



What is a Clinical Trial?

Clinical trials are scientific studies conducted to learn more about a disease and find new or better treatments. Clinical trials are the standard of care for children with Neuroblastoma – virtually all children treated for intermediate- and high-risk disease, as well as many low-risk NB patients, are enrolled on a clinical trial or treated “per” a clinical trial. The treatment is the same in either case, but only the outcomes of those enrolled on a trial are included in final trial results.

Since neuroblastoma is a rare disease, clinical trials are planned and carried out either by large single institutions, small groups of institutions, or large, international cooperative groups such as the Children's Oncology Group (COG). (See the Appendix, **What are Cooperative or Study Groups?** at the end of this section for more information.) Clinical trials may study therapeutic results of patient treatment or examine non-therapeutic issues such as what causes a type of cancer, similarities and differences between tumors, or what late effects patients may experience as a result of cancer treatment.

The current focus of clinical trials for low- and intermediate-risk neuroblastoma is on reducing treatment toxicity while maintaining high survival rates, and determining ways to identify at diagnosis the small subset of patients with higher risk of treatment failure or relapse. By contrast, the focus of trials for high-risk neuroblastoma is on increasing the survival rate.

There are four different types, or phases, of therapeutic clinical trials: Phase I, II, III or IV.

Phase I Clinical Trials

Phase I pediatric clinical trials are an initial attempt to use a drug or drug combination in children, and often enroll small numbers of patients (e.g., 10 to 30). Phase I trials are open only to children who have “refractory” disease that has not responded to other treatments or children who have relapsed. In addition to measurable or detectable disease, eligibility criteria usually include adequate organ function such as liver, kidney and heart test values, and specified blood cell counts. Some trials do not allow brain metastases or other conditions. Prior treatments such as, radiation to bone marrow, allogeneic transplants, or particular drugs used may affect eligibility to participate in a trial.

Phase I trials are not intended to cure a child of disease, but to learn more about potentially effective new agents. Although individual beneficial results are hoped for and do happen, children enrolled on a Phase I study often do not benefit directly from the drug; other children may benefit from what researchers learn about the drug, its administration and side effects.

The goals of a Phase I clinical trial will usually include one or more of the following:

- **Pediatric use:** To determine whether a drug or drug combination can safely be used in children. Drugs or drug combinations in a Phase I trial have been shown to be effective against neuroblastoma cell lines in the laboratory – and usually have been previously studied in adults – but have not been tried in children.
- **Toxicity:** To determine what side effects and toxicities the drug causes when used in children. Toxicity is quantified (grade 1, 2, 3 or 4) and reported according to NCI's Common Toxicity Criteria.

- **Dosage:** To determine the highest tolerated dose of the drug or drugs in children. You may hear such studies referred to as “dose escalation studies.” In these studies, a small number of children (usually three) are given the same dose of a drug and their responses to the drug, including any adverse effects, are observed. If the first group of children tolerates the treatment well, the next group of children enrolled on the study will receive an increased dosage, until the doctors determine the maximum tolerated dose (MTD) that can be given without serious side effects. “Inpatient dose escalation” is a trial design that allows for increasing the dose in each patient as tolerated.
- **Absorption (pharmacokinetics):** To determine how well a new drug or a new method or formulation for delivering an old drug or combination of drugs is absorbed in the child’s system, and how long it remains in the system before being eliminated.

The extent of a child’s disease is monitored periodically during the clinical trial and is reported commonly as reduced (response to treatment), stable or progressive (disease is growing). A child whose disease progresses will be removed from the trial and other treatment options will be explored. Children who have severe adverse reactions will also be removed from the study. In some cases, trials have been closed when several children experienced very serious side effects.

Phase II Clinical Trials

Like Phase I trials, Phase II clinical trials are generally open to refractory or relapsed patients who have not responded to more conventional treatments. Drugs or drug combinations in a Phase II trial have undergone Phase I testing, so the recommended maximum tolerated dose has been established and toxicities are generally known.

The primary goal of Phase II trials is to determine if the drug or drug combination is active against neuroblastoma – whether the drug will shrink tumors or, in some cases, prevent the cancer from recurring. In addition, researchers may learn more about side effects and toxicities associated with taking the drug. Phase II trials typically enroll more patients than Phase I trials, often 30-60 children in the case of neuroblastoma.

Some Phase II trials are designed specifically to test new frontline treatment regimens on newly diagnosed patients. Such Phase II trials are available only at certain large institutions and are often referred to as “pilot” studies or protocols. These studies determine toxicity and survival rates for new treatment regimens for frontline therapy. If the results are promising, future Phase III trials may incorporate the new regimens to verify that they are more effective.

Phase III Clinical Trials

Children in the US newly diagnosed with high-risk neuroblastoma usually are enrolled on the current or recently completed COG Phase III clinical trial, unless their hospital runs single-institution trials, which may be a Phase II trial. If your child is not either enrolled on a trial or being treated “per” a trial you should ask your doctor why your child is not receiving the newest treatments. It is worth noting that children are often treated on *closed* trials (Phase II or III protocols), so data on their response is not included in study results.

Although they utilize some of the most effective treatments against neuroblastoma, enrollment on a Phase III trial does not guarantee a cure. Because the prognosis for high-risk disease is so poor, doctors and researchers are constantly working to find more effective treatments that will improve survival and pose fewer long-term risks to children.

Phase III clinical trials require enrollment of a large number of patients for increased statistical significance, usually in the 300-500 patient range. These studies compare two or more treatments that are specific to neuroblastoma and try to determine which one is more effective. Most Phase III studies are randomized – children in a “control group” receive the “standard” treatment, while other children receive a different drug or treatment designed to answer a specific research question. A computer is used to randomly select which children receive the experimental treatment and which receive the standard treatment.

For a history of recent Phase III trials for high-risk neuroblastoma, see the Appendix to the chapter **Overview of High-Risk Treatment**.

Phase IV Clinical Trials

These trials are used to verify the safety of a newly approved treatment or drug. Known as “Post Marketing Surveillance Trials,” there currently are no studies designed for neuroblastoma.

Single or Limited Institution Trials

Some institutions, such as St. Jude’s Children’s Research Hospital and Memorial Sloan-Kettering Cancer Center, conduct trials limited to patients at their facility. Other trials are conducted at only a few institutions. Single institution and limited institution trials may take the form of pilot studies or individual drug studies – i.e., the initial study examining a new method or treatment. These smaller trials allow researchers to answer critical questions before a drug or treatment is made available to more patients through a larger study.

Non-therapeutic Clinical Trials

Non-therapeutic clinical trials generally fall into one of four categories:

- Biological studies: Studies that examine the biology of tumor samples and identify prognostic variables.
- Epidemiological studies: Studies that look for the causes of a type of cancer and the frequency with which it occurs.
- Cancer control studies: Studies designed to find the best methods for dealing with side effects.
- Late effects studies: Studies designed to identify and deal with the after-effects of treatment.

Patient Safety

Clinical trials are carefully planned and rigorously monitored. Each hospital must elect to open a study and enroll patients, a decision which must be approved by the hospital’s Institutional Review Board (IRB). Because patient safety is such a concern with experimental treatments, there are strict guidelines for carrying out clinical trials. For example, there is no flexibility in eligibility criteria. If the study requires patients to have a platelet count of at least 100,000, no patient can be enrolled with lower counts. Similarly, there are strict requirements for monitoring disease status and reporting toxicity.

Compassionate Use

Occasionally parents pursue “compassionate use” of “investigational new drugs” (INDs) from the FDA and manufacturers. Approval may be sought when a drug is offered in an open study but the child does not meet eligibility criteria, or when no study is currently open. The child’s oncologist, the principal investigator of the new drug, the manufacturer of the drug, and the FDA are all involved in obtaining approval for use on a case-by-case basis. Approval is highly variable and based on many factors.

Enrolling Your Child on a Clinical Trial

Before your child can be enrolled in a clinical trial, you must give your informed consent to treatment. As part of the informed consent process, you should receive a document that provides a summary of the clinical trial – its purpose, procedures and schedule, and potential risks and benefits – and that explains your rights (and your child’s rights) as a participant in the trial. See the chapter **Patients’ Rights & Responsibilities**.

The National Cancer Institute – a part of the US National Institutes of Health – has issued recommendations for research institutions and clinical centers to use in writing informed consent documents. Although documents may vary by institution, all informed consent documents should include the following:

- Title of the trial
- Purpose (Why the trial is being conducted)
- Description of procedures involved in the trial
- Estimated duration of the trial
- Risks of the trial
- Benefits of participating in the trial
- Alternatives to participation
- A statement explaining the extent to which information about the patient will be kept confidential
- Explanation of costs or additional expenses
- Statement of the patient’s rights as a participant
- Information about who to contact with questions or problems
- A list of additional sources of information, such as websites, community organizations, etc.
- A signature line representing the patient’s (or the parent’s) legal consent to participate in the trial

If you decide to enroll your child in a trial, you must sign the document indicating your consent. **After you sign the document, you should receive a copy to keep for yourself and to use as a source of information throughout the course of the trial.**

After you have read the trial document, but before you sign and give your consent, you should have an opportunity to discuss the trial and the information in the document with your doctor. During this conversation, your doctor should review all of the information in the consent document, such as the purpose of the trial, potential risks and benefits, and your child’s rights as a participant, and give you the opportunity to ask any questions you may have.

Even after you have given your informed consent to enroll your child in a clinical trial, you should feel free to ask questions and raise concerns about the treatment at any time. You are also free to

take your child off of the trial at any time – for any reason, or no reason at all – without giving up the ability to receive other treatments for your child.

Informed assent. Children under 18 cannot legally consent to participate in a clinical trial – consent must be given by a parent or legal guardian. However, if your child is over the age of 7, he or she may be asked to agree to participate in the trial in a process known as informed assent.

Your child will not be asked to give informed assent to a treatment unless you have already given informed consent to his or her participation. Once you have done so, the child can be provided with a form that explains in age-appropriate terms the purpose of the research, what your child will be asked to do and procedures that may be performed. For teenagers over 16 this form may be very similar to the informed consent document parents are asked to sign. Forms used with younger children use simpler language. All forms should state clearly that the child has the right to leave the trial at any time, for any reason, without penalty, and that information will be kept confidential.

There are two exceptions to the requirement for informed assent by the child:

- If the child is incapable of participating in the process, or
- If the trial “holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the research.” This exception applies when the treatment offered in the study is believed to be a better option than other currently available treatments, or when the treatment is the only alternative available. This exception often applies to patients with stage 4 neuroblastoma and those who have relapsed, because most of the available treatments are clinical trials.

Even in situations where one of the exceptions applies, the research team is still expected and encouraged to obtain the child’s assent. Many medical professionals believe that involving the child in these decisions is empowering, giving the child a feeling of control and a sense of ownership in what happens during the trial.

Sources:

CureSearch/National Childhood Cancer Foundation, www.curesearch.org.
National Cancer Institutes, www.cancer.gov.
ACOR Ped-Onc Resource Center, www.acor.org/ped-onc.
NCI Clinical Trials, www.cancer.gov/clinicaltrials.

Appendix

What are Cooperative or Study Groups?

In an effort to improve survival rates and therapies for neuroblastoma, various clinical trials are planned and carried out by cooperative pediatric oncology groups. Individual or small groups of institutions may carry out smaller “pilot” studies to test new therapies. Many patients are needed for Phase III randomized trials to determine the effectiveness of new therapies. Because neuroblastoma is a rare disease with relatively few diagnoses, cooperative groups are often international.

Pediatric oncology study groups are found around the globe and some conduct significant studies on neuroblastoma. Group sizes range from a single country, such as Japan’s Study Group; to one or two countries, such as Germany’s GPOH (*Gesellschaft für Pädiatrische Onkologie und Hämatologie*), a German language study group including institutions in Germany and Switzerland; to large international groups such as the *Société Internationale d’Oncologie Pédiatrique* (SIOP), which conducts large studies on neuroblastoma in 17 countries including the UK and Israel. SIOP, (also known as the “International Society of Paediatric Oncology) which held its first annual general meeting in Madrid in 1969, includes a distinct focus on neuroblastoma, among other pediatric cancers.

Annual meetings of cooperative groups and professional societies are important occasions for researchers to present study results. Hundreds of researchers interested in neuroblastoma also present findings at the “Advances in Neuroblastoma Research” ([ANR](#)) meeting, a conference held every two years.

In North America, a 1999 [merger](#) of the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) created the [Children's Oncology Group \(COG\)](#), which currently has over 230 member institutions in the US, Canada, Australia, New Zealand, the Netherlands and Switzerland. Not all COG member institutions participate in every trial run by the group. Despite being a COG institution, your hospital may not be enrolling patients in a particular COG trial. The Institutional Review Board (IRB) of each member hospital must approve participation in *each* trial.

COG is the largest pediatric cancer study group. Approximately [40,000](#) children with all types of pediatric cancers are currently treated on approximately 150 COG protocols. [Requirements](#) for membership as a COG institution and principal investigator include treating a minimum average of twelve newly diagnosed pediatric cancer cases annually. COG investigators also must enroll a minimum average of six children annually on COG therapeutic trials and a minimum of two children on non-therapeutic trials. Specific [support](#) specialists and facilities must also be provided in COG institutions. **All pediatric cancer patients treated at a COG hospital must be registered in the COG database, even if they are not treated on a COG protocol.**

The [New Approaches to Neuroblastoma Therapy](#) (NANT) consortium is a smaller group of investigators at 14 institutions who specialize in Phase I and Phase II trials for refractory and relapsed neuroblastoma.

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