

AMERICAN BRAIN TUMOR ASSOCIATION

Clinical Trials



American
Brain Tumor
Association®

Providing and pursuing answers®

ABOUT THE AMERICAN BRAIN TUMOR ASSOCIATION

Founded in 1973, the American Brain Tumor Association (ABTA) was the first national nonprofit organization dedicated solely to brain tumor research. The ABTA has since expanded our mission and now provides comprehensive resources to support the complex needs of brain tumor patients and caregivers, across all ages and tumor types, as well as the critical funding of research in the pursuit of breakthroughs in brain tumor diagnoses, treatments and care.

To learn more, visit **abta.org**.

We gratefully acknowledge Susan Chang, MD, director of Clinical Services, Neuro-Oncology Service of the Brain Tumor Research Center, Department of Neurological Surgery, School of Medicine, University of California, San Francisco, for her review of this edition of this publication.

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Clinical Trials

INTRODUCTION

This booklet describes how research studies, called clinical trials, are used to develop new treatments for brain tumors. Because clinical trials represent an additional treatment option for some, we will present basic information about what they are, how they work, and how you can find and evaluate a clinical trial to determine if it is right for you.

In general, there are several different types of clinical trials, including:

- Supportive care trials (also called quality-of-life trials)
- Prevention trials
- Early detection or screening trials
- Diagnostic trials
- Treatment trials

WHAT IS A CLINICAL TRIAL?

A clinical trial is a research study. It is an organized way of testing a new investigational treatment to determine if it is safe and effective to use. The participants in clinical trials are human patients who volunteer

for this opportunity to obtain a treatment that otherwise wouldn't be available to them. Clinical trials also add to our overall understanding of brain tumors.

No one knows in advance if the new treatment being tested in a clinical trial is as effective as, or better than, the standard therapy currently in use. The results of clinical trials are measured against the best standard therapy available for the particular condition.

Although researchers truly do not know whether the new treatment or the current treatment is the "best," the new substances or devices being investigated must have some potential for success before a trial is allowed to begin. That potential is based on previous laboratory experience, animal trials or the results of other earlier clinical trials.

Trials are designed to answer the following questions about the new treatment:

- Is it safe?
- Is it effective?
- Is it more effective than standard treatment?
- Does it provide any benefit or advantage over standard treatment?

WHY ARE CLINICAL TRIALS NECESSARY?

Clinical trials play an important part in whether new drugs and medical devices eventually get to market. The U.S. Food and Drug Administration (FDA) requires any new drug or device to be approved before being sold. To gain FDA approval, the manufacturer or distributor of the drug or device must submit full reports of the studies carried out to show

that the drug or device is safe and effective for its intended use. Clinical trials act as the primary way for manufacturers to prove that their product is safe and effective.

HOW DO CLINICAL TRIALS BEGIN?

If, after several years of laboratory and animal study, researchers believe their drug or device will be safe and effective against a particular disease, the next step is to test it in humans. This is important because what works in the laboratory or in animals might not work in people. A clinical trial is designed to answer the crucial questions regarding safety and effectiveness of the product in humans.

A clinical trial can be initiated by a researcher at a single medical facility or by an organization such as:

- National Institutes of Health (NIH)
- National Cancer Institute (NCI)
- National Institute of Neurological Disorders and Stroke (NINDS)
- A pharmaceutical, device or biomedical company
- Clinical cooperative group or consortia

Before the clinical trial can begin, an application to conduct a trial of a new agent must be approved from the FDA. The application includes a description of the protocol or process the clinical trial will follow. If the trial is sponsored by an organization, such as the National Cancer Institute, then the protocol must also be approved by other review boards.

WHERE ARE CLINICAL TRIALS CONDUCTED?

Clinical trials are conducted throughout the world at university hospitals, cancer centers, medical centers and hospitals, and doctors' offices and clinics. The National Cancer Institute sponsors or co-sponsors the majority of clinical trials in the United States and it does so through its clinical trials cooperative groups and consortia, cancer centers and clinical grant programs.

CLINICAL TRIAL COOPERATIVE GROUPS

Because brain tumors are relatively rare, many single institutions could not enroll sufficient numbers of patients into a clinical trial to derive meaningful data or it would take too long to do it. A clinical trials network was created by the National Cancer Institute to overcome those obstacles. Groups of hospitals work together as though they were one, coordinating their reports, reviews and administrative functions. There are several groups within the network offering brain tumor trials, including:

Alliance for Clinical Trials in Oncology
allianceforclinicaltrialsinoncology.org

ECOG-ACRIN Cancer Research Group
ecog-acrin.org

Radiation Therapy Oncology Group
rtog.org

Children's Oncology Group
childrensoncologygroup.org

Brain tumor consortia conducting phase I and II clinical trials:

Adult Brain Tumor Consortium
abtc.org

Pediatric Brain Tumor Consortium
pbtc.org

CANCER CENTERS

There are about 50 NCI-designated clinical and comprehensive cancer centers and each participates in at least one cooperative group.

CLINICAL GRANT PROGRAMS

NCI also supports clinical trial protocols at single institutions through peer-reviewed grants.

IN ADDITION

Pharmaceutical and biomedical companies, cancer centers, university hospitals, major medical centers and community medical centers may conduct their own trials. They often partner with one another, the NCI or local doctors to carry out their trials. They may also contract with other companies whose only purpose is to conduct clinical trials.

WHO PAYS FOR CLINICAL TRIALS?

The majority of clinical trials are paid for by the sponsor of the trial, which may be the federal government or the company that makes the new drug or device. The sponsor of the research hires physicians, who may work in a wide variety of health care settings, to conduct the clinical trial. The routine costs of care, such as surgery to remove the tumor or the usual follow-up MRI scans, may be covered by an insurance company with the patient paying their usual deductibles and out-of-pocket expenses. Some, although not many, clinical trials provide small reimbursements to cover a patient's costs of participating in the trial, such as travel or parking. Expenses for the trials offered at the NIH Clinical Center in Bethesda, Maryland are paid for by the NIH.

In some instances, health insurance and managed care providers will not cover any patient costs in a clinical trial, nor expenses that occur because of side effects of treatment received in a clinical trial. This is because some health plans define clinical trials as “experimental” or “investigational” procedures. As a result, the patient may be responsible for certain costs. Before making a decision to enroll in a clinical trial, contact both the sponsor of the trial and your insurance company to learn what coverage is available to you. For more information about costs and insurance issues pertaining to clinical trials, see the Learning About Clinical Trials section of the National Cancer Institute web site, located at www.cancer.gov.

HOW ARE CLINICAL TRIALS ORGANIZED?

Each trial follows a protocol – a detailed, written plan that explains why there is a need for the study, what it is intended to do and how it will be conducted. The protocol is written by the trial’s principal investigator (the physician or scientist in charge of the trial) with input from other physicians, researchers, patient advocates and statisticians.

A protocol specifically includes:

- The reason (scientific rationale or basis) for conducting the trial
- Objectives of the study
- The number of volunteers that must be enrolled for the data to be meaningful
- Eligibility criteria – the types of tumors to be treated, acceptable age ranges, health

requirements and need for informed consent, and any exclusions due to previous treatments

- The drugs, treatments or devices to be used
- A detailed explanation of how the treatment is to be given, its duration and schedule
- Possible side effects and permitted interventions to ease the side effects
- How patient progress is to be evaluated – required medical and neurological tests, questionnaires, scans and follow up visits
- The endpoints of the trial – such as disease free survival (DFS), overall survival, quality of life (QOL), recurrence, time to progression (TTP) and toxicity/safety

Everyone enrolled in a clinical trial must meet the same eligibility criteria, receive the same treatment process and be evaluated the same way. This uniformity enables researchers to objectively measure the results of a new treatment. This means that patients involved in the same clinical trial will most likely have the same type of tumor in the same location, along with many other similarities, in order to ensure that the results are valid and not due to some other factor.

It is also important that an adequate number of patients be enrolled in the study to determine if effects (good and bad) are due to the treatment or to individual differences among the patients. The protocol helps ensure that these types of issues are addressed in the study.

Most studies that are conducted to assess the effectiveness of a new treatment divide participants into two groups: the investigational group (the one receiving the new treatment) and

the control group (the one that receives the standard treatment or placebo). Participants are typically assigned to one of the two groups randomly. In this way, the two groups are as similar as possible at the start of the study. A randomized clinical trial (where participants are randomly assigned to each group) is considered the most reliable and impartial method for determining which treatment works best. In a double-blind study, neither the doctor nor the patient knows which treatment is being given. In a single-blind study, only the patients don't know which treatment they are receiving. At the end of the study, if one group has a better outcome than the other, the investigators will be able to conclude with some confidence that one intervention is better than the other. There are also non-randomized studies where patients with similar characteristics all receive the same investigational treatment.

Due to the seriousness of brain tumors, placebos are rarely used. (The last placebo-controlled trial was done many years ago.) If placebos are used in the trial, every patient must be informed of this possibility in advance of enrolling. Every patient must also receive, at minimum, standard therapy. No one in a brain tumor trial can be "untreated."

HOW MANY CLINICAL TRIALS ARE NECESSARY BEFORE A NEW TREATMENT IS APPROVED?

Clinical trials are conducted in phases. Each phase focuses on answering a specific question about the new treatment.

PHASE I

A phase I trial is designed to answer the question: How much of the new substance can be safely given and what is the best way to give it? The research team monitors the patient carefully to assess the side effects of the treatment. Although no one knows the effectiveness of the new treatment, the tumor – fighting effects are also evaluated, but this is not the primary purpose of a phase I study. Some of these trials are dose escalation studies – studies in which the dose is increased gradually to determine the best amount. The result of this type of study is a determination of the point at which a balance is reached between dose and acceptable side effects.

When a balance is reached between dosage and acceptable side effects, the treatment moves into a phase II study. The trial is stopped if unacceptable side effects occur. The trial typically lasts between a few months and a year, and involves a small group of about 20 patients.

If the drugs under investigation are already well known for treatment of other disease, but the correct dosage for brain tumors has not been determined, phases I and II may be combined in the same trial.

PHASE II

A phase II trial is designed to answer the question: Is the new treatment effective against a specific type of tumor? An effective treatment causes tumors to shrink in size or stop growing. There are very specific guidelines phase II trials study on how to evaluate the effectiveness of the response to treatment in new treatment solid

tumors. With a complete response (CR), the tumor or tumors disappear on scan. A partial response (PR) means that the tumor has shrunk in size by the amount described in the guidelines. Stable disease (SD) means little or no change in size of the tumor. Progressive disease (PD) means that the size of the tumor has increased per the guidelines.

A phase II brain tumor trial might last as long as two years and require about 75 patients, but can vary depending on the design of the trial. Patients are monitored according to the protocol outline and side effects are carefully evaluated.

If a positive response occurs in enough patients to be statistically significant (results which are not due to chance or error), research will move to a phase III trial. If the treatment is found to be ineffective, testing stops. If testing ceases, patients enrolled in the trial may be offered other treatment options or participation in another trial.

PHASE III

A phase III trial is designed to answer the following questions: Is this new drug more effective than already approved drugs or standard treatments? Are there fewer side effects than the standard treatment? Also, if the new treatment is as effective as standard treatment, does it offer some other advantage?

For example, is the new drug given orally rather than intravenously or is it safer to administer? A phase III trial usually involves hundreds or even thousands of participants so the effectiveness

of the different treatments can be statistically measured and compared on a large scale.

Once a new treatment has been proven successful in a phase III trial, an application for FDA approval can be submitted. If data from the clinical trials meet the FDA's standards, the treatment will be approved for use.

PHASE IV

A phase IV trial might be required by the FDA to evaluate side effects that were not apparent in the phase III trials or to answer unresolved questions. This phase is conducted after the drug or device has already received FDA approval. Again, large numbers of people are enrolled in this type of trial.

WHAT ARE MY RIGHTS AND PROTECTIONS AS A CLINICAL TRIAL VOLUNTEER?

As you investigate and consider your treatment options, remember that your voluntary participation in a clinical trial affords you a number of rights and protections.

LEAVING THE TRIAL

You may end your participation in a clinical trial at any time for any reason. If you decide you want to leave the study, you have the right to learn about other treatment options. After leaving the trial you may remain with physicians at the trial treatment facility, return to your regular doctor to receive another treatment or consult with other experts.

INFORMED CONSENT

Prior to any kind of treatment, you have a right to know the exact nature of the treatment: the known risks, the prospects of success and if there are standard therapies. Informed consent means

that the information must be explained to you by a member of the trial treatment team, all your questions must be answered and you must fully understand the explanation. You will be asked to sign a consent form once you are satisfied that you have all the information you need and have decided to participate in the study. Parents or guardians may sign for minors. Minors might be given an assent form which provides information appropriate to their age and allows them to be involved in the process.

UPDATES

If additional information about treatment is learned during the study, you will be kept informed.

ONGOING MONITORING

You will be closely monitored by doctors and nurses throughout the study for any changes in your overall health, not just your brain tumor. A data monitoring committee looks at the statistical parts of the study and alerts physicians if something unsafe seems to be happening.

PRIVACY

The study administrators must make every effort to keep your personal and health-related information confidential. To do this, most of your records will be identified by a number, rather than your name.

RISK ASSESSMENT

Institutional Review Boards (IRBs) composed of experts and lay people at hospitals and research institutions throughout the U.S. work to ensure you are not exposed to any unnecessary risks during the clinical trial. Trials sponsored by the National Cancer Institute

(NCI) and some drug companies will have their own Data Monitoring Committee (DMC) or Data Safety Monitoring Board (DSMB) to review the potential risks.

These boards act as independent groups of experts who, at periodic intervals during the trial, review accumulated data to make sure you continue to be protected.

HOW LONG DOES IT TAKE A SPONSOR TO COMPLETE A CLINICAL TRIAL?

The answer to this question depends on the phase of the trial and the number of people participating. Phase I trials can last from several months to a year but involve small numbers of people. Phase II trials may take up to two years to complete. Phase III trials often require several years to enroll and monitor the progress of the hundreds or thousands of study volunteers.

However, if a particular trial is of interest to many people, the trial may “accrue” participants faster than expected.

HOW ARE THE FINAL RESULTS OF A TRIAL MADE KNOWN?

After all patients have been treated and followed for the prescribed length of time, the results are analyzed. It is the sponsor's obligation to distribute the results as quickly and widely as possible. In reality, this can take months or even years. However, as electronic communication becomes more commonplace, this information is being shared more rapidly. Trial results are made known in several ways:

- A poster or presentation at a scientific meeting
- An article published in a scientific journal (this may take months before the article appears in

print; some journals make available electronic versions of the article as soon as they are reviewed)

- Electronic bulletins from NCI
- New trials citing results of the prior study
- An application to the FDA for a New Drug Application (NDA)
- Word of mouth among the researchers or sponsors
- News media reports, press releases, etc.

HOW DO I FIND CLINICAL TRIALS?

The two best options for finding clinical trials are to use your health care team for direction and/or to seek out clinical trials on your own.

ASK YOUR HEALTH CARE TEAM

Since your doctors know your physical condition, it makes good sense to start talking with them about treatment options. One of your physicians may already be an investigator in a trial located near your home. Or, your physician may know of trials for which you would qualify. Additionally, your health care team can contact their colleagues in the field or specialists at brain tumor referral centers on your behalf. Don't hesitate to ask for their advice and help.

SEEK OUT CLINICAL TRIALS ON YOUR OWN

If you decide to pursue treatment information on your own, let your doctor know of your desire to learn more about clinical trials as a treatment option. Then, collect all your diagnostic information. Ask your doctor's office staff to help you obtain the correct information. You will need to know the following:

- The exact spelling of the tumor

- The location of the tumor within the brain or spine
- The size of the tumor

ZUBROD (AND KARNOFSKY) PERFORMANCE SCALES

- 0 Fully active, able to carry on all pre-disease activities without restriction (Zubrod 0 equates to a Karnofsky score of 90–100)
- 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky score 70–80)
- 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky score 50–60)
- 3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky score 30–40)
- 4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky score 10–20)

- The number of tumors
- The type of treatments you've already received (biopsy or surgery, radiation therapy or stereotactic radiosurgery, chemotherapy, etc.). If you've received chemotherapy or radiation, you'll need to know the specifics: type of radiation or drug, dose, dates of treatment. Eventually, you will need copies of your medical records. When you find a trial of interest to you, the trial coordinators will provide a list of the records they need for review, i.e. copies of scans

(and which dates), laboratory tests, operative reports, pathology reports, pathology slides, etc. Your medical records belong to you and there should be no problem in getting the copies you need (although you may be charged copying fees, postage, etc.) In a few states, medical records are released only to another physician. Be aware, though, that copying costs are sometimes expensive.

HOW DO I EVALUATE CLINICAL TRIALS?

Now that you've learned how to locate trials, you'll need to begin narrowing down your choices. As you look over the various trials, consider the entry criteria first. Initially, look for:

- Age requirements
- Tumor types
- Previous treatments allowed (or not)
- Medical history
- Minimum performance status required (performance status expresses a person's ability to function and perform normal daily activities. See the scale below)

If you are considering a specific clinical trial, seek out as much information as you can about that new treatment. Because phase I trials are just beginning their testing, little might be published about them. On the other hand, a considerable amount of information is available by the time a trial reaches phase III. You can search the medical literature for more information about the treatment. To find results of prior clinical trials in the medical literature, visit: www.cancer.gov/clinicaltrials/results. Results from the last few years of clinical trials are archived at this site.

PubMed, a database of medical literature dating back to the mid-1960s, can help you search the literature for abstracts of case reports or review articles about past trials and studies involving the treatment you are considering. If you retrieve the actual articles, note the date the article was submitted for publication. Additional patients might have been treated since then, or the results of the trial might have changed.

CONTACT THE STUDY COORDINATOR FOR THE CLINICAL TRIAL(S) IN WHICH YOU HAVE INTEREST

Call the contact number for the trial location you are interested in, or ask your doctor to call for you. Depending on the institution, a study coordinator, protocol assistant, research associate, or nurse may accept telephone or e-mail inquiries to verify that the trial is still open. Before you call, make a list of questions that concern you most and that you need answered before you can make a decision.

Some of the most common questions include:

- Why is the new treatment thought to be effective? Has it been tested before?
- When did the trial begin?
- How many people have been treated so far?
- How many have my type of tumor?
- How well are they doing?
- What are the known possible side effects? Are they temporary or permanent? Can they be controlled or lessened some way (medications, diet, etc.)? How will they affect my daily activities?
- How is the treatment administered and where will the treatment take place? Can it be given close to my home?
- How many treatments will there be? How long will each one take?
- Will the study doctors work with my regular doctors while you participate in the study?
- Will I have to be hospitalized as part of the study?

You'll also want them to give you a preliminary opinion about your eligibility, and answer your questions. A definitive answer on eligibility may require copies of your medical records, including blood test reports, operative reports, scans, pathology reports, etc. Find out which documents are needed to determine your eligibility, and the best way to send them. (Be sure to obtain a shipping address that will accept overnighted packages and be sure to send your package with a carrier that will provide you with a tracking number.)

Ask for a copy of the complete protocol and the informed consent form. The informed consent form includes information about the hoped-for benefits, the known risks and reported side effects of the new treatment. The protocol is probably the only document that contains the full rationale for the study. It documents the reason the study is being done and the results of earlier testing on the new substance. Some clinical cooperative groups offer their complete protocols at their web site; if not, request it from a research associate or investigator associated with the clinical trial.

Lastly, ask how you will learn whether you qualify for the trial – should you call them, or will they contact you?

DECIDING

Once you've learned about the trials that are open to you, and talked with your doctor about the standard therapies available to you, it becomes time to decide the next course of action. You should now have enough information to make your decision about whether it is in your best interest to participate in a clinical trial. Remember, clinical trials are medical research – they can't promise you'll be cured, or even helped, by the treatment being studied. There are pros and cons to investigational treatments, just as there are for all the other treatment options. Discuss the results of your research with your doctor, your family and others whose judgment you value and trust. If you have researched your options well, you should be able to make an educated choice on how to proceed.

AMERICAN BRAIN TUMOR ASSOCIATION INFORMATION, RESOURCES AND SUPPORT

BROCHURES

Educational brochures are available on our website or can be requested in hard copy format for free by calling the ABTA. Most brochures are available in Spanish, with exceptions marked with an asterisk.

GENERAL INFORMATION

About Brain Tumors: A Primer for Patients and Caregivers

Brain Tumor Dictionary*

Brain Tumors Handbook for the Newly Diagnosed*
Caregiver Handbook*

TUMOR TYPES

Ependymoma

Glioblastoma and Anaplastic Astrocytoma

Medulloblastoma

Meningioma

Metastatic Brain Tumors

Oligodendroglioma and Oligoastrocytoma

Pituitary Tumors

TREATMENT

Chemotherapy

Clinical Trials

Conventional Radiation Therapy

Proton Therapy

Stereotactic Radiosurgery*

Steroids

Surgery

AMERICAN BRAIN TUMOR ASSOCIATION INFORMATION, RESOURCES AND SUPPORT

INFORMATION

ABTA WEBSITE | ABTA.ORG

Offers more than 200 pages of information, programs, support services and resources, including: brain tumor treatment center and support group locators, caregiver resources, research updates and tumor type and treatment information across all ages and tumor types.

EDUCATION & SUPPORT

- **ABTA Educational Meetings & Webinars**
In-person and virtual educational meetings led by nationally-recognized medical professionals.
- **ABTA Peer-to-Peer Mentor Program**
Connect with a trained patient or caregiver mentor to help navigate a brain tumor diagnosis.
- **ABTA Connections Community**
An online support and discussion community of more than 25,000 members.
- **ABTA CareLine**
For personalized information and resources, call 800-886-ABTA (2282) or email abta cares@abta.org to connect with a CareLine staff member.

GET INVOLVED

- Join an ABTA fundraising event.
- Donate by visiting abta.org/donate.

CONTACT THE ABTA

CareLine: 800-886-ABTA (2282)

Email: abta cares@abta.org

Website: abta.org

AMERICAN BRAIN TUMOR ASSOCIATION

8550 W. Bryn Mawr Avenue, Suite 550

Chicago, IL 60631

For more information contact:

Website: abta.org

CareLine: 800-886-ABTA (2282)

Email: abta-cares@abta.org



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