

Evolving Barriers to Clinical Trial Enrollment and Clinical Care in Neuro-oncology in the Face of COVID-19

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Abstract

The lack of treatments with durable response in neuro-oncology highlights the critical need for clinical trials to advance patient care. The intersection of relatively low incidence, evolving classification schema, and entrenched community, healthcare provider, and organizational factors have been historic challenges against successful trial enrollment and implementation. The additional need for multidisciplinary, often tertiary-level care, further magnifies latent national and international health inequities with rural and under-served populations. The COVID-19 pandemic both unveiled fundamental weaknesses in historical approaches and prompted the necessity of new approaches and systems for conducting clinical trials. Here, we provide an overview of traditional barriers to clinical trial enrollment in neuro-oncology, the effect of COVID-19 on these barriers, and the discovery of additional systemic weaknesses. Finally, we discuss future directions by reflecting on lessons learned with strategies to broaden access of care and streamline clinical trial integration into clinical practice.

Keywords

- ▶ neuro-oncology
- ▶ clinical trials
- ▶ barriers
- ▶ COVID-19
- ▶ inequities

Patient enrollment in clinical trials remains a vital part of the treatment of high-grade gliomas, where survival remains poor and durable treatments remain lacking. Only 20% of patients with primary brain tumors enroll in clinical trials; while higher than the 5% enrollment rate for general cancer patients, it is still not enough to move our field forward.^{1,2} Despite concerted efforts to increase enrollment and expand access, a patient survey by the National Brain Tumor Society in 2016 revealed participation remained static at 21%.³ Top reasons included provider recommendation against participation, ineligibility, and lack of knowledge on where to find a trial.³ A provider survey of the Society for Neuro-Oncology (SNO) also reported referral of under 30% of patients for clinical trials consideration.⁴ This led to collaborative efforts between key parties including providers, patient advocacy groups, trial cooperative groups/consortiums, and key orga-

nizations (including SNO and the Response Assessment in Neuro-Oncology [RANO] Working Group) to identify current barriers, with a goal of doubling trial enrollment over the next 5 years.⁵ Unfortunately, the rapid spread of coronavirus disease 2019 (COVID-19) over 2020 and its associated direct and indirect effects on patients, caregivers, and available resources led to a dramatic upending of patient care in the subsequent years. In this review, we will survey historical barriers to trial enrollment in neuro-oncology with a focus on adapting lessons learned from the COVID-19 pandemic.

Global Factors: Tumor-Related Barriers

Lee and colleagues identified four major classes of barriers to trial enrollment: (1) patient/community factors including disparities, (2) provider factors, (3) clinical trial factors, and

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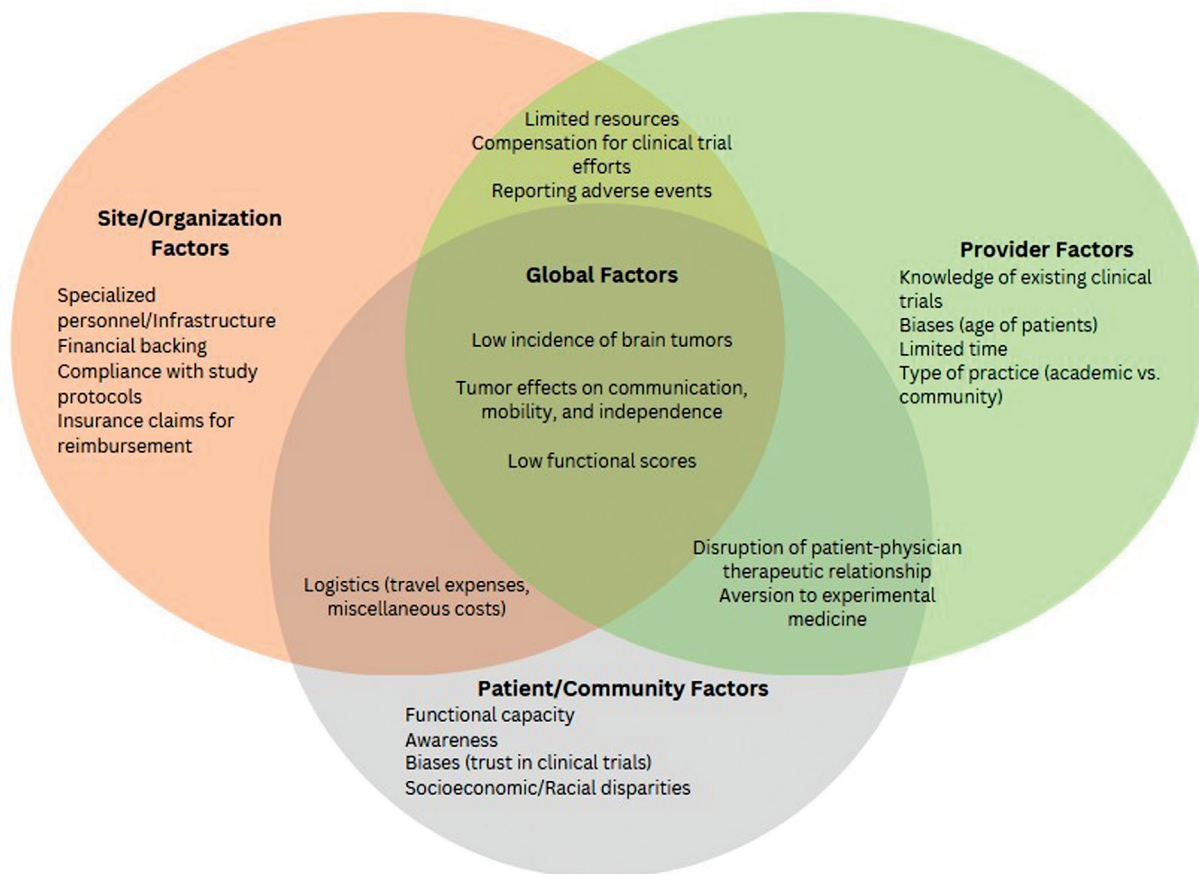


Fig. 1 Major classes of barriers for clinical trial enrollment (adapted with permission from Lee et al⁵).

(4) site/organizational factors (► **Fig. 1**).⁵ Intrinsic tumor-related factors have a cascading effect across all four classes and warrant initial discussion. Tumor-related factors include the low incidence of gliomas and other primary brain tumors. With an average of 5 to 8 gliomas diagnosed per 100,000 person-years (of which about half are glioblastoma⁶), the overall incidence remains lower than most other cancer types.^{6,7} This directly adds to the difficulty designing strong clinical trials, as obtaining robust results with the necessary statistical power requires a large study size and high enrollment rate. To accomplish this, trials need to pool from a larger catchment area, which in turn adds to the logistical burden (travel, cost, time) for patients. Rarer tumor subtypes may not have a relevant clinical trial available at many sites, which further impairs access.

A second major intrinsic tumor-related factor relates to the intracranial localization and, at times, effect on communication, mobility, function, and independence of a patient with a primary brain tumor. For example, gliomas often rob patients of language fluency, thereby impairing nuanced communication and ability to understand trial consents.⁸ In severe cases, the burden may be placed on the family and caregivers to make decisions on their behalf, further compounding communication and complicating the provider-patient relationship. Low functional scores as measured by the Karnofsky Performance Scale or Eastern Cooperative Oncology Group (ECOG) Performance Status may directly

exclude trial enrollment.^{9,10} Neurologic weakness, incoordination, or sensory changes/loss directly and indirectly hinder enrollment. Where generous inclusion criteria do permit possible enrollment, logistical issues such as travel/transport/visit or treatment frequency may effectively exclude patients. While both low incidence and neurological effects are fundamental aspects that are not easily overcome, downstream effects on the other factors that influence clinical trial enrollment do warrant individual discussion.

Patient and Community Factors

Lee and colleagues identified patient and community factors as one of the major groups of barriers to trial enrollment.⁵ Factors include awareness, education, biases about clinical trials and other experimental therapies, financial toxicity/cost, logistics (time/travel/transportation), and functional capacity. Note the aforementioned factors exist as a continuum from the individual patient to caregiver and family to community and more broadly at the systems level. For example, under-represented minorities (URMs), elderly individuals, women, and urban or rural communities with limited access to tertiary care are all traditionally under-represented in clinical studies. The COVID-19 pandemic worsened this divide by disproportionately affecting women, minority populations, and people of lower socioeconomic classes.¹¹⁻¹³ Healthcare mistrust, with spillover from divisive beliefs and misinformation about the

COVID-19 pandemic, contributed to erosion in the patient-provider relationship, trust in experimental therapies, and lay understanding of the role and driving motivation for clinical trials. In addition to distrust, patients and families delayed medical care, particularly early in the pandemic.¹⁴ This is directly supported by data from our two-site retrospective study examining the impact of the COVID-19 pandemic on neuro-oncology care.¹⁵ We observed in-person visits were delayed by 20.7 days, systemic or radiation treatments by 15.6 days, and MRI by 14.7 days. Similarly, in a multi-institutional retrospective cohort study analyzing the impact of the COVID-19 pandemic on survival of high-grade glioma patients, Vogel and colleagues found that time between cranial MRI and biopsy was significantly longer during the pandemic (21 days in pandemic time compared to 11 days in pre-pandemic times).¹⁶ As a result, sicker patients presented with more advanced stages of disease, thereby precluding them as ideal clinical trial candidates.

Finally, clinical trials are inherently complex constructs designed by humans: no study will be perfectly implemented to optimize the patient experience on first rollout. Here, engaging with participants and their families early in trial enrollment can bring to light patient-level challenges to initial and ongoing participation that can then be mitigated with minor revisions to a study protocol (► **Table 1**).

Provider Factors

In addition to patient-specific and community factors, providers play a vital role in the clinical trial enrollment process. As primary providers of care, physicians and other healthcare providers are responsible for being knowledgeable of ongoing clinical trials, identifying patients for relevant trials, having informed conversations about participation, assessing eligibility,

and coordinating care. Difficulty performing these duties is compounded when relevant clinical trials are not available at a provider's own institution, and they need to facilitate participation at another institution.

Limited time during appointments to discuss clinical trials, lack of knowledge about ongoing or upcoming clinical trials, hesitancy over interrupting continuity of care by referring to another institution, personal biases over patients' age and performance status, and concern of disrupting the therapeutic patient-provider relationship are common barriers to trial enrollment.⁵ It is also important to note that willingness to recommend clinical trials varies based on the type of practice (community vs. academic), location (rural/suburban vs. urban), and compensation models.^{17,18} Educating patients and addressing logistical issues such as documentation, setting up travel arrangements, and monitoring for adverse effects are time-consuming processes that may dissuade from trial enrollment.

The COVID-19 pandemic exacerbated these aforementioned barriers. Decreased frequency of educational programming such as lectures, conferences, and multidisciplinary meetings may have reduced access to information about ongoing trials. Providers may have been hesitant to engage in complex or weighted conversations over virtual visits, especially when introducing them as a treatment option for the first time. Participation in a clinical trial traditionally involved increased frequency of visits, obtaining serial imaging studies, scheduling regular follow-up visits, or more lab testing. Yet this is the opposite of one of the core tenants of the COVID-19 pandemic, namely, minimizing exposure/visits/number of interactions both in terms of frequency and number of people.⁵ This may have further de-incentivized providers from encouraging enrollment to reduce patient burden of travel and exposure to the virus.

Table 1 Provider level solutions targeting established barriers

Goal	Barrier	Provider level solution	Examples of potential implementation strategies
"Trial-positive" culture	Mistrust of the experimental therapies/interventions	Normalization of clinical trials as part of standard practice	<ul style="list-style-type: none"> • Priming: patients/families primed by first-line (e.g.) referring providers of the potential benefit • Habitualization: Remove potential stigma of enrollment through HIPAA-complaint exposure and outreach
Study awareness	Knowledge of available trial options	Integration in a broader landscape/platform	<ul style="list-style-type: none"> • Early engagement in brain tumor foundations • Multi-media access (websites, registries, patient advocacy groups) • Patient liaisons/advocates
Study selection	Logistics of screening + consent	Streamlining study screen, consent, on-boarding	<ul style="list-style-type: none"> • Patient navigators • Digital consents • Virtual visits • Local baseline labs/testing (where able)
Study assessments	Logistics of testing + intervention (s)	Streamlining study visits/testing/treatments	<ul style="list-style-type: none"> • Virtual/Tele-visits • Local testing/blood work • Financial assistance/reimbursement for travel expenses • Home or secondary site drug administration and accounting (e.g., through local provider) • Periodic review of participant experience

Lee and colleagues proposed several possible solutions in their 2021 roundtable report, with broader implementation of telehealth services being a key cornerstone.¹⁹ While telehealth offers the promise of increased access, clinical implementation varies widely. In our two-site retrospective study, we observed a wide difference in telemedicine use between two peer tertiary care centers during the same time (84.6% at Washington University vs. 14.3% at Duke University).¹⁵ When approached more broadly, at their core, Lee and colleagues' proposed solutions build on advances in technology and inter-institutional/community/sponsor partnerships to fundamentally improve direct and logistical access for a border gamut of patients.

At some level, the provider elements can be both easily modifiable but also intractably rooted in traditional practice. Many common sense approaches require both provider and institutional buy-in (► **Table 1**). The use of directed incentives and implementation of models successful at other institutions are two solutions which can aid in evolving practice norms.

Site/Organization Factors

As previously highlighted, execution of clinical trials imposes a significant need for specialized personnel and infrastructure that makes it a viable option primarily for resource-rich institutions. Trial patients may need access to specific or special purpose imaging studies and/or infusion centers. This requires financial support that is sometimes provided from philanthropic efforts at major institutions, raising the bar of entry for smaller hospitals to engage with clinical trials. Moreover, clinical trial care requires additional time and logistical/administrative efforts to monitor/report adverse events, comply with sponsor reviews/protocols, and stay updated with changes in trial design. These hidden costs often go unreimbursed and add to the difficulty of getting buy-in from institutions. Additional barriers such as IRB reviews and compliance, contracting issues, delineating the nuances of costs for various studies and procedures, and ensuring appropriate insurance claims for reimbursement are often factors that need to be dealt with from an organizational standpoint. The majority of cancer patients are treated in the community setting, where addressing the above issues poses a significant challenge given the lack of incentive to establish a costly and complex support apparatus with limited secondary use/gain for community hospitals. The COVID-19 pandemic only further shifted resource prioritization (financial, personal, structural/space/logistical) away from these areas. A recent systematic analysis of 161,377 non-COVID-19 trials showed that there was a statistically significant increase in the stoppage of non-COVID-19-related clinical trials compared to pre-pandemic years.²⁰ A major decrease in new trial initiation was also seen in the early stages of the pandemic.²⁰ While it may be difficult to address the greater financial factors, efforts can be made to improve accrual at the downstream level through enhanced community and tertiary-center partnerships and patient-optimized trial design (discussed below) permitting

a more decentralized approach to care. This would allow patients greater flexibility and convenience to pursue clinical trial care.

Clinical Trial Factors

Traditional clinical trial design is centered on a site-centralized approach where patients travel to a specialized center/location on rigidly defined intervals for close monitoring and intervention. Shortcomings of this bulky and at times unyielding centralization of care were witnessed during the COVID-19 pandemic, including at our two respective institutions.^{15,21} Limitations of in-person staff, non-essential visits, and imaging all increased trial drop out while impairing new enrollment at all stages. Loss of available regulatory staff further delayed trial optimization/streamlining to directly address some of these issues. Other major issues include loss or lack of available clinical coordinators, and increased burnout of over-stretched remaining staff. Coupled with rapid staff turnover, this confluence of factors further hampered efficient trial implementation and access. Normalization and integration of advances in communication technology provide a near-term solution, while a more radical decentralization approach to trial design addresses systemic issues (► **Table 1**).

Challenges to Addressing Barriers: The Promise and Risk of Decentralization

Approaches to mitigate barriers to enrollment, though theoretically possible, are difficult to implement in practice. Logistical issues include financial barriers, time, staffing, access to available technologies, and regulatory hurdles (state, national, and international). The COVID-19 pandemic exposed the shortcomings of traditional clinical trial design and implementation, but also provided an opportunity to reconsider fundamental trial design going forward.²¹ Practical realities and changes in reimbursement strategies during the COVID-19 pandemic led to the rapid integration of non-traditional (i.e. non in-person) patient care modalities including virtual/remote care services. Even if the integration of remote services varied between sites, the subsequent rise of decentralized clinical trials (DCTs) built on this newfound apparatus to offer a boarder range of options for patients.^{15,22}

At its core, DCTs offer an intuitive solution: harness technology to bring the trial to the patient and not the patient to the trial. This is not an entirely novel concept: community partnership and wide-scale engagement remains an active focus of the NCI Community Oncology Research Program (NCORP). NCORP brings cancer research studies to patients in community settings across the United States and includes protocols specifically for patients with primary brain tumors (e.g., NCT03475186). This "top-down" approach still fundamentally relied on "hub" institutional partners where patients would obtain care. Partners included community hospitals and clinics that may not otherwise have the range of services (advanced imaging, treatments/infusions, specialists) of larger tertiary-care centers, though this is not always necessary for every trial. Instead, by intentional design, these streamlined trials focused

on defined tractable endpoints targeting the so-called real-world scenarios. With the rise of HIPAA-compliant remote/tele services in 2020, a new “bottom-up” approach revolutionized DCTs and gave rise to new “hybrid” approaches, which combined features of both traditional and early decentralized trials. By allowing patients to participate regardless of location, this removes logistical barriers and provides access to more diverse populations.²³

DCTs are particularly useful in cases where it is difficult for patients to travel, and serve to improve access and enrollment in rare cancers, like primary brain tumors. However, not all clinical trials are suitable for complete decentralization given unique logistical considerations. It is here that hybrid solutions may be more reasonable, depending on the specific trial, population, and patient complexity. Given the nature of the multidisciplinary neuro-oncology care required for primary brain tumor patients in clinical trials, a one-size-fits-all approach may not be appropriate. In the neuro-oncology population, trials that require specialized imaging or interventions (e.g., laser interstitial thermal therapy, proton-based radiotherapy) will always need in-person visits. Even here, however, hybrid techniques like remote screening, monitoring, and follow-up can offset total person visits. Alternatively, a supportive care trial investigating the efficacy of an online symptom monitoring application may be very amenable to a DCT that does not require any in-person visits. It is through this adaptability that DCTs promise a new era where trial design emphasizes the needs and preferences of participants rather than sponsors or sites.²⁴

The promise as well as challenge of DCTs lies in implementation. Advantages of DCTs include enrolling subjects who are unlikely to be able to take part in conventional trials, improving patient and caregiver convenience, collecting real-world data while patients are in their home environment, and saving travel time and reducing patient expenses. There may also be disadvantages to DCTs: there is the potential to enhance inequities (also known as the “digital divide”) since groups with reduced access to technology may not be able to participate. DCTs may also introduce points of vulnerability with electronic data transmission, challenges in providing technical support to participants, and place the burden of wearing/charging devices on the patient. Large-scale DCTs also require further delineation of some clinical practice norms and other factors that may lead to biases as a result of site-to-site variability in treatment or data recording of factors not explicitly included in protocols. Statistical concerns and generalizability of hybrid type trials versus on-site trials are less of a concern.²⁵ However, a major concern about DCTs is that despite advances in technology to be able to administer trials remotely, there remains a lack of directly comparable data on key performance indicators such as recruitment, retention, adherence, and cost metrics to confirm if DCTs are actually beneficial.²⁶ Finally, the infrastructure required to advance DCTs varies across individual countries and health systems. Creating DCTs is not just an issue of developing newer and better digital health technologies. There are legal, regulatory, and ethical considerations

that will need to evolve in order to make DCTs successful for neuro-oncology patients.

Conclusion

Patients with neurologic malignancies are especially vulnerable, and efforts must be made to provide them access to the maximal therapies, which include clinical trials, to ensure the best possible outcomes. To advance patient care, it is imperative that we encourage enrollment and participation in clinical trials in the neuro-oncology population. The COVID-19 pandemic not only exacerbated historically known barriers present at various levels of patient care but also introduced new challenges that impede trial accrual. Importantly, it acted as an impetus for the neuro-oncology community to re-consider clinical trial design. We believe that DCTs, particularly hybrid models designed to overcome common barriers, serve as a promising option to improve access to and engagement in clinical trials. By prioritizing the needs and preferences of patients in their design and mitigating the barriers that impede delivery of care in their implementation, DCTs may offer the best chance of streamlining clinical trials in care models. As they become more common, it is important to anticipate and address the various ethical, legal, regulatory, and practical challenges that may arise.

Conflict of Interest

None declared.

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