

CLINICAL TRIALS

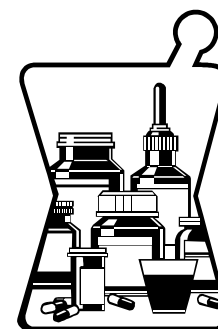
How Clinical Trials Work for Children

Today, there are only a handful of drugs approved by the U.S. Food and Drug Administration (FDA) to treat hepatitis B, C or D in adults. There are even fewer for children.

Most drugs used to treat children with viral hepatitis-related liver disease have been formally tested only in adult patients. Just two or three drugs have been fully tested in pediatric clinical trials involving children and adolescents ranging in age from infancy through age 17.

In general, more than 60 percent of all drugs used on children today have not been tested in pediatric clinical trials. According to the American Academy of Pediatrics, only a small fraction of drugs and biological products marketed in the United States, including Ritalin used to treat attention deficit disorder in children and Albuterol nebulizers used to treat asthma in children, have had extensive clinical trials performed in pediatric populations.

In 1991, 56 percent of new drugs (new molecular entities) approved by FDA that had potential usefulness in pediatric patients had some pediatric labeling that documented effectiveness and safety in children at the time of approval. In 1996, that number had dropped to only 37 percent.



The FDA is now developing new guidelines to force pharmaceutical companies to accelerate drug testing in children to ensure pediatric safety and effectiveness.

Drugs used to treat children with hepatitis are no exception in this pediatric drug oversight. There are only a few drugs and drug combinations now being tested in pediatric clinical trials. In some cases, especially in the treatment of children with hepatitis C with serious liver disease, doctors are permitted to use drugs that have only been tested and approved by the FDA for use in adults.

In an ideal world, researchers would have followed children with this disease for years and tested drugs in large groups of children of varying ages. But in the world of chronic viral hepatitis today, researchers have had limited time and limited numbers of young

patients to study in the search for a cure.

Before using “adult-tested” drugs in children with advanced liver disease, doctors must first obtain permission from their hospital or institutional review boards. According to guidelines, there should be some research or knowledge gained from this “one-child clinical trial” that can be shared with the entire medical community.

This case-by-case treatment can occur even if there are no other doctors or established pediatric clinical trials investigating the drug. A doctor can use the drug even if the pharmaceutical company has produced little research or documentation on the safety or efficacy of the drug in children. This is known as an “off label use” of a drug.

These single-child clinical trials are slowly building a core of information that will be tested out in comprehensive pediatric clinical trials that involve a larger group of children in the future.

But until that time, pediatric hepatologists and gastroenterologists are treating some children with viral hepatitis outside pediatric clinical trials, blazing new trails with each individual treatment along the way.

How Do Clinical Trials Work?

When a pharmaceutical company develops a new drug, it typically spends years developing the compound and testing it in a laboratory setting on human and animal cells. Then the drug is tested on living animals.

If these tests are successful, the pharmaceutical company provides its data to the FDA and requests permission, through an Investigational New Drug Application, to test the drug in humans in clinical trials, also known as medical research or research studies.

When it has the FDA go-ahead, clinical testing of experimental drugs is conducted in three phases. Each phase involves a larger number of people. Once the FDA has granted a New Drug Approval, pharmaceutical companies also conduct post-marketing or late Phase III or Phase IV studies.

- Phase I:

Phase I studies focus primarily on the drug's safety. This initial phase tests a small number of healthy volunteers, anywhere from 20 to 100, who are usually paid for participating in the study.

The study is designed to determine what happens to the drug in the human body, how it is absorbed, metabolized and excreted. A Phase I study investigates side effects that occur as dosage levels are increased. This initial phase of testing typically takes several months. About 70 percent of experimental drugs pass this initial phase of testing.

All studies are based on a set of rules called a protocol. A protocol describes what types of people may participate in the trial (age, illness, gender); the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

- Phase II:

Once a drug is proven safe, it must be tested for efficacy. This phase may last several months to two years and involve up to several hundred patients. Most Phase II studies are randomized trials. One group of patients will receive the experimental drug, while a second “control” group will receive a standard treatment or placebo.

Often these studies are “blinded” or “masked,” which means the patients do not know who is getting the experimental drug. In this manner, the study can provide comparative information about the relative safety of the new drug and its effectiveness. About one-third of experimental drugs successfully complete both Phase I and II studies.

A double-blind or double-masked study is one in which neither the participants nor the study staff know which participants are receiving the experimental treatment and which ones are getting either a standard treatment or a placebo. These studies are performed so neither the patients’ nor the doctors’ expectations about the experimental drug can influence the outcome.

- Phase III:

In a Phase III study, a drug is tested in several hundred to several thousand patients. This large-scale testing provides the pharmaceutical company and the FDA with a more thorough understanding of the drug's effectiveness, benefits and the range of possible adverse reactions. Most Phase III studies are randomized and blinded trials.

Phase III studies typically last several years. Seventy to 90 percent of drugs that enter Phase III studies successfully complete this phase of testing. Once a Phase III study is successfully completed, a pharmaceutical company can request FDA approval to market and sell the drug. Typically, this process can take years to complete.

- Late Phase III/Phase IV Studies

In late Phase III/Phase IV studies, pharmaceutical companies have several objectives:

- They can compare a drug with other drugs already in the market.
- They monitor a drug's long-term effectiveness and impact on a patient's quality of life.
- They determine the cost-effectiveness of this new drug therapy, compared to other traditional and new therapies.

Funding for clinical research comes from the federal government through the National Institutes of Health (NIH) and from private industries, such as pharmaceutical and biotech companies.

The sponsor of the research hires physicians who may work in a wide variety of healthcare settings and institutions to conduct the clinical trial. Physicians are typically paid on a per-patient basis. The medical care is often provided free to the patient and in some studies patients are paid a fee to participate.

People participate in clinical research for a variety of reasons. Patients who volunteer for Phase II and III trials can gain access to promising drugs long before these compounds are approved for the marketplace. They typically will get excellent care from the physicians during the course of the study. The care also may be free.

Protecting Patients in Clinical Trials

The patients' rights and safety are protected in two important ways. First, any physician awarded a research grant by a pharmaceutical company or the NIH must obtain approval to conduct the study from their hospital or medical center's Institutional Review Board.

All institutions that conduct medical research involving people must, by federal regulation, have a review board that initially approves and periodically reviews the research.

The institutional review board, usually made up of physicians, statisticians, community advocates and lay people, examines the study's protocols to ensure that the patients' rights are protected and that the study does not present an undue or unnecessary risk to the patients.

There are about 3,000 institutional review boards connected to research centers and hospitals in the United States. Any federally-funded clinical trial and any trial that evaluates a new drug regulated by the FDA is subject to an institutional review board.

When a clinical trial involves researchers and doctors in several hospitals and research centers across the country, a Data Safety Monitoring Board may be appointed to keep track of the data to ensure participants' safety.

Second, anyone participating in a clinical trial in the United States is required to sign an "informed consent" form. This form details the nature of the study, the risks involved, and what may happen to a patient in the study. The informed consent tells patients that they have a right to leave the study at any time.

Before agreeing to have their child participate in clinical research, parents should talk about it with their child's pediatrician and specialist. They also should seek to understand the credentials and experience of the individuals and the facility involved in conducting the study.

Parents should know as much as possible about the research study. It is important to feel very comfortable asking questions and the staff should answer them in a way you can understand.

- Plan ahead and write down the questions you want to ask.
- Ask a friend or relative to come with you for support and to hear the responses to your questions.
- Bring a tape recorder so you can replay the discussion after you get home.

Some questions you might ask about the research include:

- Why is this research being done?
- What is the purpose of the study?
- Who is sponsoring the study?
- Who has reviewed and approved this study?
- Why does the research team think the treatment will work?

Other questions to ask include:

- How long will the trial last?
- Where is the trial being conducted?
- What treatments will be used and how?
- What is the main purpose of the trial?
- How will my child's safety be monitored?
- Are there any risks involved?
- What are the possible benefits?
- What are the alternative treatments besides the one being tested in the trial?
- Who is sponsoring the trial?
- Do I have to pay for any part of the trial?
- What happens if my child is harmed by the trial?
- How will my child's confidential medical information be protected?
- Can my child opt to remain on this treatment, even after termination of the trial, if it appears successful?

How Untested Drugs Can Be Used on Children with Viral Hepatitis

The reason FDA gives physicians latitude in using drugs that have been tested only in adults is to hasten testing of life-saving drugs in children and adolescents.

The FDA spells this out in its guidelines to pharmaceutical companies developing and testing drugs for use in the pediatric population: "The presence of a serious or life-threatening disease for which the [drug] represents a potentially important advance in therapy suggests the need for relatively urgent and early initiation of pediatric studies. In such cases, medicinal product development should begin early in the pediatric population, following assessment of initial safety data and reasonable evidence of potential benefit."

If there are substantial data and reports from the pharmaceutical company and other independent doctors that show the drug is effective against hepatitis in adults, is safe in adults and should be safe in children, and if doctors can attempt to scale dosages appropriately for children, the FDA allows physicians to use the drug in young patients.

The FDA expects these doctors to share any information gained from this one-child clinical trial with others who are treating viral hepatitis in children and adolescents.

If there are no independent reports or research on the drug, but the pharmaceutical company has data reportedly documenting safety in children despite the lack of clinical

trials, then a doctor can use the drug on a child, provided the findings are shared with the medical community.

“Sometimes, you have little or no safety or efficacy information about a drug in the pediatric population and there is no other hospital using it, then a doctor will ask the institutional review board to use the drug as part of a study,” explained Dr. Paul Offit, Chief of Infectious Diseases at The Children's Hospital of Philadelphia and the Henle Professor of Immunologic and Infectious Diseases at the University of Pennsylvania School of Medicine.

If a doctor is treating a child with life-threatening liver disease, and a potential drug is in Phase II or III of a clinical trial and the child doesn't meet the study's criteria for age or symptoms, the physician can still use the drug. This is called a one-time compassionate release use. Cases of compassionate releases are not designed for research or for publication; the drug is tried simply to save the patient's life as a last resort.

“You can eventually publish and report about the anecdotal experience, but learning from that one case and publishing the results is not the main purpose,” observed Dr. Lynda Brady, a pediatric hepatologist with the University of Chicago Children's Hospital.

Doctors must also obtain permission from their institutional review boards for compassionate release use of drugs.

The decision to allow such experimental treatments, either off label or for compassionate purposes, will be based on the severity of illness, whether there are any alternative drugs available, the patient's quality of life issues, legal liability if something goes wrong and if there is insurance for the drugs. Often, insurance companies refuse to cover certain experimental drug therapies that have not yet been approved by the FDA for use in children.

“Like politics, the use of new drugs ultimately is a local issue,” Dr. Offit observed. “With experimental drugs, both the consent form patients sign and the approval to do trials are all generated locally, not from the FDA.”

“Once a drug has been FDA-approved, any physician can prescribe it,” Dr. Brady added. “It doesn't matter that most drugs are approved because of adult trials. Most drugs used by pediatricians were never tested in pediatric trials. In the case of lamivudine, it had a good safety record in kids with HIV, so I was even less hesitant to use it in children with hepatitis B outside the pediatric trial.”

Dr. Brady explained that when using an experimental drug in children outside of a clinical trial, she carefully reviews the drug's performance record in adults with the child's parents and explains that no one is certain how the drug will behave in children. "The parents sign a consent form, and then I monitor and document the children's reactions to the drug carefully," she explained.

"In my practice, I try to hold onto my patients until a trial is available that benefits them; that way, the experience is useful for all children," she added. "Unfortunately, you can't always do that. Right now, the current pegylated interferon trial for children with hepatitis C has an age cut-off of 8, so anyone age 8 to 18 cannot be enrolled in either the pediatric or adult trials. Once pegylated interferon is approved, I would consider using it in two children I am now following."

Doctors point out that such experimentation, with minimal pediatric data from either the drug company or other doctors and researchers, should be tried only at reputable hospitals and medical centers, or by pediatric specialists in close consultation with a pediatric gastroenterologist or hepatologist who specializes in hepatitis.

"I do not condone children treated off-trial by physicians who don't really know what they are doing, especially if the disease is not serious or life-threatening," observed Dr. Maureen Jonas, a pediatric gastroenterologist with Children's Hospital Boston.

Involving Children in the Decision to Enter a Clinical Trial

During the past 20 years, medical and legal experts have studied the issues surrounding a child's participation in clinical trials. In the eyes of the law, children 17 and younger are not adults and parents or guardians must grant legal permission for their participation after reviewing all the possible ramifications of the trial. This is called the informed consent process.

However, many health care practitioners believe that a child or adolescent should play a role in the decision to enter a research study. The American Academy of Pediatrics calls this "empower[ing] children to the extent of their capacity" and talks about this approach in its policy statement on Informed Consent, Parental Permission and Pediatric Practice, issued in February 1995.

The Academy stated that "informed consent" should have the following qualities:

- Helps the patient achieve a developmentally-appropriate awareness of the nature of his or her condition.

- Tells the patient what he or she can expect from tests and treatment(s).
- Makes a clinical assessment of the patient's understanding of the situation and the factors influencing how he or she responds (including whether there is inappropriate pressure to accept testing or therapy).
- Solicits an expression of the patient's willingness to accept the proposed care. The Academy noted that in situations in which the patient will have to receive medical care despite his or her objection, the patient should be told that fact and should not be deceived.

The National Commission for Protection of Human Subjects of Biomedical and Behavioral Research established age 7 as a reasonable minimum age for involving children in some kind of assent process. The commission asserted that most children at this age can understand information tailored for their knowledge and developmental level.

“Encouraging their involvement in decision-making is done out of respect for their rights as individuals and the desire to give them a sense of ownership in what happens during the trial,” according to an article on “Children's Assent to Clinical Trial Participation: A Unique Kind of Informed Consent,” published by the National Cancer Institute. “Even though children cannot ‘consent,’ because true consent implies full understanding, they are now routinely asked whether they agree (assent) or do not agree (dissent) to participate. Their parents or guardians are no longer asked to give ‘proxy consent’ but instead give ‘informed permission.’”

Where to Find Clinical Trials of Drugs Used to Treat Hepatitis

CenterWatch Clinical Trials Listing Service

<http://www.centerwatch.com>

Hepatitis Clinical Trials – <http://www.centerwatch.com/patient/studies/cat79.html>

CenterWatch is a Boston-based information services company that provides information about clinical trials for use by patients, pharmaceutical, biotechnology and medical device companies and research centers involved in clinical research around the world.

Clinical Trials.gov

<http://www.clinicaltrials.gov>

The U.S. National Institutes of Health, through its National Library of Medicine, has developed *ClinicalTrials.gov* to provide patients, family members and members of the public current information about clinical research studies. Before searching, you may want to learn more about clinical trials. The site is updated regularly with new trials. Visitors may search by disease to find hepatitis trials.

Veritas Medicine

<http://www.veritasmedicine.com>

Veritas Medicine's goal is to improve patient access to clinical trials and information about therapies in development for serious medical conditions. The centerpiece of the Veritas Medicine website is a comprehensive clinical trials database that allows patients to be matched to clinical trials based on information submitted confidentially.

Acurian

<http://www.acurian.com>

Patients can search a database of clinical trial listings, register to be considered for specific clinical trials, and read breaking news of advances in therapies.

National Institute of Allergy and Infectious Diseases (NIAID)

<http://www.niaid.nih.gov>

This offers a comprehensive view of clinical trials and explains the steps necessary for pharmaceutical companies to secure approval for drug therapies.

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