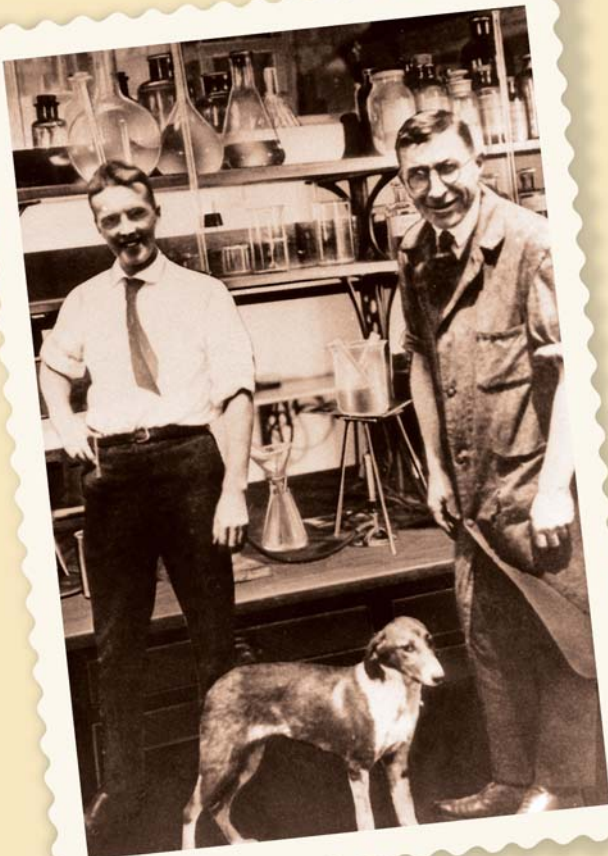


Why are pediatric clinical trials important?

As a parent or caregiver of a child with diabetes, one of the most important aspects of learning to deal with a diabetes diagnosis involves understanding the medications and treatments that will help your child be as healthy as possible.

Clinical research is the key to making new drugs and treatments available to people who need them. We would not be able to treat diabetes as successfully as we can today without the many important clinical trials that have taken place over the past 85 years. In fact, one of the most exciting moments in medical history involved a research study testing a newly discovered hormone called insulin. In 1921, Canadian surgeon

Charles H. Best (left) and Frederick G. Banting



Dr. Frederick G. Banting and his student assistant, Charles H. Best, began their search for the pancreatic substance that could safely treat diabetes. They were successful and, after being joined by biochemist James B. Collip, were able to develop a purified form of insulin. In early 1922, the researchers injected pancreatic extracts (later known as insulin) into diabetic dogs and then into themselves before giving injections to a 14-year-old boy named Leonard Thompson who lay dying of diabetes in a Toronto hospital. The boy, who had been surviving on the “starvation” diet prescribed to most diabetics of the day, showed greatly improved blood glucose levels and lived for an additional 13 years. This important discovery earned Dr. Banting the Nobel Prize in Physiology and Medicine in 1923.

Since then, further research and development of human insulin and other drugs have led to better treatments and even longer survival. Today, an adult with diabetes can choose from a variety of insulin formulations and oral drugs; however, this is not the case with children.

Unfortunately, children have not always been at the top of the list when it comes to clinical research. Until recently, there were no federal laws protecting children in clinical trials, nor were there any laws encouraging researchers and drug companies to include infants, children and adolescents in clinical trial research. In the past, many of the same drugs and treatments given to adults were also given to children without having been clinically tested in children for either their ability to treat the illness or harmful side effects.

Children are not “small adults.” It is important to include children in clinical trials in order to develop drug formulations children can tolerate (such as chewable or liquid forms of medication), to understand the child’s

response to the medication and determine how medications are distributed throughout the child's body, and to understand the short- and long-term effects of medications in children. In addition, clinical research in children is necessary to address unique pediatric diseases which require unique medications and treatments.

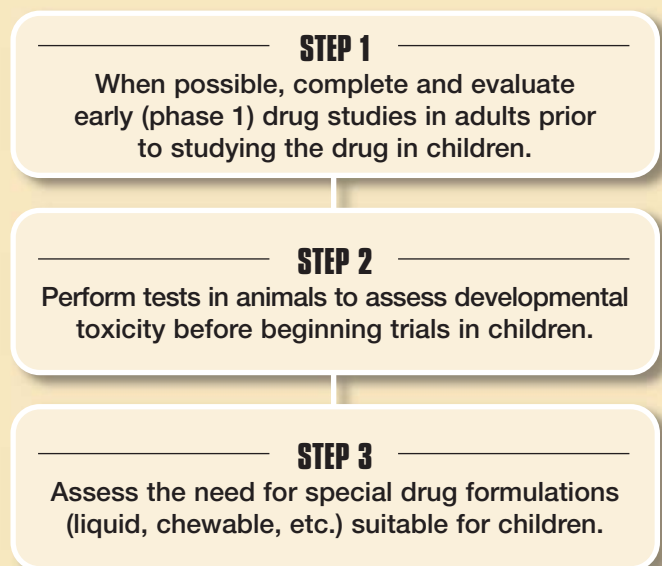
According to a 2003 article by Michelle Meadows published in the U.S. Food and Drug Administration (FDA) Consumer magazine, only 20 to 30 percent of FDA-approved drugs are labeled for pediatric use. This means that doctors, out of necessity, regularly prescribe drugs to children even though the drugs have not been proven safe or effective in children. You may be surprised to find that this also applies to diabetes. Only a few of the insulins commonly used in the United States today have undergone any clinical testing in children or adolescents and the only drug approved to treat the rapidly growing incidence of type 2 diabetes in children is metformin (Glucophage). Only a few ACE inhibitors for treatment of high blood pressure or statins for treatment of high cholesterol have been approved by the FDA for use in adolescents and older children.

While it is imperative that we keep children safe and prevent them from being exposed to high risk treatments, it is also important that we not exclude children when developing new drugs and therapies. In this way, children have the opportunity to receive the same health benefits as adults. For example, the newly approved inhaled insulin, Exubera, was approved for use in adults but has not yet been approved for use in children or adolescents due to lack of studies on the long-term effects of the drug. Islet cell transplant experiments which have been occurring in adults for several years are still limited to adults only.

Challenges of pediatric clinical trials

Initiating pediatric clinical trials can sometimes be difficult since studies in children can be harder to design and more time-consuming to recruit. Outcome measures need to be developmentally appropriate for different age children. Pediatric research should also accommodate children's physical, cognitive and emotional development, meaning that it should be conducted in a child-friendly environment by researchers and staff who have experience working with children. And, perhaps most importantly, pediatric research requires parent or caregiver involvement and family decision-making as well as compliance with additional ethical and regulatory protections for children.

According to the 2004 report, *Ethical Conduct of Clinical Research Involving Children* by the Institute of Medicine Committee on Clinical Research Involving Children, there are generally three steps which should be taken in order to minimize the number of children needed for a trial while maximizing the quality of the data obtained.



In 1974, the first diabetes law in U.S. history, the National Diabetes Research and Education Act, was established. This law requires the government to coordinate national research on diabetes and distribute diabetes information. However, it was not until 1988 that the National Institutes of Health (NIH) developed its Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. These guidelines state that it is the policy of NIH that children (those under age 21) “must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.”

In 1997, Congress enacted the FDA Modernization Act which provided incentives to drug companies to conduct pediatric studies. The Best Pharmaceuticals for Children Act renewed those incentives in 2002 and called for NIH to sponsor pediatric tests of certain drugs which had already been approved, but which had not been tested (or fully tested) for their effects in children. This Act also requires the FDA to publish a list of drugs for which additional pediatric information may provide health benefits. In 2001, the diabetes drugs on this list included insulin aspart recombinant (NovoLog) for treatment of type 1 diabetes, and acarbose (Precose), repaglinide (Prandin), rosiglitazone (Avandia) and sulfonylurea drugs (such as Amaryl and Glucotrol) to treat type 2 diabetes. The list also included more than 50 drugs which, if studied further in children, could be used to treat high blood pressure or high cholesterol—two serious complications of diabetes.

Some of these diabetes drugs have been studied since they were included on the FDA list in 2001. For example, the FDA reports that a 2005 study of the sulfonylurea Amaryl in children age eight to 17 years did not provide sufficient data to recommend pediatric use. A 2004 study of Avandia in children age 10 to 17 years revealed the same. A 2005 study of NovoLog,



however, provided evidence that NovoLog is safe and effective in treating type 1 diabetes in children and adolescents age two to 18 years.

The FDA Modernization Act and the Best Pharmaceuticals for Children Act were followed by the Pediatric Research Equity Act of 2003 which empowered the FDA to *require* pediatric studies of certain drugs. Fortunately, all of these policies and laws have had a definite impact on increasing child participation in research. Following the FDA Modernization Act there were many more drugs developed exclusively for children, and many drugs which obtained new pediatric labeling information thanks to pediatric studies. The Institute of Medicine Committee on Clinical Research Involving Children performed a search of clinical trials on the NIH website www.clinicaltrials.gov circa 2004 and found 29 studies on all types of diabetes for children age birth to 17 years. A January 2006 search of diabetes clinical trials in children on the same website found 77 studies.

Protection of children participating in clinical trials

In 1978, the Belmont Report was issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The current federal regulations protecting infants, children and adolescents in clinical research are closely based on recommendations from the Belmont Report.

Federal regulations now require all institutions to have a written assurance that they will comply with human research protection regulations. Each institution must have a “statement of principles” that governs them in protecting humans, regardless of whether the research is subject to federal regulation. This is where development of Institutional Review Boards comes into play. Institutional Review Boards, or IRBs, are groups of professionals and lay people who review and monitor

research involving human participants and provide the written assurance necessary to confirm that the researchers and institution where the research is being conducted will comply with human research protection regulations. According to the FDA, the IRB group “has the authority to approve, require modifications in,...or disapprove research.” Institutional Review Boards assess the risks and benefits to the child participating in the research and use tools, such as informed consent documents, to ensure parent/guardian permission from one or both parents depending on level of risk and potential benefit. Federal regulations also state that there should be an effort to obtain the child’s assent to the research. Other protections include the requirement to report adverse events and serious adverse events, and monitoring of large, multisite clinical trials by separate Data Safety & Monitoring Boards.



The American Diabetes Association promotes clinical diabetes research

Because the American Diabetes Association sees clinical research as being the key to bringing research discoveries from the laboratory to everyday use in people who need them, we have recently doubled the amount of our Clinical Research Awards from \$100,000 per year for three years to \$200,000 per year for three years. This will allow the Association to remain competitive in attracting the best clinical grant applications to our program.

As you may have read in previous *Forefront* issues, the ADA also supports several of the National Institutes of Health trials to prevent diabetes from developing in children and to improve care in children who have already developed the disease. These include *Type 1 Diabetes TrialNet*, *HEALTHY*, formerly known as *Studies to Treat or Prevent Pediatric Type 2 Diabetes (STOPP-T2D)*, *Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY)* and *Environmental Determinants of Diabetes in the Young (TEDDY)*.

Besides supporting federal research projects already underway, the Association continues to fight for increased diabetes research funding by our federal government. In addition to joining the bipartisan House and Senate Diabetes Caucuses, the American Diabetes Association calls on members of Congress to take action against diabetes by:

- **Supporting increased funding** for diabetes prevention research at the Centers for Disease Control and Prevention and the National Institutes of Health.
- **Supporting stem cell research** that offers significant new hope in finding a cure and new treatments for many serious diseases, including diabetes.



What parents and children should know

There can be many benefits to joining a clinical trial but there can also be risks. Participating in a trial might give your child access to a revolutionary new drug or cutting-edge procedure. There is also the satisfaction that comes with knowing you and your child have helped the research community to better understand or treat diabetes and that your contribution could help millions of other people in the future.

However, before jumping into a clinical research study, it is important to be able to give “informed consent.” Informed consent is a process of communication between parents, children and researchers. The decision to allow your child to participate in a trial should be made freely and with understanding.

How to become informed:

- Understand the purpose of the research and procedures your child will/may undergo.
- Understand the potential for harm and/or benefit. Harm includes psychological, physical and social distress.
- Understand your right to accept or refuse research participation and to withdraw your child from the study once it has started.
- Understand your and your child’s responsibilities for participating in the research.
- Understand the responsibility of the researcher to you and your child, including answering your questions, maintaining confidentiality, minimizing the risks of participation and revealing information about study findings.

If your child has diabetes or is ill or has another medical condition, you should also know:



- What your child’s medical condition and prognosis are.
- The difference between receiving usual clinical care and participating in a trial.
- Your child’s options for care outside the trial.
- Research methods, such as the method for assigning research participants to intervention or control groups.
- Potential harms and benefits of participating or not participating in the trial given your child’s illness/condition.

(Source: Committee on Clinical Research Involving Children, Board on Health Science Policy, Institute of Medicine of the National Academies: *Ethical Conduct of Clinical Research Involving Children*. Field MJ, Behrman RE, Eds. Washington D.C., The National Academies Press, 2004)

To find more information on clinical trials and how you can participate in a trial, visit the National Institutes of Health Web site at www.clinicaltrials.gov for a list of diabetes-related trials in your area. You can also visit the American Diabetes Association Web site at www.diabetes.org/diabetes-research/clinical-trials/trials-home.jsp for links to more clinical trials information and a database of clinical trials currently enrolling diabetes patients. ■