



## Prospective clinical trials of brain tumor therapy: the critical role of neurosurgeons

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*Key words:* brain tumor, clinical trial, glioblastoma, molecular endpoint, molecular profile

### Summary

Prospective clinical trials are critical to the scientific evaluation of new treatments for brain tumors. This paper reviews basic concepts of early and late phase prospective clinical trials that are most relevant to neurosurgical oncologists, with an emphasis on the challenges associated with conducting clinical trials of brain tumor therapies. Novel clinical trial designs that meet these challenges by incorporating pretreatment ‘molecular profiling’ and post-treatment ‘molecular endpoints’ are described. Because of their ability to obtain brain tumor specimens from patients before and after treatment, neurosurgeons have been required to play an increasingly important role in the execution of these molecular-based clinical trials. Potential avenues for enhancing the participation of neurosurgeons in the design and development of clinical trials are discussed.

### Introduction

Prospective clinical trials are the foundation of scientific advancements in all areas of medicine. Properly designed and executed clinical trials are the best mechanism through which the safety and efficacy of new treatments are assessed or through which competing strategies are evaluated [1]. This is particularly true in the field of neuro-oncology, where definitive therapies for the most commonly occurring primary brain tumors, particularly glioblastoma multiforme (GBM), remain elusive and in which new strategies for eradicating these tumors are constantly being developed and tested. Indeed, there are many examples of prospective clinical trials that have influenced neuro-oncologists’ practices, including studies of adjuvant radiation therapy [2], temozolamide [3,4], and BCNU wafers [5,6]. However, many more treatment strategies, including commonly employed surgical therapies, such as radical resection of GBMs, remain controversial because of the lack of prospective randomized clinical trials addressing these approaches [7,8].

Given the importance of clinical investigations in defining treatment strategies and the prominent role neurosurgeons play in the treatment of patients with brain tumors, it is essential for neurosurgeons with an interest in advanced brain tumor therapy to have a solid working knowledge of clinical research methodologies. Indeed, new information about the molecular biology of brain tumors and the development of new ‘targeted’ therapies has made neurosurgeons particularly valuable to the successful execution of many clinical trials [9]. Although it is difficult to determine the number of neurosurgeons who participate in prospective trials, data from a recent neurosurgical review suggests that only 13–20% of patients operated on for gliomas are entered into clinical studies [10,11]. It is equally difficult to ascertain the clinical research experience of most neurosurgeons. Whereas research training opportunities in neuro-oncology exist in a number of fellowship programs [12], the majority of neurosurgeons lack formal education in prospective clinical trial design, and many others are simply not aware of the evolving need for neurosurgical

expertise in the setting of oncological clinical trials.

The purpose of this paper is to provide a brief overview of clinical research, with an emphasis on prospective clinical trials of brain tumor therapies. The chapter begins with a review of basic concepts focusing on the goals and methods of early and late phase prospective clinical trials. We then examine the unique challenges associated with conducting clinical trials of brain tumor therapies, and point out potential avenues for improving clinical trial designs with an emphasis on the importance of neurosurgical participation and expertise in these trials. The chapter concludes with suggestions for increasing clinical trial awareness and participation among members of the neurosurgical community.

### **Basic principles of oncologic clinical trials**

Clinical trials (Table 1) are scientific experiments conducted on people that evaluate the effects of a drug, intervention, or therapeutic strategy [13,14]. Much has been written about the principles of clinical trial design and the reader is referred to several comprehensive reviews for details [15–18]. Here we address the basic elements of trial design that are most relevant to neurosurgeons. The majority of brain tumor investigations involve the evaluation of drugs or new therapeutic strategies; therefore, information regarding treatment trials is emphasized.

#### *Prospective vs. retrospective clinical studies*

Clinical studies can be performed retrospectively, prospectively, or a combination of both (e.g. retrospectively looking at prospectively acquired data) [17]. Given the multiple biases and confounding factors associated with retrospective analyses, the best clinical studies are prospective trials (Table 1) in which the objectives, patient eligibility criteria, treatment plan, outcome measures, and data analysis are established in a written protocol (Table 1) before enrolling patients, and patient outcomes are followed forward in time [14,17]. In fact, authoritative texts often include the concept of prospective design as a defining criteria of a true clinical trial [14]. Deviations from the predefined protocol, as well as *post hoc* ana-

lyses of data using different strata or statistical methods than those initially defined in the study should be discouraged, as these departures introduce confounding factors that may lead to erroneous conclusions.

#### *Phases of clinical trials*

Evaluations of new cancer therapies are conducted in a progressive series of clinical trials or phases (Table 2). The process usually begins with small nonrandomized studies testing the feasibility, safety and applicability of an agent or intervention (Phase I), progressing to evaluations of the biological activity of an agent (Phase II trials) and culminating in large randomized controlled studies (Phase III trials) evaluating the new intervention in comparison with a currently accepted standard treatment. On occasion post-marketing studies are conducted to explore long term side effects, adverse reactions, or effectiveness in patients with diverse demographic features (Phase IV).

The first step transitioning laboratory observations (e.g. a new drug, a new dosing schedules of an established drug, or a new combinations of accepted drugs) into clinical care is typically the phase I trial (Table 2). The primary goals of these early trials are to define the profile of unwanted toxicities or side effects associate with the agent or strategy, and to determine a dose that can be administered safely to human subjects. Phase I trials typically involve small numbers of subjects (usually less than 30) who are divided into ‘cohorts’ that are entered at a particular dose level. Serial escalation to higher doses depends upon the low occurrence of adverse events (Table 1). Adverse events are graded from mild to severe (i.e. grade 1– grade 5) based on specific standards that have been developed by the National Cancer Institute (NCI) as published in the Common Terminology Criteria for Adverse Events [19]. Adverse events are also assessed for their causal relationship to the study drug (i.e. unlikely, possibly, probably or definitely related to the drug). Adverse events that prevent escalation to the next drug level are generally ‘serious adverse events’ (grade 3 or 4 in severity) (Table 1) that are ‘probably’ or ‘definitely’ related to the study drug. The highest dose with acceptable toxicity is defined as the maximal tolerated dose (MTD) and is used

Table 1. Glossary of terms

Term	Definition
Clinical trial	An experimental study on a defined population of human subjects that is performed in a prospective manner in which the outcome of specific intervention is analyzed usually in comparison with a control group.
Prospective trial	A scientific investigation in which study participants are followed forward in time. After a baseline enrollment evaluation, an investigative intervention is undertaken and subjects are analyzed for their outcome over time.
Protocol	A written document that provides the background, objective, specific study designs and organization of a clinical trial.
Adverse event	Any event that is unfavorable or unintended that occurs after the administration of an investigational drug, biological agent or device, regardless of whether it is considered related to the medical procedure. A 'side effect' of an investigation therapy.
Serious adverse event	Any adverse event that results in death; or that is life-threatening; or that required inpatient admission or prolongation of an existing hospitalization; or that resulted in persistent or significant disability; or that produced a congenital anomaly or birth defect in offspring of the subject.
Response	A term used to describe outcomes measured during the course of a trial. For oncology trials, response is generally used to describe the measurable effect of a drug or intervention on a tumor mass. Responses are often defined as complete, partial, stable or progressive based on criteria established in individual studies.
Parallel design	A common Phase III trial design utilizing two groups of patients in which patients receive the assigned treatment throughout the trial.
Crossover design	A common Phase III trial design utilizing two groups of patients in which each patient receives sequentially both treatments being compared in the trial.
Randomization	The process by which patients in a clinical trial are assigned 'by the toss of a coin' or 'by chance' to one of the treatments being evaluated. Randomization ensures that biases do not influence whether a particular patient receives the study treatment or the control treatment.
Stratification	The process of identifying characteristics (clinical, radiographic, or laboratory) that may influence outcome, and then grouping patients based on these criteria. Once patients are assigned to the group (stratified) they can then be randomized. Stratification ensures that the group receiving a new intervention is similar in characteristics to the group receiving the control intervention.
Blinding	Lack of knowledge about whether a patient received the study treatment or the control treatment.
Type I error	False positive error.
Type II error	False negative error.
Sponsor	The entity, individual or organization that takes responsibility for the initiation and management of a clinical trial.
Institutional review board	Government mandated group that is independent of institutional authority and that is designated to review and approve all clinical trials to guarantee the safety of human subjects and to ensure that the study meets all FDA requirements.
Informed consent	A process defined as a patient's being given adequate information about a clinical trial, understanding and accepting the terms of a clinical trial, and agreeing to cooperate in its conduct.
Source documentation	Original records that describe clinical findings. All data in clinical trials must be supported by the original records to be considered valid. This process prevents falsification of information.
Audit	Independent examinations of trial-related activities and documents to determine whether these activities were conducted, and the data were recorded and reported according to the protocol, GCP and applicable regulatory requirements.

in subsequent studies. In the classic '3 + 3' Phase I design cohorts are divided into groups of three and observation of drug related adverse events in 33% of subjects warrants adding an additional three patients to the cohort or terminating the dose escalation (Figure 1). Several investigators have advocated alternative designs using more sophisticated statistical modeling, such as the continual reassessment method, that aim to identify the MTD more rapidly and with fewer patients [20–

22]. Phase I studies also commonly complete the safety analysis by analyzing serum pharmacokinetics of the new agent in subsets of participants.

Phase II trials (Table 2) are designed to assess whether the agent has biological activity (i.e. determine efficacy) and to provide additional safety data in larger groups of subjects using the dosage determined to be safe in Phase I studies (i.e. the MTD). In classic Phase II designs, all subjects receive the same dose of the experimental agent and

Table 2. Clinical trial phases

Trial phase	Objective	Prospective	Randomized	Control group	Sample size
I	Establish MTD Define toxicity profile	Yes	No	No	Small (usually <30)
II	Establish biological activity or efficacy	Yes	No	No (may use histological controls)	Small (~30–40)
III	Establish the effectiveness of a new intervention compared to a standard	Yes	Yes	Yes	Large (often >100)
IV	Post-marketing study to establish long term effects or adverse reactions	Yes	No	No	Large (variable)

### Common Dose Escalation Method for Phase I Trial

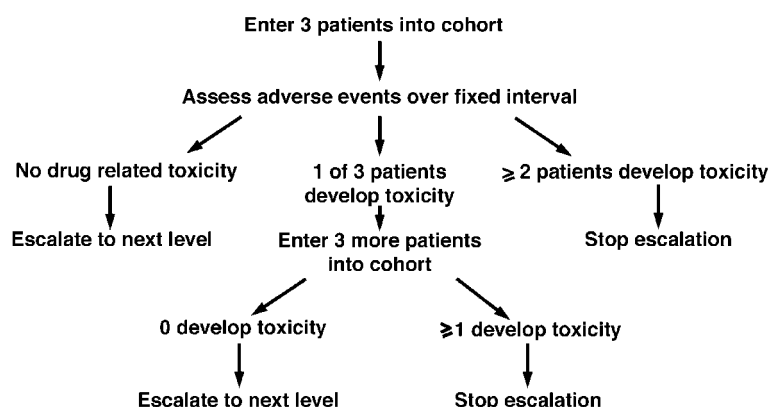


Figure 1. Common dose escalation scheme used in Phase I clinical trials. Three patients are entered at a given dose. If none of the patients experience a drug related toxicity the dose is escalated to the next level. If two patients experience toxicity the dose escalation is stopped. If one patient experiences toxicity, three more patients are added at the same dose level. If any of these three new patients experience toxicity, the escalation is stopped; otherwise the dose is escalated to the next level. Dose escalation continues until the MTD is identified.

the patient's tumor is analyzed for 'response' (Table 1) based on serial assessments of radiographic images or a known tumor marker. Responses are judged as 'complete' if the tumor disappears, 'partial' if there is a significant decrease in tumor size, or 'stable' if a previously growing tumor remains unchanged over time. Agents that exceed a predetermined response rate (e.g. 20% of patients with a partial or complete response) are considered suitable for further study. Because Phase II trials do not allow for a direct comparison of the experimental drug with other therapies, include relatively small numbers of patients (30–40 subjects), have a relatively short follow-up period and are associated often with narrow patient

demographics, definitive conclusions about efficacy cannot be drawn from these analyses. Nevertheless, Phase II studies are important as they provide enough data to prevent unwarranted pursuit of agents that have limited promise.

Agents that are safe (Phase I trial) and potentially efficacious (Phase II trial) must ultimately be tested in Phase III trials (Table 2), the goal of which is to determine whether the agent or treatment strategy is more effective than a standard therapy. The critical eliminates of Phase III trials are that they are prospective, there is a control group, and subjects are randomized. A variety of study designs can be used. The two most common designs are parallel (non-crossover) and crossover

designs (Table 1). Although the variability in data is generally less and the sensitivity generally greater in cross-over studies, parallel designs are not as affected by many types of problems that can occur in clinical trials, such as incomplete follow-up [17]. For oncological trials where irreversible responses to a drug are anticipated, or in surgical trials where reversing an intervention is not possible, parallel designs are the only option. Thus subjects in these parallel studies are randomly assigned to an investigational group, which receives the therapy under study, or to a control group that is given the standard therapy. Depending on the scientific question being asked, more than two treatment groups may be used.

After a drug or therapy is approved by regulatory agencies (see below), continued testing is often undertaken to evaluate the drug or therapy under more standard clinical circumstances. These Phase IV trials (Table 2) typically involve large numbers of patients with broader demographic features than earlier phase trials. The goal of these studies is to clarify the effectiveness of a therapy as it is used in general clinical practice and, more importantly, to identify side effects or adverse reactions that occur over the long term and at lower rates than could be detected with the number of patients entered into Phase III trials.

#### *Randomization vs. stratification*

A critical aspect of clinical studies is the concept of randomization (Table 1), i.e. the process that assigns treatments 'by chance' [23–25]. Randomization is not used in Phase I, II or IV studies, but is a critical and necessary aspect of Phase III trials. Randomization is required to ensure that statistically significant tests comparing the outcome of two (or more) groups can be used in a valid fashion [26]. Randomization decreases the chance of assigning treatments based on personal biases. It must be emphasized, however, that randomization is not a method to ensure that patients with similar characteristics are distributed equally between treatment groups. For this to be guaranteed, patients must be stratified prior to randomization [26]. Stratification (Table 1) is the process of grouping patients according to specified criteria that are generally thought to influence outcome. Thus, for trials of glioma it is important to stratify

patients by histology, age and KPS, for example, prior to randomization in order to assure that the comparison groups are equal. *Post hoc* stratification after completion of the trial is generally not a statistically valid approach.

Physicians are often concerned about whether randomization is ethical. Most investigators agree that properly randomized and carefully conducted trials that have a high probability of yielding meaningful results are ethical. Because individual investigators may have a preference at the start of a trial for one treatment over another, the concept of 'clinical equipoise' has been proposed [27]. This concept states that 'the presence of uncertainty as to the benefits or harm from an intervention among the experienced medical community, rather than in the investigator, is justification for a clinical study involving randomization.' [27].

#### *Blinding*

Another aspect of clinical trials, specifically Phase III trials is blinding (Table 1), which refers to the lack of knowledge about to which treatment the patient has been assigned [14,17]. Patients, investigators, or trial monitors can be blinded to the treatment assignment. In 'open label' trials no blinding is used and both patient and investigator know which treatment is applied. In 'single blinded' studies the patient is unaware of the treatment, but the investigator knows. In 'double blinded' studies, both investigator and patient are unaware of which treatment group the patient has been assigned. Double blinded studies are the most valid as investigators are less likely to bias their interpretation of data and patients are less prone to overstate or under emphasize their symptoms [17]. However, in many studies, especially those involving a surgical intervention, double blinding is difficult.

#### *Statistical considerations*

It is beyond the scope of this review to describe all the statistical aspects of clinical trial (see references [28–30] for review). However, several issues need emphasis.

Although statistics should not overshadow the critical issues of formulating a clear question and developing a carefully planned protocol design,

statistics remain an important part of any clinical trial, and the involvement of statisticians early in the design process is imperative. Most importantly, methods of data analyses must be determined and agreed upon by the statisticians prior to commencing the study.

In addition to traditional analytic statistics, which use a variety of mathematical techniques to analyze data and to compare differences between groups [28], investigators must be aware of other approaches. For example, Bayesian analysis is an alternative statistical approach that, unlike traditional methods, incorporates information from the past when analyzing the data [28,31]. For example (and to greatly simplify the concepts), in Phase II trials, classic analytic statistics dictate that the probability of response to the agent under study in the 15th patient entered into the trial is equal to the probability of response in the first patient, even if the 14 previous patients did not respond to the agent. With Bayesian statistics, the probability of response in the 15th patient takes into account the lack of response in the first 14 patients. These type of statistical methods are becoming increasingly popular because they derive predictive models that permit early stopping of trials of agents with not clear benefit, or that encourage investigators to keep entering patients to trials for agents that show promise.

A major goal of statistical analyses is determining sample size, a process that depends at least in part on minimizing type I and II errors (Table 1) [29,32–34]. Type I error describes the chance that a positive result is actually incorrect. For example, if a difference is observed between the survival of two treatment groups, but in fact the difference is false, detection of a difference (i.e. false positive result) is a type I error. In contrast, if the data shows no difference, but in fact a difference exists (i.e. false negative result) the error is a type II error. The goal of clinical trials is to eliminate these types of errors, which is generally accomplished by calculating a proper sample size given certain constraints based the expected outcome.

### *Regulatory issues*

New drug evaluation in the United States takes place under the supervision of the Food and Drug

Administration (FDA), one of the 17 federal agencies within the Department of Health and Human Services (DHHS). The FDA is required by law to review all data related to the evaluation of new drugs to ensure that the agents are safe and effective for specific indications. The FDA also oversees the evaluation of new medical devices.

Before a new drug or biologic agent can be tested in humans, preclinical data must be accumulated related to the activity, potential toxicity, pharmacokinetics and bioavailability of the substance. If the agent shows promise in preclinical studies, the agent's sponsor (Table 1) can submit an Investigational New Drug Application (IND-FDA form 1571) to the FDA. Once the application is approved, the sponsor can begin testing the drug in human subjects after review and approval by the relevant Institutional Review Boards (IRBs) (Table 1) (see below). If the new drug or biologic agent is found to be safe and/or more effective than standard therapies in clinical trials, the sponsor can file a New Drug Application (NDA) or a Biologics License Application (BLA) to the FDA. Once the FDA approves the NDA or BLA, the sponsor can market the drug.

Our society now demands that researchers involved in human trials adhere to strict ethical principals. The FDA has established regulations and guidelines that specify the responsibilities of individuals who are involved in the conduct of clinical research [35]. FDA regulations are found in Title 21, Chapter 1 of the code of federal regulations (21 CFR) and should be familiar to all investigators who conduct clinical research. All clinical researchers should also review 21 CFR Title 45, Part 46, which outlines protection of human subjects.

All investigators participating in the evaluation of a new drug or agent must sign and submit form 1572 to the FDA. Investigators signing a 1572 commit to a number of responsibilities that are outlined in Table 3. It is vital that investigators understand each of these points. It is particularly important to note that investigators signing a form 1572 are agreeing to *personally* conduct the trial and to comply with all requirements regarding the obligations of a clinical investigator as outlined in 21 CFR. Form 1572 is a legally binding contract with the FDA.

In 1990, six regulatory parties representing the regulatory bodies of the European Union, Japan

Table 3. Responsibilities of clinical investigators defined in FDA Form 1572, Section 9

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- To conduct the study in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
  - To personally conduct or supervise the described investigation.
  - To inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and IRB review and approval in 21 CFR Part 56 are met.
  - To report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.
  - To understand the information in the investigator’s brochure, including the potential risks and side effects of the drug.
  - To ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
  - To maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
  - To ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.
  - To promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others.
  - To not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
  - To comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.
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and the United States initiated the International Conference on Harmonization (ICH), in order to develop international coordination of regulatory requirements for human drug trials [36]. Guidelines developed by this group are published in the federal register and their content is available for review. One particularly noteworthy ICH guideline is referred to as E6, the ‘Guideline for Good Clinical Practice’ (GCP), which defines an international ethical and scientific quality standard for designing, conducting recording and reporting trials involving human subjects [36,37]. GCP is meant to protect the safety, rights and welfare of patients in addition to ensuring the accuracy of the collected study data and clinical investigators should be knowledgeable of its key principals. Investigators should also be aware of the ethical standards for clinical research set forth in three pivotal documents, the Nuremberg Code (1947) [38], the Declaration of Helsinki (1964-with 6 amendments to date) [39] and the Belmont Report (1979) [40], all of which affirm the rights of individuals who participate in clinical trials. Among the many important principals designed to protect human subjects that were introduced in these documents are those of the IRB (Table 1) and Informed Consent (Table 1).

IRBs are independent groups of professionals designated to review and approve clinical protocols in order to ensure that the study is safe for

human participation and that it adheres to FDA regulations [41]. Importantly, the approval of an IND by the FDA is not an approval to proceed with clinical research; only IRBs may approve research activity. IRBs are generally based in the individual institutions through which clinical research is being conducted, but function independently of any institutional authority. After IRB approval of a protocol, informed consent must be obtained from any potential trial participant prior to initiating any study-related procedures. Informed consent should be viewed as a *process* by which a subject voluntarily confirms his/her willingness to participate in a trial after having been informed of all relevant aspects of a given study.

Once a clinical trial has been initiated, the study sponsor is required to monitor the progress of the study. Monitors are charged with verifying to the sponsor that the study principal investigator and staff are performing as required. One very important aspect of monitoring is the review of study data for accuracy and completeness. Data accumulated in clinical studies is generally recorded on Case Report Forms (CRF) and all data recorded in CRFs must be backed up by Source Documentation (Table 1), the original records of clinical findings (the medical record). Once verified, these data, particularly in blinded, randomized studies of drugs, are often reviewed by Data and Safety Monitoring Boards (DSMB) that are

typically composed of researchers independent of the clinical trial. The DSMB may stop a trial early if excessive toxicities are found or if the treatment is found to be beneficial. From time to time, the study sponsor and or the FDA will choose to conduct an audit (Table 1) of an individual clinical site. Common inadequacies found in audits include insufficient source documentation, improperly obtained informed consent, lack of investigator oversight, failure to perform all protocol-required procedures and failure to account for the investigational drug. These regulatory reviews are intended to ensure proper conduct of clinical trials.

### **Challenges of brain tumor clinical trials**

Because of their unique location and distinct biology, brain tumors pose several challenges that add to the complexity of conducting clinical trials and interpreting the results [9,42,43].

#### *Rarity of brain tumors*

Compared with other cancers in adults, brain tumors are relatively rare. Whereas the incidence of lung cancer in the USA, for example, is 170,000 new cases per year [44], the incidence of GBM, the most common primary brain tumor is only approximately 17,000 per year [45]. Thus patients who can be enrolled in brain tumor trials are a limited resource, and completing studies for even the most common primary brain tumor, GBM, can be quite challenging. Accruing sufficient numbers of patients into studies devoted exclusively to the other less common glioma types, such as low grade astrocytomas or oligodendrogliomas, is even more difficult, and very few prospective studies focus on these important but less prevalent tumors.

Because of the rarity of brain tumors, many drug development programs do not give brain tumors high priority, particularly those programs from within the pharmaceutical industry, where many new drugs originate. Most new agents are considered for gliomas only late in the drug development process. Therefore, many agents are often rejected, even before they are tried in gliomas; and agents that are ultimately tested against

brain tumors are evaluated in a delayed fashion. The low priority of gliomas has slowed the progress of brain tumor therapy relative to other cancer types.

#### *Problems of classification*

Inclusion and stratification of patients in brain tumor clinical trials depends highly on proper diagnosis of tumor type. Histological stratification is based primarily on pathological review of tumor specimens at the microscopic level. This diagnostic process is subjective and its difficulty is compounded by the variability of histological features within brain tumors. Confusion is added by multiple grading systems and lack of uniformity about diagnostic criteria [42]. For example, some classification schemes require necrosis in order to make the diagnosis of GBM, whereas this is not a requirement of other grading systems (i.e. WHO classification) [46,47]. Although brain tumor clinical trials rarely account for this variability by including large numbers of patients, methods for stratifying based on more objective measures, such as molecular profiles of the tumor, have not to date been routinely applied in brain tumor clinical trials.

#### *The blood brain barrier (BBB)*

Delivering agents to brain tumors is significantly hindered by the BBB. The infiltrative tumor cells that extend away from the solid tumor mass usually reside within areas where the BBB is relatively intact. In contrast to most systemic tumors (e.g. lung cancer), the variable presence of the BBB in gliomas raises significant concerns about drug delivery to the tumor [9]. Indeed, for most agents, only a fraction of the serum plasma concentrations will penetrate within gliomas. Moreover, anti-convulsants and other medications can interfere with drug metabolism, altering serum drug levels and bioavailability to the tumor [48]. Although most drugs undergo preclinical evaluations to determine the levels of drug that are achieved in brain tissue, during human clinical trials specific testing for the presence of drug in the tumors is usually not performed [9,49–51]. Uncertainty therefore exists about the adequacy of drug delivery to the tumor – a prerequisite for response.

### *Evaluating response to therapy*

Determining the effectiveness of an agent against gliomas can be difficult [52]. In the majority of brain tumor clinical studies, response to an agent is based on measures of tumor regression determined on radiographic studies such as magnetic resonance imaging (MRI) or computer tomography (CT). Unfortunately, the complex nature of many gliomas renders most measurement techniques (including the common use of cross sectional areas or volume assessments) inaccurate estimates of changes in tumor size [52]. Additionally, drugs used in the routine care of patients, particularly corticosteroids, alter the amount of tumor enhancement and thus interfere with measurements of response [42,52]. Many treatments cause changes, such as necrosis, that appear similar to tumor on radiographic studies [53,54]. Alternatively, many agents, such as cytostatic agents, are not expected to alter tumor size dramatically. Many drugs are ineffective against gliomas when given alone, but can act synergistically when combined with other agents. Unfortunately, it is difficult to identify such agents, because initial single agent studies that use radiographic response to determine drug activity do not provide insight into the direct activity of the drug on the tumor cells. Hence, there is a potential disconnect between biological response and clinical/radiographic response.

### **Application of molecular biology for improving prospective clinical trials**

In the past decade major advances have been made in elucidating the molecular pathways underlying brain tumor formation and progression [46,55]. Molecular techniques have led to the identification of a variety of molecular alterations that provide tumor cells with growth advantage. This new knowledge has encouraged new insights into ways of meeting the challenges associated with performing trials of brain tumor therapies [9]. It has become clear that many molecular techniques, from gene or protein expression profiling to analyses of specific protein modifications (e.g. phosphorylation), can be applied to tumor samples acquired from patients in prospective clinical trials. Although a new concept, carefully planned

incorporation of these techniques into clinical trials has the potential of improving the information gained from brain tumor studies. Molecular profiling prior to drug treatment and analyses of molecular endpoints after drug treatment have gained particular attention.

### *Molecular profiling prior to drug treatment for tumor stratification and predicting response in clinical trials*

In the past decade molecular analyses of brain tumors have shown that tumors with similar histological features in patients with similar clinical characteristics may be sub-classified at the molecular level [56]. Thus, GBMs can be classified into primary and secondary types based on their molecular signature [46], and the response of anaplastic oligodendrogliomas to chemotherapy can be correlated to a first approximation with deletion of chromosomes 1p and 19q [57]. Although molecular profiling has been used substantially in retrospective analyses of tumors, clinical investigators are becoming increasingly aware of the potential application of molecular profiling in prospective clinical trials of new therapeutic agents.

Problems associated with classification of tumors based on microscopic review can be addressed by including molecular analyses of specimens obtained prior to treatment (i.e. pretreatment) as part of the stratification of patients. For example, differences in diagnostic criteria, such as whether necrosis is required to diagnose GBM (see above), may be addressed by adding molecular profiling into the stratification process, decreasing the emphasis on histological correlates and increasing the emphasis on tumor biology. In such a trial, tumors are not simply classified as GBM, but they are further divided based on specific molecular alterations (e.g. EGFR amplification, p53 mutations), or based on genome-wide RNA expression patterns or protein status as defined, for example, by micro-array or protein array technology, respectively.

Molecular profiling of pretreatment specimens has the added advantage that correlations between specific molecular profiles and a response to the drug under study can be established in early phase trials. In other words, response to a new therapy can be correlated to particular molecular

signatures. This type of information can be further applied in later Phase III trials that may require a certain molecular profile for inclusion or that may stratify patients based on the presence of a particular molecular signature. Although to our knowledge there are as of yet no published prospective clinical trials of brain tumor therapy using this approach, it is currently being applied in several prospective trials evaluating new drug therapies for brain tumors. For example, a trial of the tyrosine kinase inhibitor OSI774 is currently underway in which the molecular profile, particularly the EGFR status, of pretreatment specimens are being correlated with patient response to the drug (see [www.nabtc.org](http://www.nabtc.org) for trial description).

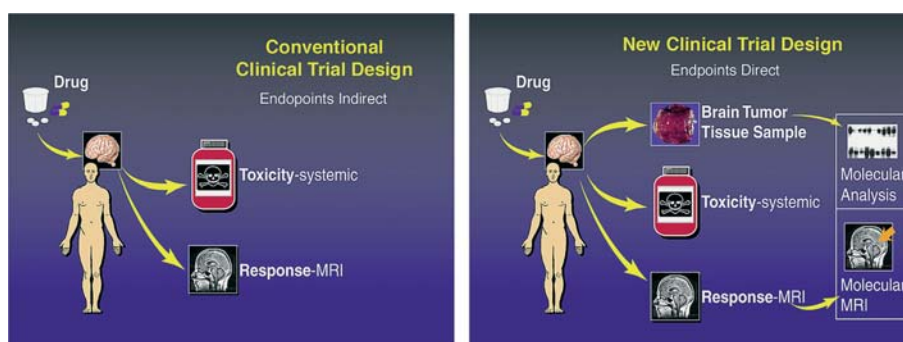
*Molecular analyses of tumor specimens after treatment for defining dose and response in clinical trials*

Another important consequence resulting from the identification of specific molecular alterations in brain tumors, has been the development of drugs that are specifically targeted to inhibit particular proteins within those molecular pathways that are critical to tumor survival [9]. These so called ‘targeted’ agents, which specifically inhibit proteins within critical signal transduction pathways, are distinct from the classic cytotoxic anticancer agents (e.g. BCNU), which cause ‘nonspecific’ injury to cells. For example, new targeted drugs are now available for clinical application that specifi-

cally inhibit the action of molecules within the PI3 kinase/AKT signal transduction pathway [9], a cascade that is critical to glioma survival, or that inhibit the activity (i.e. phosphorylation) of EGFR, a growth factor receptor whose increase expression has been associated with tumor progression [9]. Multiple other targeted agents continue to be developed.

The targeted nature of these agents has led to new clinical trial design concepts [9,49–51]. Specifically, because these agents are known to interfere with the function of a particular protein, the direct effect of the agent on a tumor can be measured in clinical trials by assessing with molecular techniques the inactivation of the targeted protein in specimens obtained from patients that have been treated with the drug (i.e. post-treatment specimens) (Figure 2). In other words, molecular analyses, or so called ‘molecular endpoints’, can be part of the design of prospective trials evaluating new drug therapies.

Whereas classic Phase I trials identify a MTD through indirect means (i.e. assessments of systemic toxicity), Phase I trials that incorporate molecular analyses of post-treatment tumor specimens can identify directly the dose of a drug that actually alters the tumor biology, which ultimately is the endpoint that is most critical to therapy. Thus Phase I trials that include molecular endpoints can determine what has been referred to as the *appropriate biological dose (ABD)*, the *optimal biological dose (OBD)*, or the *maximal target*



*Figure 2.* Comparison of classic Phase I and II trials with newer Phase I and II trials incorporating molecular endpoints. From the perspective of tumor biology, the endpoints of classic Phase I trials are indirect (left panel). Thus, classic Phase I trials determine an MTD, based on assessments of systemic adverse events. Similarly, classic Phase II trials assess response based on evaluations of radiographic images. In contrast, trials that incorporate molecular analyses of specimens obtained after treatment provide direct measures of the effect of the drug on the tumor (right panel). In the future, molecular imaging may further enhance direct molecular analyses of tissue specimens.

*inhibitory dose* (MTID) [50]. The dose that inhibits the target can thus be compared to the dose that results in systemic toxicity (MTD). In Phase II trials the efficacy of an agent can be determined by defining the relationship between radiographic tumor response and inhibition of the molecular target when the agent is given at the OBD.

The incorporation of molecular end points has been used in several published early phase clinical trials and is becoming an increasingly common approach. An important aspect of this paradigm is the inclusion of molecular endpoints without abandoning classic endpoints of toxicity and response [9]. A recent Phase I trial of adenoviral-mediated p53 gene therapy exemplifies the feasibility of such studies [58]. The goal in this trial was to determine the biologic effect of intratumoral administration of a replication-deficient type 5 adenovirus vector containing cDNA from the p53 gene (Ad-p53), while also determining the clinical toxicity customarily assessed in standard Phase I trials. Therefore, a two-stage surgical approach was established in which patients underwent a biopsy and injection of Ad-p53 via a catheter implanted in the center of the tumor. Several days after injection, the tumor was resected *en bloc* with the catheter. Tissue from the pretreatment biopsies allowed p53 mutational status to be assessed in the tumors before treatment. The post-treatment surgical specimens were analyzed for p53 gene expression with the catheter serving as a reference for the site of Ad-p53 delivery. After tumor resection, the walls of the post-resection tumor cavities were injected with Ad-p53 so that patients could be followed to identify clinical toxicity related to Ad-p53 and to determine treatment efficacy. The dose of Ad-p53 was escalated among four cohorts, permitting determination of an ABD (based on a gene expression endpoint) and a MTD (based on a clinical toxicity endpoint).

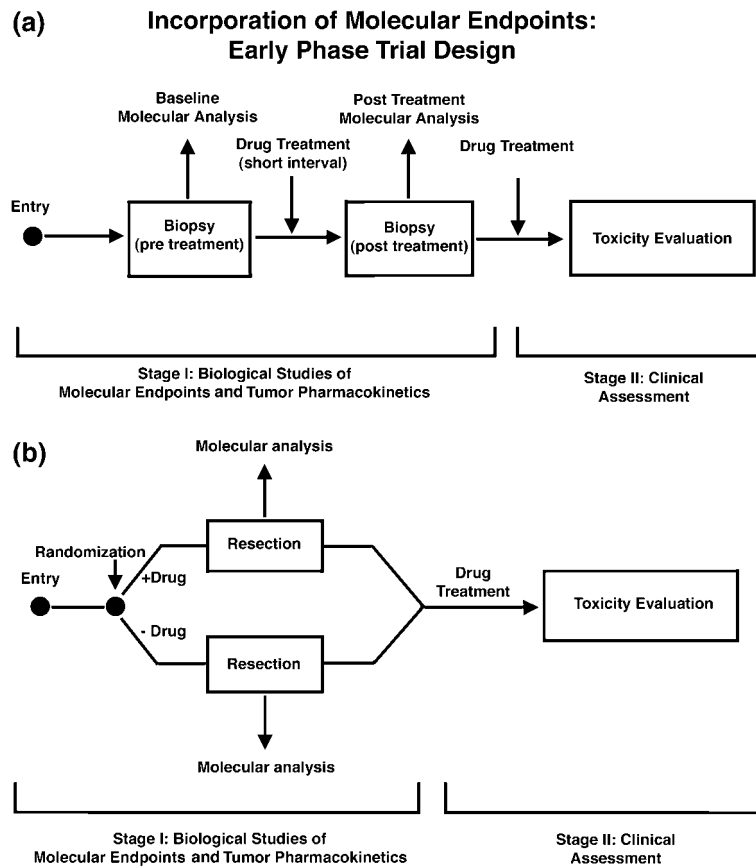
This two-stage paradigm has been used as a working model for trials that seeks to incorporate molecular endpoints (Figure 3) [9]. In the ideal design (Figure 3a) patients undergo biopsy to obtain tissue to establish a pretreatment baseline evaluation of the molecular target. The experimental drug is then administered for a predetermined short interval after which resection of the drug-treated tumor is performed in order to provide tissue for analysis of drug levels and drug-related molecular changes. After surgery, the

experimental drug is administered in order to determine clinical toxicity, according to standard criteria. This ideal two-stage model allows comparisons to be made between treated and untreated specimens from the same patient and also allows for conventional toxicity assessments. However, because of the need for two procedures, issues of enrollment and cost exist.

Other approaches are also possible and are beginning to be applied in studies that are currently underway. For example, baseline biopsies may be avoided using an alternative approach in which patients are randomized to a preoperative drug administration group or to a placebo/no-drug group (Figure 3b). Patients in both groups undergo surgical resection and the tumor specimens from the untreated cohort serve as controls for the specimens from the drug-treated group. After surgery all patients are administered the agent and are followed for clinical toxicity using standard criteria. This design has the advantage of requiring only one surgical procedure. It suffers from its dependence on population analyses to determine the baseline variability of the targeted molecule and will require enrolling more patients per cohort.

For Phase II trials, similar two-stage paradigms can be used. Biologic efficacy or 'molecular response' can be demonstrated by evaluating the molecular endpoint in post-treatment specimens, and clinical response can be determined using standard radiographic criteria. Thus, biologic efficacy can be correlated with clinical efficacy. As a consequence of extensive tumor resection, criteria for assessing clinical response may need to be re-evaluated. Because the majority of tumors will undergo gross total or near total resection of enhancing tumor, response measurements (i.e. radiographic assessments of tumor reduction) may not be possible. Consequently, clinical efficacy with this approach may best be assessed based on determination of time to recurrence and progression-free survival. Precedent for the use of progression free survival in brain tumor studies has already been established [59].

Although details of the methodology will require continued refinement, the inclusion of molecular endpoints provides several clear advantages. Most importantly, evaluating molecular changes in post-treatment tumors specimens can provide answers to important questions about a therapeutic agent, e.g. about drug delivery and



*Figure 3.* Examples of designs of clinical trials that incorporate molecular endpoints. (a) Optimal design. In the first stage (biological stage) of the trial, tissue specimens are obtained before treatment to determine the baseline value of the target in each patient. Patients then receive the drug for a predetermined interval, after which tissue is again obtained from the same patient and the effects of the drug on the target are assessed. In the second stage (clinical stage) of the study, patients are treated with the drug over a longer interval and observed for adverse events. (b) Avoidance of pretreatment biopsy. An alternative design for obtaining post-treatment specimens is to randomize patients in the biological stage of the trial to either receive the drug or not to receive the drug prior to biopsy or craniotomy. The tissue specimens from patients who received the drug are compared with the specimens from patients who did not receive the drug; thus the latter group acts as the control for the patients who did receive the drug. Although statistically more complex, this design avoids two procedures in individual patients. In the clinical stage, the drug is administered to all patients and assessments of clinical adverse events are determined.

effect of treatment on tumor biology. Ironically, answers to these questions may be most valuable in assessing agents that are considered failures because they do not produce a radiographic response in classic trials. In these situations, molecular endpoints can provide insight into the cause of failure. Was the problem with drug delivery? Did the drug not exert its desired molecular effect? Did the drug alter the tumor biology, but the alteration was not sufficient to induce a radiographic response? Taking a molecular approach may avoid continuing studying drugs that are not

effective, or prematurely eliminating agents that do not meet traditional response criteria, but that effectively alter an important molecular pathway underlying tumor growth and that, therefore, may be efficacious when combined with other agents.

#### **Critical role of neurosurgeons in brain tumor clinical trials**

Neurosurgeons are uniquely positioned to play a pivotal role in the development and performance

of prospective clinical brain tumor trials. This involvement may be particularly valuable in drug development trials, which are typically viewed as being within the purview of medical neuro-oncology. However, collaboration between neuro-oncologists and neurosurgeons would enhance several areas of clinical trials design and execution.

#### *Patient access*

Because neurosurgeons evaluate the majority of patients with newly diagnosed or recurrent brain tumors, neurosurgeons are particularly cognizant of the fundamental problems surrounding brain tumor therapy and can, therefore, formulate pertinent clinical questions and posit novel therapeutic approaches. Their front-line interaction with patients also affords significant opportunities to educate patients and referring physicians about the benefits of clinical trial participation. This includes participation in standard therapeutic clinical trials, but also cooperation with other important forms of clinical research, such as those that include molecular endpoints.

#### *Tissue acquisition*

Neurosurgeons are the only specialists who can directly access living brain tumor specimens and who can acquire human brain tumor tissue for microscopic and molecular study. This has been important in the past as removal and testing of brain tumor specimens has been the basis for many retrospective correlative pathological-clinical studies.

However, the recent movement to incorporate molecular endpoints into clinical trials, has greatly increased the need for and the importance of neurosurgical participation in prospective clinical trials, particularly Phase I and II studies. As described above, the assessment of many targeted, novel anti-glioma agents may ultimately rest upon the identification of a desired molecular effect within freshly acquired post-treatment tumor specimens. Acquisition of this tissue rests solely on the meaningful participation of neurosurgeons, without whom access to human tissue specimens will not be possible. To properly participate, however, neurosurgeons must be fully knowledgeable of the properties of the drug under study,

especially because these molecular-based trials require the administration of the agent prior to tumor removal. Because drug related intra-operative or post-operative complications may increase with this type of approach, neurosurgeons must be active in the development of these trials. Effects of the drug on coagulation (increased intra-operative bleeding) and immune responses (increased risk of infection) must be understood and evaluated by neurosurgeons. Likewise, systemic effects of the drug, such as adverse cardiac and respiratory toxicities, must be taken into consideration. Neurosurgeons must also be familiar with the molecular assays to be performed so that appropriate collection of tissue is achieved. For example, processing of tissue for protein analyses is different from that for RNA. Details such as the time between resection and tissue preservation must be worked out by the neurosurgeon in collaboration with the individuals performing the assays so that the molecular target is appropriately preserved for analysis.

#### *Delivery methods*

The special skills of neurosurgeons may also be applied in the delivery of many novel therapies to brain tumors. Recent studies have shown that the concept of locally applied chemotherapeutic agents released from polymers or other carriers may be a useful paradigm for bypassing the BBB [5]. In addition, the emerging technology of convection-enhanced delivery (CED) [60] depends upon the placement of infusion catheters within brain tissue, an expertise that can only be achieved by neurosurgeons. The development and safe application of these types of novel delivery strategies rely heavily upon neurosurgical input, and will only be realized if neurosurgeons take a leading role in their development through carefully run clinical trials.

#### **Clinical trial organizations**

Because collaboration between neurosurgeons and medical neuro-oncologists is critical to the further development of new treatment strategies, it is important for neurosurgeons to participate in the clinical trial process at the local, national and international levels. Clinical trials can be performed at single institutions, multiple institutions

(multi-center) or as part of national groups. There are advantages and disadvantages associated with each of these venues.

Complex trials that are in their early stages (Phase I and II) of development in which methodological details are evolving (e.g. initial gene therapy studies, trials evaluating a particular molecular target, or trials using novel surgical procedures such as CED) are probably best carried out in one or a few institutions that are committed to solving the many complexities associated with these novel approaches. However, universal acceptance of new treatment strategies requires testing in multiple centers on patients enrolled from broad demographic areas.

In the USA there are currently two Brain Tumor Consortia that are funded by the NCI (Table 4). Membership in these consortia is based on a competitive grant application. The North American Brain Tumor Consortium (NABTC) currently includes eight centers. The central administrative headquarters of the NABTC is at the University of California San Francisco, and the data base coordination is at The University of Texas MD Anderson Cancer Center. The New Approaches to Brain Tumor Therapy (NABTT) consortium is comprised of eleven academic centers. This consortium headquarters and data management site is located at Johns Hopkins Hospital. Both consortia have been mandated by NCI to evaluate novel

therapies in early phase clinical trials, and both have successfully tested a variety of drugs or drug combinations in many clinical trials (see websites, Table 4). These consortia have undertaken novel study designs, such as incorporation of molecular endpoints. Participation in these groups represents one avenue for increasing neurosurgical involvement in early phase clinical trials.

Most recently, the American College of Surgeons Oncology Group (ACOSOG) has funded a Central Nervous System Working Group whose goal has been to carry out Phase III clinical trials. This group represents the only neurosurgeon-specific clinical trial group in North America. Although early in development this working group may represent one of the few venues for neurosurgeons to specifically test novel agents that require surgical intervention, such as gene therapy, convection delivery, and other local-delivered anti-glioma strategies.

#### **Final thoughts: potential role of AANS/CN joint section on tumors in clinical trials**

Neurosurgeons are becoming an increasingly important component in the process of evaluating new brain tumor treatments through clinical trials due, at least in part, to the development of novel trial designs requiring pre- and post-treatment

Table 4. Brain tumor consortia in the USA

	New approaches to brain tumor treatment (NABTT)	North american brain tumor consortium (NABTC)
Chair	Stuart A. Grossman, MD (Neuro-Oncologist, Johns Hopkins University)	Michael Prados, MD (Neuro-Oncologist, The University of California San Francisco)
Co-Chair		W.K. Alfred Yung, MD (Neuro-Oncologist, The University of Texas MD Anderson Cancer Center)
Member institutions	Cleveland clinic, Emory University Henry Ford Hospital Johns Hopkins University Massachusetts General Hospital Moffitt Cancer Center NCI Intramural Program University of Alabama The University of Pennsylvania  Wake Forest University Emory University University of Texas, San Antonio	The University of California San Francisco The University of California Los Angeles Memorial Sloan Kettering Cancer Center The University of Wisconsin Hospital Neuro-Oncology Branch, NIH The University of Pittsburgh Medical Center Dana Farber Cancer Institute The University of Texas MD Anderson Cancer Center
Website Address	<a href="http://www.nabtt.org">www.nabtt.org</a>	<a href="http://www.nabtc.org">www.nabtc.org</a>

surgically acquired tissue. In this context, the occasion of the 20th Anniversary of the founding of the AANS/CNS Joint Section on Tumors, may be a good time to reassess one of the primary purposes of the organization stated in the preamble of the Rules and Regulations of the Section [61], namely 'to provide a forum for ... research on tumors of the nervous system.' Whereas the Section has clearly met this goal through organization of scientific meetings, forums, and symposia, one also might argue that, similar to other surgical specialties [62], there has been less emphasis on prospective clinical trials. Thus a goal of The Tumor Section for the next decade may be to formalize mechanisms for educating members about developing and participating in prospective clinical trials. Clearly the future of brain tumor therapy would benefit from the Section on Tumors taking a leading role in the promotion of clinical trials in neurosurgical oncology.

### Acknowledgements

This study was supported by a Grant (to FFL) from The Elias Harrison Family Fund for Brain Tumor Research, The Anthony Bullock III Brain Tumor Research Fund, and The Brian McCulloch Memorial Brain Tumor Fund. The authors thank Wei Ming Shi and Ian Suk for their expert assistance with the figures. Special appreciation goes to Sandra Flores and Maricela Emery for their diligent assistance with the preparation of the manuscript.

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