COVID SAFE 2.0
COVID-19 Screening Program
Study Protocol

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1. Abstract

In view of the recent COVID surge and difficulties in obtaining testing, we aim to increase Point of Care (POC) testing, whereby University of Pennsylvania (Penn) faculty, staff, and trainees who are working in person at Perelman School of Medicine (PSOM) laboratories can self-test. The purpose of this study is to evaluate the implementation of this POC testing program. We will not be collecting any samples as part of this study. This will ensure that individuals can rapidly identify if they have COVID-19 while balancing use, acceptability, appropriateness, and feasibility. We will start with a pilot phase whereby we will evaluate the implementation of a POC version of COVID-19 screening program that will coordinate several existing systems at the University of Pennsylvania including voluntary, self-administered saliva-based viral testing. We will pilot this program to a small cohort of PSOM labs and then test implementation of the self-testing of the POC version of COVID-19 screening across all PSOM labs for those who wish to participate. All results will be self-reported and will not be used to validate any tests or support any future approval from the FDA. No data from this study will go into the participants' EMR.

2. Overall objectives

The primary objective of the study is to evaluate the use, acceptability, appropriateness, and feasibility of implementing a voluntary COVID-19 Point of Care (POC) screening program with Penn faculty, staff, and trainees that uses saliva-based self-collection followed by testing in their own PSOM laboratories. A secondary objective is to learn about self-reported test results, program usability, user burden, participant experience, program ease, program continuation and availability. Another secondary objective is to learn about individual's perspectives about the program.

3. Aims

3.1 Primary outcome

The primary implementation outcomes include self-reported quantitative survey data from Penn faculty, staff, and trainees related to use, acceptability, appropriateness, and feasibility collected weekly. We will collect this data for up to four weeks.

3.2 Secondary outcomes

The secondary implementation outcomes include self-reported quantitative survey data about test results, program usability, user burden, participant experience, program ease, program continuation and availability. Secondary outcomes also include qualitative data about participants' perspectives of the program implementation and change in behavior or decision-making process, which will be collected during virtual interviews conducted after primary data collection has completed.

4. Background

The coronavirus disease (COVID-19) pandemic has resulted in close to 300,000,000 reported cases worldwide, including more than 58,000,000 reported cases and 800,000 deaths in the United States [1,2]. Initial efforts to address the COVID-19 pandemic were aimed at testing symptomatic individuals, implementing stay-in-place orders, and at increasing hospital capacity to meet surge demands [3]. Currently, we are going through an unprecedented surge in the total number of cases – mostly due to the spread of the Omicron variant. While we continue to confront the current crisis, a complete lockdown as seen in 2020 is not desirable or being planned. We must address the current issue and also plan for the future by putting in place tools to enhance our ability to conduct effective screening, containment, and case management. Future variants may cause similar delays in testing availability.

Widespread COVID-19 testing is needed to safely and effectively operate schools, workplaces, and businesses across the US. However, currently approved clinical testing options require reagents that are limited in supply and expensive qPCR machines, severely hindering scalability [4] coupled with acute shortage of person-power. In response to limited clinical testing options, rapid antigen tests that are available to purchase over-the-counter and can be self-administered have become recently a popular testing approach; however, these tests are expensive, in short supply, and may not be as sensitive in detecting Omicron variant compared to PCR tests [5]. Emerging evidence indicates that saliva testing with the option of self-administration of testing can accurately identify COVID-19 viral infection [6]. Moreover, this approach provides an option for the easy, safe and convenient collection of samples required for testing without traveling to a doctor's office, hospital, or testing site. Point of care testing (i.e. using saliva-based self-collection to administer screening for COVID-19 in one's own laboratory setting) utilizes testing equipment that is readily available to our workforce, leverages their existing training, and benefits from existing institutional health and safety infrastructure.

Self-administration of saliva testing also reduces exposure of health care workers to the virus and preserves limited personal protective equipment [7]. Additional diagnostic testing options will continue to increase staff access and decrease resources needed from the health system to support testing.

For these reasons, we propose to evaluate the implementation of a COVID-19 POC screening program that uses saliva-based self-testing and to pilot test approaches to improve program enrollment.

5. Study design

5.1 Design

This is an implementation clinical trial that we anticipate lasting up to two months. In the first phase, we will pilot the approach with four PSOM laboratories. We plan to enroll up to 50

people across these labs during the pilot phase. Labs will be located either in the CRB, Smilow, or the BRB II/III buildings. We will pilot test the best manner to distribute saliva collection test kits and assay tests to participants and elicit rapid feedback for one week. We will apply feedback in real time to improve the distribution method. In the second phase, we will roll out the clinical trial more broadly across all interested PSOM laboratories. We anticipate enrolling up to 500 participants across all PSOM laboratories. All participants will be Penn employees (faculty, staff, and trainees) who work in a PSOM laboratory.

All participants will be required to provide informed consent and watch a training video before self-collecting their first saliva sample. All participants will be told they can collect saliva samples as much or as little as they want – but no more than daily for up to four weeks. They will also be asked to complete online surveys weekly for up to four weeks. These surveys are expected to take about 15 minutes to complete. See below for table of survey measures and frequency. A subset of participants will also be asked to participate in a one-time qualitative interview after the point of care testing program is over. This interview is expected to take about 30 minutes.

5.2 Study duration

The study is expected to begin as soon as necessary approvals are obtained. Study participation in the point of care testing will last for up to four weeks. A subset of participants will be asked to participate in a qualitative interview after study participation is over. If they agree to participate, they will engage in a one-time interview with the research team which will last approximately 30 minutes.

5.3 Target population

The target population is Penn faculty, staff, and trainees that work in person on campus at a PSOM laboratory.

5.4 Accrual

Up to 50 participants will be enrolled in the pilot phase. Up to 500 participants will be enrolled in the second phase.

5.5 Key eligibility criteria

To be eligible, participants must:

1) Be 18 years or older
2) Be University of Pennsylvania staff, faculty or trainee who is working in person on campus at a PSOM laboratory
3) Have knowledge of safe practices in and access to a biological safety cabinet
4) Have knowledge and access to pipet and PCR machine

6. Subject recruitment

Penn Medicine leadership will email PIs of PSOM laboratories about this project and ask them to forward a recruitment email to the personnel who work in their laboratories. The recruitment email will include a link to a screening questionnaire in REDCap (a secure, web-based application for collecting and managing survey data that can be completed via computer or mobile device). All individuals who are interested in participating will click the link and answer the screening questions. The research team will collate interest and deliver saliva collection test kits and assay tests to a location in or close to each laboratory. The team will also share this location with potential participants, who will visit the location and scan a QR code. This QR code will direct them to REDCap, where they will be able to click a link to review the full consent. If participants decide they want to participate, they will indicate this by checking a box and proceeding to the next page. If they do proceed, they will be considered enrolled in this study.

7. Subject compensation

Participants in the point of care testing portion of this study who complete surveys will be entered into a lottery to receive one of four $100 e-gift cards to Starbucks. Participants who engage in the qualitative interview will receive $25 e-gift cards to Starbucks.

8. Study procedures

8.1 Consent & HIPAA Authorization

We have requested ***waiver of written documentation of consent*** from the Penn IRB. The required elements of informed consent and HIPAA Authorization for the study will be described in a consent form that participants can access via REDCap. If they agree to participate, participants will consent by checking a box and and proceeding to the second page. Only participants who click this box will be able to proceed to the next page. Additionally, only individuals who consented to the point of care testing program will be invited to participate in the qualitative interview. Before the interview is conducted, participants will be consented using a separate consent document that will be submitted to the IRB prior to use.

During the consenting process, participants will have the opportunity to reach out to the research team with any questions the participant might have. All potential participants will be asked to confirm that they understand the information provided, understand that participation is voluntary, and feel able to make an informed choice. All participants will be assured during the informed consent process that their decision to participate or not will not impact employment status at Penn.

8.2 Procedures

Once participants provide consent in REDCap, they will be directed to a page that provides an instructional video on what to do next. Participants will be instructed to take a saliva collection test kit. When they are ready to self-collect their saliva sample, they will be instructed to not eat or drink for 30 minutes prior to collecting their saliva and to collect saliva in an isolated room. Participants will then be instructed on how to inactivate the virus and bring their sample to their laboratory's central PCR machine, where they will take an assay test. They will be instructed to collect saliva into a 1.5mL collection tube containing inactivation buffer (TCEP and EDTA) using a small funnel and inactivate at 95°C for 10 minutes. Participants will then transfer 6ul of saliva into 2 PCR tubes containing amplification master mix and primers, put tubes in a heat block or PCR machine at 65°C for 45 minutes and assess fluorescence using a simple battery-powered fluorescence viewer. Once they assess their sample, they will be instructed to dispose of the saliva sample safely and in accordance with best laboratory practices. No saliva samples will be collected by the research team at any time as part of this study.

Each time a participant self-collects a saliva sample and runs the assay test, they will have the opportunity to pick up another saliva collection test kit. Each time they take another saliva collection test kit, they will scan a QR code (labeled for returning users) which will direct them to a simple REDCap prompting them for their name. We will use this data to record how many saliva collection kits are taken by each participant. Participants will be told they can do this point of care testing as frequently as they want (but no more than once a day for up to four weeks).

Each week for up to four weeks, consented participants will also be emailed a link to the online REDCap survey. Based on the week of their participation, they will be asked a battery of survey measures (see below list of surveys along with survey frequency table).

COVID SAFE 2.0 SURVEY MEASURES

Measures	Pre-consent	After training video and completing first test*	Week 1	Week 2	Week 3	Week 4
Screening Questions	X					
Use & POC testing		X	X	X	X	X
AIM, IAM, & FIM		X		X**		X**
Intervention Usability Scale (IUS)		X				X
User Burden Scale (UBS)		X				X
Participant Experience & Program Ease		X		X		X
Program Continuation & Availability		X				X
Demographics		X				

*depending on what day of week participants consent to participate, these surveys will be collected at the Week 1 timepoint.
**At Weeks 2 and 4, we will use a single item adapted version of AIM, IAM, FIM

Survey Measures

- Questions about participant's use and results of test
    - Note, results of test are self report. No saliva samples will be collected as part of this study. If participants self-report a positive result, they will be asked to self-report if they confirmed the positive result (i.e. by getting a CLIAA-approved test). Note, the confirmatory results are also self-report. No data will be entered into the EMR as part of this study.
- The 4-item Acceptability of Intervention Measure (AIM); the 4-item Intervention Appropriateness Measure (IAM); and the 4-item Feasibility of Intervention Measure (FIM; Weiner et al., 2017). We will also use a modified 1-item version of each of these measures. See table of survey measures.
- The Intervention Usability Scale (IUS)
- The User Burden Scale (UBS)
- Questions about the participant's experience with point of care testing and program ease
- Questions about program continuation and availability of testing to family members
- Demographics questions

During the pilot phase, we will check in with participants once to get real time feedback on changes to our test distribution method and rapidly adjust our workflow to refine our distribution method. During the second phase, we will scale up the program and make study enrollment available to all Penn faculty, trainees, and staff who work in person at a PSOM laboratory.

Participants will be instructed to follow standard university and department specific guidelines for isolation and return to work if the assay is positive.

The COVID-19 screening test was developed by University of Pennsylvania faculty and staff on the Rapid Assay Task Force. The task force was assembled under the direction of Dr. Jon Epstein, Chief Scientific Officer and Executive Vice Dean at the Perelman School of Medicine and is led by Dr. Arupa Ganguly, Professor, Department of Genetics. The assay is developed by Dr. Scott Sherrill-Mix, Department of Microbiology. The saliva-based test is conducted using a highly sensitive reverse-transcription loop-mediated isothermal amplification (RT-LAMP) assay compatible with reagents developed at the University of Pennsylvania to detect SARS-CoV-2 viral RNA. LAMP is a method of isothermal DNA replication that utilizes DNA oligos that hybridize with different regions of the target molecule to form loops in the DNA. Utilizing a strand displacing polymerase, a fast amplification reaction can occur upon proper oligo binding to the desired target. Such reactions are capable of generating microgram quantitates of DNA in a very short period of time at a single reaction temperature. Furthermore, although the strand-

displacing polymerase has reverse transcriptase activity, a reverse transcriptase can be included to improve sensitivity within the reaction when detecting an RNA target (RT-LAMP). The saliva test developed by the University of Pennsylvania uses SARS-CoV-2 specific primer sets along with molecular beacons, fluorescent reporter oligonucleotides designed to only fluoresce in the presence of amplified SARS-CoV-2 sequence. The protocol is simple, inexpensive, and rapid. Results are typically available in about one hour. Positive samples are called by comparison to positive and negative controls; reactions displaying a characteristic color under illumination by blue light and orange filtering indicate that the target sequence is present. Positive results are indicative of the presence of SARS-CoV-2-RNA but must be confirmed by a CLIA approved test. Our research suggest that assays based upon these protocols allow for a sensitivity down to about 20 genomes per microliter of saliva or further with increased reaction volume[8,9]. As an assay control, an additional primer set and molecular beacon targeting a common human mRNA and fluorescing in a different color will be included in reactions.

Quality control (QC) checks will occur at multiple points in this protocol:

1) Kit QC – Each batch of kits will be tested to ensure all components are functioning as expected.
2) A positive control QC step, consisting of a LAMP reaction spiked with synthetic SARS-CoV-2 RNA, will be included in each assay to validate LAMP function and provide a visual reference.
3) A negative control QC step, consisting of LAMP reaction spiked with oligonucleotide matching the human control mRNA, will be included in each assay to ensure that no contamination of LAMP reagents has occurred and provide a visual reference.
4) A primer set and molecular beacon targeting human mRNA will be included in each reaction to ensure that sample has been correctly added and no inhibition of the reaction has occurred.

9. Analysis plan

We will measure the primary outcomes of use, acceptability, appropriateness, and feasibility and the secondary outcomes of test results, program usability, user burden, participant experience, program ease, program continuation, and availability of testing to others using descriptive statistics. To evaluate the use of the program, we will evaluate the reported frequencies of self-testing performed by participants. We will look at the relationship between these outcomes using regression. Qualitative analysis to achieve our additional secondary outcomes will be guided by an integrated approach, which provides a rigorous, systematic method to analyzing qualitative data and has been shown to produce robust theoretical models of social behavior in healthcare settings. This approach uses an inductive and deductive process of iterative coding to identify recurrent themes, categories, and relationships in qualitative data. A comprehensive coding scheme to produce a fine-grained descriptive analysis of the role of multilevel contextual characteristics on implementation. Using Nvivo, we will then separately code a sample of

transcripts and compare their application of the coding scheme to assess reliability and robustness. Disagreements will be resolved through discussion.

10. Investigative Team

- Rinad Beidas, PhD, Professor, Psychiatry, Medical Ethics and Health Policy, and Medicine, Perelman School of Medicine, rinad.beidas@pennmedicine.upenn.edu
- Arupa Ganguly, PhD, Professor of Genetics at the Hospital of the University of Pennsylvania, ganguly@mail.med.upenn.edu
- Scott Sherrill-Mix, PhD, Postdoctoral Researcher, shescott@pennmedicine.upenn.edu.

11. Human research protection

11.1 Data confidentiality

Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Wherever feasible, identifiers will be removed from study-related information. Lab staff may be privy to participant identity in that they will see participants pick up test kits but have been trained to maintain confidentiality. Precautions are in place to ensure the data are secure by using passwords and encryption, because the research involves web-based surveys.

11.2 Subject confidentiality

Research data will be obtained from participant surveys and interviews. All participants will provide informed consent prior to study participation. Research data that is obtained will be used for research purposes only. Patient identifiers will be used only for linkage purposes or to contact patients. The study identification number, and no other identifying information, will be used on all data collection instruments. All study staff will be reminded to appreciate the confidential nature of the data collected and contained in these databases. The Penn Medicine Academic Computing Services (PMACS) will be the hub for the hardware and database infrastructure that will support the project and is where the REDCap portal is based. The PMACS is a joint effort of the University of Pennsylvania's Abramson Cancer Center, the Cardiovascular Institute, the Department of Pathology, and the Leonard Davis Institute. The PMACS provides a secure computing environment for a large volume of highly sensitive data, including clinical, genetic, socioeconomic, and financial information. Among the IT projects currently managed by PMACS are: (1) the capture and organization of complex, longitudinal clinical data via web and clinical applications portals from cancer patients enrolled in clinical trials; (2) the integration of genetic array databases and clinical data obtained from patients with cardiovascular disease; (3) computational biology and cytometry database management and analyses; (4) economic and health policy research using Medicare claims from over 40 million Medicare beneficiaries. PMACS requires all users of data or applications on PMACS servers to complete a PMACS-hosted cybersecurity awareness course annually, which stresses federal data security policies

under data use agreements with the university. The curriculum includes Health Insurance Portability and Accountability Act (HIPAA) training and covers secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server. We will implement multiple, redundant protective measures to guarantee the privacy and security of the participant data. All investigators and research staff with direct access to the identifiable data will be required to undergo annual responsible conduct of research, cybersecurity, and HIPAA certification in accordance with University of Pennsylvania regulations.

Data will be stored, managed, and analyzed on a secure, encrypted server maintained by Penn Medicine Nudge Unit and/or the Penn Center for Mental Health. All study personnel that will use this data are listed on the IRB application and have completed training in HIPAA standards and the CITI human subjects research. Data access will be password protected. Whenever possible, data will be de-identified for analysis.

11.3 Subject privacy

Interested participants will be directed to the REDCap platform where they will be asked to enter data related to eligibility. Participants can choose when and where to access this platform, maintaining their own privacy. There is the possibility that a participant's involvement in the study may be made known to other participants, as other study participants may be visiting the central lab location at the same time to pick up saliva sample collection kits. Other study participants will not have access to any personal information or other information collected throughout this study. All efforts will be made by study staff to ensure subject privacy.

11.4 Data disclosure

The following entities, besides the members of the research team, may receive protected health information (PHI) for this research study. The Office of Human Research Protections at the University of Pennsylvania -Federal and state agencies (for example, the Department of Health and Human Services, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes.

11.5 Data safety and monitoring

The Principal Investigators and research team will closely monitor the safety, privacy, and data integrity of the study. Patients will be provided contact information for study staff and if adverse events are identified, events will be reported and brought to the PI's attention.

11.6 Risk/benefit

11.6.1 Potential study risks

All data described previously will be protected as described in the Subject confidentiality section. There is minimal risk to subjects as there is minimal risk of breach of data. Our team has extensive experience working with these types of data. We will use commercial-grade encryption to protect participant information. Their personal information will only be used by study team members who have been trained to use secure protocols to maintain the privacy of data. Risks and side effects related to this study include the possibility that answering certain questions on the surveys about symptoms may make study participants feel slightly uncomfortable or may be inconvenient. The risks of self-collecting a saliva sample for testing may include the possibility for false positives or false negatives, testing may induce feelings of fear or anxiety, a positive test result may cause participants to miss days of work, and individuals may experience mild discomfort if they receive the CLIA approved test. We expect the risks of picking up and dropping of test kits to be no more than the risk of returning to campus.

11.6.2 Potential study benefits

This unique program could improve the health of individuals by picking up on changes in symptoms earlier allowing individuals with COVID-19 to be identified quickly and reduce the spread of the virus. However, participants may receive no benefit from the study.

11.6.3 Risk/benefit assessment

There is minimal risk of breach of data and appropriate measures have been taken. Therefore, we believe the risk/benefit assessment is favorable given the potential insights that could be yielded from the findings of this study.

12. References

1. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus Disease 2019 Case Surveillance—United States, January 22 – May 30, 2020. MMWR Morb Moral Wkly Rep 2020;69:759-765.
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis; published online Feb 19.
3. McClellan M, Gottlieb S, Mostashari F, et al. A national COVID-19 surveillance system: Achieving containment. Accessed June 29, 2020. https://healthpolicy.duke.edu/sites/default/files/atoms/files/covid-19_surveillance_roadmap_final.pdf
4. Association of State and Territorial Health Officials, Association of Public Health Laboratories, and Council of State and Territorial Epidemiologists. COVID-19 Testing Needs to Be Limited to Priority Groups Unit Sufficient Testing Supplies and Personal Protective Equipment is Available Nationwide. Accessed June 29, 2020.

https://www.astho.org/Press-Room/COVID-19-Testing-Needs-to-Be-Limited-to-Priority-Groups-for-Now/03-20-20/
5. Ferré VM, Peiffer-Smadja N, Visseaux B, Descamps D, Ghosn J, Charpentier C. Omicron SARS-CoV-2 variant: What we know and what we don't [published online ahead of print, 2021 Dec 10]. Anaesth Crit Care Pain Med. 2021;41(1):100998. doi:10.1016/j.accpm.2021.100998
6. U.S. Food & Drug Administration. Coronavirus (COVID-19) Update: FDA Authorizes First Diagnostic Test Using At-Home Collection of Saliva Specimens. Accessed June 29, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-diagnostic-test-using-home-collection-saliva
7. Tu YP, Jennings R, Cangelosi GA, et al. Swabs collected by patients or health care workers for SARS-CoV-2 Testing. N Engl J Med. 2020. PMID: 32492294.
8. Rabe BA, Cepko C. SARS-CoV-2 detection using an isothermal amplification reaction and a rapid, inexpensive protocol for sample inactivation and purification. medRxiv preprint doi: https://doi.org/10.1101/2020.04.23.20076877. Accessed July 7, 2020.
9. Sherrill-Mix S, Hwang Y, Roche AM, et al. Detection of SARS-Co-V-2 RNA using RT-LAMP and molecular beacons. Genome Biol 22, 169 (2021). https://doi.org/10.1186/s13059-021-02387-y