

Roadmap for Conducting Neuroscience Research in the COVID-19 Era and Beyond: Recommendations From the SNACC Research Committee.

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encountered during the COVID-19 pandemic along with possible strategies for facilitating research activities. These challenges and recommendations are included in this consensus statement. The objectives are to: (1) provide an overview of the disruptions and challenges to neuroscience research caused by the COVID-19 pandemic, and; (2) put forth a set of consensus recommendations for strengthening research sustainability during and beyond the current pandemic. Specific recommendations are highlighted for adapting laboratory and human subject study operations to optimize safety. Complementary research activities are also outlined, for both laboratory and clinical researchers, if specific investigations are impossible due to regulatory or societal changes. The role of virtual platforms is also discussed with respect to fostering new collaborations, scheduling research meetings, and holding conferences such that scientific collaboration and exchange of ideas can continue. Our hope is for these recommendations to serve as a valuable resource for investigators in the neurosciences and other research disciplines for current and future research disruptions.

The Coronavirus Disease 2019 (COVID-19) pandemic has created a global crisis with grave public health and economic consequences. The pandemic has also left a severe impact on laboratory and clinical research, as many hospitals and universities have halted or significantly reduced research activities except for those directly relating to COVID-19. Some scientists are contemplating leaving research entirely due to the high levels of psychological stress incurred by the pandemic.^{1, 2} COVID-19 has particularly affected clinical neuroscience research by suspending trials that are testing novel therapies for neurologically vulnerable patients.^{3, 4} Given the lack of validated biomarkers for adverse neurological outcomes of interest to perioperative physicians, chart review-based strategies are frequently unavailable, or of limited benefit. There is thus a critical need to develop a well-articulated, programmatic strategy for advancing neuroscience research during the COVID-19 pandemic, which might also be beneficial in future situations that could similarly impact research activity.

The objectives of this manuscript are to: (1) summarize effects of the COVID-19 pandemic on research in the neurosciences, and; (2) provide systematic recommendations for improving neuroscience research sustainability during such challenging conditions. The themes and recommendations discussed may also apply to other research disciplines, and may be useful in the event of a future disruption that similarly impedes neuroscience research. Sections are devoted to laboratory science, non-clinical human volunteer studies, and clinical research. Within each section, specific challenges are highlighted, possible solutions are reviewed, and alternative activities are suggested in the event that certain studies are unable to resume.

The writing group consists of members from the Society for Neuroscience in Anesthesiology and Critical Care (SNACC) Research Committee. An outline of the proposed recommendations was drafted and accepted by all authors. The manuscript was then reviewed and approved by the SNACC Executive Committee and Board of Directors. Lastly, the manuscript was made available to active SNACC members for review and comment before publication.

The COVID-19 pandemic has adversely impacted neuroscience research in profound ways. Researchers have faced decreased funding, resource limitations, restrictions to laboratory and hospital access, and reductions in available personnel (e.g., layoffs, hiring freezes, re-deployments) for multiple aspects of research operations. Scientists have also experienced furloughs in research activities, which has hindered collaboration within the neuroscience community. These suspensions in operations have also led to social isolation, as many investigators have been required to work remotely. Such isolation may contribute to emotional and psychological strain. Physicians may also experience stress and anxiety from emergency redeployment and additional clinical responsibility because of increases in volume or staff shortages, resulting in reduced research time.

Indeed, COVID-19 has imparted a burden of psychological stress on researchers. These issues are highlighted in a recent survey of UK neuroscientists conducted by the British Neuroscience Association.² Nearly 80% of respondents to this survey were concerned that their research would be impacted by insufficient funding; 88% have seen negative progression in their research, and

approximately 32% reported considering leaving neuroscience research altogether. This phenomenon is particularly concerning for early-stage investigators who are reliant upon funding and resources to launch new research programs. In addition, there are clear indications that women researchers, as well as researchers with young children, are disproportionately affected because of the closure of childcare facilities and schools.^{5 - 7} This disadvantage is likely to expand, as many institutions have resumed research activities while schools cycle between open and closed as community spread varies. Work-life balance issues can be further exacerbated if physical distancing in the work environment has forced personnel to work shifts outside of normal working hours. Additionally, researchers caring for sick or older family members are absorbing increased burden and may become less productive academically.

An additional consideration is the effect that a COVID exposure, directly attributable to a research project, may have on researchers. During periods of high community spread, it is not uncommon that potential transmission may have occurred in the workplace. Typically, if the exposure was prolonged and indoors, even with precautions in place, post-exposure isolation would be required. Such an event can have consequences for research productivity as the majority of a laboratory group may need to quarantine. There may also be psychological consequences, including feelings of anxiety and guilt over potential exposure to staff or participants as a result of continuing research during the pandemic.

Overall, scientists face novel and considerable challenges with conducting research during the COVID-19 era. Limited resources and funding, suspension of activities, reduced collaboration, personnel reductions, and preexisting disparities in sex or heritage have created barriers to research productivity.^{2, 5 - 7} In the following sections, we will propose possible solutions to improve sustainability for both laboratory and human subject research in the neurosciences.

Despite the current challenges posed by the COVID-19 pandemic, many research activities remain possible. Researchers can use this time to analyze previously collected data, complete manuscripts, write protocols for future studies, and prepare new grant applications, including neuroscience funding opportunities for COVID-19 research. Some have successfully pivoted their research focus away from hands-on laboratory and clinical research towards “dry-lab” and “in silico” projects. With neuroscience research in particular, many projects are designed around the use of animal or human electrophysiological databases and may be suited for remote analysis. Some funding agencies, such as the U.S. National Institutes of Health and Canadian Institutes of Health Research, may offer grant extensions on a case-by-case basis depending on circumstances.

Digital platforms can also be utilized to advance research activities. Virtual meetings can be scheduled with colleagues to foster new collaborations and generate new hypotheses for future testing. The increased fluency in digital communication methods has enabled some groups (including SNACC) to hold virtual conferences that, at least theoretically, lower barriers to collaboration. The virtual format may also help to reduce costs and promote diversity by improving inclusivity.⁸ However, this virtual format does not necessarily replace spontaneous discussions and brainstorming triggered by chance encounters at meetings and conferences, though it does result in time and cost savings for researchers.⁸ Further growth of digital platforms hopefully will better support such creative encounters. Switching to digital communication methods also allows for regularly scheduled interactions, weekly group or individual meetings, and “flexible availability” (i.e., short meetings and windows of access to principal investigators). Similarly, team meetings, seminars, and journal clubs can also be conducted via digital platforms. This virtual technology has also allowed faculty and instructors to invite guest speakers to classes and seminars, which facilitates inter- and intra-institutional networking with colleagues, and enriches curricula without the usual expenses associated with guest faculty travel. Lastly, investigators can also use this time to explore opportunities for committee service and tend to administrative responsibilities. These recommendations are summarized in Table 1.

Laboratory research is predominantly a hands-on activity conducted in space-constrained environments. At most institutions, a shut-down of all in-person activities occurred in the face of

COVID-19, due to both concern for the safety of laboratory staff and the need to divert resources to pandemic management. This produced an unprecedented crisis for global research enterprises, particularly relating to the neurosciences. 2 In many cases, the only activities permissible were those required for the long-term continuation and upkeep of biological stocks or for COVID-19-related research activity. Laboratory facilities have gradually reopened with ongoing restrictions, such as physical distancing, maintaining low personnel density, and implementation of sanitization protocols. Although permissive of some research activities, these restrictions continue to hamper progress due to restricted laboratory access and lack of research personnel available to conduct study protocols that span multiple days. Research progress, particularly experimental data generation, has slowed dramatically for many researchers, negatively impacting the timely completion of grant objectives, manuscripts, and, in many cases, the graduation of students. In addition, many future physicians are not receiving exposure to laboratory science. The laboratory workforce traditionally includes undergraduate and post-baccalaureate students applying to medical school; because of ongoing restrictions, many of these students have not worked in laboratories during the pandemic. The lack of exposure to scientific methods and training may also affect the career choices and opportunities for students who may have otherwise pursued graduate studies in the neurosciences.

It is also important to note that the psychological stress on laboratory assistants and technicians could be severe. Besides the direct roles in experimental work, research technicians are likely to be responsible for housekeeping needs and might be required to continue working in the laboratory despite the high exposure risk. Furthermore, technicians and assistants may operate on reduced salary, as funding from internal sources has diminished at many institutions due to budgetary constraints. Some funding agencies have provided additional funds to help laboratories cope with diminished productivity, including the U.S. National Institutes of Health National Research Service Awards for fellows and trainees, which offers continued stipend payments. However, these support mechanisms often do not apply to technical staff and, in many cases, only partially compensate for lost productivity.

With the gradual reopening and resumption of research activities, many laboratories have temporarily repurposed workspaces to meet the personnel density and physical distancing goals set by institutions. Where spatial constraints have remained an ongoing issue, some laboratory groups have implemented staggered schedules, rotating personnel to work different shifts (e.g., hours, days). Night and weekend shifts could also be considered when possible. Finally, many labs have diversified their effort “portfolios” by starting new projects that are less reliant on in-person bench data collection, such as computational modeling, programming, and database analysis. Laboratory groups can also use this time to acquire new skillsets. These recommendations are summarized in Table 2 .

There are also opportunities for studying the neurobiological mechanisms and consequences of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus and the resulting COVID-19 disease. Unraveling the mechanisms behind central nervous system manifestations of SARS-CoV-2 will represent a new frontier for neuroscientists. Such research will be particularly important for understanding lingering chronic fatigue and other adverse neurological outcomes associated with the so-called “long COVID” syndrome. 9 Laboratory groups that are already working on these problems will have valuable tools and experience in place to facilitate collaboration and pivot effort towards this important work.

Non-clinical research involving volunteer human participants poses a unique set of challenges during a pandemic. Some of these challenges overlap with those in basic research, including using time and space to distance research staff from one another. For research involving human subjects, space and time between consecutive participants must be sufficient to obviate the need for a waiting room with multiple people. This particularly affects research that inherently involves multiple participants, such as educational intervention and clinical simulation research. Additionally, the interaction between participants and researchers poses an exposure risk that must be mitigated. This is particularly important from a research ethics standpoint, as most non-clinical human

volunteer studies have no direct benefit for participants aside from monetary compensation, and participation in any in-person activity now carries risk of contracting SARS-CoV-2.

As conditions evolve, investigators should continuously monitor and abide by all applicable institutional policies and local health department recommendations. It is important to note that regulations, policies, and protocols may vary widely across institutions and countries. Guiding principles for conducting research during the pandemic generally balance risk to participants and staff against benefits of research progress. 10 Some universities have incorporated COVID-19 relative risk tools, whereby research is precluded for participants meeting high-risk thresholds. 10 In some instances, volunteer research activities may be suspended during COVID-19 surges. Exceptions and restart plans for human subjects research projects have required investigators to submit specific protection plans for Institutional Review Board approval. Principles for promoting safety and reducing risk of transmission are described in the following sections.

Recruitment for some volunteer studies has been more challenging compared to pre-pandemic interest. This may be due to decreased participant availability, as potential volunteers that live or work near academic institutions where the research is being performed may be working or learning remotely. Research focused on volunteers from high-risk groups, such as the elderly or those with chronic medical conditions, may experience even more reluctance to participate. This can be somewhat offset by more targeted advertising via university research portals and registries. Some reduced enthusiasm for volunteering for research participation may be mitigated with modestly increased compensation. Taking such a strategy is meant to offset the increased inconvenience with participating, as most daily activities have become more complicated. For example, compensation could be increased to at least meet minimum wage requirements, and costs could be covered for parking and transportation. Many clinical-translational science institutes also offer programs for engaging historically underrepresented communities for increasing enrollment diversity. 11

Although the risk of disease transmission during study operations cannot be eliminated, it can be minimized. Effective mitigation efforts reduce the risk to both subjects and researchers to levels commonly experienced in other essential aspects of daily life, such as grocery shopping. Virtual informed consent and remote assessments should be considered when possible. From a safety standpoint, COVID-19 screening should be implemented for study staff and participants before study in-person procedures. This screening should occur as close as possible to the scheduled study visit, and study team members should conduct a comprehensive screen for COVID-19 symptoms and contactless temperature checks upon participant arrival. Best practice would err on the side of rescheduling any subject that reports any symptoms of illness, even in the absence of fever or respiratory symptoms. Based on regional supplies and availability, point-of-care antigen testing could be considered as part of the screening process. Such testing should be strongly considered regardless for high-risk studies (i.e., those that may include aerosol-generating procedures).

During study activities, distance between participants and researchers should be maximized and close contact time should be minimized. This may be challenging for studies that involve direct data collection, such as obtaining biological samples, imaging, or physiological recordings. In these cases, appropriate personal protective equipment should be used. Medical or surgical masks and eye protection should be worn throughout the study period, and hand hygiene should be meticulously observed with the use of gloves and hand sanitizing solutions. N95 masks should be used in the event of aerosol-generating procedures. Adequate supplies of gloves, other relevant personal protective equipment, cleaning solutions, and hand-sanitizing solutions should be in place. Should a shortage of personal protective equipment occur for clinical care, these supplies should be diverted and research operations would need to be temporarily suspended. The number of researchers present for a given experiment should be also minimized, particularly in small spaces that prohibit physical distancing. Further engineering protections, such as installation of plexiglass shielding, can also be considered for dedicated human subjects research space.

All non-disposable equipment used for a participant visit must be thoroughly cleaned and disinfected between subjects. Research staff performing these procedures should continue to wear masks and gloves while using disinfectant. Manufacturer recommendations for application and dwell time for the disinfecting agent should be followed. Many experimental setups include rough or porous surfaces that are also “high-touch” areas that need to be cleaned and disinfected frequently. Disposable plastic wrapping could also be considered for covering these surfaces. Adequate time should also be allowed for air exchange between studies, particularly in small and poorly ventilated spaces. Patient interviews could also be conducted outside of such settings when possible.

Overall, these principles and recommendations could facilitate the continuation of human subjects research programs without having to pause activities. While external factors, such as COVID-19 surges, might force suspension of research operations, incorporating the preventive measures described above could reduce the risk of needing to put studies and programs on hold.

As elective surgery and other non-essential medical procedures were postponed during the first surge of COVID-19, opportunities to recruit patients for non-COVID-19 clinical research studies declined dramatically, and many trials and observational studies were suspended. Clinical neuroscience research has been particularly impacted, as advances in this field are often reliant on prospective study designs. Validated biomarkers of neural injury are unavailable via retrospective chart review, and screening results for cognitive impairment are inconsistently incorporated into medical records.¹² As the pandemic progressed, clinical research was further impeded by quarantines, site closures, travel limitations, and supply chain interruptions for research equipment. Asynchronous peaking of COVID-19 across geographic regions may also impact multi-institutional collaborative projects. Clinical research has since gradually ramped up, with investigators and institutions demonstrating ingenuity, adaptability, and persistence with research re-engagement. Safety protocols continue to evolve for human subject research, and digital platforms are available for informed consent and study assessments.^{10, 13}

Despite the considerable disruptions and impediments posed by the current COVID-19 pandemic, these challenges can also be viewed as an opportunity to transform clinical research. The pandemic has constrained conditions for conducting clinical research, and, in response, novel strategies are being tested and implemented to facilitate research operations and improve sustainability. In the following sections, we will review challenges to, and novel strategies for, conducting clinical neuroscience research during a major pandemic.

Before the COVID-19 pandemic, recruitment and retention of research study participants could be fundamentally challenging, but the pandemic has only exacerbated these challenges. As clinical practice moves towards less direct contact with patients, so too must our clinical research efforts.

New approaches to subject recruitment are needed during the COVID-19 pandemic. Subjects may need to be actively sought-out and recruited, rather than researchers passively relying on clinic and operating room schedules for screening procedures. For example, clinical-translational science institutes offer community engagement programs that foster connections between clinical research teams and interested communities.¹¹ These services can also help to improve enrollment diversity by connecting with historically underrepresented communities.¹¹ Moreover, text messages and email links can be automatically sent to prospective community participants, identified via university health research portals. Research teams can thus leverage such digital, university-based resources to adapt recruitment and retention strategies during an era where conventional, in-person clinic recruitment may not be feasible. Active recruitment strategies may also help overcome the significant healthcare disparities that were unmasked by the pandemic and allow for more appropriate representation of all ethnic and racial groups in clinical studies.

For trials and observational studies that have resumed, appropriate safety protocols should be implemented to protect the health of participants, research personnel, and clinicians. Similar to human volunteer studies, virtual- and telephone-based informed consent should be considered, and protocols should also include baseline COVID-19 screening procedures, mask requirements,

physical distancing measures, and appropriate hand hygiene. Online team training modules are encouraged where such resources are available. The World Health Organization offers basic online training videos for public health professionals. 14 Telephone- and virtual video-based assessments could also be utilized when in-person interactions are not possible or required. The U.S. Food and Drug Administration, World Health Organization, and European Medicines Agency provide systematic guidance for ensuring the safety of trial participants, maintaining compliance with good clinical practice, and minimizing risks to trial integrity for the duration of the public health emergency. 15 - 17 These guidelines could serve as valuable resources, particularly for study teams without local institutional protocols available.

While some prospective trials and observational studies have resumed, we recognize that some clinical research activities remain suspended. In these scenarios, investigators could consider retrospective studies for which data have already been made available. Indeed, clinical data repositories are available from entities such as the U.S. Neuroscience Information Framework and U.K. Data Service. 18 , 19 The U.S. National Surgical Quality Improvement Program and Multicenter Perioperative Outcomes Group provide repositories specific to the surgical and anesthetic care. 20 , 21 Certain limitations are present, as there are no validated biomarkers for perioperative neurological injury that would be found in electronic health records or data warehouses. Nonetheless, these resources may still be useful depending on the line of investigation and outcomes under consideration. Investigators can also use this time to consider survey research for social and behavioral questions relevant to perioperative neuroscience. Clinical trials and observational studies could also be considered for urgent and emergent surgeries that remain ongoing. Recommendations for human volunteer and clinical research studies are summarized in Table 3 .

Many neuroscientific questions have arisen with respect to SARS-CoV-2 and COVID-19 pathophysiology. Mechanisms by which SARS-CoV-2 enters the central nervous system and mediates downstream injury need to be elucidated. Understanding these mechanisms is particularly important, as SARS-CoV-2 appears capable of affecting brainstem autonomic control centers, generating epileptiform activity, and causing encephalopathy and related brain states. 22 , 23 Direct invasion may occur via olfactory transmucosal transmission, axonal transport, leukocytes, and endothelial cells, 24 though these mechanistic pathways remain incompletely understood. SARS-CoV-2 may also cause central nervous system injury via indirect, immune-mediated pathways that can also affect blood-brain barrier permeability. 25 COVID-19 patients also demonstrate an increased risk of thromboembolic events, 26 and processes that support thromboembolic propagation throughout the cerebral vasculature require advanced understanding. This foundational work is critically important for understanding the underlying neurobiology of encephalopathy, seizures, cerebrovascular events, and other neurological syndromes associated with COVID-19.

From a clinical standpoint, risk factors need to be identified for adverse neurological outcomes, such as delirium, seizures, and stroke. This could be addressed via retrospective case-control studies. Large-scale cohort studies can also be conducted to determine long-term neurological sequelae of COVID-19. These studies could include prospective neuropsychological tests and screens for neurocognitive disorders to understand the longitudinal impact of COVID-19 on cognitive function. For those with impairment, cognitive rehabilitation therapies could be considered and tested. The Global Consortium to Study Neurological Dysfunction in COVID-19 (GCS-NeuroCOVID) represents a major, large-scale collaboration to harmonize these data collection efforts. 27 Neuroscientific and medical societies could play a role in advancing such research via funding mechanisms, where possible. These research topics are outlined in Table 4 .

The lessons learned from the COVID-19 pandemic can be applied to neuroscience research practices for improving sustainability. For example, for future disruptions during which research activities are paused, investigators can consider analyzing previously collected data, writing new manuscripts and grants, and shifting to new research activities with methods that are otherwise feasible as outlined in Table 1 . Safety protocols that require physical distancing and other

preventive measures have been developed, tested, and implemented should this need arise again. The current pandemic has also catalyzed growth of virtual platforms, which can be used to continue certain activities if in-person alternatives are not available. Digital communication methods may also now serve as a permanent tool for conducting some operations, including informed consent and questionnaire completion. This pandemic has also prompted many clinical-translational groups to reflect on recruitment practices, with renewed emphasis on proactive strategies that include focus on engaging historically underrepresented communities. Overall, the COVID-19 pandemic may have improved resiliency of research enterprises by generating flexible, adaptive, and inclusive strategies for improving neuroscience research practices and adding to sustainability.

The COVID-19 pandemic has been detrimental to research communities. Nevertheless, resolve is strengthened by adversity, and researchers have demonstrated considerable ingenuity, perseverance, and collaboration to solve manifold challenges that have arisen during this pandemic. Biomedical societies such as SNACC have dedicated significant time and resources to the advancement of neuroscience during this challenging era. The ideas and recommendations in this Consensus Statement may also help to make research more flexible and adaptable, particularly in the event of a future, similar disruption of research activity.

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This Consensus Statement has been reviewed and approved by the Society for Neuroscience in Anesthesiology and Critical Care (SNACC) Executive Committee and Board of Directors. It has not undergone review by the Editorial Board of the Journal of Neurosurgical Anesthesiology.

Disclosures : The authors have no conflicts of interest to declare.

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Recommendations and activities provided may apply to both laboratory scientists and research groups conducting human subject studies.

Laboratory Science – Research Activity Recommendations

COVID-19 indicates coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Human Subjects Research – Recommendations

COVID-19 indicates coronavirus disease 2019.

Neuroscientific Research Pertaining to COVID-19

CNS indicates central nervous system; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.