Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Official Title: Randomized trial of adding pulse oximetry to an automated text-messaging program for remotely monitoring patients at home with Covid-19

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This supplement contains the following items:

1. Original protocol, final protocol, summary of changes
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

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A. Original Protocol

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A. Original Protocol

1. Abstract

The clinical guidance for 90 percent of infected COVID-19 adult patients who do not meet eligibility for inpatient admission is to self-isolate. To support these patients, alternatives to in-person care are needed to manage an unpredictable clinical course; identify and intercept patients rapidly deteriorating at home, prevent viral spread during in-person visits; and minimize future surges in emergency departments (EDs). In addition, fingertip pulse oximeters have been proposed to improve in-home early detection of respiratory deteriorations but are untested and the operational infrastructure to support large-scale monitoring is limited.

While telemedicine has been widely adopted during the pandemic as an alternative to conventional outpatient care, limited telemedicine access may be exacerbating observed disparities for Black and Latino patients. In this health system, Black and Latino patients used video-visits 15 percent less often than white patients. Text messaging and phone calls may improve healthcare access for communities of color, but the evidence for these telecommunication modalities to be effective and improve equity are limited.

The University of Pennsylvania Health System (UPHS) developed and deployed COVID Watch to improve access to health care for COVID-19 patients who are self-isolating at home. COVID Watch sends twice-daily, scheduled text messages to assess patients for shortness of breath using a clinical algorithm to determine whether patients need an urgent escalation to a team of dedicated, on-call nurses within one hour. These nurses are supported by an on-call team of clinicians who can conduct urgent phone or video assessments. Patients can also trigger the algorithmic assessment independent of the scheduled messages. As of May 21, 2020, COVID Watch has managed 3,628 COVID-19 patients at home, of which 1,295 are confirmed COVID-19 positive; of these, 61 percent are Black or Latino, higher than the proportion of all UPHS COVID-19 positive patients that are Black or Latino (55 percent).

2. Overall objectives

The objective of this study is to conduct a pragmatic randomized controlled trial to determine the incremental benefit of providing home pulse oximetry for patients enrolled in COVID Watch.

3. Aims

3.1 Primary outcome

The primary outcome measure is the difference in Days Alive and Out of Hospital.

3.2 Secondary outcomes

The secondary outcome measure is the difference in level of Emotional Distress and Anxiety on day 0, 7, and 14 after enrollment in COVID Watch as measured by Emotional Distress-Anxiety Short Form 4a scale.

3.3 Exploratory outcomes

The research team will explore several other outcomes of interest. These included differences in: 1) 30-day mortality; 2) incidence and timing of remote monitoring escalations to nursing care and subsequent emergency department referrals; 3) health care utilization including

outpatient, emergency department, inpatient, and ICU care; 4) self-perceptions of feeling safe at managing illness; and 5) rates of discordance between dyspnea symptoms and hypoxia as measured on home pulse oximetry.

4. Background

Most (80-90%) COVID-19 positive patients are asked to self-isolate at home because they do not qualify for home care or inpatient admission.1,2 Alternatives to in-person care are urgently needed to: (1) manage an unpredictable clinical course; (2) identify and intercept patients rapidly deteriorating at home, (3) prevent viral spread during in-person visits; and (4) triage symptoms to minimize surges to emergency departments (EDs).3-9 In addition, fingertip pulse oximeters ("pulse oximetry") have been proposed to improve in-home early detection of respiratory deteriorations but are untested and the operational infrastructure to support large-scale monitoring is limited.10-12 While telemedicine has been widely adopted during the pandemic as an alternative to conventional outpatient care, worse COVID-19 outcomes observed among Black and Latino patients may be due, in part, to worse telemedicine access for these socially and medically disadvantaged groups.13-20

To improve in-home monitoring and health care access for patients with suspected or confirmed COVID-19, the team in the University of Pennsylvania Health System ("UPHS") developed COVID Watch, a free of charge, 24/7, automated, text message-based, home monitoring program across UPHS' large geographic catchment area. This study will answer the question, "How does the addition of pulse oximetry affect clinical outcomes for COVID-19 patients?"

COVID Watch was first implemented on March 24, 2020 and has enrolled 3,628 patients through May 21, 2020 of which 1,295 were COVID-19 positive. Understanding the effect of COVID Watch with and without pulse oximetry on Black and Latino patients is important because communities of color have had disproportionately higher rates of COVID-19 morbidity and mortality nationally,21-23and locally in Pennsylvania, ranking 5th total deaths, 24 and New Jersey, ranking 2nd.24 Symptom monitoring apps and programs are commercially available.25-30 However, COVID Watch is uniquely embedded into its host healthcare system, UPHS. Patients are enrolled using the electronic medical record (EMR), escalations are addressed by UPHS nurses, and they are referred to UPHS-based telemedicine, primary care, and social services when appropriate. COVID Watch is a scalable operational platform for monitoring patients with home pulse oximetry readings. Whether remote monitoring with or without pulse oximetry helps COVID-19 patients stay safe at home is an urgent, patient-centered question.10,31,32 Finally, with COVID-19 surges projected in late 2020, health systems will need to be prepared with evidence-based strategies for managing more COVID-19 patients at home.33,34

COVID Watch (https://covidwatch.waytohealth.org/) is powered by UPHS' NIH-funded research and operational texting platform (www.waytohealth.org), integrated with UPHS' EMR. Since hypoxemia is the primary driver of admission and fatality among COVID-19 patients, the researchers focused their algorithm (Appendix Fig 1-3) on shortness of breath, the researchers' closest approximation for concerning hypoxemia.9,35,36 Given the rapid and unpredictable decompensation of COVID-19 patients, patients receive clinical support 24 hours/day, 7 days/week.4,37-39 COVID Watch sends twice-daily, scheduled text messages to assess patients for shortness of breath using an algorithm to determine whether patients need an urgent escalation to a team of dedicated nurses within 1 hour (Appendix Fig 4). These nurses are supported by an on-call team of clinicians who can conduct urgent phone or video assessments. At each level patients' clinical needs are either managed with self-care advice, prescriptions, or a referral to the ED. The majority of COVID Watch patients (83.7%) have been enrolled by outpatient providers conducting telephone and video visits; 8.7% and 7.6% have been enrolled at ED and inpatient discharge, respectively. The program is available at all six of UPHS's hospitals and EDs, and all 530 affiliated ambulatory settings using the EMR. Any clinical staff member (e.g., RN, physician, medical

assistants) logged on to the EMR is able to enroll patients (Appendix Fig 5). Patients can also trigger the algorithmic assessment independent of the scheduled messages. Patients only receive the intervention if they are agreeable ("opt-in") and can stop anytime. Patients are scheduled to be in COVID Watch for 14 days, with the option to extend to 21 days if interested. A Spanish-language version of COVID Watch was made available to patients on May 18, 2020, with nurses using translation lines to communicate with patients.

COVID Watch engagement is high. To date, nearly 80% of enrolled patients have engaged with the program, defined as responding to scheduled text messages at least once every two days. RNs have managed over 600 calls with a mean response time (median) of 25 minutes (11 minutes). Of the calls, 37% were asked to continue to monitor at home, 41% were scheduled for an urgent follow-up telemedicine visit, and 9% were sent to the ED for emergent evaluation.

Here the researchers provide a conceptual model of how adding home pulse oximetry may potentially improve outcomes. Preventing or aggressively treating respiratory failure is essential for patients infected with COVID-19. Among all infected patients, an estimated 10-20% of patients with COVID-19 develop severe illness requiring hospitalization, of which 30-40% develop critical illness requiring support in an intensive care unit.40 Among the critically ill, respiratory failure is common and results from acute hypoxemic respiratory failure due to acute respiratory distress syndrome (ARDS).40 ARDS is a clinical manifestation of pulmonary tissue inflammation, preventing the exchange of oxygen between inhaled air and blood circulating in patients' lungs ("hypoxemia"). Increasing the concentration of oxygen in the air that patients breathe (e.g., supplemental oxygen) and reducing the degree of pulmonary inflammation can support patients with COVID-19 by reducing the severity of hypoxemia and providing sufficient oxygen supply to vital organs. Measures of pulse oximetry – the oxygen saturation in the blood – can provide an objective measure to identify which patients have or are beginning to experience declines in their respiratory function.41

The research team's conceptual model (Figure 1) is based on emerging evidence that early medical interventions can improve clinical outcomes for COVID-19, resulting in less severe clinical sequelae and reduced mortality. For COVID-19 patients requiring supplemental oxygen, new preliminary data from a large multicenter randomized controlled trial of dexamethasone indicates that patients have markedly reduced mortality when given dexamethasone.42 This corticosteroid likely reduces pulmonary inflammation and prevents the development of severe ARDS. These findings suggest that earlier treatment for patients who develop more severe forms of COVID-19 may prevent unwanted outcomes. Secondly, there is additional evidence that remdesivir can speed recovery and reduce hospital days among patients with COVID-19.43 Finally, there is promising data that simple changes in ED care and hospital practices may improve outcomes. For example, "awake proning," which involves positioning an awake, non-intubated patients at regular intervals onto their abdomen with their face down can enable greater recruitment of lung tissue for oxygen exchange and reduce the need for subsequent intubation and mechanical ventilation.44,45 These sorts of interventions can reduce the days that patients spend in the hospital, prevent complications such as ventilator associated pneumonia, and reduce mortality related to COVID-19.

Respiratory decline needs to be identified early for patients to benefit from early medical interventions. Respiratory decline can be (a) signaled when patients report the sensation of feeling "shortness of breath" or "difficulty breathing" (i.e., dyspnea), or (b) identified when the concentration of oxygen in patients' blood or oxygen saturation are objectively measured. Current models of care ("Usual Care"), even with expanded telemedicine access, rely on patients contacting providers - a reactive process. This reactive process can delay care because most primary care practices use an intermediary (e.g., a staff member or message inbox) to screen communications for busy clinicians. Many practices do not respond to patients' concerns efficiently overnight or on weekends. These processes frustrate patients

because they are concerned about contacting their providers for mild changes, irrespective of the time or day the event is occurring, because they are concerned about respiratory failure. This process is even harder for patients with limited primary care or telemedicine access or language barriers, problems disproportionately faced by Black and Latino communities. In contrast, COVID Watch is a proactive process, requesting patients report symptoms twice a day, and patients can trigger a phone call to a nurse within an hour by simply texting. COVID Watch + pulse oximetry mirrors COVID Watch but can proactively detect respiratory decline using an objective measure of oxygen saturation. In addition, COVID Watch is available free of charge and is now available in Spanish, with over 85 Spanish speaking patients enrolled to date.

To not overburden emergency departments (EDs), respiratory decline needs to be identified accurately. Both unnecessary escalations of care to the ED for patients with mild COVID-19 and delayed detection of respiratory decline in patients with severe COVID-19 may occur when managing patients with COVID-19. For usual care and COVID Watch, clinicians are reliant on the subjective sensation of dyspnea. Dyspnea is concerning enough that patients are often redirected to an urgent care center or emergency department so patients can have their oxygen saturation measured. Referring patients with an oxygen saturation <94% would justify redirecting patients to the ED for additional clinical evaluation and supportive therapy. Referring patients with mild dyspnea who turn out to have a normal oxygen saturation (Figure 2A) may be a burden to patients and their families and requires additional resource from EDs and hospitals. During times of rapid rises in community infection rates, or surges, efficient resource allocations are imperative for supporting patients who are critically ill. At the same time, patients still benefit from enhanced connections with clinical providers to reassure them that they are not experiencing respiratory decline. COVID Watch, supplemented by pulse oximetry, could provide this highly responsive team of clinicians objective data so they can accurately assess a patient's respiratory state.

In an alternative scenario, patients may have low oxygen saturation without the sensation of dyspnea, a phenomenon unique to COVID-19 infected patients, and is commonly known as "silent" or "happy" hypoxemia (Figure 2B).31 These patients receive medical interventions late because they are unaware they are hypoxemic. There have been reports of COVID-19 patients arriving in EDs with profoundly low oxygen saturation levels with relatively little or no dyspnea.10 This has led to proposals to use home pulse oximetry to detect silent hypoxemia which have been widely reported in the media (e.g. New York Times) and resuscitation medicine forums.46,47 To address this phenomenon, the Vermont Department of Public Health has implemented a program to mail pulse oximeters to newly diagnosed COVID-19 cases 24-48 hours after contact tracing interviews.48 But as reported in Science: "No one, however, has studied whether early detection of hypoxia might head off bad outcomes. Some physicians believe pulse oximeters are best used with a doctor's guidance, perhaps through telemedicine. With many COVID-19 patients frightened to visit a hospital and arriving only when their symptoms have dangerously advanced, doctors also wonder whether home monitoring could hasten treatment—and whether, for some, that could make all the difference."31

Based on lack of studies determining whether pulse oximetry can hasten treatment for patients deteriorating at home relative to the current standard of care in the health system of automated text messaging paired with telemedicine, the researchers believe there is equipoise between these two treatment strategies: automated text messaging with telemedicine vs. automated text messaging with telemedicine plus pulse oximetry. Therefore, a randomized comparison is needed to guide health system programs to better address this pandemic.

5. Study design

5.1 Design

Study design and hypotheses. This will be a pragmatic randomized controlled trial to test the effect of adding home pulse oximetry to patients being started on COVID Watch as part of their routine care.49 In this adaptation to COVID Watch, after being deemed safe for outpatient management and started on COVID Watch patients will be randomly selected to receive a pulse oximeter via overnight mail with educational materials (Appendix Fig 6).

Patients sent a pulse oximeter will be prompted twice daily to text their oxygen saturation level after walking in place for 1 minute. If the oxygen saturation is ≥3% lower than the baseline first O2 sat measurement, or if it falls below an absolute level of 90%, the patient will receive an immediate call from the same on-call RNs for COVID Watch and undergo the same triage protocol. Hypotheses: Provision of pulse oximetry will lead to a higher number of Days Alive and Out of Hospital and Emergency Department (H2a), particularly among Black and Latino patients (H2b) compared to COVID Watch alone.

Choice of study design. The research team has chosen a pragmatic randomized control trial because it is the most rigorous design for obtaining causal effects of providing pulse oximeters to a remote home monitoring program for COVID-19 in real world settings with diverse populations while accounting for time-varying trends, such as advances in treatment that occur during the study period.

5.2 Study duration

The study is expected to take 18 months to conduct, an expedited time frame in order to make results available as quickly as possible in the midst of the COVID-19 pandemic: 2 months for planning and approvals; a minimum of 5 months for data collection to reach the target sample size; 3 months for analysis, and 8 months for dissemination of results.

5.3 Target population

The study population will be COVID-19 patients enrolled in COVID Watch as routine care via (1) outpatient testing or (2) who were tested and discharged from the ED. Patients will be excluded from the trial if they have already been provided a fingertip pulse oximeter as part of routine care. Recruitment will begin as soon as possible (target October 1) and proceed to approximately March 1, 2021 in order to provide reports in Year 1 of this investigation and meet the enrollment quota based on the sample size calculations (see below) and current COVID Watch patient volume (currently ~60 patients per week as of August 21. 2020).

5.4 Accrual

This is an evaluation of a health system intervention involving patients treated in 5 emergency departments and 530 affiliated outpatient practice sites at the University of Pennsylvania Health System that already places patients with suspected COVID-19 into a remote home monitoring program as part of usual care.

5.5 Key inclusion criteria

The study population will be patients with suspected or confirmed COVID-19 started on COVID Watch as routine care via (1) outpatient COVID-19 testing or (2) who were tested for COVID-19 and discharged from the ED.

5.6 Key exclusion criteria

Patients will be excluded if they are: 1) less than 18 years of age; or 2) were provided a pulse oximeter upon discharge from the ED (available for distribution as usual care for patients with suspected COVID-19 being discharged from the ED with an ED pulse ox less than 95%, who have an infiltrate on chest x-ray, are greater than 60 years of age, or who are deemed by the ED clinician to have significant comorbid conditions).

6. Subject recruitment

Since this is an evaluation of a health system intervention, patients will not be recruited or enrolled individually but instead an analysis will be conducted based on interactions with the health system. Based on target sample size estimates below, the team is seeking to enroll at least 850 patients.

7. Subject compensation

No compensation will be offered in this study.

8. Study procedures

8.1 Consent

This trial will be conducted under a waiver of the requirement for informed consent based on the following criteria set for forth by the Federal Policy for the Protection of Human Subjects (the "Common Rule"):

1. The research involves no more than minimal risk to subjects.
2. The waiver will not adversely affect the rights and welfare of the subjects.
3. The research cannot be practicably conducted without a waiver of the requirement for informed consent.

The research involves no more than minimal risk to subjects. The risks to subjects of participating in this study is no more than minimal because both interventions exceed the standard of care routinely provided to patients diagnosed with COVID-19 managed at home. The current standard of care for patients with COVID-19 who are residing at home is to go to the ED for worsening symptoms. UPHS has implemented COVID Watch to enhance this standard of care by providing text-based assessments, two times a day for 14 days and escalates care to a nurse via telemedicine for any reported worsening of symptoms not severe enough to recommend going to the ED immediately. This service is provided free of charge to patients, a benefit to patients without insurance or established primary care. UPHS already offers a version of COVID Watch with pulse oximetry to patients with COVID-19 being discharged from the ED who meet specific criteria: a discharge pulse ox less than 95%, an infiltrate on chest x-ray, are or age of 60 years or older, or who are deemed by the ED clinician to have significant comorbid conditions. For this study, additional patients will be offered pulse oximetry, those eligible for COVID Watch but not meeting these additional criteria used in the ED. These individuals will be randomized to receive a pulse oximeter via overnight mail. Patients who prefer not to use the pulse oximeter will be free not to and continue on in COVID Watch. Those who use the pulse oximeter will still be escalated to a nursing assessment if they report a worsening of their respiratory symptoms even if they report a normal pulse oximetry reading. Furthermore, pulse oximetry devices are commercially widely available for patients to purchase, and patients may choose to use a pulse oximetry device irrespective of randomization for this study.

The waiver will not adversely affect the rights and welfare of the subjects. The intervention arm of this study (i.e., those randomized to receive a pulse oximetry) does not disrupt their eligibility or ability to receive care from the COVID Watch program. Therefore, the researchers do not anticipate the waiver will adversely affect the rights and welfare of subjects. Patients will retain the full right not to use the mailed pulse oximeter in addition to COVID Watch. A statement on the existing COVID Watch website will indicate that their data may be anonymized and used to study the impact of the program. The website will provide the contact information for a research coordinator if the patient wishes to not have their data to be analyzed for research purposes. The text message invitation to enroll in COVID Watch will include a link to this information. This statement will continue to be pushed to all patients placed into COVID Watch during the course of this trial.

The research aims cannot be practicably conducted without a waiver of the requirement for informed consent. This trial seeks to evaluate the effectiveness of adding home pulse oximetry to the existing, standard of care COVID Watch remote monitoring program in an overall population of patients with suspected or confirmed COVID-19. Requiring individual informed consent would introduce important selection biases. Specifically, socioeconomically disadvantaged populations who have experienced the greatest burden from COVID-19 have historically participated in research at lower levels than the general population and would be less likely to enroll in this study. A major goal of this study is to understand and create knowledge that is generalizable to these marginalized populations. Furthermore, unlike a drug trial where outcomes are primarily determined by physiologic effects of a medication, in this study of behavioral interventions, those who consent are likely to have behavioral characteristics that are not representative of those who would not consent and therefore potentially biasing the outcomes of a behavioral study. Therefore, requiring consent would render the study invalid since it would not have generalizability in applying to the desired population, particularly those experiencing the greatest disparities in outcomes due to COVID-19. Second, requiring informed consent would lead to delays in the distribution of pulse oximeters for a condition with an intense, but short disease course that could further reduce the generalizability of study results for health systems considering pulse oximeters for COVID-19 patients.

8.2 Procedures

1. Patients are started on COVID Watch as routine care based on confirmed or clinical suspicion for COVID-19 via the integration of the Way To Health (W2H) platform with the electronic health record.

2. Patient receives a text message to proceed in COVID Watch as is current routine care.

3. For this study, W2H auto-generates and sends the study's Research Coordinator (RC) a daily excel report with a list of new COVID Watch enrollees at regular intervals (e.g., every 2 hours). The report includes the randomized arm assignment (COVID Watch or COVID Watch + Pulse Oximetry), along with the patient's phone number.

4. The RC alerts patients randomized to COVID Watch + Pulse Oximetry via phone call and/or text message that there will be a next day pulse ox device delivery and that once received, the patient will start to measure and report their oxygen levels. The RC confirms the patient's mailing address and instructs patients that in the meantime, they should continue to respond to COVID Watch check-ins per standard protocol. The patient is instructed to text or call once they have received the pulse oximetry device. If language preference is Spanish, an interpreter is required on the call.

i. If the patient cannot be reached by text, the RC calls and if necessary leaves a voicemail and the patient will still be sent a pulse ox.

5. The RC sends a pulse oximetry device via UPS 11am and 5pm. The package will include a pulse oximetry device (with barcode), printed patient instructions in the appropriate language, and prepaid, labeled return envelope to be used at the end of their COVID Watch enrollment

6. The RC logs device identifier, date and time of drop off of package for each patient

7. The RC tracks device receipt (via both UPS tracking and/or patient self-report) and contacts the patient via text and/or phone call to ensure the patient understands how to use the device. If language preference is Spanish, an interpreter is required on the call.

8. The RC changes patient protocol from COVID Watch to COVID Watch + Pulse Oximetry.

9. The RC follows up with patients via text and/or phone call in the event that the device is not returned within 2 weeks of being discharged from COVID Watch

9. Human research protection

COVID Watch patients. The target population for the COVID Watch program will be any patient 18 or older evaluated and tested for suspected COVID-19 throughout any of the Penn Medicine access points, including the Emergency Department, calls to the hospital or outpatients centers, occupational health, and testing sites. Using established clinical resources as well as Penn OnDemand telehealth system, patients will be presented the option to enroll in the COVID-Watch program.

COVID Watch (https://covidwatch.waytohealth.org/) is an automated, text-based, remote monitoring program for patients infected with COVID-19 (i.e., laboratory confirmed). The intervention was designed by a team of clinical, technological, innovation, and analytic experts. Since hypoxemia is the primary driver of admission and fatality among COVID-19 patients, the researchers focused the algorithm on dyspnea, or shortness of breath, the closest approximation for concerning hypoxemia. Given the rapid and unpredictable decompensation of COVID-19 patients, patients receive clinical support 24 hours/day, 7 days/week. COVID Watch sends twice-daily, scheduled text messages to assess patients for shortness of breath using an algorithm to determine whether patients need an urgent escalation to a team of dedicated, on-call nurses within 1 hour. These nurses are supported by an on-call team of clinicians who can conduct urgent phone or video assessments. At each level patients' clinical needs are managed either via self-care advice, prescriptions, or referral to the ED. Patients are able to text the dedicated COVID Watch phone number and receive a response from clinical support within an hour.

Pulse Oximeter. The pulse oximeter device is used to monitor a patient's oxygen saturation levels in the body. The device is small and lightweight and is placed on the finger for measurement. As part of COVID Watch, patients are instructed on how to use the device and understand and report its readings. During enrollment into COVID Watch, the patient's baseline oxygen saturation level (SpO2) is collected and entered into Way to Health. During COVID Watch monitoring period the patient will collect SpO2 measurements. Care escalation is triggered in Way to Health under the following conditions:

If (baseline 95-100 AND >3 drop) OR (baseline 92-94 AND > 2 drop) OR level <90

If (baseline 95-100 AND >3 drop) OR (baseline 92-94 AND > 2 drop) OR level <90

If (baseline 95-100 AND <3 drop) OR (baseline 92-94 AND < 2 drop) OR level > 90

Pulse Oximeter data is automatically stored in Way to Heath and will be extracted from Way to Health platform in .csv format and stored on PMACs secure server.

9.1 Data confidentiality

All data will be stored on Penn Medicine Computing Services Servers. The Penn Medicine Academic Computing Services (PMACS): PMACS will store all data securely. The data center is housed in Information Systems and Computing at 3401 Walnut Street. All data for this project will be stored on the secure/firewalled servers of the PMACS Data Center, in data files that will be protected by multiple password layers. These data servers are maintained in a guarded facility behind several locked doors, with very limited physical access rights. They are also cyber-protected by extensive firewalls and multiple layers of communication encryption. Electronic access rights are carefully controlled by UPenn system managers. This multi-layer system of data security, identical to the system protecting the University of Pennsylvania Health Systems medical records, greatly minimizes the risk of loss of privacy.

Patient medical record data: electronic medical record data will be extracted from patient medical records (EPIC) via a report created by the Data Analytics Center (DAC) at Penn Medicine. The report will run weekly and be placed in a folder in a PMACs or UPHS secure shared drive. This DAC report has already been created by staff on the Penn Medicine COVID-19 Registry team. The Penn Medicine COVID-19 Registry team will provide support for this project and their staff will access the report to save data points needed for this project in a different file described below. Access to this DAC report is limited to those with institutional approval to access the report. Approval is granted only for staff with HIPAA and CITI training. The file created by the Penn Registry team for this project will be saved onto a secure PMACs or UPHS drive only accessible by the team on this protocol (via password protection) or using the Penn Secure Share encrypted document sharing mechanism. The file will then be saved to a secure shared drive on PMACs server for staff access. The file will be saved with password protection and only those staff who need access to the file will be provided the password. The limited dataset will remain on this secure shared drive until the follow-up data collection and analysis is complete. Participants will be assigned a STUDY ID listed on the DAC report to match data from other sources (i.e., Way to Health).

Way to Health data: Any datasets and computer files are referred to by study ID. The study ID is also used on all analytical files. All personal information that the participant is asked to provide will be collected via Penn's Way To Health study platform. Way To Health collects subjects' names and phone numbers. They also request the name and phone number of an alternate contact. To assure that participant confidentiality is preserved, individual identifiers are stored in a single password protected system that is accessible only to study research, analysis and IT staff. An investigator or statistician who logs in will be able to access only non-identifiable data. The Way To Health administrative group and research coordinators responsible for contacting participants for follow-up study visits or responding to questions about the study are able to view participant names and contact information. The WTH web development team and Project Director currently have administrative access to PHI. All of these personnel will have completed Human Subjects Protection and HIPAA privacy training. The system automatically generates logs of all data queries which can be reviewed by research staff to ensure that no unauthorized persons have gained access to identifiable information. This system is hosted on site at The University of Pennsylvania and is protected by a secure firewall and several layers of operational security. Once a participant has been entered into this system, they are given a unique study identification number (ID). Any datasets and computer files that leave the firewall are stripped of all identifiers and individuals are referred to by their study ID. The study ID is also

used on all analytical files. The Penn Medicine Academic Computing Services (PMACS) is the hub for the hardware and database infrastructure that supports the project and the Way To Health web portal is built on this infrastructure. The data collected for Way To Health based studies is stored in mySQL databases on a PMACS-operated blade server environment devoted specifically to Way To Health. Every SQL transaction, including accessing and changing data, is logged for auditing purposes. Data are entered into the database through several different mechanisms. Participants enter their own personal information and respond to surveys through a PHP-based web interface. Researchers have a separate interface that allows them to manually enter data if needed. Datasets are stripped of all personally identifiable information when exported for analysis. The web application automatically removes all identifiers when a researcher requests an analytic dataset. The only people with access to identifiable participant information are pre-specified Research Coordinators responsible for contacting participants for follow-up. Personal information and research data will be stored in separate SQL tables and will be linked by a computer-generated ID number. Additionally, any information that leaves this system to communicate with third party data sources (i.e., survey software) is stripped of any identifiers and transmitted in encrypted format.

9.2 Subject confidentiality

All participant data will be through COVID Watch or the electronic medical record. There will be no paper records or other forms of data collection. Therefore, subject confidentiality will be maintained through the data protections described above in section 11.1.

9.3 Subject privacy

All data abstracted from the medical chart will be placed onto PMACS servers, all text responses will be secured on the Way to Health platform and no one but the PI, project manager, and study staff responsible for the will have access to these databases. Participants are educated about best practices for mobile phone privacy upon enrollment into the program. Patients are encouraged to contact a medical provider via telephone to discuss escalating symptoms or other symptoms they wish to speak about privately.

9.4 Data disclosure

Research data will not be shared with anyone outside of the University of Pennsylvania.

9.5 Data safety and monitoring

The researchers will form a Data Safety Monitoring Board only if the Penn IRB requests or recommends it.

9.5.1 Research Materials and Maintenance of Data Security

The study involves data collected with protection of confidentiality. Study and survey data collected during the baseline and subsequent visits will be kept electronically secure as described in the Data confidentiality above. No one but the PI, project manager, and study staff responsible for the follow up will have access to these files. Any data used for results will only be presented in a de-identified manner in the aggregate.

9.5.2. Study Monitoring

All protocols and consent forms belonging to this project will be fully approved by the IRB before implementation. The Co-PIs (Delgado and Chaiyachati), co-investigators, the project managers, and others will monitor study accrual, data quality and adverse events continuously.

9.5.3. Monitoring Procedures

The researchers will form a Data Safety Monitoring Board only if the Penn IRB requests or recommends it.

If the researchers are requested to form a DSMB, authority for monitoring data and safety will reside exclusively with an independent external DSMB in collaboration with the study statistician and one patient investigator (non-voting members); ultimate responsibility for the conduct of this study will reside with the CO-PIs (Delgado and Chaiyachati). Written standard operating procedures and standard best practices regarding the protection of Human Subjects will be used to guide the training of involved research staff and the enrollment and interventions with subjects during and after their clinical visit.

9.5.4. Data Management

The project managers (Hemmons and Kelly) will oversee data management and management procedures will be developed and monitored by the CO-PIs (Delgado and Chaiyachati). The project managers will conduct monthly quality assurance on the various data streams to ensure consistency and validity. They will make the PIs aware of any missing data and/or issues with data collection, storage, or management.

9.5.5. Unanticipated Problems

All unanticipated problems related to the treatment or assessment sessions will be reported to the primary PI for the duration of the study. The PI is responsible for identifying potential unanticipated problems experienced by study participants, adjusting the intervention accordingly and reporting the experience.

9.6. Risk/Benefit Assessment

9.6.1 Potential study risks

Patients with COVID-19 may have quickly deteriorating health conditions. Penn Medicine OnDemand was created to ensure patients have access to COVID-19 related clinical support 24/7. Patients enrolled in COVID-Watch are monitored by Penn Medicine OnDemand and patients who report escalated symptoms are instructed to go to the Emergency Department or contacted by a clinician within an hour.

There is a risk of breach of confidentiality for participants, as they participate in the COVID-Watch programs through their personal mobile phones. As with all forms of electronic communication there is risk that information may not remain confidential through individual access. All participants have been made aware of this through the enrollment process, and participants are notified how to unenroll at any time if they feel they or their data are not safe.

Additionally, there is a risk of breach of confidentiality of data extracted from patient medical records. The steps taken to mitigate this risk are provided in the Data Management section. Only those on the research team will have access to the Way to Health platform study page, and will need to sign in with their unique username and password to access records. Way to Health is maintained on secure PMACS servers that are encrypted.

9.6.2 Potential study benefits

There is a direct benefit to patients that enroll into the COVID-Watch program. Patients enrolled into the program will have constant monitoring of their symptoms and a direct pathway to escalation of care if warranted by their care team. There is also an indirect benefit for patients, as this builds a network of rigorously and academically tested telemedicine for patients that have historically and disproportionally had lower access to care, while having higher rates of underlying chronic illness.

9.6.2.a. Importance of the knowledge to be gained

There is a lack of evidence and rigorous evaluations regarding telemedicine. Knowledge gained from this research could optimize how providers interact with patients that have traditionally had lower access to care. Traditional in-person ambulatory care visits risk spreading infection. The efficacy of telemedicine must be analyzed, as the pandemic has caused an exponential increase in its use to ensure patients are receiving proper care through this transition.

9.6.3 Risk/benefit assessment

This study is minimal risk.

10. Investigators

Principal investigators: Overall responsibility for protocol development, intervention development, budget overview, data dictionary development, ethical approval, trial registration, trial oversight, and the data and safety monitoring board, assessment of overall recruitments, potential, data analysis, and dissemination and presentation of results.

Co-Investigators: Also, protocol development, data dictionary development, trial oversight, dissemination of results.

10.1 Principal Investigators

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B. Final Study Protocol

1. Abstract

The clinical guidance for 90 percent of infected COVID-19 adult patients who do not meet eligibility for inpatient admission is to self-isolate. To support these patients, alternatives to in-person care are needed to manage an unpredictable clinical course; identify and intercept patients rapidly deteriorating at home, prevent viral spread during in-person visits; and minimize future surges in emergency departments (EDs). In addition, fingertip pulse oximeters have been proposed to improve in-home early detection of respiratory deteriorations but are untested and the operational infrastructure to support large-scale monitoring is limited.

While telemedicine has been widely adopted during the pandemic as an alternative to conventional outpatient care, limited telemedicine access may be exacerbating observed disparities for Black and Latino patients. In the health system, Black and Latino patients used video-visits 15 percent less often than white patients. Text messaging and phone calls may improve healthcare access for communities of color, but the evidence for these telecommunication modalities to be effective and improve equity are limited.

The University of Pennsylvania Health System (UPHS) developed and deployed COVID Watch to improve access to health care for COVID-19 patients who are self-isolating at home. COVID Watch sends twice-daily, scheduled text messages to assess patients for shortness of breath using a clinical algorithm to determine whether patients need an urgent escalation to a team of dedicated, on-call nurses within one hour. These nurses are supported by an on-call team of clinicians who can conduct urgent phone or video assessments. Patients can also trigger the algorithmic assessment independent of the scheduled messages. As of May 21, 2020, COVID Watch has managed 3,628 COVID-19 patients at home, of which 1,295 are confirmed COVID-19 positive; of these, 61 percent are Black or Latino, higher than the proportion of all UPHS COVID-19 positive patients that are Black or Latino (55 percent).

2. Overall objectives

The objective of this study is to conduct a pragmatic randomized controlled trial to determine the incremental benefit of providing home pulse oximetry for patients enrolled in COVID Watch.

3. Aims

3.1 Primary outcome. The primary outcome measure is the difference in Days Alive and Out of Hospital.

3.2 Secondary outcomes. The secondary outcome measure is the difference self-reported anxiety on a single question adapted from the Emotional Distress-Anxiety Short Form 4a scale on day 0, 7, and 14 after enrolment in COVID Watch.

3.3 Exploratory outcomes. The researchers will explore several other outcomes of interest. These included differences in: 1) 30-day mortality; 2) incidence and timing of remote monitoring escalations to nursing care and subsequent emergency department referrals; 3) health care utilization including outpatient, emergency department, inpatient, and ICU care; 4) self-perceptions of feeling safe at managing illness; and 5) rates of discordance between dyspnea symptoms and hypoxia as measured on home pulse oximetry.

4. Background

Most (80-90%) COVID-19 positive patients are asked to self-isolate at home because they do not qualify for home care or inpatient admission.1,2 Alternatives to in-person care are urgently needed to: (1) manage an unpredictable clinical course; (2) identify and intercept patients rapidly deteriorating at home, (3) prevent viral spread during in-person visits; and (4) triage symptoms to minimize surges to emergency departments (EDs).3-9 In addition, fingertip pulse oximeters ("pulse oximetry") have been proposed to improve in-home early detection of respiratory deteriorations but are untested and the operational infrastructure to support large-scale monitoring is limited.10-12 While telemedicine has been widely adopted during the pandemic as an alternative to conventional outpatient care, worse COVID-19 outcomes observed among Black and Latino patients may be due, in part, to worse telemedicine access for these socially and medically disadvantaged groups.13-20

To improve in-home monitoring and health care access for patients with suspected or confirmed COVID-19, the team in the University of Pennsylvania Health System ("UPHS") developed COVID Watch, a free of charge, 24/7, automated, text message-based, home monitoring program across UPHS' large geographic catchment area. This study will answer the question, "How does the addition of pulse oximetry affect clinical outcomes for COVID-19 patients?"

COVID Watch was first implemented on March 24, 2020 and has enrolled 3,628 patients through May 21, 2020 of which 1,295 were COVID-19 positive. Understanding the effect of COVID Watch with and without pulse oximetry on Black and Latino patients is important because communities of color have had disproportionately higher rates of COVID-19 morbidity and mortality nationally,21-23and locally in Pennsylvania, ranking 5th total deaths, 24 and New Jersey, ranking 2nd.24 Symptom monitoring apps and programs are commercially available.25-30 However, COVID Watch is uniquely embedded into its host healthcare system, UPHS. Patients are enrolled using the electronic medical record (EMR), escalations are addressed by UPHS nurses, and they are referred to UPHS-based telemedicine, primary care, and social services when appropriate. COVID Watch is a scalable operational platform for monitoring patients with home pulse oximetry readings. Whether remote monitoring with or without pulse oximetry helps COVID-19 patients stay safe at home is an urgent, patient-centered question.10,31,32 Finally, with COVID-19 surges projected in late 2020, health systems will need to be prepared with evidence-based strategies for managing more COVID-19 patients at home.33,34

COVID Watch (https://covidwatch.waytohealth.org/) is powered by UPHS' NIH-funded research and operational texting platform (www.waytohealth.org), integrated with UPHS' EMR. Since hypoxemia is the primary driver of admission and fatality among COVID-19 patients, the researchers focused the algorithm (Appendix Fig 1-3) on shortness of breath, the closest approximation for concerning hypoxemia.9,35,36 Given the rapid and unpredictable decompensation of COVID-19 patients, patients receive clinical support 24 hours/day, 7 days/week.4,37-39 COVID Watch sends twice-daily, scheduled text messages to assess patients for shortness of breath using an algorithm to determine whether patients need an urgent escalation to a team of dedicated nurses within 1 hour (Appendix Fig 4). These nurses are supported by an on-call team of clinicians who can conduct urgent phone or video assessments. At each level patients' clinical needs are either managed with self-care advice, prescriptions, or a referral to the ED. The majority of COVID Watch patients (83.7%) have been enrolled by outpatient providers conducting telephone and video visits; 8.7% and 7.6% have been enrolled at ED and inpatient discharge, respectively. The program is available at all six of UPHS's hospitals and EDs, and all 530 affiliated ambulatory settings using the EMR. Any clinical staff member (e.g., RN, physician, medical assistants) logged on to the EMR is able to enroll patients (Appendix Fig 5). Patients can also trigger the algorithmic assessment independent of the scheduled messages. Patients only receive the intervention if they are agreeable ("opt-in") and can stop anytime. Patients are scheduled to be in COVID Watch for 14 days, with the option to extend to 21 days if interested. A Spanish-language version of COVID Watch was made available to patients on May 18, 2020, with nurses using translation lines to communicate with patients.

COVID Watch engagement is high. To date, nearly 80% of enrolled patients have engaged with the program, defined as responding to scheduled text messages at least once every two days. RNs have managed over 600 calls with a mean response time (median) of 25 minutes (11 minutes). Of the calls, 37% were asked to continue to monitor at home, 41% were scheduled for an urgent follow-up telemedicine visit, and 9% were sent to the ED for emergent evaluation.

Here the researchers provide a conceptual model of how adding home pulse oximetry may potentially improve outcomes. Preventing or aggressively treating respiratory failure is essential for patients infected with COVID-19. Among all infected patients, an estimated 10-20% of patients with COVID-19 develop severe illness requiring hospitalization, of which 30-40% develop critical illness requiring support in an intensive care unit.40 Among the critically ill, respiratory failure is common and results from acute hypoxemic respiratory failure due to acute respiratory distress syndrome (ARDS).40 ARDS is a clinical manifestation of pulmonary tissue inflammation, preventing the exchange of oxygen between inhaled air and blood circulating in patients' lungs ("hypoxemia"). Increasing the concentration of oxygen in the air that patients breathe (e.g., supplemental oxygen) and reducing the degree of pulmonary inflammation can support patients with COVID-19 by reducing the severity of hypoxemia and providing sufficient oxygen supply to vital organs. Measures of pulse oximetry – the oxygen saturation in the blood – can provide an objective measure to identify which patients have or are beginning to experience declines in their respiratory function.41

The conceptual model (Figure 1) is based on emerging evidence that early medical interventions can improve clinical outcomes for COVID-19, resulting in less severe clinical sequelae and reduced mortality. For COVID-19 patients requiring supplemental oxygen, new preliminary data from a large multicenter randomized controlled trial of dexamethasone indicates that patients have markedly reduced mortality when given dexamethasone.42 This corticosteroid likely reduces pulmonary inflammation and prevents the development of severe ARDS. These findings suggest that earlier treatment for patients who develop more severe forms of COVID-19 may prevent unwanted outcomes. Secondly, there is additional evidence that remdesivir can speed recovery and reduce hospital days among patients with COVID-19.43 Finally, there is promising data that simple changes in ED care and hospital practices may improve outcomes. For example, "awake proning," which involves positioning an awake, non-intubated patients at regular intervals onto their abdomen with their face down can enable greater recruitment of lung tissue for oxygen exchange and reduce the need for subsequent intubation and mechanical ventilation.44,45 These sorts of interventions can reduce the days that patients spend in the hospital, prevent complications such as ventilator associated pneumonia, and reduce mortality related to COVID-19.

Respiratory decline needs to be identified early for patients to benefit from early medical interventions. Respiratory decline can be (a) signaled when patients report the sensation of feeling "shortness of breath" or "difficulty breathing" (i.e., dyspnea), or (b) identified when the concentration of oxygen in patients' blood or oxygen saturation are objectively measured. Current models of care ("Usual Care"), even with expanded telemedicine access, rely on patients contacting providers - a reactive process. This reactive process can delay care because most primary care practices use an intermediary (e.g., a staff member or message inbox) to screen communications for busy clinicians. Many practices do not respond to patients' concerns efficiently overnight or on weekends. These processes frustrate patients because they are concerned about contacting their providers for mild changes, irrespective of the time or day the event is occurring, because they are concerned about respiratory failure. This process is even harder for patients with limited primary care or telemedicine access or language barriers, problems disproportionately faced by Black and Latino communities. In contrast, COVID Watch is a proactive process, requesting patients report symptoms twice a day, and patients can trigger a phone call to a nurse within an hour by simply texting. COVID Watch + pulse oximetry mirrors COVID Watch but can proactively detect respiratory decline using an objective measure of oxygen saturation. In addition,

COVID Watch is available free of charge and is now available in Spanish, with over 85 Spanish speaking patients enrolled to date.

To not overburden emergency departments (EDs), respiratory decline needs to be identified accurately. Both unnecessary escalations of care to the ED for patients with mild COVID-19 and delayed detection of respiratory decline in patients with severe COVID-19 may occur when managing patients with COVID-19. For usual care and COVID Watch, clinicians are reliant on the subjective sensation of dyspnea. Dyspnea is concerning enough that patients are often redirected to an urgent care center or emergency department so patients can have their oxygen saturation measured. Referring patients with an oxygen saturation <94% would justify redirecting patients to the ED for additional clinical evaluation and supportive therapy. Referring patients with mild dyspnea who turn out to have a normal oxygen saturation (Figure 2A) may be a burden to patients and their families and requires additional resource from EDs and hospitals. During times of rapid rises in community infection rates, or surges, efficient resource allocations are imperative for supporting patients who are critically ill. At the same time, patients still benefit from enhanced connections with clinical providers to reassure them that they are not experiencing respiratory decline. COVID Watch, supplemented by pulse oximetry, could provide this highly responsive team of clinicians objective data so they can accurately assess a patient's respiratory state.

In an alternative scenario, patients may have low oxygen saturation without the sensation of dyspnea, a phenomenon unique to COVID-19 infected patients, and is commonly known as "silent" or "happy" hypoxemia (Figure 2B).31 These patients receive medical interventions late because they are unaware they are hypoxemic. There have been reports of COVID-19 patients arriving in EDs with profoundly low oxygen saturation levels with relatively little or no dyspnea.10 This has led to proposals to use home pulse oximetry to detect silent hypoxemia which have been widely reported in the media (e.g. New York Times) and resuscitation medicine forums.46,47 To address this phenomenon, the Vermont Department of Public Health has implemented a program to mail pulse oximeters to newly diagnosed COVID-19 cases 24-48 hours after contact tracing interviews.48 But as reported in Science: "No one, however, has studied whether early detection of hypoxia might head off bad outcomes. Some physicians believe pulse oximeters are best used with a doctor's guidance, perhaps through telemedicine. With many COVID-19 patients frightened to visit a hospital and arriving only when their symptoms have dangerously advanced, doctors also wonder whether home monitoring could hasten treatment—and whether, for some, that could make all the difference."31

Based on lack of studies determining whether pulse oximetry can hasten treatment for patients deteriorating at home relative to the current standard of care in the health system of automated text messaging paired with telemedicine, the researchers believe there is equipoise between these two treatment strategies: automated text messaging with telemedicine vs. automated text messaging with telemedicine plus pulse oximetry. Therefore, a randomized comparison is needed to guide health system programs to better address this pandemic.

5. Study design

5.1 Design

Study design and hypotheses. This will be a pragmatic randomized controlled trial to test the effect of adding home pulse oximetry to patients being started on COVID Watch as part of their routine care.49 In this adaptation to COVID Watch, after being deemed safe for outpatient management and started on COVID Watch patients will be randomly selected to receive a pulse oximeter via overnight mail with educational materials (Appendix Fig 6).

Patients sent a pulse oximeter will be prompted twice daily to text their oxygen saturation level after walking in place for 1 minute. If the oxygen saturation decreases by 3 percentage points or more to a level below 95% or if it falls below an absolute level of 90%, the patient will receive an immediate call from the same on-call RNs for COVID Watch and undergo the same triage protocol. Hypotheses: Provision of pulse oximetry will lead to a higher number of Days Alive and Out of Hospital and Emergency Department (H2a), particularly among Black and Latino patients (H2b) compared to COVID Watch alone.

Choice of study design. The researchers have chosen a pragmatic randomized control trial because it is the most rigorous design for obtaining causal effects of providing pulse oximeters to a remote home monitoring program for COVID-19 in real world settings with diverse populations while accounting for time-varying trends, such as advances in treatment that occur during the study period.

5.2 Study duration

The study is expected to take 18 months to conduct, an expedited time frame in order to make results available as quickly as possible in the midst of the COVID-19 pandemic: 2 months for planning and approvals; a minimum of 5 months for data collection to reach the target sample size; 3 months for analysis, and 8 months for dissemination of results.

5.3 Target population

The study population will be COVID-19 patients participating in COVID Watch as part of routine care via (1) outpatient testing, (2) ED/Inpatient COVID-19 testing with subsequent ED discharge or (3) ED/Inpatient testing with subsequent hospital discharge. Patients will be excluded from the trial if they are: 1) less than 18 years of age; or 2) were already participating in an alternate monitoring program (e.g., home health care, inpatient rehab, specialized remote monitoring programs for a defined patient group such as those with pregnancy, cancer, or deemed high-risk upon ED discharge). Recruitment will begin as soon as possible (target October 1) and proceed to approximately March 1, 2021, in order to provide reports in Year 1 of this investigation and meet the enrollment quota based on the sample size calculations (see below) and current COVID Watch patient volume (currently ~60 patients per week as of August 21. 2020).

5.4 Accrual

This is an evaluation of a health system intervention involving patients treated in 5 emergency departments and 530 affiliated outpatient practice sites at the University of Pennsylvania Health System that already places patients with suspected COVID-19 into a remote home monitoring program as part of usual care.

5.5 Key inclusion criteria

The study population will be patients with suspected or confirmed COVID-19 started on COVID Watch as routine care via (1) outpatient COVID-19 testing or (2) ED/Inpatient COVID-19 testing with subsequent ED discharge or (3) ED/Inpatient testing with subsequent hospital discharge.

5.6 Key exclusion criteria

Patients will be excluded if they are: 1) less than 18 years of age; or 2) were already participating in an alternate monitoring program (e.g., home health care, inpatient rehab, specialized remote monitoring programs for a defined patient group such as those with pregnancy, cancer, or deemed high-risk upon ED discharge)

6. Subject recruitment

Since this is an evaluation of a health system intervention, patients will not be recruited or enrolled individually but instead an analysis will be conducted based on interactions with the health system. Based on target sample size estimates below, the researchers are seeking to enroll at least 1078 patients.

7. Subject compensation

No compensation will be offered in this study.

8. Study procedures

8.1 Consent

This trial will be conducted under a waiver of the requirement for informed consent based on the following criteria set for forth by the Federal Policy for the Protection of Human Subjects (the "Common Rule"):

1. The research involves no more than minimal risk to subjects.
2. The waiver will not adversely affect the rights and welfare of the subjects.
3. The research cannot be practicably conducted without a waiver of the requirement for informed consent.

The research involves no more than minimal risk to subjects. The risks to subjects of participating in this study is no more than minimal because both interventions exceed the standard of care routinely provided to patients diagnosed with COVID-19 managed at home. The current standard of care for patients with COVID-19 who are residing at home is to go to the ED for worsening symptoms. UPHS has implemented COVID Watch to enhance this standard of care by providing text-based assessments, two times a day for 14 days and escalates care to a nurse via telemedicine for any reported worsening of symptoms not severe enough to recommend going to the ED immediately. This service is provided free of charge to patients, a benefit to patients without insurance or established primary care. UPHS already offers a version of COVID Watch with pulse oximetry to patients with COVID-19 being discharged from the ED who meet specific criteria: a discharge pulse ox less than 95%, an infiltrate on chest x-ray, are or age of 60 years or older, or who are deemed by the ED clinician to have significant comorbid conditions. For this study, additional patients will be offered pulse oximetry, those eligible for COVID Watch but not meeting these additional criteria used in the ED. These individuals will be randomized to receive a pulse oximeter via overnight mail. Patients who prefer not to use the pulse oximeter will be free not to and continue on in COVID Watch. Those who use the pulse oximeter will still be escalated to a nursing assessment if they report a worsening of their respiratory symptoms even if they report a normal pulse oximetry reading. Furthermore, pulse oximetry devices are commercially widely available for patients to purchase, and patients may choose to use a pulse oximetry device irrespective of randomization for this study.

The waiver will not adversely affect the rights and welfare of the subjects. The intervention arm of this study (i.e., those randomized to receive a pulse oximetry) does not disrupt their eligibility or ability to receive care from the COVID Watch program. Therefore, the researchers do not anticipate the waiver will adversely affect the rights and welfare of subjects. Patients will retain the full right not to use the mailed pulse oximeter in addition to COVID Watch. A statement on the existing COVID Watch website will indicate that their data may be anonymized and used to study the impact of the program. The website will provide the contact information for a research coordinator if the patient wishes to not have their data to be analyzed for research purposes. The text message invitation to enroll in COVID Watch will include a link to this information. This statement will continue to be pushed to all patients placed into COVID Watch during the course of this trial.

The research aims cannot be practicably conducted without a waiver of the requirement for informed consent. This trial seeks to evaluate the effectiveness of adding home pulse oximetry to the existing, standard of care COVID Watch remote monitoring program in an overall population of patients with suspected or confirmed COVID-19. Requiring individual informed consent would introduce important selection biases. Specifically, socioeconomically disadvantaged populations who have experienced the greatest burden from COVID-19 have historically participated in research at lower levels than the general population and would be less likely to enroll in this study. A major goal of this study is to understand and create knowledge that is generalizable to these marginalized populations. Furthermore, unlike a drug trial where outcomes are primarily determined by physiologic effects of a medication, in this study of behavioral interventions, those who consent are likely to have behavioral characteristics that are not representative of those who would not consent and therefore potentially biasing the outcomes of a behavioral study. Therefore, requiring consent would render the study invalid since it would not have generalizability in applying to the desired population, particularly those experiencing the greatest disparities in outcomes due to COVID-19. Second, requiring informed consent would lead to delays in the distribution of pulse oximeters for a condition with an intense, but short disease course that could further reduce the generalizability of study results for health systems considering pulse oximeters for COVID-19 patients.

8.2 Procedures

1. Patients are started on COVID Watch as routine care based on confirmed or clinical suspicion for COVID-19 via the integration of the Way To Health (W2H) platform with the electronic health record.

2. Patient receives a text message to proceed in COVID Watch as is current routine care.

3. For this study, W2H auto-generates and sends the study's Research Coordinator (RC) a daily excel report with a list of new COVID Watch enrollees at regular intervals (e.g., every 2 hours). The report includes the randomized arm assignment (COVID Watch or COVID Watch + Pulse Oximetry), along with the patient's phone number.

4. The RC alerts patients randomized to COVID Watch + Pulse Oximetry via phone call and/or text message that there will be a next day pulse ox device delivery and that once received, the patient will start to measure and report their oxygen levels. The RC confirms the patient's mailing address and instructs patients that in the meantime, they should continue to respond to COVID Watch check-ins per standard protocol. The patient is instructed to text or call once they have received the pulse oximetry device. If language preference is Spanish, an interpreter is required on the call.

i. If the patient cannot be reached by text, the RC calls and if necessary, leaves a voicemail and the patient will still be sent a pulse ox.

5. The RC sends a pulse oximetry device via UPS 11am and 5pm. The package will include a pulse oximetry device (with barcode), printed patient instructions in the appropriate language, and prepaid, labeled return envelope to be used at the end of their COVID Watch enrollment

6. The RC logs device identifier, date and time of drop off of package for each patient

7. The RC tracks device receipt (via both UPS tracking and/or patient self-report) and contacts the patient via text and/or phone call to ensure the patient understands how to use the device. If language preference is Spanish, an interpreter is required on the call.

8. The RC changes patient protocol from COVID Watch to COVID Watch + Pulse Oximetry.

9. The RC follows up with patients via text and/or phone call in the event that the device is not returned within 2 weeks of being discharged from COVID Watch

9. Human research protection

COVID Watch patients. The target population for the COVID Watch program will be any patient 18 or older evaluated and tested for suspected COVID-19 throughout any of the Penn Medicine access points, including the Emergency Department, calls to the hospital or outpatients centers, occupational health, and testing sites. Using established clinical resources as well as Penn OnDemand telehealth system, patients will be presented the option to enroll in the COVID-Watch program.

COVID Watch (https://covidwatch.waytohealth.org/) is an automated, text-based, remote monitoring program for patients infected with COVID-19 (i.e., laboratory confirmed). The intervention was designed by a team of clinical, technological, innovation, and analytic experts. Since hypoxemia is the primary driver of admission and fatality among COVID-19 patients, the researchers focused the algorithm on dyspnea, or shortness of breath, the closest approximation for concerning hypoxemia. Given the rapid and unpredictable decompensation of COVID-19 patients, patients receive clinical support 24 hours/day, 7 days/week. COVID Watch sends twice-daily, scheduled text messages to assess patients for shortness of breath using an algorithm to determine whether patients need an urgent escalation to a team of dedicated, on-call nurses within 1 hour. These nurses are supported by an on-call team of clinicians who can conduct urgent phone or video assessments. At each level patients' clinical needs are managed either via self-care advice, prescriptions, or referral to the ED. Patients are able to text the dedicated COVID Watch phone number and receive a response from clinical support within an hour.

Pulse Oximeter. The pulse oximeter device is used to monitor a patient's oxygen saturation levels in the body. The device is small and lightweight and is placed on the finger for measurement. As part of COVID Watch, patients are instructed on how to use the device and understand and report its readings. During enrollment into COVID Watch, the patient's baseline oxygen saturation level (SpO2) is collected and entered into Way to Health. During COVID Watch monitoring period the patient will collect SpO2 measurements. Patients with a decrease in SpO2 by 3 or more percentage points to a level below 95% or with a reading below an absolute value of 90% triggered a care escalation alert to COVID Watch telemedicine clinician team via Way to Health.

Pulse Oximeter data is automatically stored in Way to Heath and will be extracted from Way to Health platform in .csv format and stored on PMACs secure server.

9.1 Data confidentiality

All data will be stored on Penn Medicine Computing Services Servers. The Penn Medicine Academic Computing Services (PMACS): PMACS will store all data securely. The data center is housed in Information Systems and Computing at 3401 Walnut Street. All data for this project will be stored on the secure/firewalled servers of the PMACS Data Center, in data files that will be protected by multiple password layers. These data servers are maintained in a guarded facility behind several locked doors, with very limited physical access rights. They are also cyber-protected by extensive firewalls and multiple layers of communication encryption. Electronic access rights are carefully controlled by UPenn system managers. This multi-layer system of data security, identical to the system protecting the University of Pennsylvania Health Systems medical records, greatly minimizes the risk of loss of privacy.

Patient medical record data: electronic medical record data will be extracted from patient medical records (EPIC) via a report created by the Data Analytics Center (DAC) at Penn Medicine. The report will run weekly and be placed in a folder in a PMACs or UPHS secure shared drive. This DAC report has already been created by staff on the Penn Medicine COVID-19 Registry team. The Penn Medicine COVID-19 Registry team will provide support for this project and their staff will access the report to save data points needed for this project in a different file described below. Access to this DAC report is limited to those with institutional approval to access the report. Approval is granted only for staff with HIPAA and CITI training. The file created by the Penn Registry team for this project will be saved onto a secure PMACs or UPHS drive only accessible by the team on this protocol (via password protection) or using the Penn Secure Share encrypted document sharing mechanism. The file will then be saved to a secure shared drive on PMACs server for staff access. The file will be saved with password protection and only those staff who need access to the file will be provided the password. The limited dataset will remain on this secure shared drive until the follow-up data collection and analysis is complete. Participants will be assigned a STUDY ID listed on the DAC report to match data from other sources (i.e. Way to Health).

Way to Health data: Any datasets and computer files are referred to by study ID. The study ID is also used on all analytical files. All personal information that the participant is asked to provide will be collected via Penn's Way To Health study platform. Way To Health collects subjects' names and phone numbers. They also request the name and phone number of an alternate contact. To assure that participant confidentiality is preserved, individual identifiers are stored in a single password protected system that is accessible only to study research, analysis and IT staff. An investigator or statistician who logs in will be able to access only non-identifiable data. The Way To Health administrative group and research coordinators responsible for contacting participants for follow-up study visits or responding to questions about the study are able to view participant names and contact information. The WTH web development team and Project Director currently have administrative access to PHI. All of these personnel will have completed Human Subjects Protection and HIPAA privacy training. The system automatically generates logs of all data queries which can be reviewed by research staff to ensure that no unauthorized persons have gained access to identifiable information. This system is hosted on site at The University of Pennsylvania and is protected by a secure firewall and several layers of operational security. Once a participant has been entered into this system, they are given a unique study identification number (ID). Any datasets and computer files that leave the firewall are stripped of all identifiers and individuals are referred to by their study ID. The study ID is also used on all analytical files. The Penn Medicine Academic Computing Services (PMACS) is the hub for the hardware and database infrastructure that supports the project and the Way To Health web portal is built on this infrastructure. The data collected for Way To Health based studies is

stored in mySQL databases on a PMACS-operated blade server environment devoted specifically to Way To Health. Every SQL transaction, including accessing and changing data, is logged for auditing purposes. Data are entered into the database through several different mechanisms. Participants enter their own personal information and respond to surveys through a PHP-based web interface. Researchers have a separate interface that allows them to manually enter data if needed. Datasets are stripped of all personally identifiable information when exported for analysis. The web application automatically removes all identifiers when a researcher requests an analytic dataset. The only people with access to identifiable participant information are pre-specified Research Coordinators responsible for contacting participants for follow-up. Personal information and research data will be stored in separate SQL tables and will be linked by a computer-generated ID number. Additionally, any information that leaves this system to communicate with third party data sources (i.e., survey software) is stripped of any identifiers and transmitted in encrypted format.

9.2 Subject confidentiality

All participant data will be through COVID Watch or the electronic medical record. There will be no paper records or other forms of data collection. Therefore, subject confidentiality will be maintained through the data protections described above in section 11.1.

9.3 Subject privacy

All data abstracted from the medical chart will be placed onto PMACS servers, all text responses will be secured on the Way to Health platform and no one but the PI, project manager, and study staff responsible for the will have access to these databases. Participants are educated about best practices for mobile phone privacy upon enrollment into the program. Patients are encouraged to contact a medical provider via telephone to discuss escalating symptoms or other symptoms they wish to speak about privately.

9.4 Data disclosure

Research data will not be shared with anyone outside of the University of Pennsylvania.

9.5 Data safety and monitoring

The researchers will form a Data Safety Monitoring Board only if the Penn IRB requests or recommends it.

9.5.1 Research Materials and Maintenance of Data Security

The study involves data collected with protection of confidentiality. Study and survey data collected during the baseline and subsequent visits will be kept electronically secure as described in the Data confidentiality above. No one but the PI, project manager, and study staff responsible for the follow up will have access to these files. Any data used for results will only be presented in a de-identified manner in the aggregate.

9.5.2. Study Monitoring

All protocols and consent forms belonging to this project will be fully approved by the IRB before implementation. The Co-PIs (Delgado and Chaiyachati), co-investigators, the project managers, and others will monitor study accrual, data quality and adverse events continuously.

9.5.3. Monitoring Procedures

The researchers will form a Data Safety Monitoring Board only if the Penn IRB requests or recommends it.

If the researchers are requested to form a DSMB, authority for monitoring data and safety will reside exclusively with an independent external DSMB in collaboration with the study statistician and one patient investigator (non-voting members); ultimate responsibility for the conduct of this study will reside with the CO-PIs (Delgado and Chaiyachati). Written standard operating procedures and standard best practices regarding the protection of Human Subjects will be used to guide the training of involved research staff and the enrollment and interventions with subjects during and after their clinical visit.

9.5.4. Data Management

The project managers (Hemmons and Kelly) will oversee data management and management procedures will be developed and monitored by the CO-PIs (Delgado and Chaiyachati). The project managers will conduct monthly quality assurance on the various data streams to ensure consistency and validity. They will make the PIs aware of any missing data and/or issues with data collection, storage, or management.

9.5.5. Unanticipated Problems

All unanticipated problems related to the treatment or assessment sessions will be reported to the primary PI for the duration of the study. The PI is responsible for identifying potential unanticipated problems experienced by study participants, adjusting the intervention accordingly and reporting the experience.

9.6. Risk/Benefit Assessment

9.6.1 Potential study risks

Patients with COVID-19 may have quickly deteriorating health conditions. Penn Medicine OnDemand was created to ensure patients have access to COVID-19 related clinical support 24/7. Patients enrolled in COVID-Watch are monitored by Penn Medicine OnDemand and patients who report escalated symptoms are instructed to go to the Emergency Department or contacted by a clinician within an hour.

There is a risk of breach of confidentiality for participants, as they participate in the COVID-Watch programs through their personal mobile phones. As with all forms of electronic communication there is risk that information may not remain confidential through individual access. All participants have been made aware of this through the enrollment process, and participants are notified how to unenroll at any time if they feel they or their data are not safe.

Additionally, there is a risk of breach of confidentiality of data extracted from patient medical records. The steps taken to mitigate this risk are provided in the Data Management section. Only those on the research team will have access to the Way to Health platform study page and will need to sign in with their unique username and password to access records. Way to Health is maintained on secure PMACS servers that are encrypted.

9.6.2 Potential study benefits

There is a direct benefit to patients that enroll into the COVID-Watch program. Patients enrolled into the program will have constant monitoring of their symptoms and a direct pathway to escalation of care if warranted by their care team. There is also an indirect benefit for patients, as this builds a network of rigorously and academically tested telemedicine for patients that have historically and disproportionally had lower access to care, while having higher rates of underlying chronic illness.

9.6.2.a. Importance of the knowledge to be gained

There is a lack of evidence and rigorous evaluations regarding telemedicine. Knowledge gained from this research could optimize how providers interact with patients that have traditionally had lower access to care. Traditional in-person ambulatory care visits risk spreading infection. The efficacy of telemedicine must be analyzed, as the pandemic has caused an exponential increase in its use to ensure patients are receiving proper care through this transition.

9.6.3 Risk/benefit assessment

This study is minimal risk.

10. Investigators

Principal investigators: Overall responsibility for protocol development, intervention development, budget overview, data dictionary development, ethical approval, trial registration, trial oversight, and the data and safety monitoring board, assessment of overall recruitments, potential, data analysis, and dissemination and presentation of results.

Co-Investigators: Also, protocol development, data dictionary development, trial oversight, dissemination of results.

10.1 Principal Investigators

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C. Summary of Amendments and Clarifications to Protocol

There were four modifications to the protocol. First, the researchers corrected the care escalation algorithm based on peripheral oxygenation saturation (SpO2) levels to more accurately reflect the original design and operating procedures of the COVID Watch + Pulse Oximetry program. Patients with a decrease in SpO2 by 3 or more percentage points to a level below 95% or with a reading below an absolute value of 90% triggered a care escalation alert to COVID Watch telemedicine clinician team.

Second, prior to randomizing the first participant, the researchers updated study eligibility criteria to include hospitalized patients who were initiated on COVID Watch as part of routine discharge care and exclude any patient already participating in an alternate monitoring program. The rationale for this change was that this design enabled the comprehensive capture of all patients initiated on COVID Watch and more accurately reflect the COVID Watch program's standard operating procedures.

Third, the researchers simplified the patient survey emotional distress and anxiety measure. This modification was also performed prior to randomizing the first patient. The rationale for this change was based on the feedback the researchers received from the community and patient stakeholder advisory committee.

Lastly, the researchers increased the sample size. The rationale for this change was due to a lower-than-expected COVID positivity rate and standard deviation in Days Alive Out of Hospital (DAOH) based on baseline COVID Watch program data through November 30, 2020.

Protocol Version	Amendment or Clarification	Dates
Final	Sample size was increased based on analysis of baseline data prior to trial (see amendment to statistical analysis plan)	12/17/20
	Patient survey emotional distress and anxiety measure was simplified to a single-item anxiety measure	11/02/20
	Eligibility criteria were updated to include hospitalized patients who were initiated on COVID Watch as part of routine discharge care and exclude any patient already participating in an alternate home monitoring program	11/02/20
	Care escalation algorithm based on peripheral oxygenation saturation (SpO2) corrected to reflect original COVID Watch + Pulse Oximetry program design and operation	11/02/20
Original	The approved IRB protocol was considered the original protocol. Approval was granted 10/8/20.	10/08/20

D. Original Statistical Analysis Plan

The primary analysis will be an intention to treat analysis among randomized patients with confirmed COVID-19. The researchers seek to enroll at least 259 Black or Latino patients in each arm to achieve 90% power to detect a mean difference of 2 DOAH, assuming a type I error rate of 0.05. Given that Black and Latino patients comprise 61% of the COVID Watch sample, this indicates a target minimum sample size of at least 850 patients with confirmed COVID-19.

Linear mixed effects models will be used to assess the incremental effect of home pulse oximetry on DAOH relative to COVID Watch alone. Random intercepts will be used to account for clustering by testing site. Randomization will theoretically ensure balance of measured and unmeasured covariates between arms. Factors deemed to be associated with the outcome a priori will be adjusted for to increase efficiency. These include: age, sex, race, ethnicity, insurance, median income of residential ZIP code and ED vs. outpatient enrollment.

The researchers will examine heterogeneity in treatment effects using interaction terms by treatment comparator group and: the following (1) location of enrollment (outpatient vs ED); (2) primary care in the health system (yes or no); (3) insurance (none/Medicaid/Medicare/private); and (4) race/ethnicity, including an evaluation of Black and Latino patients separately. A sensitivity analysis will be performed to compare outcomes to UPHS COVID-19 patients not enrolled in COVID Watch using a propensity score analysis. The researchers will record and report all reasons for dropout and missing data, and account for all patients in reports. Because this research is being conducted in the context of routine care and COVID Watch requires a working cell phone, the researchers anticipate fewer losses to follow-up than is typical.

As secondary analyses, the researchers will repeat the above analyses in the full population of randomized patients now including the population of patients placed into COVID Watch who had suspected COVID-19 but ended up having negative COVID-19 tests.

E. Final Statistical Analysis Plan

The primary analysis will be an intention to treat analysis among randomized patients with confirmed COVID-19. The researchers seek to enroll at least 204 Black or Latino patients in each arm to achieve 90% power to detect a mean difference of 1 DOAH, assuming a type I error rate of 0.05. Given that Black and Latino patients comprise 61% of the COVID Watch sample, this indicates a target minimum sample size of at least 1078 patients with confirmed COVID-19.

As the primary analyses, the researchers will use an intention-to-treat approach. The researchers also performed a per protocol analysis including only those patients who actively participated on their allocated protocol (e.g., responded to at least one text-message check-in). For both analyses, the researchers compared mean DAOH between study groups using two-sample t-tests. Adjustment for covariates via regression was not deemed necessary as all sociodemographic and clinical characteristics were well balanced between arms. The researchers also compared continuous secondary outcomes including mean number of outpatient visits, emergency department encounters, and hospitalizations using t-tests. The researchers compared categorical secondary outcomes using Fisher's Exact test. A prespecified subgroup analysis was completed by comparing outcomes for Black and Hispanic patients to White patients. Exploratory subgroup analyses were conducted for age strata and enrollment context (inpatient, outpatient, and ED). All tests were two-sided and a p-value < 0.05 was considered statistically significant in the primary analyses. In subgroup analyses, to account for multiple testing, Bonferroni corrected p-value cut-offs are provided for the results in the supplementary tables. All analyses were conducted using R statistical software version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

[Below is from original SAP]

Linear mixed effects models will be used to assess the incremental effect of home pulse oximetry on DAOH relative to COVID Watch alone. Random intercepts will be used to account for clustering by testing site. Randomization will theoretically ensure balance of measured and unmeasured covariates between arms. Factors deemed to be associated with the outcome a priori will be adjusted for to increase efficiency. These include: age, sex, race, ethnicity, insurance, median income of residential ZIP code and ED vs. outpatient enrollment.

The researchers will examine heterogeneity in treatment effects using interaction terms by treatment comparator group and: the following (1) location of enrollment (outpatient vs ED); (2) primary care in the health system (yes or no); (3) insurance (none/Medicaid/Medicare/private); and (4) race/ethnicity, including an evaluation of Black and Latino patients separately. A sensitivity analysis will be performed to compare outcomes to UPHS COVID-19 patients not enrolled in COVID Watch using a propensity score analysis. The researchers will record and report all reasons for dropout and missing data, and account for all patients in reports. Because this research is being conducted in the context of routine care and COVID Watch requires a working cell phone, the researchers anticipate fewer losses to follow-up than is typical.

As secondary analyses, the researchers will repeat the above analyses in the full population of randomized patients now including the population of patients placed into COVID Watch who had suspected COVID-19 but ended up having negative COVID-19 tests.

F. Summary of Amendments and Clarifications to Statistical Analytic Plan

There were three modifications to the statistical analytic plan. All modifications were made prior ascertaining outcome.

First, the researchers clarify that Bonferroni was used for corrected p-value cut offs to adjust for multiple comparisons for the race subgroup analyses.

Second, the researchers increased the sample size. The rationale for this change was due to a lower-than-expected COVID positivity rate and SD in Days Alive Out of Hospital (DAOH) based on baseline COVID Watch program data through November 30, 2020.

Plan Version	**Amendment or Clarification**	**Dates**
Final	Sample size was increased	12/17/20
	Clarified plan to use Bonferroni corrected p-value cut offs to adjust for multiple comparisons for the race subgroup analyses	11/02/20
Original	The approved IRB protocol was considered the original statistical analysis plan. Approval was granted 10/8/20.	10/08/20

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