Am J of Geriatric Psychiatry 28:9 (2020) 913–920

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ajgponline.org

Special Issue Article

Clinical Trials and Tribulations in the COVID-19 Era

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ARTICLE INFO

Article history:
Received April, 13 2020
Revised May, 9 2020
Accepted May, 15 2020

Key Words:
Alzheimer disease
clinical trials
geriatrics
telemedicine

ABSTRACT

Advances in treating and preventing Alzheimer disease and other neurocognitive disorders of aging arise from rigorous preclinical and clinical research, with randomized controlled treatment trials as the last and definitive test. The COVID-19 pandemic has greatly disrupted ongoing interventional studies and researchers are scrambling to find ways to safely continue this critical work amidst rapidly shifting guidelines from sponsors, institutions, and state and federal guidelines. Here the authors describe novel approaches and work-flow adaptations to study visits, drug delivery and interim and endpoint safety and outcomes assessments to avoid sacrificing years of preparation and substantial financial investments, to work in the best interest of participants and their caregivers, and to continue on the path toward discovering disease-modifying treatments for the millions of individuals impacted by major neurocognitive disorders. (Am J Geriatr Psychiatry 2020; 28:913–920)

As of May 2020, there are 275 ongoing interventional trials for Alzheimer disease (AD) in the United States which are recruiting, active and no longer recruiting, or not yet recruiting subjects for enrollment.[1] There have been no new drugs approved for this disease since 2003, and to date there is still no approved disease-modifying drug aiding the over five million people diagnosed with AD and their caregivers in the United States.[2] These stark figures warrant dedicated attention and resources. A global catastrophe resulting from the COVID-19 pandemic has shifted the inertia of progress. Here we describe these sudden changes to interventional protocols, how the field has thus far responded, and the consequences borne by not only researchers, but by study participants and their caregivers.

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https://doi.org/10.1016/j.jagp.2020.05.016

TOUGH DECISIONS

There was a sense of understanding mixed with nervous concern each time one research coordinator at Massachusetts General Hospital's (MGH) Alzheimer's Clinical and Translational Research Unit (ACTRU) reached out to subjects and study partners to inform them that their clinical trial screening visit or follow-up investigational drug infusion had been put on hold. Some participants offered to keep their scheduled visit regardless of risk. Some were angry and others expressed sadness. Nearly all participants were eager to continue on their medication (or perhaps placebo), even if this meant learning how to attend a virtual visit or drive to another site. The imminent risk of exposure to SARS-CoV-2, the virus responsible for COVID-19, in our multi-vulnerable population has made some decisions seem obvious, such as safety over research. But how have necessary public health restrictions affected their treatment of dementia and our search for medical treatment in the short term and long term? How do we adapt to these circumstances?

On April 2nd, the U.S. Food and Drug Administration (FDA) released a 16-page document entitled: *Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic,*[3] encouraging sponsors to use their best judgment in deciding whether and how to continue or stop drug trials, with the safety and best interest of the subjects in mind. This came weeks after some sponsors offered tentative, broad guidelines to local sites, an improvement from the initial weeks of the crisis, when e-mail inquiries to sponsors from site coordinators landed in a vacuum; most never receiving a reply. Sites followed hospital and local institutional review board (IRB) policy, or in some cases helped their hospitals to develop such policy. Some staff were ordered to work from home, while others were re-deployed to medical clinics. Safety labs, biomarkers (including neuroimaging, neurophysiological, and biofluids), and neurocognitive endpoints were unable to be performed.

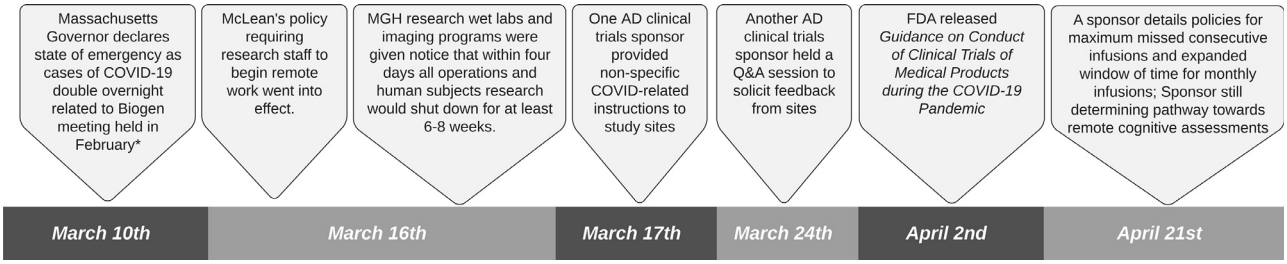
The older adult research subject population has a high risk of severe illness and mortality resulting from COVID-19,[4] and with safety always the highest priority, our initial response has been to minimize risk of exposure to the virus. We are adopting in real-time a formula of risk calculus: how do we adapt and salvage the potential healthcare benefits to patients in their participation, the scientific integrity, and value of the trial in the face of missing and uncontrolled data, navigate interruption in treatment, and preserve economic investments toward the long-term search for better treatments for dementia? In response to the pandemic, study clinicians and participants began experimenting with virtual visits; safety checks and assessments were retooled, infusions were delayed indefinitely, and enrollment was halted. Faced with great uncertainty, this experience has been challenging for the clinicians, researchers, coordinators, subjects, and their support partners to navigate. Here we attempt to provide a personal inside view of the whirlwind pace of change, uncertainties, decisions and indecisions, and their collective impact on the operation of clinical trials at the ACTRU, and McLean's Geriatric Psychiatry Research Program (GPRP) over the first month of COVID-19 social distancing restrictions.

BOTTOM-UP POLICY

McLean Hospital issued a policy requiring research staff to begin remote work on March 16, 2020, based on a tiered system of risk to staff and patients, and potential loss of data (Fig. 1). The GPRP, conducting trials with multiple putative disease-modifying drugs, sought approval to continue with already scheduled infusions. On March 17, one sponsor provided instruction on how sites should proceed if visits are missed in the context of the pandemic but did not give specific guidelines for when to suspend in-person visits. On March 24, another sponsor held a Q&A to solicit feedback, again offering no recommendations for pausing visits or assessments, essentially leaving such decisions to local policy. Umbrella hospital policies drove decision-making as well: amyloid and tau positron emission tomography scans, for instance, were deemed nonessential and suspended, resources and staff were re-allocated to the crisis.

After consideration of what constituted adequate reduction of infection exposure, the GPRP obtained an exception to McLean's policy, allowing for two continued infusions on-site over the following week, along with cognitive testing and collection of blood samples for biomarker analysis. Staff, in the meantime, began

FIGURE 1. Timeline of policy and protocol changes around Alzheimer disease clinical trials as experienced by researchers at Massachusetts General Hospital and McLean Hospital. *[5]



receiving a deluge of COVID-19-related e-mails, filled with questions of availability of continued infusions and anxiety regarding risk of exposure. Based on the many concerns of caregiver, patient and staff related to a growing risk of community exposure in the context of a voluntary clinical trial, the GPRP team decided to halt infusions. Research coordinators reached out to each of the subject-caregiver dyads to inform them that subsequent infusions, imaging, and cognitive assessment visits were placed on hold, with plans for reassessment in late April.

On March 16, MGH research wet labs and imaging programs were told that within 4 days all operations and human subjects research with few exceptions would shut down for at least 6−8 weeks. In response ACTRU took similar bottom-up actions as GPRP, suspending its own studies that could be suspended or judiciously adapting sponsored studies in the absence of guidance from sponsors reluctant to risk breaching IRB or FDA guidelines too unclear to interpret for their individual studies. This left the sites operating under hospital guidelines only. Once the ACTRU proposed novel approaches, the sponsors demonstrated varying degrees of rigidity in the approval process. For instance, with regard to virtual visit planning, two sponsors responded differently to solutions proposed by the ACTRU, leading to variable standards and added administrative efforts.

WORK-AROUNDS

From in-person visits to plans for home infusions and virtual assessments, the transition has been abrupt and variable. As new policies from hospital administration were implemented, informed by state and federal guidelines and mandates, the research groups found creative solutions, though some required further change hours later when another policy rollout emerged. Out of necessity we formed triage processes dividing ongoing or upcoming projects into one of two categories based on the premise of 1) safety first, and 2) *some* data are better than *no* data. With regard to safety prioritization, the first question was whether or not the visit or participant-involving task was truly necessary to perform without delay for patient safety or primary study outcomes. This checkpoint led to sacrificing all observational trials of healthy volunteers, to be resumed at a later date, were less costly than interventional studies, and affected fewer subjects.

Of those studies crossing the threshold of necessity, the next question became whether a visit or task could be done virtually, how to do so, and how to document such encounters for later statistical comparisons to the standard methods. When in-person visits were halted, telemedicine and virtual visits were anticipated as emergent gap-fills.[6] Several sponsors advised the GPRP to conduct phone visits if in-person visits were unable to continue, emphasizing participant safety, and changes in concomitant medications. Beyond obvious limitations imposed by the virtual visit, such as performing physical exams, geriatric subjects offer additional challenges, such as lack of access or discomfort or inexperience with technology, challenges with the transitions in care,[7] and population-specific comorbidities, such as hearing or vision loss. Another issue specific to these geriatric studies is the role of the study partner/caregiver: Isolation strategies have, in some cases, prevented study

partners from connecting with subjects. This creates a dual challenge, as not only do study partners assist with coordinating visits, but one of their primary roles in several clinical studies is study partner assessment; study partners, who contribute significantly to behavioral and cognitive assessments during visits, are intended to have contact with the subject a minimum of 2 days per week, which is less of a problem when the partner is a spouse or lives in the home with the subject. However, several study partners are adult children or other relatives of the subject and have been restricted from visitation, either to the home or assisted living facility, rendering their role in assessment less valid. Finally, many of the key staff, such as nurses and nurse practitioners who originally performed in-person visits have been redeployed toward emergency measures such as working at pop-up COVID-19 surge respiratory clinics.

Some tasks/visits are simply not amenable to a virtual session, such as drug distribution, or bloodwork, other biometric data collection, or neuroimaging. Provision of medications has proven surprisingly challenging, involving rerouting of experimental drugs normally supplied at in-person encounters through couriers or pharmacy delivery programs; for infusion-based drugs, one possible work-around is the home visit, which at least in one case was at first considered feasible, and later disallowed by the sponsor. Since late April, at least one sponsor has permitted contracting with home infusions services and is preparing to share protocols and reinstate treatments. Safety visits often include vital signs, blood tests, ECGs and neuroimaging (e.g., to evaluate for amyloid-related imaging abnormalities). Once in-person safety lab draws at Mass General Hospital's main campus in Boston became unavailable, our coordinators steered subjects to other institutional locations, which, days later, were shuttered to nonurgent appointments. Contracting with commercial labs was another alternative. This too presented difficulty, as were initially dedicating total resources to COVID-19; however, many have since reopened their services more broadly. Even this viable alternative was imperfect: smaller pharmaceutical sponsors were hesitant to reimburse the growing costs associated with outsourcing their studies. Given their limited budgets, any serious interruptions or extensions of the study could spell bankruptcy. And participants needed to agree to changes as well; when offered the option to obtain vitals and lab draws through a contract organization, some subjects and caregivers adjusted while others felt that this was still too risky, and that self-quarantine was the only safe option. Thus, the question being asked at all levels is how much we can widen the window of tolerance around missed safety visits (weeks? months?), before continuing treatment becomes unsafe? As the lapse in infusions and/or safety visits extends beyond initial expectations, contingency plans are reshaping into amended IRB protocols, and some sponsors (as of late April) are establishing site-spanning guidelines for upper limits of missed months of infusions, and maximal deviations from set infusion windows.

ASSESSING FROM AFAR

While some of the same challenges limiting safety/biomarker visits also apply to in-person clinical and cognitive scale administration, there is already a literature base providing at least provisional support for the validity and reliability of performing assessments via tele-neuropsychology (TeleNP), including in older adults (e.g.,[8–12]). As neuropsychologists around the country have rapidly begun adapting their clinical practices to telehealth formats out of current necessity, national organizations such as the American Psychological Association and Inter Organization Practice Committee have been instrumental in compiling resources pertaining to TeleNP during the COVID-19 crisis, including the development of a website for just this purpose.[13,14]

Still, a number of theoretical and practical limitations remain before most virtual assessment capabilities can be implemented in AD trials. To date, there is little existing data regarding systematic differences in measurement error between in-person versus virtual test administration in a clinical trial context. Neuropsychological testing inherently does not lend itself well to deviations in administration procedures, and accounting for potential inconsistencies related to virtual versus in-person testing across and within trial sites and participants would be a significant challenge. As an example, the Alzheimer's Disease Composite Score (ADCOMS), has been at least partially validated for use in the online setting,[15] yet one component of ADCOMS, the Mini-Mental State Examination (MMSE), relies heavily on orientation questions

(10 points out of 30). On the MMSE, an addition of five points to each subject's score for relaying their home address (over-learned information), or loss of points for not knowing the date or day of the week, which may or may not be true disorientation given the blurring-together of days for many under self-quarantine, could drastically and systematically skew the interpretation of outcomes.

Remote assessment confers myriad challenges ranging from technological barriers to the minutiae of establishing appropriate distance of a stimulus from the video camera. In cases in which record forms must be utilized by both the research participant and the administrator (as is the case with the commonly administered Repeatable Battery for Assessment of Neuropsychological Status: RBANS), arrangements must be made days in advance to ensure that both parties have access to a copyright permitted (nonphotocopied) version of the record form, and that the integrity of the testing materials and data are maintained following administration. This requires considerable additional planning on the side of the researcher and the participant, and typically requires the presence of a study partner in the case of individuals with cognitive impairment.

Testing from a remote location may also result in more difficulty establishing rapport, reduced control over the testing environment and external distractions, and inability to provide hands-on instructions and offer immediate feedback. Specific to our population, patient engagement and attention can be a challenge, and redirection via a small screen is not easy. Additionally, our subjects may be cognitively capable at the outset of a trial, but then degenerate over the course of the study due to lack of treatment response or randomization to the placebo arm, potentially rendering virtual assessments impractical or invalid over time.

While adapting to unmet needs for virtual assessment in the current crisis, neuropsychologists have taken note of promise and potential in virtualizing cognitive assessments even as they scramble to ensure validity and reliability in their work. For instance, bridging the barrier of in-person attendance for clinical and cognitive assessments would be a boon for geriatric psychiatry, particularly for some under-represented individuals with socioeconomic or geographic barriers (e.g.,[16]), who deserve equal access to potentially life-altering interventions. We also have an opportunity to realize more consistent longitudinal data collection in the face of unpredictable hurdles, such as halted drug administration. As many of the hopeful drug candidates target the long-term course of disease, collecting a more thorough dataset through convenience should confer a more accurate statistical assessment of drug effect over time. Some novel computerized assessment platforms and novel test designs have also shown immense promise over the last several years (e.g., "gameification"). Leveraging these creative new testing paradigms could fundamentally alter both how patients are assessed and the types of cognitive data that are obtained in clinical trial contexts, though further validation studies are needed (see Textbox).

Textbox. Adapting neuropsychological scales and tests to the virtual platform

The two major neuropsychological and psychiatric outcome measure categories in most AD trials are *interview-based cognitive scales* (i.e., self- or informant-rated) and *performance-based cognitive tests*. Interview-based scales can be used on telehealth platforms with minimal to no deviation from standardized administration procedures. One important consideration, however, is the assessment of suicidality (e.g., the Columbia-Suicide Severity Rating Scale,[17] which requires additional planning on the part of the trial site and/or sponsor to ensure appropriate risk management from the remote setting.

Adapting performance-based cognitive tests to a telehealth platform is more challenging than interview-based measures. There is a growing literature supporting the validity and feasibility of virtual neuropsychological assessment,[9] including in older patients with cognitive impairment.[10–12] Tests that are auditory/verbal in nature are most amenable to virtual platforms. For example, a recent review found that tasks requiring a verbal response, including digit span, verbal fluency, and list-learning, were not meaningfully affected by videoconference administration.[9] Some tasks requiring visual presentation of materials, such as the Boston Naming Test (BNT), also performed on par with in-person administration. By contrast, there was more variability in results for tests that had a stronger visuomotor component (e.g., Clock Drawing) and may require further retooling to be successfully implemented. These test-specific findings are significant because measures of verbal memory and language have been shown to yield high predictive accuracy in terms of progression from mild cognitive impairment to Alzheimer's dementia.[18] Notably, a recent study examining two global measures of cognition commonly used in AD clinical trials — the MMSE and ADAS-Cog — found no differences between in-person and videoconference administration, except in inpatients with more pronounced cognitive deficits (MMSE <17).[18] One final consideration worth noting relates to the use of so-called "synchronous" tests — i.e., tests for which administration might be negatively affected by technological disruption during administration.[9] Tests that include a timed component, or those with single trials (e.g., digit span, Stroop task, list learning) could be significantly affected by

audio and/or video latencies, whereas other nontime dependent tasks and those with more relaxed rules about repeating instructions (e.g., BNT, Figure Copy, and Recall) are less susceptible to technological interference.

CLINICAL CONSEQUENCES OF SUSPENDING STUDIES

Could missing doses of infused antiamyloid or antitau antibodies affect disease outcomes? Given that in-person visits have been largely suspended, scheduled infusions for ongoing studies are being delayed for an indefinite amount of time. Kinetics from at least one compound being studied (BIIB092, for ongoing Phase II study TANGO) showed sustained reduction in extracellular secreted tau in cerebrospinal fluid for up to 12 weeks,[19] suggesting that a short lapse in infusions may not affect outcomes. However, other results caution against assuming preserved cognitive benefits after stopping infusions. In March 2019, Eisai and Biogen announced that they would initiate an open-label extension of Study 201, a Phase II Clinical Trial of BAN2401, an anti-Aβ protofibril antibody, based on efficacy findings of decreased rate of progression of disease (ADCOMS) at 18 months in subjects treated with high-dose (10 mg/kg infusions) monthly or biweekly BAN2401.[20] After an average 2 years post stopping infusions, in order to establish a baseline for the extension study, drug- and placebo-treated subjects from the previous study were re-tested at the neurocognitive level, and the drug-treated subjects were shown to have regressed to disease progression rates of the placebo-treated subjects. This was seen despite impressive sustainment of beta amyloid depletion on positron emission tomography SUVr over the average 2-year period.[21]

In the same month that Eisai and Biogen announced that they would run an open-label extension study, Biogen halted their Aducanumab studies (EMERGE and ENGAGE) after a Phase III futility analysis initially suggested that their drug would not meet the primary therapeutic endpoint. Later, based on positive findings from a more complete analysis of data, Biogen filed to reinitiate the study.[22] In the interim, a number of clinicians have observed significant cognitive decline in subjects since the study's termination. Thus, there are risks to participant outcomes given the delay in new enrollment and freezing of infusions in ongoing antibody trials. The current suspension of new IRB submissions and clinical research has delayed Biogen's EMBARK trial (Aducanumab re-dosing, originally slated for April), leaving subjects and their families/caregivers anxiously waiting for the trial to resume.

PSYCHOSOCIAL CONSEQUENCES

Helplessness and frustration are familiar emotions for people diagnosed with neurodegenerative diseases and their support systems. As there are currently no FDA-approved disease-modifying therapies for AD, volunteers participating in clinical trials for a potential disease-modifying drug often endorse the same goal: "Let me do everything in my power to take back control of this disease or help others who come after me." What's more, both subjects and caregivers describe a sense of community and social support through participation in the trials. A 2019 retrospective study by McLean researchers (unpublished) on subjects and study partners who participated in the EMERGE trial found that subjects placed high value on the clinical care received on a regular basis in the course of their research participation. They felt that participation offered a recurrent source of hope each month, while caregivers found the experience to benefit their partner's mood, provided social contact and support, and was a comfortable place to talk about AD. Further, when EMERGE abruptly ended in March 2019, study partners/caregivers, even more than subjects, felt a sudden loss of social support (Multidimensional Scale of Perceived Social Support) and hope, expressing both disappointment and a return to states of relative helplessness (unpublished). In the wake of COVID-19, when enrollment has ceased, and infusions are delayed until an unknown time, subjects and study partners wonder about the hope they have invested into the process. In the wake of such sweeping changes, the GPRP is in the process of establishing a virtual support group where caregivers can join together with clinicians and researchers to address ways of caring for their loved ones and themselves, as well as combat loneliness and isolation associated with self-quarantine. It is also an opportunity for the caregivers to receive updated news and safety recommendations by clinicians in a group format.

MOVING FORWARD

The immediately known threat of COVID-19, as well as the many uncertainties about it justifiably elevates the pandemic to an international medical priority. One consequence is that medical research for almost all disease states has been disrupted, which has threatened the steady progress made toward finding effective treatments for insidious diseases like Alzheimer's. In the wake of the pandemic, what damages to ongoing studies will need managing, and what lessons will we have learned? Trial protocols are thoughtfully written to account for *most* anticipated deviations. Now, they must consider how to statistically and interpretively evaluate variable interruptions in treatment administration, delayed or missed safety visits, or delays or high-volume losses of endpoint measurements. Shifting neurocognitive assessment approaches midway through a study has not been validated and will have been applied inconsistently. While these changes borne of necessity will surely take the field to the era of virtual assessments faster than we would have arrived there otherwise, the cost of abruptly switching technological approach may be the loss of inertia toward our primary research objectives. Given the nascency of telehealth and TeleNP specifically, we are still a long way from establishing fully remote virtual assessment as a feasible and reliable option in AD clinical trials. Will statisticians offer clarity in interpretation of our disjointed study results?

The daunting nature of keeping on target with our research objectives is shared by many across the country, and we hope that in describing our experiences at the MGH's ACTRU and McLean's GPRP, we not only validate the tremendous efforts all clinical researchers are putting toward their team's projects, but start a broader dialog to collectively find solutions to the many challenges we are facing right now in the field. This crisis presents an opportunity for us to examine and redefine what we have long considered "gold standards" in testing new therapeutic interventions. In the end, it is the hope, generosity, and incredible resilience of our participants and their caregivers, and their care and support that is the heart of our work and keeps our mission clear.

AUTHOR CONTRIBUTIONS

MSW, PO, RM, REP, NAS, AM, JG, DGH, SEA, and BF contributed substantially to conception, drafting and review/revision of intellectual content, and final approval of the manuscript.

DISCLOSURE

MSW declares no conflicts. REP receives grant support from Biogen, the National Institute of Health/National Institute on Aging, and the Rogers Family Foundation, and is a clinical rater on three industry-sponsored Alzheimer's clinical trials for Biogen and Eli Lilly. JG receives support from AbbVie. RM and PO receive grant support from Biogen. NAS receives funding support from AbbVie. AJM receives funding support from the Alzheimer's Association. JG receives funding support from the Challenger Foundation. DGH receives research funding from Biogen, Eli Lilly, the National Institute on Aging, Rogers Family Foundation, and the Spier Family Foundation. SEA receives institutional research support from NIH, Abbvie, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Amylyx, Challenger Foundation, EIP Pharma, Seer and vTv and has received consultant/advisory fees from Abbvie, Athira, Biogen, Cortexyme, EIP Pharma, and vTv. BF receives research funding from Biogen, Eli Lilly, the National Institute on Aging, Rogers Family Foundation, and the Spier Family Foundation, and is a consultant for Biogen. Research reported in this publication was supported by National Institutes of Health grant number R25MH094612 (MSW).

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