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Report of National Brain Tumor Society roundtable workshop on innovating brain tumor clinical trials: building on lessons learned from COVID-19 experience

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Abstract

On July 24, 2020, a workshop sponsored by the National Brain Tumor Society was held on innovating brain tumor clinical trials based on lessons learned from the COVID-19 experience. Various stakeholders from the brain tumor community participated including the US Food and Drug Administration (FDA), academic and community clinicians, researchers, industry, clinical research organizations, patients and patient advocates, and representatives from the Society for Neuro-Oncology and the National Cancer Institute. This report summarizes the workshop and proposes ways to incorporate lessons learned from COVID-19 to brain tumor clinical trials including the increased use of telemedicine and decentralized trial models as opportunities for practical innovation with potential long-term impact on clinical trial design and implementation.

Beginning early 2020, the world faced the Coronavirus Disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which led to unprecedented changes in clinical medicine due to the need for physical distancing to minimize the spread of disease.[1] There were far-reaching consequences as many medical institutions shifted resources to manage COVID-19. These changes affected clinical trial conduct as not all protocol-specific procedures could be completed.[2,3] Indeed, in the United States, both the Food and Drug

Administration (FDA)[4] and the National Cancer Institute (NCI)[5–8] released guidance documents on the conduct of clinical trials during the COVID-19 public health emergency. These documents encouraged measures to protect participants and research staff such as limiting in-person study visits to only those needed for participant safety and clinical care, increasing flexibility for laboratory tests and imaging to be done locally, shipping oral investigational agents, and limiting unnecessary travel. Many of the administrative and bureaucratic barriers to telemedicine (including reimbursement) were loosened and the use of telehealth and virtual visits increased.[2,9]

On the one hand, COVID-19 exposed certain limitations of our current clinical trial infrastructure and conduct. On the other hand, COVID-19 has also created an opportunity to reimagine how clinical trials can be run. On July 24, 2020, a workshop sponsored by the National Brain Tumor Society (NBTS) was held on innovating brain tumor clinical trials based on ongoing lessons learned from the COVID-19 experience. Various stakeholders from the brain tumor community participated including the FDA, academic and community clinicians, researchers, industry, clinical research organizations, patients and patient advocates, and representatives from the Society for Neuro-Oncology (SNO) and the NCI. This effort was born in part out of an initiative involving SNO, the Response Assessment in Neuro-Oncology (RANO) Working Group, patient advocacy groups including NBTS, clinical trial cooperative groups, and other partners to double clinical trial participation over the next 5 years.[10,11] Despite being such a deadly disease with limited treatment options, only 8%-11% of patients with newly diagnosed glioblastoma (GBM) enroll in clinical trials.[12] Analysis of GBM clinical trials with testing locations in the United States and with start dates between 2005 and 2016 demonstrated that almost 5% of trials terminated early due to lack of accrual. As stakeholders in this initiative, NBTS and the workshop organizing committee wished to explore how lessons learned during COVID-19 could help improve clinical trial accrual. Here, we summarize the findings of the workshop and propose concrete ways to bring these lessons forward into brain tumor clinical trials in the COVID-19 and post-COVID-19 era.

The COVID-19 Experience

We heard first-hand accounts of how COVID-19 has disrupted traditional clinical trial conduct from the perspective of patients, clinicians, sponsors, and regulatory authorities. The safety of trial participants on therapeutic studies remains paramount, although the pandemic has created situations in which protocol deviations are unavoidable as a result. For example, some institutions temporarily restricted research interventions at the onset of the pandemic to only what was clinically necessary. Many correlative, nontherapeutic studies were suspended. While patients could continue to receive their study treatment, correlative studies such as on-study biopsies, specialized MRI protocols, and pharmacokinetic blood samples were halted. Although these deviations could have been viewed as potential threats to the conduct of a clinical trial, many sponsors adapted to the restrictions and created streamlined processes to ensure proper documentation, safety oversight, and consistency across patients and studies. In addition, remote monitoring, virtual investigators' meetings, and virtual site initiation visits for clinical trials have flourished during the pandemic. Although remote and virtual activities do not perfectly replace in-person activities, they are more cost-efficient for the sponsor.

Dr. Erik Bloomquist (a lead statistician in the Center for Drug Evaluation and Research at the FDA) provided an overview of the FDA's recent COVID-related clinical trial guidance.[4] While the FDA anticipates COVID-related trial modifications that could affect the statistical validity of trials such as missing data collection, changes to interim analyses, or adjustments to sample sizes, he stressed that sponsors should work to maintain the validity of trials as much as possible and encouraged communication between sponsors and the FDA to collectively determine how best to move forward. He noted that the FDA generally recommends that sponsors prospectively attempt to capture data on protocol deviations. Additionally, he stated that efforts to evaluate how aspects of the COVID-19 flexibility might be extended into the post-pandemic future are underway at the FDA.

Many agreed that the increased flexibility in trial conduct was a favorable and welcome change (Table 1). These include allowances for laboratory tests and imaging to be done locally, shipping oral study agents directly to patients, administration of some FDA-approved intravenous study agents at local partner institutions, increased use of virtual visits in lieu of in-person visits (saving on transportation costs and time spent away from family care and work as well as providing a more familiar home environment for the patient during these encounters), and remote monitoring of clinical trial sites. However, this increased flexibility does occasionally create additional logistical challenges. For example, local imaging is generally more convenient for the patient but generally less convenient for the study team. The study team must confirm that the local scan adheres to protocol requirements. Once procured, imaging must be sent to the study institution on disc via regular mail and uploaded into the study institution's medical record system after system compatibility check. In the era of COVID-19, with decreased on-site staffing, this process is more delayed than usual. That means that the patient must wait longer for the study team to determine if imaging demonstrates response, stability, or progression. Improved technology, however, offers a partial solution as software systems are currently available that allow a direct digital transfer of images from the community institutions to compatible electronic medical record systems of the study institution. These software systems could improve the efficiency of obtaining imaging studies and could be further explored for widespread adoption.

Although this roundtable primarily focused on the US experience, participants acknowledged hurdles for international patients participating in US-led studies and for global studies. The international guidance for COVID-19 has not been uniform. Patients from certain countries may be barred from traveling to other countries or may be subject to quarantine upon arrival. The shipment of oral experimental agents to a patient internationally faces additional regulatory barriers.

Table 1 Barriers to Clinical Trial Conduct During COVID-19, Opportunities Learned From COVID-19, Ongoing Limitations, and Possible Solutions to Those Ongoing Limitations

Barriers During COVID-19	Opportunities	Ongoing Limitations	Potential Solutions
Limitations to in-person study participant/provider visits	• Telemedicine visits • Partnering with local providers who can perform visits in-person • Consider new sources of data that can be collected remotely (ie, electronic patient-reported outcomes, wearable devices)	• Barriers to telemedicine including immature digital infrastructure, cross-state licensing, reimbursement, concerns over data reliability and integrity • Disparities and lack of access • Challenges for international patients given restrictions on travel • Logistical barriers to obtaining permission for local provider to participate in study care (ie, IRB approval, FDA 1572 regulatory definition of co-investigator)	• Studies to systematically examine the impact of telemedicine vs in-person visits • Ongoing efforts to make telemedicine expansion permanent • Extend care, enhance education about trials and trial opportunities for underrepresented populations • Identification of high-quality reliable community resources and partners, remote training in trial conduct
Limitations to in-person visits resulting in missed study procedures	• Electronic consenting of patients • Study procedures performed locally	• Limitations on flexibility as some visits still required in-person and some protocol required procedures cannot be done locally • Variance in quality of technology and interpretation of imaging • Lack of uniform ways in transmitting information to treating center • Added time and effort with central reviews associated with locally obtained scans (ie, cost and time in obtaining the scan and confirming that local scan adheres to protocol)	• Modifications in current protocols to accommodate remote testing • Identification of high-quality reliable community resources and partners • Use of inter-institution information transfer technology
Limitations to on-site monitoring visits	• Remote monitoring of clinical trial sites		• Modifications in current protocols to accommodate remote monitoring
Limitations to drug accessibility and distribution resulting in potential delays or missed doses or termination of treatment, protocol deviations/violations, issues with drug accountability, and federal compliance	• Oral study drugs shipped directly to patients • Some study intravenous drugs that are FDA-approved administered at local partner institutions	• Ongoing trial participant safety concerns • Not all drugs can be shipped or administered locally • Logistical barriers to obtaining permission for local provider to administer investigation drug (ie, IRB approval, FDA 1572 regulatory definition of co-investigator)	• Remote drug distribution guidelines in protocols • Develop EMR-based drug timetable and reporting • Training of home nursing or alternative sites by trained but non-study personnel • Identification of high-quality reliable community resources and partners, remote training in trial conduct

Abbreviations: EMR, electronic medical records; FDA, US Food and Drug Administration; IRB, institutional review board.

Shifting Toward Decentralization of Clinical Trials

In essence, the increased flexibility resulting from COVID-19 adaptations is shifting clinical trial conduct toward decentralized clinical trial approaches. Decentralized clinical trials refer to trials utilizing telemedicine, mobile or local health providers, and/or mobile technologies.[13] Partially centralized or hybrid approaches combine features of decentralized clinical trials with traditional approaches. This allows recruitment and participation regardless of location, possibly accelerating trial accrual and increasing diversity among participants. Historically, limitations to implementation included immature digital infrastructure, limited experience with decentralized approaches, regulatory barriers, cross-state licensing for telemedicine services, limited reimbursement for telehealth services, and concerns over data reliability and integrity.[13]

Dr. Amy Barone (a pediatric oncologist and FDA clinical reviewer on the central nervous system, pediatric solid tumor, and rare cancer review team) spoke further on decentralizing clinical trials, with an emphasis on the relevance for patients with brain tumors and for underrepresented populations. She described an ongoing FDA working group that is discussing ways to structure and facilitate the conduct of decentralized trials as well as hybrid trials. The FDA is also planning a major public workshop to discuss the potential silver linings that are emerging from the COVID-19 experience, with a specific focus on opportunities for more decentralized trials. Finally, she commented briefly about the importance of understanding the impact of COVID-19 on clinical trial eligibility criteria. The FDA's Oncology Center of Excellence (OCE) has participated in multiple efforts to rationally expand eligibility and advocates that patients with cancer not be uniformly excluded from trials due to a history of COVID-19 infection. Dr. Barone stated that there is a need to better understand how issues related to COVID-19 are being addressed in clinical trials, such as how information related to COVID-19 is captured, whether patients are routinely tested for COVID-19 prior to enrollment, what additional safety monitoring is being conducted (if any), whether patients who have had COVID-19 will be studied in a separate cohort, how post-COVID-19 morbidities are evaluated, and what the impact will be on trial screening and racial disparities.

When deciding if a trial is appropriate for partial decentralization, one must consider the type of trial, the patient population, and the phase of development. Many of the decentralized approaches may be more suitable for later phase clinical trials, particularly trials with endpoints that are less subject to variability (such as overall survival) and where "real-world experience" or generalizability may be valued. On the other hand, early clinical trials (eg, first-in-human trials, surgically based trials, trials with corollary novel imaging, or trials with biological laboratory data) may require expertise, infrastructure, and procedures that typically cannot be replicated outside of centralized clinical trial sites. Pediatric brain tumor patients on clinical trials may require clinical expertise that is not as readily available in the community and therefore pediatric trials may be less suitable for certain aspects of decentralization compared to their adult counterparts. From the regulatory perspective, it is important to evaluate how efforts to decentralize the conduct of a trial might impact the ability to achieve the primary objectives of the trial, such as characterizing safety or interpreting the primary endpoint.

Decentralization may also lead to more patient-centered clinical trials, minimize some potential barriers to clinical trial participation, and ultimately promote clinical trial participation.[10,11] For example, time and travel costs associated with traditional clinical trials are known barriers to participation, particularly for patients who live further away from academic centers and for patients with fewer economic means. By shifting study procedures such as labs and imaging locally; shifting standard of care treatments such as radiation, temozolomide, or bevacizumab to local centers; and replacing in-person visits with telemedicine visits, patients may be more able to participate in clinical trials. The group discussed additional barriers within traditional neuro-oncology clinical trials to patient accrual and participation as well as possible solutions incorporating features of decentralized clinical trials (Table 2). Several of the key barriers are discussed in more detail below.

Telemedicine

A major component of decentralized or hybrid clinical trials is telemedicine. Prior to COVID-19, telemedicine resources and initiatives were limited in most hospital systems around the United States (except in very rural areas), with much of telemedicine either not reimbursed in any way or at a low rate. Laws varied across states in terms of what was covered and how insurers paid reimbursements. There were additional concerns about cross-state provider licensing and malpractice liability when the patient resides in a different state than the one in which the provider is licensed. COVID-19 escalated the development of virtual care solutions in part because of the barrier to in-person care including the need for social distancing and limited availability of personal protective equipment. The Centers for Medicare & Medicaid Services (CMS) issued waivers during COVID-19 to allow flexibility for Medicare telehealth services and granting payment parity for Medicare between telehealth and in-person care.[14] Many states expanded telehealth services through COVID-19 emergency orders, but less than half required reimbursement parity.[15,16] The US Department of Health and Human Services (HHS) also allowed the use of video communication compliant with the Health Insurance Portability and Accountability Act (HIPAA) for virtual visits during COVID-19.[17] This led to rapid adoption of telehealth by both patients and providers with some cancer centers reporting almost two-thirds of follow up cancer care as virtual.[9] How many of these expanded services will be continued beyond the COVID-19 public health emergency is not known; this provides a point of opportunity from a legislative and policy perspective.

Table 2 Barriers Within Traditional Neuro-Oncology Clinical Trials and Possible Solutions Incorporating Features of Partially Decentralized Clinical Trials

Step	Barrier from Patient Perspective	Possible Solutions	Barrier from Physician/Institution/Sponsor Perspective	Possible Solutions
1. Consideration of trial as possible treatment option	Limited knowledge about the potential benefits of trial participation Misperception about research study involvement	• Community education • Patient navigators • Engagement with patient advocacy groups and community members, especially URMs • Trial website/App • Social media	Limited knowledge of available trials and incentive for the local team to refer outside for trials	• Trial website/App • Local team continue to co-manage (allow SOC to be done locally on trial, etc.) • Establish a partnership between community physicians and academic physicians (through brain tumor boards, etc.)
2. Identification of trial opportunities	Limited knowledge about trial options	• Patient navigators • User-friendly app/website • Brain tumor registries for easier identification of potential candidates	Limited knowledge about trial options outside the institution	• User-friendly app/website • Establish partnership between community physicians and academic physicians (through brain tumor boards, etc.)
3. Patient connects with institution to discuss trial options	Logistic barriers as visits historically done in-person	• Telemedicine consults particularly when patient lives far from the institution	Ability of trial physician to convey pros and cons of trial participation	• Provider education to improve communication with patients regarding clinical trials • Patient-friendly electronic literature explaining the trial
4. Patient signs consent for clinical trial	Logistic barriers as historically done in-person	• Electronic consent • Telemedicine for consent signing • Ensure adequate safeguards in place for truly informed consent	Some IRBs have concerns with verbal consents Institution lacks necessary systems and procedures for electronic consent	• Current COVID FDA guidance allows verbal consenting • Ensure adequate safeguards in place for truly informed consent • Institution develops necessary systems and procedures for electronic consent
5. Patient proceed with screening on trial	Logistic barriers as historically done in-person Overly restrictive trial eligibility	• Local studies for standard procedures, CLIA-certified labs, etc.	Sponsor concerns about quality of local labs, etc. Administrative burden to sites to have approval of local lab sites, etc. Overly restrictive trial eligibility	• Allowance/acceptance of CLIA-certified local labs • Study sponsors and study PIs to reassess eligibility criteria to appropriately loosen criteria
6. Patient enrolls and participates in trial	Logistic barriers as historically done in-person Burden of visits and study requirements	• Telemedicine with study team for some visits • Some visits to be done by local oncologist, supplemented if necessary by telemedicine with the study team • Allow SOC (eg, radiation, temozolomide) to be administered locally • Patient reimbursement for travel • Expansion of trial to more community sites	Sponsor concerns about quality of data Added costs if patients reimbursed for travel	• Studies to budget for added cost of patient reimbursement for travel • Study sponsors and PIs to obtain input from patients and patient advocacy groups on study • Design more patient-friendly, more efficient trials
7. Patient receipt of study drugs on study	Logistic barriers as historically done in-person	• For study visits done via telemedicine, allow oral drugs to be mailed to patient home • For IV drugs that are otherwise commercially available/FDA approved for other indications, allowance of IV administration locally from commercial supply	Concerns over mailing drugs Concerns over quality of commercially available drugs vs the study supplied drug	• Need a mechanism to ensure adequate drug accountability and compliance (drug diaries, etc.)
8. Off study assessments	Logistic barriers as historically done in-person	• Allowance of local assessments and/or telemedicine		

Abbreviations: CLIA, Clinical Laboratory Improvement Amendment; FDA, US Food and Drug Administration; IRB, institutional review board; IV, intravenous; SOC, standard of care; PI, Principal Investigator; URM, underrepresented minority.

While telemedicine is not as well studied in neuro-oncology, data support the use of telemedicine in various neurology subspecialties, particularly in acute stroke management.[18] Benefits have been noted in expediting care, increasing access, reducing patient and caregiver burden, improving patient satisfaction, and reducing cost.[19] Additional benefits specific to neuro-oncology patients include increased access for patients with limited mobility such as hemiparesis, for patients with limited transportation such as restricted driving privileges due to seizures, and for distant family members wishing to participate in telemedicine conversations and to help with decision making for patients with cognitive limitations.

Studies also suggest that the neurologic examinations performed by telemedicine can be reliable in the acute setting for stroke and non-stroke diagnoses, for standardized scales of motor assessment in Parkinson's disease, and for remote standardized examinations such as the Expanded Disability Status Scale for multiple sclerosis and common screening examinations for dementia.[19–21] Neurologic Assessment in Neuro-Oncology (NANO) is a standardized clinician-reported metric of neurologic function with high inter-observer agreement developed to permit more effective overall RANO.[22] Although originally intended to be performed in-person, NANO could likely be modified to be performed remotely via video, perhaps with the assistance of a caretaker or family member present with the patient. However, further validation would be needed to determine if NANO via telemedicine is reliable. It is also important to note that training and experience in performing examinations via telemedicine are necessary to optimize diagnostic accuracy and that sometimes telemedicine cannot replace in-person examinations. Monitoring of quality and outcomes with telemedicine in neuro-oncology will be an important area of study.

Another barrier to widespread use of telemedicine is cross-state licensing. The originating site (the location of the patient) is considered the place of service, and therefore the distant site provider must adhere to the licensing rules and regulations of the state in which the patient is located.[16] Several pieces of federal legislation have been introduced to redefine the place of service from the site of the patient to the site of provider, thus obviating the need for a cross-state medical license, but so far such bills have not been successful. Some states have provided licensing waivers or exceptions due to the COVID-19 public health emergency to provide greater access to care; however, these policies have not been adopted uniformly. To ease the burden of cross-state licensing, some professions such as the Nurse Licensure Compact (NLC) and the Interstate Medical Licensure Compact (IMLC) have created interstate licensing compacts as a pathway to licensure in multiple states, but not all states currently participate.

Loss of revenue is a disincentive to the expanded adoption of telemedicine by hospital systems. Despite the current COVID-19 public health emergency waivers from CMS, the financial impact to hospital systems results from lack of reimbursement parity, loss of facility fees, and loss of additional services (laboratory, imaging, etc.) that would have been performed at the facility if the patient had presented in-person.

Electronic Consent

Currently, many institutions require patients to come in-person to sign paper informed consent for clinical trials. Transition to electronic consent would reduce the number of visits patients are required to make and potentially aid accrual into trials. Electronic informed consent (eIC) refers to electronic systems and processes that utilize electronic media such as text, graphics, audio, video, podcasts, websites, biologic recognition devices, and card readers to convey information related to clinical trials and document informed consent.[23] In March 2015, the FDA and HHS Office for Human Research Protections (OHRP) jointly released a guidance document for institutional review boards (IRBs), investigators, and sponsors on electronic consent.[23] Critical to eIC is the need to develop systems and procedures[24] that are secure, ensure patient confidentiality, can appropriately archive and easily retrieve electronic documents, have audit trail capability, and are compliant with the US Code of Federal Regulation 21 Code of Federal Regulations part 11 requirements for electronic records and signatures.[25] However, it is the responsibility of the study team or the home institution's information technology department to build, document, test, validate, and maintain this system. As with paper consent forms, electronic consent may still contain certain elements for IRB approval and all key elements of consent are required to be communicated to the participant. The date of electronic signature must be captured. There must be methods to gauge subject comprehension of key study elements and the process must be suitable for the specific study population or procedures, which may be particularly important for neuro-oncology patients with neurocognitive limitations. The electronic consent process must have the functionality to allow patients to proceed backwards, forwards, or pause the consent process. Electronic consents are not meant to replace paper consents (which should still exist for patients who are not able to utilize electronic consents).

Leveraging Community Medical Partners

Historically, clinical trials required most (if not all) study required procedures to be done at the study center. However, during the COVID-19 pandemic, collaborations with community health partners have provided an important avenue for patients to continue their clinical trial participation safely.

From the sponsor perspective, accreditation is critical to the conduct of a clinical trial and refers to the preselection of trusted partners (such as providers, laboratories, imaging centers, and other types of facilities) to involve in a clinical trial. One key aim of accreditation is to provide greater flexibility and convenience to a patient participating in a clinical trial so that they can visit a local facility in their own community setting. The other key aim of accreditation relates to selecting facilities that can provide high-quality data while complying with

Human Subject Protection, Good Clinical Practice,[26] and other evolving regulatory requirements. There is a need to identify community practitioners and centers that have experience in trials, perhaps by engaging with national organizations and patient advocacy groups to harness existing networks/cooperative groups (eg, NCI's community clinical oncology program). Beyond allowing standard data sources such as laboratory data to be collected from an accredited local partner, decentralization of trials allows increased use of new sources of study data that can be collected remotely, such as electronic patient-reported outcomes and wearable devices.

From the principal investigator perspective, one must balance the obligations of a principal investigator to administer the clinical trial appropriately while allowing greater access to patients in the community knowing that there are varying levels of expertise, resources, and commitment in community settings. The Statement of Investigator (Form FDA 1572) is an agreement between a clinical trial investigator and the sponsor which verifies the qualifications of the investigator and the clinical site, informs the investigator of his/her obligations, and verifies that the investigator agrees to follow the FDA Code of Federal Regulations.[27] Typically, the investigator and sub-investigators (individuals who will assist the investigator and make a direct and significant contribution to the data) are listed on the 1572. While some local providers such as phlebotomists may not meet criteria to be defined as a sub-investigator, it is less clear if a local provider administering an FDA-approved drug or providing a study-specific physical examination as part of the clinical trial should or should not be added to the 1572. This requires an assessment of that provider's direct and significant contributions to meet the regulatory requirements. Adding a community partner to the 1572 can be burdensome from the administrative perspective, especially if it requires IRB clearance, study personnel training, and remote monitoring, all potentially adding sponsor costs.

With respect to imaging, as previously discussed, there is variation in the quality of technology and radiologic interpreters and challenges with the transmission of radiographic information resulting in delays. In the specific case of brain tumor trials, it is important to ensure high-quality imaging with the standardized Brain Tumor Imaging Protocol[28] that can be used for brain tumor consensus evaluations. Currently, this may not always be possible to achieve with a stand-alone radiology center or outlying hospital. One important step that would significantly improve imaging standardization would be the widespread adoption of the standardized Brain Tumor Imaging Protocol at most institutions, not only for imaging of patients on clinical trials but also for routine imaging.

With respect to local laboratory assessments, there are differences in complexity among various types of labs needed to monitor patients in clinical trials. A local center can do a more straightforward blood panel such as a complete blood count while a more specific parameter that is integral to the selection or stratification of a treatment for the patient likely should remain centralized. Ultimately, there is a need to deconstruct aspects of clinical trial protocols to evaluate which pieces can be done locally or remotely vs those that must be managed centrally or in-person.

With respect to drug accessibility and distribution, COVID-19 exposed limitations of our current systems with respect to drug supply, distribution, and investigational pharmacy functioning and an overreliance on central sites for in-person drug administration. These limitations lead to potential delays in dosing, missed doses, or even termination of treatment; protocol deviations and violations related to drug supply; and issues with drug accountability and federal compliance. Safety must remain the first consideration for a trial patient. Potential solutions discussed include incorporation of remote drug distribution guidelines in protocols, development of an electronic medical record based on drug timetables and reporting, and delivery of drug by home nursing or by trained but non-study personnel at local medical facilities. FDA provides guidance with respect to some of these issues during the COVID-19 public health emergency.[4]

Disparity and Access

Despite FDA policy initiatives to enhance the diversity of clinical trial populations, certain groups remain underrepresented in clinical trials.[29] Telemedicine is often less accessible to racial and ethnic minorities, patients who live in rural areas, patients with limited English proficiency, patients with low literacy, and patients with low income.[30] In addition, telemedicine can be a challenge to patients who are elderly or with physical disabilities or low digital literacy who live alone and cannot utilize resources without assistance even if available. Many of these disparities are driven by a variety of factors including limited access to broadband internet and related technology, financial barriers to telemedicine reimbursement, and lack of institutional commitment to equity in telemedicine. Increased use of telemedicine in clinical trials could have the unintended consequence of making clinical trial populations even less diverse than they are now. In moving forward with an expansion of telehealth, disparities might be lessened by assisting patients who need help navigating online systems and by providing medical interpretation for non-English speakers. Ultimately, decentralizing trials and improving the ease of participation may improve the participation of underrepresented populations.

Conclusion

While barriers to accrual and participation in brain tumor clinical trials have been pervasive, the COVID-19 pandemic has created a major disruption in the "traditional" approach to brain tumor clinical trials, leading to enhanced regulatory and sponsor flexibility and the opportunity for innovation. Telehealth and telemedicine trends were emerging prior to the pandemic, but COVID-19 has exposed new opportunities and challenges, including in the areas of access, reimbursement, and disparities/equity. There was consensus across workshop participants that there is an opportunity to leverage the COVID-19 experience for a future in which hybrid/decentralized trials for brain tumors become the new normal. In the near

term, the brain tumor community can engage with the broader cancer and health care field to advance issues that cut across disease-states, including policy issues impacting upon physician licensing and reimbursement for telemedicine. In advancing innovation in clinical trials, the brain tumor community can focus on issues that are specific to neuro-oncology, including:

- Developing a framework for a virtual neuro-oncology assessment by documenting and publishing the feasibility of conducting neurologic exams via video so that companies and other investigators can take this information and utilize it more broadly.
- Evaluating clinical trial protocol elements to deconstruct what is necessary to be accomplished in-person or at a central site vs what can be accomplished remotely or at a local lab or community setting.
- Promoting adoption of the Brain Tumor imaging Protocol[28] to support enhanced imaging expertise in the community setting.
- Defining what expertise and capabilities are needed for a community site to participate fully as a brain tumor clinical trial partner to support efforts to expand networks that can further engage community oncologists in brain tumor trials.
- Allowing study supply of FDA-approved medications to be administered by local physicians, reducing the number of visits to the central study site.

Keywords

clinical trials | COVID-19 | decentralization | telemedicine

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