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# Restarting Respiratory Clinical Research in the Era of the Coronavirus Disease 2019 Pandemic



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The clinical research we do to improve our understanding of disease and to develop new therapies has temporarily been delayed as the global health-care enterprise has focused its attention on those impacted by coronavirus disease 2019 (COVID-19). Although rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are decreasing in many areas, many locations continue to have a high prevalence of infection. Nonetheless, research must continue and institutions are considering approaches to restarting non-COVID-related clinical investigation. Those restarting respiratory research must navigate the added planning challenges that take into account outcome measures that require aerosol-generating procedures. Such procedures potentially increase risk of transmission of SARS-CoV-2 to research staff, use limited personal protective equipment, and require conduct in negative-pressure rooms. One must also be prepared to address the potential for COVID-19 resurgence. With research subject and staff safety and maintenance of clinical trial data integrity as the guiding principles, here we review key considerations and suggest a step-wise approach for resuming respiratory clinical research.

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**KEY WORDS:** aerosol generating; clinical research; COVID-19; SARS-CoV-2; spirometry

Clinical research is critical to our understanding of disease mechanisms and leads to life-saving therapies. During the time that worldwide efforts have been appropriately focused on describing and treating disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), most non-coronavirus disease 2019 (COVID-19) clinical research has paused and/or pivoted to a COVID-19 research focus. However, now that we have navigated the initial surge of SARS-CoV-2 cases, many are considering how to reintroduce non-

COVID-19 clinical research conduct while protecting participants and staff and ensuring data integrity. Because of the many aerosol-generating procedures (AGPs) that are necessary to generate critical outcomes in respiratory research (eg, lung sampling by bronchoscopy, nasal brushing, spirometry, administration of nebulized medications, and sputum induction, among others), the challenges to resuming clinical research in pulmonary disease are numerous, and potentially more complicated than in other areas. Here we review key considerations and

**ABBREVIATIONS:** AGP = aerosol-generating procedures; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; FDA = Food and Drug Administration; NIH = National Institutes of Health; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOP = standard operating procedure

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suggest a step-wise approach for resuming clinical research including observational research, registry trials, and interventional trials, as well as potential data confounding related to COVID-19 that is important to consider as research studies restart and data are analyzed.

### Illustrative Case

In January 2020, a 63-year-old woman enrolled in an 8-week, phase 3 randomized trial with planned open-label rollover. Because of the increasing number of COVID-19 cases in her state, clinical research conduct was put on hold with the exception of studies deemed to have potential benefits for subjects. Because the subject was scheduled to roll over to an open-label study drug at the end of March 2020, her continued participation was agreed to have benefit. The subject's local government issued a shelter-in-place notice on March 25, 2020. This ordinance, in combination with the potential risk of infection, decreased the subject's enthusiasm to travel to the research site. Development of a new process was deemed necessary to ensure her access to the open-label study drug.

### Guiding Principles

To resume clinical research in the era of COVID-19, several guiding principles should be followed:

- Research subjects must be kept safe.
- Clinical research staff must be kept safe.
- The integrity of protocols, data, and outcomes must be maintained.
- The process of resuming research should be flexible and dynamic, varying over time and by geography as dictated by the prevalence of COVID-19, the availability of testing and personal protective equipment (PPE), and local institutional and governmental policies.

### Safety of Subjects and Staff

Clinical research inherently has certain risks, due to either procedures or investigational agents. In the spirit of "Do No Harm," it is critical that institutional policies and processes be in place to ensure there is no significant additional risk of contracting viral respiratory or other infections in the normal course of participation in research studies; now, during the COVID-19 pandemic, these principles are even more critical. Careful consideration should be given regarding screening, enrollment, and continued protocol participation for high-risk participants. Equally important, it is

imperative that clinical research staff be protected from potential risks of contracting respiratory tract infections, including SARS-CoV-2, from research subjects or individuals accompanying them. Maximizing the safety of all can be addressed by adopting several strategies to reduce potential exposure to those who are infected.

**COVID-19 Screening/Testing:** The first line of protection is to prevent subjects and staff at risk of infection from contracting and propagating disease. Although there is some risk associated with asymptomatic individuals spreading disease, the vast majority of COVID-19 transmission is from symptomatic people. In that vein, all staff must self-monitor and self-report any symptoms daily. If these symptoms occur, staff must remove themselves immediately from work and from serving as vectors of infection. Similarly, research subjects should be screened for symptoms in the 2 to 14 days before each visit to evaluate whether the subjects have symptoms of COVID-19, or are otherwise at high risk of being infected or infectious. This evaluation is particularly important for immunocompromised patients, as they may shed virus longer. Screening for symptoms should also be repeated on arrival at the institution, with both survey questions and temperature checks. Symptomatic or febrile subjects must undergo COVID-19 testing with research visits postponed until test results have returned and/or symptoms have resolved. Whether all subjects, including asymptomatic subjects, should be tested before participation in research depends on several factors including local community standards of care, prevalence, and testing availability including rapid turnaround time.<sup>1</sup> Testing of some individuals before they undergo a procedure that is likely to produce a high level of aerosol generation, such as bronchoscopy, should be strongly considered and has been implemented at many academic institutions.<sup>2</sup> At this time, SARS-CoV-2 antibody testing has significant limitations due to sensitivity and specificity depending on the platform, and is currently not recommended. However, as testing characteristics improve in the future, this may be helpful in evaluating the safety of research participation and potential for confounding due to COVID-19 as noted below.

**Reducing Exposures With Administrative and Engineering Controls and Personal Protective Equipment:** Other measures should be taken to reduce potential exposure, including directing access of participants strictly to entrances where monitoring stations are present, limiting or avoiding visitors accompanying participants, minimizing the number

or duration of participant visits, using remote monitoring such as telehealth if possible, and staggering participant visits to reduce exposures. Additional administrative measures to reduce exposures include limiting nonessential/non-research staff interactions with participants and research areas, and limiting research staff from directly interacting with participants; the latter will also conserve PPE. These preventive measures can be taken by managing access to research units, developing one-way hallways for 6-min walk testing, and using Plexiglas/plastic barriers and good ventilation in areas when staff and/or participants are in close proximity. Furthermore, staff and participants should be safely positioned in workplaces and research areas to optimize social distancing.

Centers for Disease Control and Prevention (CDC), professional society, and/or local and state guidelines and policies should be followed for allocation of PPE for research, with priority of allocation for use in clinical care. As outlined by the CDC, central purchase and storage of PPE may be considered to ensure adequate supplies as well as conservation of PPE, especially for face masks and protective eyewear (eg, face shields, safety glasses, and goggles). Participants and research staff should be educated in the appropriate use of PPE, including donning and doffing, and exposure reduction measures. All must be required to wear face masks or surgical masks as well as protective eyewear for study personnel, if available, to reduce the spread of infectious droplets and aerosols. Aerosol-generating procedures, including pulmonary function testing, exhaled nitric oxide measurement, sputum induction, nasopharyngeal sampling, laryngoscopy, and bronchoscopy, require additional PPE, inclusive of at least an N95 filtering facepiece respirator and a face shield or a controlled air-purifying respirator, gown, and gloves. Although the Occupational Safety and Health Administration has currently waived the yearly fit testing requirement for filtering facepiece respirators, this testing is necessary if it has not been done recently. The AGPs should be performed with appropriate engineering controls, including negative pressure and increased air exchanges and filtration, allowing appropriate time for air clearance between procedures, as well as donning and doffing of PPE. Scheduling patients' visits must include consideration of PPE as well as air clearance and required intensified sanitization of the room and/or equipment; consideration should be given to limit the number of visits occurring at any given time and to space out participant visits. Environmental sampling for SARS-CoV-2 should be considered to evaluate

exposures and cleaning and disinfection processes. As an example, surface sampling based on World Health Organization<sup>3</sup> or other methods could be considered in potential areas of exposure, including rooms in which AGPs are performed as well as the equipment used for testing. Viral sampling of air in examination and procedure rooms and ultraviolet light decontamination of rooms and surfaces, using routine industrial hygiene techniques, may be considered depending on available resources and expertise.

### *Ensuring Protocol and Data Integrity*

A key principle of clinical research is to ensure protocol and data integrity to maximize the generalizability of clinical trial/study results including the end points, efficacy, and safety of studied interventions. Research goals include timely recruitment, proper adherence to protocol-specified procedures, high retention of participants, and proper statistical analyses to avoid undue loss of statistical power and increased risk of bias due to informative missing data. Fleming et al<sup>4</sup> recently recommended several strategies to protect scientific integrity. These approaches include potentially delaying or pausing enrollment, prespecifying analyses to address effects of the pandemic on trial integrity, and addressing analytical issues, such as missing data, by validated statistical approaches.

**Considerations for Remote Study Visits:** Another consideration is to modify protocols to accomplish study goals without interfering with the spirit of the study. These modifications may involve reconsideration of the necessity for all study visits and procedures. In that regard, one could consider implementing telehealth, home health visits, and smart technology to facilitate clinical research. Before the pandemic, the use of telehealth and home outcome assessment (eg, spirometry, sputum collection, and even patient-reported outcomes) was limited. The rapid deployment of these clinical tools has allowed their application to clinical research studies, and in some cases ensuring the continued conduct of study consent, safety visits and assessments, and collection of outcome measurements. On the basis of the positive reception from trial participants, it is anticipated that, as in clinical care, telehealth and home assessment options will continue to be incorporated into clinical trials subsequent to the pandemic. The standardization of acquisition and reproducibility of home measurements for cross-sectional and longitudinal studies will need to be established. For example, increased variability in home

**TABLE 1 ] Potential Confounders of COVID-19 in Research Study Outcomes**

Potential Confounder	Impacted Measurement
Pandemic stress/anxiety	Quality-of-life instruments
SARS-CoV-2 infection	Lung function; imaging abnormalities; pulmonary exacerbations; measures of exercise tolerance; routine blood work; potentially genomic, epigenetic, immunologic, and other assays
Decreased physical activity resulting from shelter-in-place orders	Lung function, measures of exercise tolerance
Missed clinical or safety visits (exams, laboratory tests)	Increased adverse events, reduced data available for analysis

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

spirometry measurements may lead to the need to increase sample size to maintain adequate study power to detect differences in outcomes. Use of research coordinator telecoaching for the maneuver could improve reproducibility. As another example, collection of a sputum sample at home by the participant could be inadequate, or the sample could be lost in transit, thus increasing the work of study statisticians to account for missing data points. Furthermore, assessment of physical examination findings is limited to those that can be ascertained by observation, and may limit recording of study-related adverse events. On the other hand, use of telehealth for clinical research may increase access to research for potential participants who have previously avoided participation because of time and/or distance from the research site. Sponsors and investigators will need to find the balance between access to study participation and the current limitations of telehealth and accuracy of home outcome measures.

**Reducing Confounding Due to COVID-19:** SARS-CoV-2 infection of subjects needs to be considered as a confounding factor in respiratory disease research, as the infection may mimic or even cause a disease flare in individuals with asthma, COPD, or interstitial lung disease, resulting in persistent symptoms or respiratory abnormalities and thus altering outcomes, including patient-reported outcomes, lung function, exercise, disease course, and radiologic imaging<sup>5,6</sup> (Table 1). The impact on other assays, such as genomic, epigenetic or immunologic assays, and the duration of the impact are unknown, but are likely to occur with the potential for extensive impact on the immune system<sup>7</sup> and need to be considered in analyses. Finally, for multicenter studies, the variance in regional allowance of on-site visits and study procedures will need to be considered and the resulting bias adjusted for in data analysis.

In addition, consideration may be given to modifying the study procedures to minimize risk. For example, if repeated AGPs are required to obtain specimens from bronchoscopy, induced sputum, or nasopharyngeal sampling, limiting the number of these procedures if required over multiple time points, or pairing with blood specimens to allow comparisons and/or allowing studies to substitute collection of specimens with lower risk of viral transmission more frequently, might be an option. Ensuring use of leftover specimens from procedures being done for clinical purposes, and limiting control participant procedures or number, are other possibilities. Processing of the specimens needs to be considered as a risk of exposure to staff, and some centers have used heat or ultraviolet light inactivation of biofluid samples or chemical inactivation (eg, placement of blood, nasal, or bronchial epithelial cells directly into an acid-guanidinium-phenol-based reagent such as TRIzol [Thermo Fisher] or other virus-inactivating medium) for genomic studies to minimize the possibility of viral exposure. Propagation of respiratory epithelial cells collected from a SARS-CoV-2-infected individual in submerged or air-liquid interface culture may result in the generation of high viral titers and should be done under biosafety level-3 conditions. Ideally, participants and/or their cells should be tested for SARS-CoV-2 before propagation of respiratory cells in culture.

## How to Move Forward

### *Guidance From Decision-Making Bodies*

As each clinical research unit contemplates the approach to restarting non-COVID clinical research at its institution, guidelines from national, regional, and local levels should be considered well in advance to allow appropriate preparations to be completed (Fig 1). As described above, CDC<sup>8</sup> recommendations should be considered in establishing return to clinical research

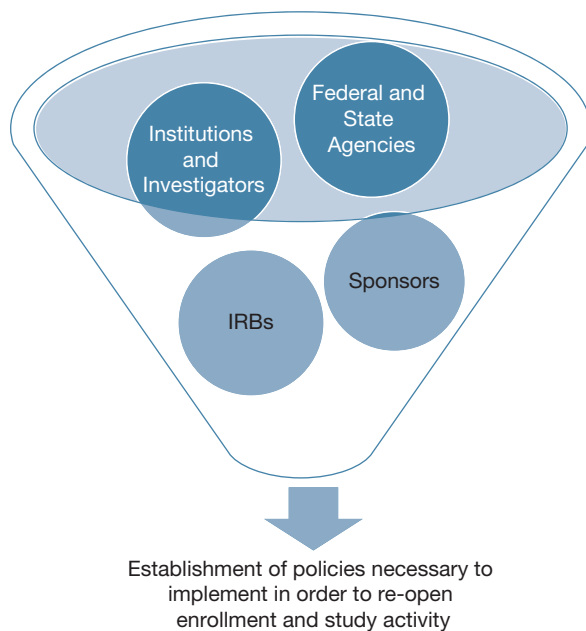


Figure 1 – Guidance from various decision-making bodies will be required to restart research in the setting of the COVID-19 pandemic. COVID-19 = coronavirus disease 2019; IRB = institutional review board.

approaches in the health-care setting and/or other setting.

**Institutional and Local Mandates:** The establishment of crisis standards of care in hospitals (eg, temporary restrictions on elective procedures), as well as at-home isolation orders and travel restrictions for state citizens, are impacted by regional variation in leadership and rates of SARS-CoV-2 infection. Similarly, the rescinding of such mandates is not uniform across the country and must be considered to determine not only when participants may travel to a research site for visits, but also when research sponsors and monitors can begin study initiation and oversight. The interpretation of city/state mandates by each institution will also dictate the revision of pandemic policies that restrict clinical study activity, including the conduct of outcome measures that result from AGPs and require PPE. Changes made to protocols must be passed by local and central institutional review boards/ethics committees as well as granting agencies and/or sponsors as appropriate.

**Federal Guidance:** Both the Food and Drug Administration (FDA) and National Institutes of Health (NIH) have issued publicly available recommendations<sup>9,10</sup> regarding conduct of research in the setting of the COVID-19 pandemic. In the midst of the pandemic, the NIH suggested limitation of study visits to those needed for participant safety or those that

would be coincident with clinical care, to consideration of the conduct of virtual visits, use of local laboratories for safety monitoring, limitation of unnecessary travel, and the cancellation of large gatherings. In acknowledgment of the potential pandemic-related delays in research progress and the incurrence of unanticipated costs, the NIH will allow for project extensions and requests for administrative supplements in some cases.

Similar to the approach of the NIH, FDA guidance has used patient safety as the overarching principle to guide recommendations. Adherence to good clinical practice and minimizing risks to trial integrity are also required. FDA guidance encourages sponsors to work closely with investigators and independent ethics committees to determine in which situations subjects' participation in a trial will continue or be paused. Furthermore, sponsors and investigators are advised to work closely with institutional review boards to address urgent or emergency changes to the protocol or informed consent that resulted from the pandemic, and to prospectively define procedures to prioritize reporting of protocol deviations that may impact participant safety. Necessary protocol modifications that will impact efficacy assessments, data management, and statistical analysis plans should be discussed with the applicable review division. As with all FDA research conduct, documentation of changes and their rationale remains critical during the pandemic, including changes that "impact on the informed consent process, study visits and procedures, data collection, study monitoring, adverse event reporting, and changes in investigator(s), site staff, and/or monitor(s) secondary to travel restrictions, quarantine measures, or COVID-19 illness itself." With the restart of clinical research, reversal of temporary changes must occur and be documented, including updates to study status at [ClinicalTrials.gov](https://ClinicalTrials.gov). Finally, when submitting clinical trial study reports to the FDA, sponsors will need to address the impact of the COVID-19 pandemic on the reported safety and efficacy results.

#### *The National Jewish Health Approach to Staged Reopening*

To restart clinical trials/studies put on hold as a result of the pandemic, and to prepare for the start of new trials, one should consider implementing a multistage, risk-based approach that continues to emphasize participant and staff safety (Table 2). In each stage, one should consider the prepandemic status of the trial (active or in

TABLE 2 ] National Jewish Health Staged Reopening Plan

Reopening Stage	Allowable Clinical Trial Activity	On-Site Visits	Participant Home Location	Allowable Procedures for Research	Factors to Consider Before Moving to Next Stage
During peak of COVID-19 pandemic	<ul style="list-style-type: none"> <li>Active (prepandemic) interventional studies with potential participant benefit</li> <li>Active (prepandemic) observational studies</li> <li>Continue with remote visit options per sponsor/participant desires</li> </ul>	+ <sup>a</sup> + <sup>b</sup>	Local only	<ul style="list-style-type: none"> <li>No aerosol-generating procedures</li> <li>Limit use of PPE</li> </ul>	<ul style="list-style-type: none"> <li>Local prevalence of SARS-CoV-2 infection is stable or decreasing</li> <li>PPE supply <math>\geq</math> 14 d on hand</li> <li>Staff available for visits</li> </ul>
Stage I	<ul style="list-style-type: none"> <li>Active observational studies: Open to new enrollment</li> </ul>	+	Local only	<ul style="list-style-type: none"> <li>No aerosol-generating procedures</li> <li>Limit use of PPE</li> </ul>	<ul style="list-style-type: none"> <li>Local prevalence of SARS-CoV-2 infection is stable or decreasing</li> <li>PPE supply ideally <math>\geq</math> 2-3 mo is on hand or available from supplier and contingency capacity per the CDC</li> </ul>
Stage II	<ul style="list-style-type: none"> <li>Active (prepandemic) interventional studies: Open to new enrollment</li> <li>Sponsor/monitor visits</li> </ul>	+	Local, out of state with negative COVID testing	<ul style="list-style-type: none"> <li>Aerosol-generating procedures (eg, nebulization, induced sputum, MBW, spirometry, NPD, nasal scraping, exhaled NO), negative-pressure room meeting institutional guided minimum air exchange requirements and full PPE required</li> </ul>	<ul style="list-style-type: none"> <li>Local prevalence of SARS-CoV-2 infection is stable or decreasing</li> <li>PPE supply ideally <math>\geq</math> 2-3 mo is on hand or available from supplier and contingency capacity per the CDC</li> <li>Staff available for visits</li> <li>Adequate space for social distancing of returning staff</li> <li>Safe space for specimen processing, eg, biosafety containment container</li> <li>Travel restrictions</li> <li>Availability of negative-pressure rooms</li> <li>Access to validated SARS-CoV-2 testing (participant and environmental)</li> </ul>
Stage III	<ul style="list-style-type: none"> <li>Observational studies: All activity and enrollment open</li> <li>New studies pending activation are open to enrollment</li> </ul>	+	Local and out of state	<ul style="list-style-type: none"> <li>At this stage, we must have the capability to conduct all protocol-required procedures and ensure that available PPE presents no limitations to procedure conduct</li> <li>Bronchoscopy and laryngoscopy (under general anesthesia only)</li> </ul>	<ul style="list-style-type: none"> <li>Local prevalence of SARS-CoV-2 infection is stable or decreasing</li> <li>PPE supply ideally <math>\geq</math> 6 mo is available from supplier and potentially 9-12 mo and at contingency capacity per the CDC</li> <li>Staff available for visits</li> </ul>

(Continued)

**TABLE 2 ] (Continued)**

Reopening Stage	Allowable Clinical Trial Activity	On-Site Visits	Participant Home Location	Allowable Procedures for Research	Factors to Consider Before Moving to Next Stage
Stage IV	<ul style="list-style-type: none"> <li>All studies open to enrollment</li> </ul>	+	Local and out of state		<ul style="list-style-type: none"> <li>Adequate space for social distancing of returning staff</li> <li>Safe space for specimen processing, eg, biosafety containment container</li> <li>Travel restrictions</li> <li>Availability of negative-pressure rooms</li> <li>Access to validated SARS-CoV-2 testing (participant and environmental)</li> </ul>

CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; MBW = multiple breath washout; NO = nitric oxide; NPD = nasal potential difference; PPE = personal protective equipment; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

<sup>a</sup>Per participant choice/sponsor requirement.

<sup>b</sup>If participant on site for scheduled clinical visit.



the study initiation phase), the location of the participant (local vs out of state requiring travel), and most importantly, the procedures that will be associated with the visit. Unlike research in many other fields, respiratory clinical trials often include a large number of potential and known AGPs that are used to measure primary or secondary efficacy and outcomes, including spirometry, induced sputum, nasal potential difference, cardiopulmonary exercise tests, laryngoscopy, and bronchoscopy, among others. As outlined above, the availability of negative-pressure rooms, PPE fit-tested staff, adequate well-ventilated space for social distancing of returning staff, safe specimen-processing areas, disinfection protocols, and availability of PPE must be established before progression to subsequent reopening stages.

To ensure that each of the guiding principles has been considered before restarting clinical research, we created the following checklists:

#### Research participant and staff safety:

- Establish standard operating procedure (SOP) for room and equipment disinfection
- Alert all research participants of new institutional protocols (eg, building entrance screening and temperature monitoring, mask expectations, SARS-CoV-2 testing)
- Alert monitors of new institutional protocols (eg, building entrance screening and temperature monitoring, mask expectations)
- Fit-test staff for N95 masks and educate them regarding appropriate PPE use and doffing/donning
- Communicate regularly with PPE committee regarding availability of equipment
- Perform weekly environmental testing of clinical research area for SARS-CoV-2
- Reconfigure workspaces to ensure social distancing between staff members and between staff and subjects
- Reconfigure clinical research examination rooms to negative-pressure rooms (if air exchange is inadequate)
- Establish guidelines for location of specimen processing based on source (low risk vs known SARS-CoV-2-infected subjects and their body fluids)
- Ensure laboratory processing space meets safety guidelines for processing of biological specimens
- Redesign 6-min walk test area to ensure social distancing between subjects/staff

- Reevaluate study design and ability to use lower risk procedures and/or samples, such as peripheral blood cells vs BAL cells, or change in study time points
- Reconsent subjects (if necessary), based on protocol modifications

#### Protocol integrity:

- Discuss all potential protocol modifications with sponsor, whether federal and/or industry, as well as the institutional review board
- Report any pandemic-related unanticipated events and protocol deviations to the sponsor/institutional review board
- Establish SOP for conducting research telehealth visits
- Establish process for shipping of investigational product, home testing kits (eg, urine, sputum)
- Submit protocol modifications to institutional review board/data monitoring committee/FDA/NIH
- Update [ClinicalTrials.gov](https://clinicaltrials.gov) with protocol modifications/enrollment holds (if indicated)
- Contact sponsor (NIH, foundation, etc.) to establish impact on study funding

#### Flexibility:

- Hold weekly COVID planning/update meetings with research managers and medical director to review local case data, changes in state/federal/institutional guidelines
- Perform a weekly review of environmental testing of clinical research areas by medical director
- Adjust newly established SOPs as indicated by changing case data and state/federal/institutional guidelines
- Create a clear plan for regular communication to investigators regarding the move forward through stages of reopening (or cessation of research based on increased infection rates, lack of PPE and/or testing capabilities)

This year has taught all of us that flexibility and adaptability are critical aspects of navigating the uncertainties caused by the pandemic. Thus, timelines for progressing to the next stage must be adjusted for subject and staff safety, based on successful transition through the previous stage. Successful transition will include objective measurements, such as the absence of positive SARS-CoV-2 environmental testing on the clinical research unit, the absence of COVID-related adverse outcomes in research subjects (eg, positive testing for SARS-CoV-2 after contact with an asymptomatic but subsequently positive member of the research staff), or local outbreaks

of disease in the community. Changes in the availability of adequate PPE could also delay the transition from one stage to the next.

Other considerations moving forward will include the criteria that would lead to another clinical research pause if there is a substantial resurgence of SARS-CoV-2 infections. This may include rates of COVID-19-positive infections, hospital and ICU capacity, availability of PPE, participant willingness to continue to be involved in research, and movement to crisis standards of care, to name a few. These measures should be discussed and outlined ahead of time so that reversion to a prior stage or staying at a current stage can be clear and transparent for staff and participants. This pandemic has taught us that, in addition to considering SARS-CoV-2 infection, we may also need to more closely scrutinize the impact of confounding by other respiratory viruses and infections in many of our vulnerable patient populations as the “cold and flu season” comes upon us.

## Case Resolution

For the subject to remain in the study and continue in the open-label arm, the sponsor was contacted to discuss and approve the plan to obtain the minimum required safety tests (urine pregnancy test, complete metabolic panel, and CBC) at the subject’s home, to conduct consent by telephone, and to ship the investigational product to the subject’s home. The sponsor reviewed FDA COVID-19 guidelines<sup>8</sup> and submitted the necessary changes to the central institutional review board. At the time of the subsequent scheduled follow-up safety visit, telehealth was in place. Therefore, rather than an on-site visit, the subject accepted the option of a study visit with the research coordinator via telehealth to review adverse events and complete quality of life questionnaires, with a separate home nurse visit for acquisition of safety laboratory values. After the sponsor was notified that research spirometry could not be performed per institutional policy, the subject was provided with a home spirometer from the sponsor. If the performance of aerosol-generating procedures is allowed at the time of her next scheduled safety visit, the subject will be given the option of a remote visit, with blood draw and home spirometry, or an on-site visit with spirometry performed in office or at home before the visit. Throughout the subject’s participation in clinical research during the pandemic, she expressed her appreciation for the opportunity to continue in the study from which she believed she was benefiting,

with minimal risk of exposure to infection with SARS-CoV-2.

## Conclusions

To summarize, although the world has appropriately focused on combating COVID-19 for the last several months, we are now shifting our focus to the resumption of clinical care and clinical research under new circumstances. The main priority in clinical research conduct should continue to be the safety of participants, while also considering the safety of staff and data integrity of trials. Flexibility, creativity, vigilance, and resilience will be critical aspects of restoring and reinventing clinical research participation, and of designing and conducting future trials.

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