



## 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 are included in the 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 Study (Cooperative) Groups?” at the end of this section for more on study groups. 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 to reduce treatment toxicity while maintaining high survival rates, as well as to determine how to identify at diagnosis the small subset of those with higher risk of treatment failure or relapse. By contrast, the focus of trials for high-risk neuroblastoma is primarily to increase the survival rate.

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

### Phase I Clinical Trials

Phase I pediatric clinical trials are the 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 specified blood cell counts, and liver, kidney, and heart test values. Some trials do not allow brain metastases or other condition. Prior treatments may affect eligibility, such as particular drugs used, radiation to bone marrow, allogeneic transplants, etc.

Phase I trials are not intended to cure a child of disease, but to learn more about potentially effective new agents. A child enrolled on a Phase I study often does not benefit directly from the drug (although individual beneficial results are hoped for and do happen), but 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 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 (grades 1, 2, 3, and 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 and their response 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 dose, until the doctors determine the maximum tolerated dose (MTD) that can be given without serious side-effects. “Inpatient dose escalation” design allows for the dose to be increased 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 before it is 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). Children who have progressive disease are removed from the trial and other treatment options are explored. Children who have severe adverse reactions will also be removed from the study. In some cases, studies 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 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, often 30-60 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 be verified as more effective.

### Phase III Clinical Trials

Children 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 their data is not included in the results of the study.

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 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 the “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 **Appendix to “Overview of High-Risk Treatment.”**

### **Phase IV Clinical Trials**

These trials are to verify the safety of a newly approved treatment or drug. None of these “Post Marketing Surveillance Trials” are currently 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; and
- 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, which requires approval from 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 less. Similarly, there are strict monitoring requirements for disease status and reporting toxicity.

### **Compassionate Use**

Occasionally parents pursue “compassionate use” of “investigational new drugs” (INDs) from the FDA and manufacturers. Reasons for this may be that the drug is offered in an open study but the child does not meet eligibility criteria, or 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 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 Patients’ Rights & Responsibilities.**

The National Cancer Institute—a part of the U.S. 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 for whom to contact with questions or problems;
- A list of additional sources of information, such as websites, community organizations, etc.; and
- Signature line representing the patient’s (or the parent’s) legal consent to participation in the trial.

If you decide to enroll your child on 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 the parents 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 be clear 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 treatments for these types of disease 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](http://www.curesearch.org).

National Cancer Institutes, [www.cancer.gov](http://www.cancer.gov).

ACOR Ped-Onc Resource Center, [www.acor.org/ped-onc](http://www.acor.org/ped-onc).

NCI Clinical Trials, [www.cancer.gov/clinicaltrials](http://www.cancer.gov/clinicaltrials).

## Appendix

### What are Study (Cooperative) 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 and small groups of institutions also carry out smaller “pilot” studies to test new therapies. Many patients are needed for phase III (randomized) trials to discern the effectiveness of new therapies. Since incidence of neuroblastoma is small, cooperative groups are often international.

Pediatric oncology study groups are found around the globe and some conduct significant studies on neuroblastoma. Some have been limited within one or more countries such as Japan’s Study Group, and Germany’s [GPOH](#) (*Gesellschaft für Pädiatrische Onkologie und Hämatologie*), a German language study group including institutions in Germany and Switzerland. The *Société Internationale d’Oncologie Pédiatrique* or [SIOP](#) conducts large studies on neuroblastoma in 17 countries including UK and Israel. It is also known as “International Society of Paediatric Oncology.” The first annual general meeting was held in Madrid in 1969 and began with a distinct focus on neuroblastoma among other pediatric cancers.

Annual meetings of cooperative study groups and professional societies are important occasions for researchers to present results of studies. Hundreds of researchers interested in neuroblastoma also have an opportunity to present findings every two years at “Advances in Neuroblastoma Research” or [ANR](#). ANR does not conduct cooperative studies.

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

COG is the largest pediatric cancer group, and [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 annual average of twelve newly diagnosed pediatric cancer cases. COG investigators must also enroll a minimum annual average of six children 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. **Every pediatric oncology patient treated at COG hospitals must be registered in the COG database, even if they are not treated on a COG protocol.**

A smaller group of investigators specializing in neuroblastoma at 14 institutions comprise the [New Approaches to Neuroblastoma Therapy](#) (NANT) consortium. This group plans and offers phase I and phase II trials for refractory and relapsed neuroblastoma.

Please contact [editors@nbhope.org](mailto:editors@nbhope.org) with any comments