Clinical Trials
ABOUT THE AMERICAN BRAIN TUMOR ASSOCIATION

Founded in 1973, the American Brain Tumor Association (ABTA) was the first national nonprofit advocacy organization dedicated solely to brain tumor research. The ABTA provides comprehensive resources to support the needs of brain tumor patients and caregivers and funds critical research in the pursuit of discovering breakthroughs in brain tumor diagnosis, treatment, and care.

To learn more about the ABTA, visit www.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.

This publication is not intended as a substitute for professional medical advice and does not provide advice on treatments or conditions for individual patients. All health and treatment decisions must be made in consultation with your physician(s), utilizing your specific medical information. Inclusion in this publication is not a recommendation of any product, treatment, physician or hospital.

COPYRIGHT © 2018 AMERICAN BRAIN TUMOR ASSOCIATION
REPRODUCTION WITHOUT PRIOR WRITTEN PERMISSION IS PROHIBITED
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 that tests a new investigational treatment (a treatment that is not yet approved for general use) to determine if it is safe and effective. Participants in clinical trials are human patients who volunteer for the opportunity to obtain a treatment that otherwise would not be available to them. Clinical trials also add to our overall understanding of brain tumors.

When you enroll in a clinical trial, there is no way of knowing if the treatment being tested is as effective as – or better than – the current standard treatment. The
results of clinical trials are measured against the best standard therapy available for the particular condition.

Before a clinical trial is allowed to begin, researchers must prove the new substance or device being investigated has some potential for success. 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?**

Any new drug or device must be approved by the U.S. Food and Drug Administration (FDA) before being sold. To gain FDA approval, the manufacturer or distributor of the drug or device must submit full reports of the studies conducted 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?**

After several years of laboratory and animal study, if researchers believe their drug or device will be safe and effective against a particular disease, the next step is to test it in humans. What works in the laboratory or in animals might not work in people, so clinical trials are 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 organizations such as:

- National Institutes of Health (NIH)
- National Cancer Institute (NCI)
WHERE ARE CLINICAL TRIALS CONDUCTED?
Clinical trials are conducted throughout the world at university hospitals, cancer centers, medical centers, hospitals, and doctors’ offices and clinics. The National Cancer Institute sponsors or co-sponsors the majority of clinical trials in the United States through its clinical trials cooperative groups and consortia, cancer centers, and clinical grant programs.

CLINICAL TRIAL COOPERATIVE GROUPS
Because brain tumors are relatively rare, most institutes are unable to enroll a sufficient number of clinical trial participants on their own. Without enough participants, trials cannot derive meaningful data, or it would take too long to collect the data. To overcome these obstacles, the National Cancer Institute created a clinical trial network that facilitates a group effort among hospitals to work together by coordinating their reports, reviews and administrative functions.

There are several groups within the network that offer brain tumor trials, including:

- Alliance for Clinical Trials in Oncology
  www.allianceforclinicaltrialsinoncology.org
- ECOG-ACRIN Cancer Research Group
  www.ecog-acrin.org
- NRG Oncology
  www.nrgoncology.org

Before the clinical trial can begin, an application to conduct a trial on a new agent must be approved by 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.

• National Institute of Neurological Disorders and Stroke (NINDS)
• Pharmaceutical, device or biomedical companies
• Clinical cooperative groups or consortia
Brain tumor consortia conducting phase I and II clinical trials:

- Adult Brain Tumor Consortium
  www.abtconsortium.org
- Pediatric Brain Tumor Consortium
  www.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
The National Cancer Institute 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, local doctors or the National Cancer Institute 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 healthcare settings) to conduct the clinical trial. 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 National Institutes of Health (NIH) Clinical Center in Bethesda, Md. 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 any 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.

**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 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 response rate (RR), progression-free survival (PFS) or disease free survival (DFS), overall survival (OS), quality of life (QOL), recurrence, 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 – along with many other similarities – in order to ensure that the results are valid and not due to other factors.

An adequate number of patients must be enrolled in the study to determine if effects (good and bad) are caused by the treatment or by individual differences among the patients. The protocol helps ensure that these types of issues are addressed in the study.

Some 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. 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 patient is unaware of the treatment being administered. 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.

Newer study designs, like platform trials, may randomize patients to different experimental therapies or to a control arm. By using one control arm to compare against several experimental arms, the scientific validity of randomized studies is preserved while allowing more patients to be randomized to experimental therapies. There are also non-randomized studies where patients with similar characteristics all receive the same investigational treatment.

Due to the seriousness of brain tumors, non-active controls are rarely used, meaning participants in a brain tumor trial will never be “untreated.” Every patient must receive, at minimum, standard therapy.

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

Clinical trials are traditionally conducted in phases, and each phase focuses on answering a specific question about the new treatment. The following phase descriptions are meant as a general guideline as newer development strategies may combine phases and there are no specific rules that state how the phases must be conducted.

**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.

Some of these trials are dose escalation studies, where 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 few years, and involves a small group of about 20 patients.
The research team will record and evaluate the tumor-fighting effects of the treatment; however, this is not the primary purpose of a phase I study.

If the drug under investigation is already well known for treating other diseases, but the correct dosage for brain tumors has not yet 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 use to evaluate the effectiveness of the response to treatment:

- **Complete response (CR):** the tumor or tumors disappear on scan
- **Partial response (PR):** the tumor has shrunk in size by the amount described in the guidelines
- **Stable disease (SD):** little or no change in size of the tumor.
- **Progressive disease (PD):** the size of the tumor has increased per the guidelines.

A phase II brain tumor trial can last as long as two years and require about 75 patients; however, that may vary depending on the design of the trial. Patients are monitored according to the protocol outline, and side effects are carefully evaluated. More phase II trials have become randomized to improve the data results.

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. If the testing shows promising results, research will move on to a phase III study.

**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 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 the standard therapies already being used (if any). Informed consent means that the information must be explained to you by a member of the trial treatment team, that all your questions must be answered and that you must
fully understand the explanation. Once you are satisfied with the information you received, you will be asked to sign a consent form that states you were given the information. Parents or guardians may sign for minors. Minors might be given an assent form which provides information appropriate to their age and so they can 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 review accumulated data at periodic intervals during the trial to make sure you continue to be protected.

**HOW LONG DOES IT TAKE A SPONSOR TO COMPLETE A CLINICAL TRIAL?**
The length of a clinical trial depends on the phase of the trial and the number of people participating. Phase I
trials can last from several months to a few years, but involve small numbers of people. Phase II trials may take up to two years or more 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 enroll 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. The sponsor is responsible for distributing 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 release electronic versions of the article as soon as they are reviewed)
  - Electronic bulletins from the National Cancer Institute
  - New trials citing results of the prior study
  - An application to the FDA for a New Drug Application (NDA)
  - Posted on clinicaltrials.gov
  - 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 healthcare team for direction or to seek out clinical trials on your own.

**ASK YOUR HEALTH CARE TEAM**

If you are considering a clinical trial, start by talking to your doctors. One of your physicians may already be an investigator in a trial located near you or may know of
trials that you would qualify for. Additionally, your healthcare team can contact their colleagues in the field or specialists at brain tumor referral centers on your behalf. Do not hesitate to ask for their advice and help.

**SEEK OUT CLINICAL TRIALS ON YOUR OWN**

If you decide to look for clinical trial options on your own, still let your doctor know as you will need to obtain your diagnostic information. Work with the staff at your doctor’s office to make sure you get all of the information you need. 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
- The number of tumors
- The type of treatments you have already received (biopsy or surgery, radiation therapy or stereotactic radiosurgery, chemotherapy, etc.).
- If you have received chemotherapy or radiation, you will need to know the type of radiation or drug, dose and dates of treatment.

When you find a trial that interests you, the trial coordinators will provide a list of the records they need for review, such as copies of scans (with dates), laboratory tests, operative reports, pathology reports and pathology slides.

Although your physical medical records belong to the doctor who created them, you own the information within the records so you should not have any issues getting copies. However, you may have to pay a copying fee, which can sometimes be expensive. Additionally, a few states only allow medical records to be released to other physicians.
HOW DO I EVALUATE CLINICAL TRIALS?

Now that you have learned how to locate trials, you will 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)

**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 or 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 percent of waking hours (Karnofsky score 50–60)

3  Capable of only limited self-care, confined to bed or chair 50 percent 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)
If you are considering a specific clinical trial, seek out as much information as you can. Phase I trials most likely will not have a lot published as they are just beginning their testing. 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.

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 may 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 email inquiries to verify that the trial is still open. Before you call, make a list of questions about aspects of the trial that concern you and anything else you need to know before you 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?
- What are the known possible side effects? Are they temporary or permanent? Can they be controlled or lessened (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 I participate in the study?
• Will I have to be hospitalized as part of the study?

You should also ask them to give you a preliminary opinion about your eligibility. A definitive answer on eligibility may require copies of your medical records. Find out which documents are needed to determine your eligibility, as well as 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 website. If they are not available online, request them 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 have learned about the trials that are available to you and talked with your doctor about the standard therapies, you have to decide what is the best 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 cannot promise that you will be cured, or even helped. It is also important to note that a
clinical trial may cause you to become worse. 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.

THE ABTA IS HERE FOR YOU
You don’t have to go through this journey alone. The American Brain Tumor Association is here to help.

Visit us at www.abta.org to find additional brochures, read about research and treatment updates, connect with a support community, join a local event and more.

We can help you better understand brain tumors, treatment options, and support resources. Our team of caring professionals are available via email at abtacares@abta.org or via our toll-free CareLine at 800-886-ABTA (2282).
AMERICAN BRAIN TUMOR ASSOCIATION
PUBLICATIONS AND SERVICES

CARE & SUPPORT
CareLine: 800-886-ABTA (2282)
Email: abtacares@abta.org

PUBLICATIONS
About Brain Tumors: A Primer for Patients and Caregivers
Brain Tumors – A Handbook for the Newly Diagnosed*
Brain Tumor Dictionary*
Caregiver Handbook*
Returning to Work: Accessing Reasonable Accommodations*

Tumor Types:
Ependymoma
Glioblastoma and Malignant Astrocytoma
Medulloblastoma
Meningioma
Metastatic Brain Tumors
Oligodendroglioma
Pituitary Tumors

Treatments:
Chemotherapy
Clinical Trials
Conventional Radiation Therapy
Proton Therapy
Stereotactic Radiosurgery*
Steroids
Surgery

Most publications are available for download in Spanish. Exceptions are marked *

CLINICAL TRIALS

More brain tumor resources and information are available at www.abta.org.
Contact the ABTA:

CareLine: 800-886-ABTA (2282)
Email: info@abta.org
Website: www.abta.org

Connect with us on social media:
Facebook.com/theABTA
Twitter.com/theABTA

To find out how you can get more involved locally, contact volunteer@abta.org or call 800-886-1281.