/my child's medical condition? If so, how can we learn more about those trials to compare them?

Notes

Privacy and rights

- How will my/my child's health information be kept private?
- Who will have access to my/my child's health information?
- What happens if I/my child want(s) to withdraw from the trial or if I want him or her to withdraw?

Notes

Location and travel

- Where/how far away are the clinics and/or hospitals we will need to visit?
- How often will I/my child have to visit these clinics and/or hospitals?
- Will I/my child have to stay in the hospital during the trial? If so, for how long?

Notes

Costs

- Will personal costs involved in any travel required by the trial (eg, gas, meals, hotel accommodations, childcare for siblings) be reimbursed?
- Who will be responsible for any medical bills if I/my child experience(s) side effects or complications as a result of this trial?
- Will someone be available to help us answer questions from our insurance company (if necessary)?

Notes

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Please discuss any medical questions with a health-care professional (HCP).

If you would like to provide feedback on this educational resource or would like additional information please contact: **patientadvocacy@amicusrx.com**.

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Making the decision to enroll

For many families, the process of deciding whether to enroll in a pediatric clinical trial can be both exciting and challenging. The amount of new information—and the complexity of some of the considerations—may feel overwhelming at times. Here are some additional steps that may help with the process of gathering and evaluating information about the trial:

- Consider contacting a patient organization about other families who have participated or are considering having their child participate in the trial. Other families may be able to provide valuable additional perspectives that complement the information the family receives from the researchers
- Provide copies of the child's medical records to the trial investigators. These should include diagnoses, reports on imaging studies or other evaluations, all medications and supplements the child is currently taking and a full description of the child's current treatment plan. Having this information may help the investigators provide more personalized answers to some questions about participation in the trial
- Encourage family members to prepare questions in advance before each meeting with the research team. This can help ensure that that all potential concerns are addressed

Some questions families may wish to consider asking trial investigators are listed on pages 7 and 9. Space is also provided for any additional questions and notes. Consider using these pages as a resource and guide to help ensure that all family members receive the information they need.

Resources

To find out about upcoming and ongoing pediatric clinical trials, visit **clinicaltrials.gov** or **clinicaltrialsregister.eu**, or talk to an HCP.

To learn more about pediatric clinical research, visit:

- *fda.gov/drugs/development-resources/pediatric-product-development*
- *ema.europa.eu/en/documents/other/preparedness-medicines-clinical-trials-paediatrics-recommendations-enpr-ema-working-group-trial_en.pdf*

Amicus offers additional resources that provide information for families about various aspects of drug development and clinical research (listed below). Please contact us at **patientadvocacy@amicusrx.com** to request copies.

- *A Guide to Informed Consent*
- *The Drug Development Process: A guide to understanding how new therapies are created (with a special focus on rare diseases)*
- *Joining Together to Make a Difference: Contributing to research and advocacy for rare diseases*

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