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Restarting Human Participant Research at Community-based Observational Studies during the COVID-19 Pandemic

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**Abstract**

At the onset of the Coronavirus Disease 2019 (COVID-19) pandemic, just as public institutions and businesses closed, research programs performing human participant research (HPR) also largely ceased operations. With the partial ebbing of the pandemic in some areas, universities and healthcare organizations conducting HPR are considering reopening. Whereas guidelines from governmental authorities and medical specialty societies currently exist to help restarting health services and resuming clinical trials, no clear guidance is available to aid resumption of HPR at community-based observational cohort studies. Indefinite stoppage of observational research at cohort studies carries many drawbacks and its safe resumption is important and feasible. In this narrative review, we describe a potential path forward for safely reopening community-based observational studies, drawing on scientific knowledge and best practices from a variety of medical and lay sources. We highlight current recommendations regarding pandemic status assessment and the metrics useful for guiding decisions regarding safe reopening/reclosing and for screening and surveillance of COVID-19 among employees and participants. We synthesize insights from contemporary literature regarding infection prevention and environmental safety into a set of easy to operationalize plans for restructuring HPR. And lastly, we suggest ways in which observational studies can potentially aid the efforts to characterize the pandemic.

**Key Words:** community-based cohort studies, observational research, COVID-19 pandemic, infection control, environmental safety, reopening
The Coronavirus Disease 2019 (COVID-19) pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) agent has resulted in unprecedented disruptions to life as usual, including the conduct of biomedical research. Of particular concern is research involving human participants, where the benefit to society from the continuation of research has to be weighed against the risk to research participants and staff/investigators (of exposure to SARS-CoV-2) from their participation. Universities and health systems that conduct human participant research (HPR) have adopted institution-specific approaches to reopening research programs, including prioritization of research activities based on potential direct benefit to the participants.\(^1\)\(^-\)\(^5\) In these prioritization schema, observational studies and other epidemiological research have been held to be of low priority owing to perceived lack of benefit to the participant,\(^6\)\(^-\)\(^8\) while entailing SARS-CoV-2 infection risk. Prioritizing participant risk in the conduct of scientific research is consistent with the ethics of HPR in which “non-malfeasance” is a paramount core value. However, there are currently no clear guidelines available to aid reopening observational studies while ensuring the safety of participants.
Whereas the argument that individuals can gain some benefit from their participation in therapeutic clinical trials carries salience, it is usually considered that no direct and/or immediate benefit accrues to participants in observational research studies.\textsuperscript{9} However, by quantifying chronic disease burden, elucidating risk factors, delineating natural history and evaluating the life course effects of chronic disease, observational research has its own unique contribution to a robust understanding of human health and disease. Indefinite stoppage of observational research also carries harms to society and the research enterprise in terms of new knowledge not generated and research programs that may fail, leading to wasted resources and unrealized gains.

We believe continuation of community-based observational studies (COS) while preserving staff and participant safety is an important and achievable goal. Recent reports indicate that risk for viral transmission is lower in healthcare settings compared with the community, suggesting that proper disinfection procedures and appropriate usage of personal protection equipment markedly reduce the risk of SARS-CoV-2 transmission.\textsuperscript{10} In addition, COS can serve as sentinel sites in an infectious disease pandemic setting, and COVID-19-related testing in their participants can provide community level information regarding the current ongoing pandemic. Such testing can also help characterize the SARS-CoV-2 infection and immunity status of participants and may indirectly benefit them.

In this report, we propose a potential pathway for safe reopening of COS and conduct of HPR in the context of an infectious disease pandemic. The key goal is minimization of SARS-CoV-2 infection risk to participants and staff/investigators, while allowing high quality data acquisition to the maximum extent possible. We describe a phased progression (composed of six distinct
phases) in the reopening of these studies. We highlight metrics that can aid decisions regarding opening/closing research programs, best practices that can aid the safe conduct of interactions with study participant, suggest measures to mitigate participant risk and creative ways to repurpose HPR at cohort studies to aid the pandemic control effort itself.

**Decision phase**

The decision as to if/when COS should reopen will be based on a complex set of considerations. Besides paying heed to recommendations national organizations (such as Centers for Disease Control and Prevention [CDC] and Occupational Safety and Health Administration [OSHA]), any mandates regarding reopening from state and local governments have to be considered because epidemics have local dynamic characteristics. In addition, many epidemiological studies either operate under the administrative oversight of a parent university or are affiliated with one or more institutions. The operational requirements recommended by the parent institution and the related review boards (IRB) must be taken into account. If there are no outright prohibitions to reopening, then the studies can reopen in a manner consistent with staff and participant safety and confirming to recommendations from state and local authorities and governing institutions.

When determining the likely risk to either participant or staff for contracting SARS-CoV-2 (because of HPR resumption), the community burden of disease and the rapidity of viral spread in the geospatial location of the study and proximity to a healthcare facility must be assessed. The capacity of the local healthcare system to evaluate and care for possible COVID-19 patients...
is also important. In their guidance for all organizations to aid reopening, the CDC has recommended several metrics (“gating criteria”; Table 1). These criteria can be used/adapted to aid the decision to reopen or reclose COS. The criteria should be evaluated using rolling averages (Table 1) over a 14-day period to assess downtrends and facilitate reopening, and over a 5-day period of increase to trigger ramp-down and reclosing decisions. In addition, participants in some COS are geographically dispersed. In such cases, the metrics for the community where the participant resides are relevant, as the risk of the participant becoming a source of infection to study staff needs to be considered carefully. There is also a risk to participant from exposure during long-distance travel. A step-by-step approach to assess these risks is presented below (reopening phase). Details regarding how to evaluate these metrics and decide on safe reopening have been published by the CDC in the document “CDC Activities and Initiatives Supporting the COVID-19 Response and the President’s Plan for Opening America Up Again”.

**Preparation phase**

Physical distancing, personal and workspace hygiene, cleaning and disinfection of equipment and premises, air sanitization, and use of protective equipment are mandatory elements that need to be addressed prior to reopening. To achieve these standards the study will require (a) reviewing and re-engineering the study processes that involve human subject interactions (b) renovating the facility to aid adherence to safety guidelines (such as physical distancing, sanitization etc.) (c) acquire the equipment to mitigate SARS-CoV-2 transmission and (d) educating the study staff and appraising the participants of the new policies and procedures.
A variety of changes to the physical building are necessary to make it safer for staff and participants during the pandemic and reduce the likelihood of SARS-CoV-2 pandemic. The layout of the facility itself can be reconfigured to reduce the frequency of interpersonal interactions. Modular facilities, where the layout allows separate entry and exit to different parts of the study building that perform different types of tests, can help minimize breadth of exposure, limit closures to that area in case of suspected SARS-CoV-2 exposure and aid employees in maintaining physical distancing. In addition, this will facilitate partial isolation of personnel interacting directly with the study participants from those who are performing other administrative functions. This minimizes the number of staff who are at risk for exposure and number of staff the participant comes into contact with.

A variety of strategies for air sanitization have been recommended to reduce risk of airborne viral transmission. Installing high-efficiency particulate air filters is an important minimum step. Increasing ventilation rates in the work environment will enhance the volume of oxygen/outdoor air mixing, an important method to provide added air clearance. Also creating a laminar airflow in as many study areas as possible will reduce the likelihood of airborne infection. Specialized negative pressure ventilation in some settings, such as for aerosol generating procedures, may be necessary. Installation of ultraviolet disinfectant equipment and/or other airborne disinfection equipment will aid sterilization of air and exposed surfaces.
All aspects of the facility that the participant or staff will likely use (e.g., water faucets, trash cans) should be changed to facilitate “no touch” operation. Wherever possible, all doors should be automatic (with air dams as necessary) as doors handles are high touch surfaces. There are also “digital identity” signal technologies available to allow a user to unlock doors, use elevators etc. without touching. Facilities will also require posting of signage regarding hand hygiene, physical distancing and mask/protective gear wearing so that both participants and staff are reminded of these important measures. Hand sanitizer dispensers should be installed at all entry and exit points of the rooms, corridors, and the facility itself. Distance markers should be placed at all areas where participants and staff might have to intermingle to aid in physical distancing. Seating/waiting areas have to be rearranged to ensure requisite spacing between people.

Staff should have dedicated workstations wherever possible. Installing physical barriers, such as clear plastic sneeze guards can help facilitate aerosol exposure protections at institutions with open-floor organization of workspaces. If resources necessitate shared workspace(s), staff scheduling can be rotated such that no two people use the same workspace on the same day, thus providing the opportunity for cleaning and disinfection in between. Interactions between staff and participants that require documentation (e.g., obtaining informed consent for study procedures) should be done with cleanable interfaces (e.g., tablet or laptop computers) instead of using paper and pens/pencils (or use disposables). The COS has to establish a robust and secure video conferencing infrastructure to perform those aspects of research that do not require an in-person presence.
And lastly, there should be a designated quarantine area, in case either a participant or staff member is deemed to be manifesting clinical features suspicious for COVID-19 after they arrive on the premises.

Infrastructure and Engineering – Equipment

The availability and proper use of personal protection equipment (PPE) is an important factor in reducing the risk of SARS-CoV-2 transmission. Staff will need masks, gowns, gloves, shoulder/neck covers and eye protection (e.g., face shields or goggles). Participants will need at least masks and depending on the nature of the particular research examination, other PPE.

“Double masking” (both participant and staff wear a mask) with simple surgical masks may suffice for most situations. Indeed, a systematic review of the literature in The Lancet concluded that for the general public, “face masks are associated with protection, even in non-health-care settings, with either disposable surgical masks or reusable 12–16-layer cotton ones.” The review also backed the use of eye protection, physical distancing, and hand hygiene, among other measures, and cautioned that masks alone do not fully supplant the benefits of these other precautions. Additional PPE, such as additional barrier protection (face shields, goggles, gowns and neck coverings) or more advanced respiratory protection (N95 respirators, N/R/P100 filtering facepiece respirators, an air-purifying elastomeric [e.g., half-face or full-face] respirator with appropriate filters or cartridges, powered air purifying respirator [PAPR] with high-efficiency particulate air filter; or supplied air respirator [SAR]) may be necessary for staff who have to engage in high proximity contact with participants or for specialized aerosol generating procedures. Given possible supply chain disruptions and shortages that cannot be
predicted, an entire examination cycle’s worth of PPE should be purchased up front, or alternate
supply chains for critical goods and services should be identified.\textsuperscript{17,32} In addition, partitions,
cleaning and disinfectant supplies, easily cleanable electronic devices for staff-participant
interaction should be readily available.

\textit{Administrative Reorganization - Operational Procedures}

A thorough review of the normal operating procedures should be performed to assess viral
transmission risk associated with each research activity. Research visits to COS are typically
organized into a set of discrete tasks or “test stations” with each station accomplishing a
particular activity such as taking a health history and doing a physical examination or performing
a noninvasive procedure (e.g., an echocardiogram). These activities can be classified into those
that can be remotely accomplished and those that require an in-person visit. For those elements
of the research program that require an in-person visit, the operating procedures can be reviewed
and modified to reduce the risk of exposure and virus transmission to both participant and staff.
Portions of the research evaluation that involve higher transmission risk such as high proximity
interactions\textsuperscript{34} (\(\geq 15\) minutes continuous contact between participant and staff member within 6
feet distance, or any closed room) or those that generate aerosol, should be reconfigured to
minimize risk as much as possible. Additional guidelines on occupancy and physical spacing
include:\textsuperscript{35}

- Limit to no more than 50\% of the building’s maximum permitted occupancy as
documented in its occupancy permit on record with the municipal building department or
other municipal record holder.
Buildings for which no permitted occupancy limitation is on record may allow 10 persons (including staff) per 1,000 square feet of accessible space.

No enclosed space within the building may exceed occupancy of 10 persons per 1,000 square feet.

All occupancy counts and calculations shall include customers, staff, and other workers.

Clear guidance should be developed regarding cleaning equipment and surfaces between participants, use of protective equipment, appropriate rooms/locations for each station to leverage airflow characteristics to mitigate risk, signage such as unidirectional passages, etc. And lastly, a protocol should be developed for (a) informing participants, their healthcare providers and their local public health authorities; and (b) isolation and contact tracing of study personnel; if within 14 days after a visit a participant and/or staff members they interacted with are found to be SARS-CoV-2 positive or have COVID-19.

Administrative Reorganization – Staff Assessment and Training

Each COS needs to develop a plan to minimize risk to staff from exposure to SARS-COV-2 from participants. As a first step, all staff will need to be screened for health conditions that put them at high risk for contracting the virus or having poor outcomes from the resulting disease. These staff can be assigned tasks that do not require direct contact with participants and/or close contact with other staff. Second, staff will need education and training on equipment and workspace cleaning, self-sanitation practices, respiratory etiquette, donning and doffing of PPE and guidance regarding physical distancing practices. They will need procedures for handling
material participants may bring to the study (e.g., health records in paper form or electronic media) Custodial staff have to be provided guidance on how to clean and sanitize areas that participants use such as changing rooms, storage spaces and or lockers etc. OSHA mandated policies and procedures that typically govern spillage of biospecimens may be adapted to include measures to eradicate SARS-CoV-2. Providing staff with a basic overview of SARS-CoV-2 and COVID-19 are also desirable. In addition, they will need focused education regarding policies and procedures, that have been developed specific to their institutions.

Management and Communications

Staff should have an assigned “point person” (COVID coordinator) available who they can contact for any questions and concerns regarding COVID-19 related issues. There should be a clearly established communication mechanism (periodic email or newsletter or virtual “townhall” style meetings) to keep the staff appraised of status of the operations during the pandemic and ongoing changes to study structure and procedures. Apart from the COVID coordinator, it would be desirable to have a designated person in charge of each aspect of pandemic related restructuring (e.g. facility changes, operating procedure restructuring, scheduling, and participant communication etc.). And lastly, there should be a designated liaison to communicate and coordinate with relevant institutional review boards regarding changes to research protocol and address and participant safety enquiries they may have.
Participant Engagement, Evaluation and Education

To aid reopening of HPR in a safe, effective, and transparent manner, the COS should strive to:

“Evaluate” participants’ individual risks and take appropriate actions to mitigate them.

‘Educate” participants regarding COVID-19 risks and the strategies COS are adopting for safe conduct of HPR

“Engage” participants in a mutual dialogue, solicit feedback and incorporate this knowledge in reengineering research processes.

The general public is bombarded by information from a variety of media sources regarding the risks of contracting SARS-CoV-2 associated with travel, common items, types of person-to-person interactions etc. They may be understandably reluctant to participate in HPR during the pandemic and may have many questions on how they can ensure their personal safety. We believe it is very important to not place the onus of acquiring this information on them and provide them clear guidance to help them travel to/from the study site and how to conduct themselves while they are there. In addition, the participants have to be screened and evaluated in terms of the risk they pose to staff if they have the disease or are asymptomatic carriers.  

Early in the reopening process, as much of the research evaluation as can be feasibly done via videoconference, should be accomplished prior their arrival for an in-person encounter. In addition, rapidly developing new technologies are allowing “tele-examinations” where-in certain portions of the physical examination (e.g. jugular venous distension assessment) can also be
accomplished via tele-visits.\textsuperscript{39} Several commercial videoconferencing platforms currently available\textsuperscript{40} enable clinical telehealth visits and are compliant with regulations regarding privacy protection (e.g. Health Insurance Portability and Accountability Act). A recent study also demonstrated feasibility of “e-consenting” i.e. obtaining informed consent remotely.\textsuperscript{41} As reopening progresses, “hybrid examinations” where certain portions are designated for face-to-face encounters and other for remote evaluations will become the norm. The time intervals between in-person and teleconference portions of the research examination should be as short as possible. A step-by-step example of how a hybrid examination involving face-to-face interactions and teleconferencing, or remote visit alone, is provided in Figure 1.

To mitigate risk of transmission from participant to staff (or other participants who visit the study campus at the same time), a symptom screen should be administered at the time of scheduling and on the morning of the scheduled visit. If they exhibit symptoms suspicious for COVID-19 on either screen, they should not visit the study. Additional information, like vital signs can also be considered provided the participants have the equipment to measure them, or appropriate equipment is mailed out to them a priori. To facilitate such data gathering, and to help participants safely make a visit to the study site, we recommend a “pandemic protection pack” (Table 2) that can be mailed to them ahead of time. This package will organize all the things necessary for them to safely visit the study center and easily comply with the new requirements.

Participants should be consented a priori to (a) inform the COS if they develop symptoms suspicious for or test positive for COVID; (b) facilitate informing their local department of

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public if they are exposed to a staff member who later develops COVID. And finally, several simulated “test runs” of a participant visit to the study site can help fine tune the new procedures and reveal any problems, before the research facility reopens.

**Reopening phase**

Prior to restarting in-person participant visits, the COS should consider having all staff tested at least once for SARS-COV-2. This could be either with a nasal-swab for viral ribonucleic acid (RNA) detection, blood sampling for antibody testing, or preferably both, to establish a “baseline” COVID-19 status for all employees. After that, all staff should perform daily self-assessment with COVID-19 symptom questionnaire and temperature check before coming to the study site.\(^{42}\) If any symptoms are present or they have a fever, they should not come to the study site, irrespective of potential alternate explanations for the manifestations (e.g., the clinical syndrome is more consistent with a common upper respiratory infection, influenza etc.).

All aspects of participant evaluation that can be accomplished remotely (i.e. via teleconference, mobile/remote sensing technologies etc.) should be completed prior to an in-person visit. The study will initially schedule participant visits in a non-overlapping fashion i.e. no two participants will be on site at the same time. During this phase, studies can also consider alternate day scheduling, as they can continuously debrief staff and iteratively learn about any inefficiencies in the new procedures that become evident once they are executed.
Risk for SARS-CoV-2 transmission during HPR can be conceptualized into the following components.

1. Risk to the participant during travel to and from the study site.
2. Risk to the participant from interactions with the study personnel.
3. Risk to the participant from interactions with other participants during the study visit.
4. Risk to the staff of SARS-CoV-2 transmission from participants to staff.
5. Risk of staff to staff SARS-CoV-2 transmission.

These risks can be largely mitigated by the use of PPE and disinfection procedures.\textsuperscript{30,31} Education of participants regarding measures to mitigate travel risks will also help. If funding permits, all participants can be tested for SARS-CoV-2 when they arrive on site. Current rapid throughput technologies allow results under an hour.\textsuperscript{43} The combination of a negative symptom screen and a negative viral RNA test will have a high negative predictive value for presence of infection.\textsuperscript{44}

In addition, participants can be scheduled in an order of priority that minimizes risk of COVID-19 to both them and the staff.\textsuperscript{45} The risk stratification process should include the following aspects.

1. Participant location assessment: Is participant living in a high prevalence/transmission area?
   Participants living in a low prevalence area (stable county prevalence of less than 10/100000 cases for 2 weeks) OR areas with improving COVID-19 metrics (prevalence 0.5% plus
continuously decreasing gating criteria for 2 weeks) will be invited initially, with ramp up/down based on each subsequent period of 2 week improvement (for ramp-up) or 5 day worsening (for ramp-down) of CDC gating criteria,\textsuperscript{14} assessed as described above and in Table 1.

2. Participant assessment
Participant risk of contracting virus (e.g. owing to occupational exposure; Figure 2)\textsuperscript{18} and risk of poor outcomes from disease (co-morbidities)

3. Household assessment
Nuclear family vs. extended family vs. multigenerational household (crowded living conditions pose increased risk for SARS-COV-2 transmission; in addition, infection acquired during travel/study site visit will be taken back to a large family).\textsuperscript{46}

4. Travel risk\textsuperscript{15,16}
Can participant drive to the study site vs. has to fly there or use other forms of public transportation?

After assessment based on the above factors, the study can then prioritize least risk participants for the initial phase of reopening. We suggest a schema to assess “risk levels” as follows:

Least risk = age < 65 years and no high-risk comorbidities + low risk occupation + lives in a nuclear household + can drive to the study site.
Low risk = age < 65 years and no high-risk comorbidities; any one of either moderate risk occupation or need for public transportation or living in a larger household

Moderate risk = age < 65 years and no high-risk comorbidities; any combination of moderate-to-high-risk occupation or public transportation usage or larger household size

High-risk = age > 65 years and/or comorbidities that will put the participant at risk for poor outcomes if SARS-CoV-2 is contracted OR is very high-risk occupation; temporarily defer in-person visit.

A separate check in area with laminar airflow\textsuperscript{22} can be created where participants can complete the formalities for initiating their in-person visit. This is also where COVID-19 screening and testing can be done, and PPE provided to participants before they enter the rest of the study site.

**Ramp-up phase**

As the pandemic abates, the pace and scope of in-person interactions can increase. The number of participants who can be accommodated on any given day can be steadily increased to approximate pre-pandemic levels. This phase would also involve ongoing debriefing of front-end staff to identify any problems with the new policies and procedures instituted as part of adaptation to the current pandemic and correct them accordingly.

To ensure the safety of participants and staff and also provide reassurance to them that the maximum possible risk mitigation efforts are being undertaken, we recommend a proactive surveillance approach. Such a surveillance plan can be initiated and formalized during this phase.
as other immediate considerations due to the pandemic are ebbing. Participants should receive a follow-up phone call at 7 days post visit or 14 days post visit (or both) to screen for symptoms or any intercurrent testing for COVID-19. If any participant went on to develop a clinical syndrome suspicious for COVID-19 or has tested positive for SARS-CoV-2 within 14 days, the procedures for reporting to the relevant authorities, and for contact tracing within the study itself can be initiated. Although this may seem burdensome in terms of staff time and effort and administrative workload, it will ensure the participant and employee safety, and instill confidence that HPR is being continued in a responsible manner.

Similarly, ongoing surveillance of staff will allow early detection of any exposure of a participant to staff who are under investigation for COVID-19. The participant, their primary care physician and their local department of public health have to be informed right away. In addition to triggering the in-house contact tracing protocol, the staff member will be advised to get tested for SARS-COV-2 and be required to self-quarantine until test results become available (and are negative) or for 2 weeks if they test positive.

It is noteworthy that the ramp-up will not be to the maximum participants accommodated per day pre-pandemic, but to the maximum that can be accommodated, keeping in mind the occupancy and physical distancing requirement. Thus floor area, number of examination stations, duration of the research visit and number of staff necessary to complete the examination will all have to be taken into account to calculate the “new maximum” of participants per day which will be the goal for the ramp-up. Each COS will have to evaluate these factors to determine their individual target number. If the COS location has achieved either six periods of continuously improving gating criteria, or 2 periods of low stable prevalence, the number of participants can return to the
previous maximum. Similarly, if the pandemic worsens (as determined by worsening gating criteria as a rolling average over a 5-day period) or if guidance from CDC or OSHA change regarding occupancy and physical distance requirements, COS should have a plan in place for a commensurate “ramp-down” of operations. If gating criteria worsen for three consecutive 5-day periods, then COS should re-close.

“New normal” phase

Challenging times often create opportunities for reimagining the way we normally conduct life and research is no exception. Just as the COVID-19 pandemic opened up the opportunity to realize the promise of “Telehealth”, the processes of HPR can be reinvented. Many aspects of research conducted at COS, such as questionnaire administration, history taking etc. can just as well be done remotely via teleconferencing, without any loss of data-collection fidelity.

In addition, advances in remote monitoring technology and “M-health” (mobile phone-based healthcare applications) platforms can be repurposed to obtain portions of data that previously were collected in person. This reduces the time spent by a participant during in-person visits thus reducing fatigue, amount of time required to stay fasting for certain tests etc. It also reduces their exposure time to study staff, and vice versa. Disaggregating the research visit into a combination of in-person visit, and one or more virtual sessions (taking care to minimize time-gap between them and attendant biases in data) will help maintain on-going engagement with participants. In addition, participant preferences for virtual versus in-person evaluations can be incorporated in the structure of the revised study examinations, striving to create a “right mix”
that will serve to preserve participant safety and data integrity. Cumulatively, these measures may help develop a better “participant-study relationship” (akin to a doctor-patient relationship) and reduce loss to follow-up.

We acknowledge that there are potential disadvantages to HPR performed without any in-person interactions at all. Non-verbal communication is an important aspect both in the data gathering and trust building aspects of HPR and even videoconferencing is not an adequate substitute for human interaction. In our experience, many participants anticipate and enjoy the social interactions with the study staff and each visit to the COS constitutes a distinct “memory”, an important element that decreases loss to follow-up. The altruistic impulse that motivates participation in HPR may not be adequately “emotionally rewarded” when research interactions seem remote and depersonalized. We believe these disadvantages can be overcome by carefully crafting a mix of remote and face-to-face interactions that simultaneously preserve the participant experience, ensure safety and reduce the burdens of volunteering for HPR. As we note above, engagement with the participants themselves is key in creating such a win-win situation. Whereas some aspects of pandemic related changes (like PPE use, disinfection procedures, distancing guidelines) can eventually return to pre-pandemic behavior, it may be advantageous to maintain the well-crafted new structural elements indefinitely. We, therefore, term this “new normal” as we do not see any compelling reason why COS should completely revert to the “old normal”. The “new normal” can and should be better.

Thus, this phase (during the tail end of the pandemic) is about on-going assessment of changes made to the conduct of research at COS during the pandemic, gather lessons learned regarding
what worked well and what did not, and work towards creating a new and improved research process that will become permanent. Many of the restrictions on in-person interactions between staff, investigators etc. can be relaxed. Rotating telework policies can also be consolidated to provide staff with the ease of working from home, while allowing for intermittent workplace interaction that can facilitate the advantages of working together. Teleworking infrastructure developed during the pandemic can also be repurposed to help remotely located investigators collaborate with in-study scientists, and thus increase the utilization of study data and improve scientific productivity.

Vigilance phase

Even with the establishment of a new normal, a portion of HPR will still be conducted face to face. In this phase (“inter-pandemic” [between this pandemic and a future one] or post-pandemic period), COS will proceed with research at full capacity, while continuously monitoring for a recrudescence of COVID-19.

An intriguing possibility will be the use of COS themselves as avenues for monitoring the infectious disease pandemic. As screening questionnaires will be administered to participants to determine the safety of research visits, these data can be used to assess the incidence and prevalence of COVID-like illness in the community. If studies chose to perform SARS-CoV-2 RNA tests or serologies on participants, the prevalence of asymptomatic SARS-COV-2, prevalence of COVID-19 and prevalence of seropositive individuals can be determined. If
antibodies are subsequently deemed to provide durable protection (an unknown at the moment) it will help determine the status of “herd immunity” in the community.

And lastly, COS can potentially serve as sentinel or early warning sites. Currently a variety of infectious disease-specific surveillance systems are available. In addition, the CDC and World Health Organization monitor several syndromic passive surveillance networks. However, to detect a new infectious epidemic, a syndromic active surveillance system may be desirable. Most infectious disease epidemics stem from airborne or water borne illnesses. It is conceivable that a generic questionnaire can be created for common such symptoms that occur in time-limited fashion. Such a screening for “Acute Limited Illness without Diagnosis” (ALID) can potentially serve as an advance warning system for a newly emerging infectious disease pandemic. (e.g. COVID-19 was an acute respiratory illness which was self-limited in most patients but was only realized to be a new epidemic when a cluster of hospitalizations came to the attention of public health officials in Wuhan; it is conceivable that a community-based ALID screening system could have alerted physicians and healthcare authorities about an emerging epidemic earlier). COS also typically have stored bio-samples, so testing samples banked prior to the detection of an epidemic via clinical syndromes may help identify the true “left end” of the pandemic curve. The questionnaires can also be potentially standardized across multiple COS, adding increased power to the detection efforts. A “Cross-cohort Collaboration Consortium” already exists to facilitate chronic disease epidemiology; this can serve as a template of collaboration to develop and maintain an ALID surveillance system.
We acknowledge that what we suggest is not a proven method and analogous attempts may have been made in the past without success. The suggested framework warrants additional discussions among public health experts engaged in infectious disease surveillance to assess its feasibility, potential utility (or lack thereof) and limitations. Such discussions could guide informed decisions regarding whether an ALID surveillance system based at COS is truly worthwhile.

Conclusions

COS and affiliated investigators rightly recognize that the COVID-19 pandemic poses health risks to participants of HPR. However, we submit that it also provides the opportunity to rethink and reconfigure the conduct of observational research. With thoughtfully redesigned research policies and procedures and a cautious approach to reopening, it is possible to resume this important research while simultaneously mitigating risk to participants and staff. The breadth and depth of changes required for safe conduct of HPR during the pandemic may initially seem daunting, but we believe they can be implemented successfully. Our suggested approach can be a potential path forward not just for current resumption of COS, but also reengineer them to improve research participant experience and cope with possible future infectious disease pandemics.

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Table 1. CDC recommended COVID-19 pandemic evaluation criteria to aid reopening of institutions.

|   |   |
|---|---|
| 1. | Downward trajectory for influenza-like illness (ILI) |
| 2. | Downward trajectory for COVID-19-like illness (CLI) |
| 3. | Downward trajectory for documented COVID-19 cases |
| 4. | Downward trajectory of positive tests as a percentage of total tests for SARS-CoV-2 |
| 5. | Adequate ability of local hospitals to treat patients without crisis care |
| 6. | A robust testing program for SARS-CoV-2 is in place |

*To assess a downward trajectory, CDC recommends a 3-day rolling average and applying a spline curve. A period of 14 days of declining cases occurs when fewer cases are reported at the end of the 14 days compared with the number at the beginning of the period, using the 3-day rolling average fitted with the spline curve to define the number of cases. In addition, a "grace period" of 5 days may be applied during a downward trajectory, during which cases may increase for no more than 5 consecutive days.**

** The four disease occurrence gating indicators (1-4) should be interpreted collectively to reach a determination on the trajectory of COVID-19 activity within a jurisdiction, bearing in mind that the measures differ significantly in their lag, specificity, and sensitivity. Laboratory testing and syndromic data sources generally have less lag than COVID-19 case report data relative to when transmission occurred. SARS-CoV-2 testing, and COVID-19 case reports are more specific measures of COVID-19 activity than the CLI syndrome.

CDC - Centers for Disease Control and Prevention; COVID-19 – Coronavirus Disease 2019; SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2
Table 2. Pandemic protection pack to prepare participants for in-person visit.

|   |                                                                 |
|---|-----------------------------------------------------------------|
| 1 | Mask                                                            |
| 2 | Sanitizer lotion or solution                                    |
| 3 | Gloves                                                          |
| 4 | Face shield                                                     |
| 5 | Touchless thermometer                                           |
| 6 | Pulse oximeter                                                  |
| 7 | A short video of study activities to ensure participant protection |
| 8 | CDC travel guidelines in print or electronic media              |
| 9 | Small installable camera to facilitate video conferencing from participants’ home if they do not already have such equipment |
|10 | A list of symptoms and signs they should monitor for in the 2 weeks preceding their visit and guidance on how to reach the study if they occur. |

CDC - Centers for Disease Control and Prevention
Figure Legends:

Figure 1. Example of a step-by-step approach to structuring research evaluations during the pandemic.

Figure 2. Occupational exposure risk categories as designated by the Occupational Safety and Health Administration.
Evaluate participant to assess safety and feasibility of in-person visit

In person visit safe & feasible

- Visit is scheduled on a date convenient for participant
- Within 2 weeks prior to visit, “pre-televisit” (a) screen for COVID-19 symptoms; (b) complete some elements of research evaluation
- Morning of visit, screen for COVID-19 symptoms OR test for SARS-CoV-2
- In-person visit for research examination

In person visit not safe & feasible

- Schedule teleconference for (a) health history (b) any research questionnaires
- During tele-visit, assess participant willingness/ability to provide objective data/samples with mailed equipment (e.g. vital signs, anthropometric measures, ECG, blood-spot testing, buccal swabs, urine samples etc.)
- If participant willing and able, mail biosample collection and telemonitoring equipment to participant
- Schedule 2nd tele-visit to occur after equipment arrives
- Participant education/coaching on equipment use to complete desired tasks. Depending on type of data, participant can directly read out measurements during tele-visit; samples will be mailed back
No contact with known/suspected SARS-CoV-2 infected people AND

No frequent close contact with (i.e., within 6 feet of) the general public

e.g.: Administrative staff without front-end duties.

Frequent and/or close contact (i.e., within 6 feet of) with people who may be infected with SARS-CoV-2, but who are not known or suspected COVID-19 patients.

e.g.: workers in travel industry, food industry workers, retail sales etc.

High potential for exposure to known or suspected COVID-19 cases

e.g.: Healthcare delivery staff; medical transport workers; mortuary workers

Exposure in special settings

e.g.: Physicians performing invasive procedures (intubation, bronchoscopy etc.)
Healthcare workers handling biospecimens from known/suspected COVID-19 cases; morgue employees handling bodies of people with known/suspected SARS-CoV-2 infection.