

Short Communication

Maximizing Safety in the Conduct of Alzheimer's Disease Fluid Biomarker Research in the Era of COVID-19

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Accepted 11 June 2020

Abstract. The coronavirus disease 2019 (COVID-19) pandemic led to an abrupt halt of many Alzheimer's disease (AD) research studies at sites spanning the world. This is especially true for studies requiring in-person contact, such as studies collecting biofluids. Since COVID-19 is likely to remain a threat for an extended period, the resumption of fluid biomarker studies requires the development and implementation of procedures that minimize the risk of in-person visits to participants,

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staff, and individuals handling the biofluid samples. Some issues to consider include structuring the visit workflow to minimize contacts and promote social distancing; screening and/or testing participants and staff for COVID-19; wearing masks and performing hand hygiene; and precautions for handling, storing, and analyzing biofluids. AD fluid biomarker research remains a vitally important public health priority and resuming studies requires appropriate safety procedures to protect research participants and staff.

Keywords: Alzheimer's disease, biofluids, biomarkers, COVID-19, safety

The coronavirus disease 2019 (COVID-19) pandemic has caused major disruptions throughout the world. One of the many important activities affected is Alzheimer's disease (AD) research [1]. To reduce transmission of the virus that causes COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), most research institutions closed during the initial phase of the pandemic in early 2020, abruptly halting many AD clinical research studies, including observational and treatment trials. Several months later, the risk of COVID-19 appears to vary widely by location [2, 3]. In some areas, SARS-CoV-2 transmission appears relatively well controlled, while in others areas SARS-CoV-2 is still being rapidly transmitted [3]. Many experts suspect that COVID-19 will remain a threat for an extended period, until an effective vaccine is available, and that all people will have to find ways to continue life in a world where SARS-CoV-2 transmission is a risk.

In many regions, stay-at-home orders have been lifted and research institutions are starting to re-open, but currently there is not clear guidance on when and how to resume clinical research activities. Despite this uncertainty, many investigators are considering how to safely resume clinical research. This is particularly challenging in AD clinical research because most of the participants are older, which is a risk factor for severe complications and death from COVID-19 [4, 5]. Although clinical and cognitive assessments, which are typically performed during in-person visits, are being adapted to be performed remotely via telephone or real-time video, it is not possible to remotely obtain fluids (e.g., blood and cerebrospinal fluid [CSF]) for biomarker studies. For fluid biomarker studies to resume, procedures for in-person visits must be developed that minimize risk of SARS-CoV-2 transmission to both participants and staff. Research may only resume if investigators, institutions and regulatory agencies are convinced that participants and staff are safe. Since so many research groups (in AD and other fields) face similar challenges, we have described herein some of the rel-

evant considerations for biofluid collection, handling, storage, and analysis (Box 1).

As investigators are developing site-specific procedures, they should be fully informed on national, state, local, and institutional guidelines regarding COVID-19 protections, which may change over time. Investigators should consider the characteristics of each study participant, including their age, comorbidities, and living situation, along with the potential benefit of study participation. It may be advisable not to perform in-person visits with participants in certain highly vulnerable groups (e.g., residents of nursing facilities) in whom no additional risk of SARS-CoV-2 transmission is acceptable. For other participants, protections should be implemented such that the risk of SARS-CoV-2 transmission from a research visit is minimal and likely below the risk of other routine activities (e.g., going to the grocery store). The investigator should also consider any potential risks associated with a research visit, such as the use of public transportation or parking in a garage connected to a medical facility, and work to mitigate these risks. Regardless of the procedures implemented, some individuals may choose not to participate in research visits during the pandemic because of concern about SARS-CoV-2 transmission. However, many participants may be comfortable in accepting a minimal level of risk, especially in communities where SARS-CoV-2 transmission is relatively low.

Before in-person biofluid collections resume, the visit workflow should be reviewed in detail. Facilities and entry/exit routes should be chosen to minimize the contacts between participants and other individuals, especially individuals with possible COVID-19. For example, investigators should try to avoid situations where participants may share exam rooms, waiting rooms, elevators, or stairwells with individuals who are being evaluated for COVID-19 symptoms. Social distancing reminder signs should be placed where appropriate, such as at the check-in desk. Waiting rooms should be arranged to facilitate social distancing, with groups of chairs spaced greater

than six feet apart. Participants should be scheduled to minimize the overlap of entries and exits with other participants.

Investigators should consider whether SARS-CoV-2 testing of the participant and/or staff is indicated prior to an in-person visit. Institutional policies may provide specific guidance. In general, if participants live in communities where the prevalence of COVID-19 is relatively high, SARS-CoV-2 testing may be prudent. Some staff performing in-person biofluid collection, such as nurses collecting blood or neurologists performing lumbar punctures, may also serve as healthcare providers in higher risk settings. Given the relatively high rate of COVID-19 infection in healthcare workers [6, 7], it is reasonable to consider testing staff with possible COVID-19 exposure in the previous fourteen days for SARS-CoV-2 before they interact with research participants, irrespective of the safety precautions used during the potential COVID-19 exposures and during the research visit.

The number of study partners accompanying the participant to the in-person visit should be minimized to only those that are essential, such as one caregiver for a cognitively impaired participant. Before travel to the study site (preferably one day before), the participant and study partner should be contacted and pre-screened for COVID-19 exposures and symptoms [8]. Any concerning responses should be reviewed with the study investigator before confirming the study visit. Depending on local guidelines, the participant and study partner should be advised to wear a mask to the research visit and be given detailed directions to the study location, including any areas to avoid. Study partners should be encouraged to help cognitively impaired participants observe social distancing guidelines during the visit.

The day of an in-person visit, staff should undergo screening for COVID-19 exposures and symptoms per institutional guidelines. Staff should not have contact with research participants if they have been exposed (without proper personal protective equipment [PPE]) within the past fourteen days to an individual known to have COVID-19, are feeling unwell, or have a fever. All surfaces that contact participants and/or staff (e.g., doorknobs, pens, clipboards, and exam tables) should be cleaned and disinfected before and after each use. Staff should consider wearing a mask or face shield throughout all participant contacts. Additional PPE, such as gloves and eye protection, should be worn as required by the procedure. Hand hygiene should be performed fre-

quently, including before and after each participant contact.

Upon arrival to the study site, the participant and study partner should be asked to perform hand hygiene, given masks if needed, and screened for COVID-19 exposures and symptoms. Any concerns should be reviewed with the study investigator before the visit proceeds. All procedures should be performed with careful attention to universal precautions. Eating and drinking should be avoided if possible. At the end of the visit, the participant and study partner should perform hand hygiene and be asked to promptly leave the study site through the designated exit route.

Several small studies have demonstrated the presence of SARS-CoV-2 in biofluid samples collected from COVID-19 patients. SARS-CoV-2 was detected in some blood samples collected from COVID-19 patients: six of forty-one patients (15%) [9], six of fifty-seven patients (11%) [10], and 3 of 307 patients (1%) [11]. No SARS-CoV-2 was detected in the CSF of two patients with COVID-19 and strokes [12], seven COVID-19 patients with neurological symptoms [13], or ten individuals who died from COVID-19 [14]. However, SARS-CoV-2 was detected in the CSF of a single individual with COVID-19 and meningoencephalitis [15]. Notably, these studies were performed using samples from individuals with symptomatic, and typically severe, COVID-19. It is unknown whether SARS-CoV-2 is present in blood and CSF samples from individuals who are mildly affected or asymptomatic.

Although it is unknown whether the SARS-CoV-2 that is occasionally present in biofluids is infectious, a general laboratory principle is that all biofluid samples should be treated as potentially infectious. Adherence to universal precautions and biosafety level-1 protocols are recommended at this time for most laboratory procedures that do not generate aerosols (Box 2) [16]. If procedures are performed that could potentially generate aerosols, investigators should consider use of additional safety measures [16, 17]. Given uncertainties about the infectivity of samples, it may be reasonable for investigators to flag samples collected from individuals with known COVID-19 and to forward this information to anyone receiving aliquots of the sample. Especially given the high rate of asymptomatic infection, all samples collected during the pandemic should be handled as if they contain SARS-CoV-2.

Long after the COVID-19 pandemic subsides, AD will remain a major cause of dementia, death, and

healthcare burden. AD fluid biomarker research has been gaining momentum, with recent progress in blood-based biomarkers [18], and may speed the development of effective therapies for AD. By instituting procedures that minimize risks for participants and staff, it may be possible to safely resume AD fluid biomarker research before the pandemic has fully passed. As investigators work to safely re-start their research, they should consider the effects of the pandemic on their study design and planned analyses, which may be impacted by issues such as missing data and altered protocols [1, 19]. Even amidst a pandemic, it is important to resume rigorous research because AD also represents a major health care crisis that will worsen until effective therapies are found.

Box 1. Recommended clinic procedures:

- Identify participants in highly vulnerable groups (e.g., residents of nursing facilities);
- Encourage modes of transportation that present a low risk for SARS-CoV-2 exposure for participants and staff;
- Establish entry and exit routes to the research facility that minimize contacts between individuals, especially individuals that may have COVID-19;
- Facilitate social distancing in waiting rooms and other shared areas;
- Consider whether testing participants or staff for SARS-CoV-2 is warranted;
- Minimize the number of individuals accompanying the participant;
- Pre-screen participants and study partners for COVID-19 exposures and symptoms before travel to the study site;
- Screen participants, study partners, and staff for COVID-19 exposures and symptoms prior to the procedure;
- Perform frequent hand hygiene and consider wearing masks during biofluid collection;
- Use additional personal protective equipment as appropriate for the procedure;
- Follow universal precautions for the collection and handling of biofluid samples.

Box 2. Recommended laboratory procedures:

- Perform hand hygiene frequently;
- Avoid touching the eyes, nose, and mouth;
- Facilitate social distancing;
- Post biohazard signs;
- Decontaminate all work surfaces at task completion and between shift changes;

- Wear personal protective equipment that is appropriate to the task, such as a lab coat or gown, mask, gloves, and eye protection;
- Avoid splashes or aerosols (e.g., vortexing samples);
- Decontaminate immediately after spills;
- Handle sharps safely;
- Use centrifuges that are equipped with a double cover, safety buckets, and sealed rotors.

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