Curr. Treat. Options in Oncol. (2021) 22:78
DOI 10.1007/s11864-021-00875-8

Neuro-oncology (GJ Lesser, Section Editor).

Clinical Trial Considerations in Neuro-oncology

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This article is part of the Topical Collection on *Neuro-oncology*

Keywords Clinical trials · Clinical trial disparities · Clinical trial accrual · Clinical trial design · Response assessment

Opinion statement

Clinical trials play a critical role in discovering new treatments, but the path to regulatory approval can be cumbersome and time consuming. Efforts to increase the efficiency and interpretability of clinical trials within the neuro-oncology community have focused on standardization of response assessment, development of consensus guidelines for clinical trial conduct, decentralization of clinical trials, removal of barriers to clinical trial accrual, and re-examination of patient eligibility criteria.

Introduction

Clinical trials play a critical role in discovering new treatments. Over the past decade, the neuro-oncology community has worked on improving the design, interpretation, accrual, and conduct of clinical trials. The effort has been spearheaded predominantly by the Response Assessment in Neuro-Oncology (RANO) working group, a multidisciplinary international working group consisting of neuro-oncologists, medical oncologists, neuroradiologists, neurosurgeons, radiation oncologists, neuropsychologists, and experts in clinical outcomes assessments, working in collaboration with government and industry. Their initial papers focused on the limitations of endpoint assessments in gliomas [1] and updating response criteria for high-grade glioma [2], which has now become the standard method for radiographic assessment in high-grade glioma clinical trials. Over the past decade, RANO efforts have expanded into other central nervous system (CNS) tumors including low-grade gliomas, meningiomas, brain metastases, leptomeningeal metastases, pediatric CNS tumors, and spine tumors as well as other aspects of response assessment including seizure endpoints, standardization of neurologic examination assessment, use of PET imaging, the impact of immunotherapy in response assessment, corticosteroid use, pathologic assessments, and patient-reported outcomes (Table 1). More recently, RANO has collaborated with the Society for Neuro-Oncology (SNO), patient advocacy groups, clinical trial cooperative groups, and other partners to increase clinical trial accrual [37••]. This review explores

Published online: 02 July 2021

Table 1. Clinical trial outcome assessments and guidelines developed by RANO working groups

Name of working group	Reports/guidelines published to date
RANO HGG (high-grade glioma)	• Limitations of endpoint assessments for high-grade gliomas [3] • Proposed response assessment criteria for high-grade glioma [2] • Clinical trial design and endpoints [4, 5] • Challenges in brain tumor related phase 0 and window of opportunity clinical trials [6•]
iRANO (immunotherapy)	• Proposed radiographic response assessment for brain tumor patients receiving immunotherapy [7]
RANO LGG (low-grade glioma)	• Proposed response assessment criteria for low-grade glioma [3]
Response Assessment in Pediatric Neuro-Oncology (RAPNO)	• Challenges in pediatric neuro-oncology clinical trials [8] • Proposed response assessment in pediatric medulloblastoma and leptomeningeal seeding tumors [9] • Proposed response assessment in pediatric high-grade glioma [10] • Proposed response assessment in pediatric low-grade glioma [11] • Proposed response assessment in pediatric diffuse intrinsic pontine glioma [12]
RANO BM (brain metastases)	• Challenges in brain metastases clinical trials [13, 14] • Proposed response assessment criteria for brain metastases [15] • Clinical trial design and endpoints for systemic therapies [16] and local therapies [17]
RANO LM (leptomeningeal disease)	• Review of challenges in leptomeningeal disease clinical trials [18] • Proposal for response assessment criteria for leptomeningeal metastases [19] • Revised proposal for response assessment criteria for leptomeningeal metastases [20]
RANO Meningioma	• Review of PFS6 benchmarks in meningioma clinical trials [21] • Review of meningioma treatments and patient outcomes following standard surgery and radiotherapy to help inform clinical trial design [22]
Neurologic Assessment in Neuro-Oncology (NANO)	• Standardized neurologic assessment metric for clinical trials [23]
RANO Seizures	• Proposed seizure assessment as a metric in brain tumor treatment trials [24]
SPIne response assessment in Neuro-Oncology (SPINO)	• Challenges in standardizing imaging-based assessment of local control and pain for spinal metastases [25] • Proposed response assessment following spine stereotactic body radiotherapy for spinal metastases [25] • Recommendations for patient- and clinician-reported measures in clinical trials for spinal metastases [26]
RANO Steroid	• Recommendations for evaluating corticosteroid use in endpoint assessment for clinical trials [27]
RANO Patient Reported Outcomes (PRO)	• Guidance on the use of patient-reported outcome measures in clinical trials and practice for adult patients with brain tumors [28] • Consensus recommendations for core set of symptom and functional constructs as represented in existing PRO measures for use in clinical care and trials for patients with high-grade gliomas [29]
RANO PET	• Recommendations for use of PET imaging in gliomas [30, 31] • Recommendations for use of PET imaging in meningiomas [32] • Recommendations for use of PET imaging in brain metastases [33]
RANO Surgery	• Recommendations for surgically related endpoint assessment [34]

Table 1. (Continued)

Name of working group	Reports/guidelines published to date
RANO Pathology	• Standardization of histological, biological, and molecular characteristics of adult recurrent glioma [35]
RANO Liquid Biopsies	• Review of literature on liquid biopsies for diagnosis and monitoring of leptomeningeal and parenchymal brain metastases [36]

recent advances in neuro-oncology clinical trial design, accrual, and conduct in clinical trials.

Clinical trial design

- Window of opportunity clinical trial designs, in which tumor tissue is sampled from patients pre-treated with the experimental agent, allow us to determine tumor tissue penetration as well as the biochemical, physiologic, and molecular effects of the agent [6•].
- Master protocols help improve the efficiency of clinical trials by creating a common trial infrastructure to test multiple treatments under a single protocol.

Few effective treatments exist for primary and metastatic brain tumors. With a plethora of experimental systemic agents in development for oncologic indications, how do we best choose which drugs to test in brain tumors? Sufficient blood-brain barrier (BBB) penetration is a particular challenge to overcome, and even for drugs that can sufficiently penetrate the BBB, how do we ensure that the drug has the intended biochemical, physiologic, and molecular effects in patients? Phase 0 clinical trials are early (sometimes first-in-human) clinical trials that provide preliminary information about drug pharmacokinetics, target engagement, mechanism of action, and pharmacodynamics to help inform decisions about drug candidate selection and development [6•, 38]. In a window of opportunity trial, study participants may be pre-treated with the experimental agent prior to surgery, thus allowing tissue-based pharmacokinetic and pharmacodynamic assessment. The RANO working group provides consensus guidance regarding the use of Phase 0-like/window of opportunity clinical trial designs in neuro-oncology [6•].

For drugs much further in development, traditional randomized controlled trials represent the gold standard for testing efficacy but are expensive, inefficient, and slow, and answer limited questions [39]. Novel designs such as master protocols aim to increase the efficiency of clinical trials. Master protocols specifically create a common trial infrastructure and design to test multiple hypothesis [40], thus improving efficiency via uniformity and standardization. Types of master protocols include basket

trials, umbrella trials, and platform trials. In a basket trial, the same targeted therapy is evaluated across different diseases that share a common molecular alteration. For example, a trial of an NTRK inhibitor may allow accrual of different cancers with *NTRK* fusions, which can be seen in a small subset of adult and pediatric primary and metastatic CNS tumors [41]. In contrast, an umbrella trial evaluates multiple targeted therapies for a single disease stratified by molecular subgroups. Alliance A071701 is a multi-arm phase II genomically guided treatment trial for brain metastases patients [42]. Previously obtained tissue from brain metastases and extracranial sites are screened for molecular alterations associated with sensitivity to the drugs available on study (currently CDK, PI3K/mTOR, and NTRK/ROS1 inhibitors). If determined to harbor such a molecular alteration, then the patient enrolls into the corresponding arm of the trial. Finally, platform trials (also known as multi-arm, multi-stage design trials) are trials that evaluate several treatments in a single disease against a common control group. Examples of platform trials include GBM Adaptive Global Innovative Learning Environment (GBM AGILE) [43], INdividualized Screening trial of Innovative GBM Therapy (INSIGhT) [44], and Neuro Master Match (N^2M^2) [45]. Adaptive platform trials can continue in a perpetual manner, adding or dropping arms [39]. Some may incorporate Bayesian approaches, which allow the ability to accumulate data in real time to alter the course of the trial, thus allowing for ineffective arms to be dropped sooner and for preferential enrollment to promising arms. Mathematical modeling suggests that the use of Bayesian adaptive designs in glioblastoma (GBM) trials results in trials requiring substantially fewer overall patients [46].

Clinical trial conduct

- Decentralized clinical trials utilize novel technologies or processes to collect study data, thus allowing the study to be designed around patients and not sponsors or sites [47].
- The COVID-19 pandemic has changed the way we practice medicine and allows us to re-envision the conduct of clinical trials [48].

Traditional clinical trial design generally requires all study-related visits and procedures to be performed at the research site. Because most academic centers are in large urban centers, this creates a barrier for trial participants who live far from these centers and/or do not have the resources to travel. Decentralized clinical trials utilize telemedicine, mobile technologies, and/or local health providers to collect study data [47]. The goal is to make clinical trials easier for patients by reducing the need to travel, thus improving trial accrual and retention. During the COVID-19 pandemic, trial conduct adapted to incorporate decentralized approaches in order to minimize travel and physical contact, including increased use of telemedicine, remote work by research staff, shipping of oral investigational agents, and remote monitoring [47, 49]. Such flexibility in clinical trial care was bolstered by guidance by regulatory agencies [50•, 51•,

Table 2. Summary of recommendations for neuro-oncology clinical trial eligibility [63]. Reprinted with permission from Lee EQ et al. Neuro Oncol 2020 May 15;22(5):601-612

Criterion	Types of trials	Recommendation
Age	Primary brain tumor	• Allow children (age ≥ 12) to participate in adult trials when disease biology and clinical course is similar in children and adults • Allow older patients (age ≥ 65) to participate on trials, particularly in diseases such as GBM where older patients represent a significant portion of the patient population
Functional status	Solid tumor phase 1 trials	• Performance score requirement can be of ECOG ≤ 2 or equivalent KPS of ≥ 60 for selected Phase 1 clinical trial based on mechanism of action and expected toxicity profile.
Co-morbid medical conditions	Primary brain tumor	• Allow participation of patients with a prior or concurrent history of malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen, rather than specifying a specific time frame since completion of treatment
	Immunotherapy	• Allow patients with select, well-controlled, autoimmune diseases to enroll on immune checkpoint inhibitor trials, e.g., thyroiditis
Concomitant medications	Immunotherapy	• Allow corticosteroids at baseline but consider limiting maximum total daily doses of 2 mg dexamethasone and/or stratification according to dexamethasone dose in randomized trials
Long washout	Primary brain tumor	• Use 5 half-lives rather than a 4 week washout for investigational agent. A general statement that the patient must have recovered from the effects of prior treatment would allow for even broader participation.
Archival tissue requirements	Primary brain tumor	• The amount of tissue required for study enrollment needs a strong rationale and should be limited to what is necessary
Laboratory values	Primary brain tumor	• Only the relevant laboratory tests based on the safety profile of the study agent should be used as the basis for eligibility criteria • For those laboratory tests included as eligibility criteria, allow for a safe range above normal parameters
	Immunotherapy	• Depending on the trial design and primary outcome, baseline ALC > 1000 cells/μL is ideal, but > 500 cells/μL may be reasonable
Pathology	GBM	• Patients with tumors meeting criteria for "diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV" should be allowed to participate on GBM clinical trials • Patients with IDH-mutant GBM can be included in phase 0/I GBM studies where efficacy is not primary endpoint or patients can be stratified by IDH status in randomized studies
	Solid tumor phase 1 trials	• Patients with primary brain tumors including lower grade gliomas and other rare CNS tumors should be included in dose escalation phases of solid phase I clinical trials • Exploratory expansion cohorts of specific brain tumor histopathology should be included if there is a biologic rationale for efficacy
Prior therapy	Phase I	• Allow inclusion regardless of prior therapy unless a particular study question makes the prior therapy relevant • Allow prior exposure to bevacizumab
	Phase II/III recurrent GBM	• When efficacy is an important endpoint and there is a high likelihood that outcomes may be influenced by prior therapies, strategies to allow broader

Table 2. (Continued)

Criterion	Types of trials	Recommendation
		enrollment include specifying separate analyses for patients who have or have not received the particular treatment (e.g., bevacizumab refractory versus bevacizumab naïve), enrolling separate arms for these patient populations, or stratifying randomization based on prior exposure.
Number of relapses	Recurrent GBM and phase I	• Allow any number of prior relapses, especially in phase 0/I trials and especially in bevacizumab-naïve patients
	Recurrent GBM and phase II	• Allow at least 2 prior relapses in bevacizumab-naïve patients

52–54]. Which (if any) of these flexible policies will continue after the pandemic is unclear.

Policies supportive of telemedicine driven by COVID-19 [55] led to the increased use of telemedicine in oncologic clinical care [49]. However, to sustain widespread use of telemedicine after the pandemic, legislative and policy changes are needed to resolve ongoing issues such as reimbursement, disparities in access, cross-state medical licensure, and cross-state medical malpractice coverage.

Procurement of imaging on study also shifted from central sites to local sites. While more convenient for the patient, this created additional work for study teams given time and effort to collect and review imaging centrally as well as the variability in the quality of imaging in the community. To overcome this obstacle, study sites can develop partnerships with qualified local sites [56] who can follow standardized imaging protocols for primary brain tumor trials [57••] as well as for brain metastases trials [58••].

Clinical trial accrual and enrollment

- Despite their important role in finding better treatments for patients, accrual to oncology clinical trials (including neuro-oncology) is generally poor.
- SNO, RANO, patient advocacy groups, clinical trial cooperative groups, and other partners are working together to improve clinical trial accrual.

Studies suggest that more than 50% of patients will enroll when offered a clinical trial for which they meet eligibility criteria [59]. However, a survey of brain tumor patients and caregivers revealed that only 21% participated in a clinical trial and only 24% were even informed about clinical trial options at the time of diagnosis [60]. In addition, a survey of neuro-oncology providers revealed that less than 30% of patients were even referred by their provider for a clinical trial [61]. In response to these sobering statistics, SNO, RANO, patient advocacy groups, clinical trial cooperative groups, and other partners banded together to improve trial accrual and enrollment.

The group's first task was to explore the barriers to neuro-oncology trial accrual, with a particular focus on modifiable barriers [37••]. From the

perspective of patients and caregivers, barriers to clinical trial participation include lack of awareness of trial opportunities, misconceptions about research participation, and cost and travel constraints, as well as study burden and inconvenience. Gathering input from patients during the clinical trial design process as well as decentralization of clinical trials may be helpful in developing more patient-friendly clinical trials. In the USA, age, race, gender, and socioeconomic status influence treatment delivery in glioblastoma [62]. Racial bias and mistrust in the medical community may impact the enrollment of underrepresented minorities. Recommendations for improving diversity in study populations include community outreach and education of providers on gender and racial disparities.

The group next re-examined clinical trial eligibility for brain tumor studies [38]. Table 2 summarizes consensus recommendations for neuro-oncology clinical trial eligibility. Overly restrictive eligibility criteria may impair trial accrual, limit patient access to investigational treatments, and limit generalizability [64]. Overly permissive eligibility criteria may increase the risk of harm to patients. In general, eligibility criteria should be tailored depending on the study population, the toxicity and mechanism of action of the study agent, the phase of the study, and the objectives of the study. For example, only the relevant laboratory tests based on the safety profile of the study agent should be used as the basis for eligibility criteria. The group also recommended expanding eligibility criteria for GBM trials when appropriate to include patients with diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV [65].

Summary

Various groups within the neuro-oncology community continue efforts to improve the accrual, design, conduct, and interpretability of clinical trials. Working groups within RANO, including iRANO and RANO-BM, continue to validate and refine their initial radiographic response criteria. The National Brain Tumor Society held a workshop in July 2020 on innovating brain tumor clinical trials based on lessons learned from the COVID-19 experience with participation from various stakeholders including the US Food and Drug Administration (FDA), academic and community clinicians, researchers, industry, clinical research organizations, patients and patient advocates, and representatives from SNO and the National Cancer Institute [48]. Consensus recommendations from the workshop include further development of virtual neuro-oncologic assessment, evaluation of which clinical trial elements can be decentralized, and more widespread adoption of the standardized imaging protocols for primary brain tumor [57••] and brain metastases [58••] trials to support enhanced imaging expertise in the community setting.

Declarations

Conflict of Interest

Eudocia Q. Lee has received honoraria from MedLink, prIME Oncology, and the American Academic of

Neurology (Continuum), and receives royalties from Wolters Kluwer Health (UpToDate).

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