Title

Effect of Antiseptic Mouthwash/Gargling Solutions and Pre-procedural Rinse on SARS-CoV-2 Load (COVID-19): A Structured Summary of a Study Protocol for a Randomized Controlled Trial

ClinicalTrials.gov Identifier:

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Effect of Antiseptic Mouthwash/Gargling Solutions and Pre-procedural Rinse on SARS-CoV-2 Load (COVID-19): A Structured Summary of a Study Protocol for a Randomized Controlled Trial

Protocol contributors

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Abstract

Background: SARS-CoV-2, the virus causing the COVID-19 pandemic, is a health threatening disease especially for people with comorbidities, and for people with high exposure such as health care workers (HCWs) and frontline workers. The virus typically first colonizes in the upper respiratory tract (URT) and can cause clinical symptoms such as cough and sore throat; the virus can move to the lower respiratory tract (LRT) potentially leading to severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and death. The aim of this pilot clinical trial is to investigate the ability of four over-the-counter (OTC), alcohol-free and fluoride-free antiseptic mouthwashes to inactivate SARS-CoV-2 *in vivo* versus distilled water as a control. Another objective of the study is to assess changes in self-reported clinical symptom onset or worsening (e.g. healthcare utilization and hospitalization). In addition, this study will also examine tobacco use, marijuana smoking, or electronic cigarette vaping as possible effect modifiers of the effect of OTC antiseptic mouthwash on SARS-CoV-2.

Methods: In this trial, 150 confirmed COVID-19 positive volunteers will be randomly assigned to 1 of 5 groups: distilled water (H_2O); Chlorine Dioxide (ClO_2) (CloSYS Ultra Sensitive,

Rowpar Pharmaceutical Inc., USA); Hydrogen Peroxide (H_2O_2) (Oral-B Mouth Sore, Proctor & Gamble, USA); Cetylprydinium Chloride (CPC) (Crest Pro-Health Multi-Protection, Proctor & Gamble, USA); or Essential Oils (EO) (Listerine Zero, Johnson & Johnson, USA). Study participants will be masked to the extent possible to the rinse assigned. After collecting a baseline unstimulated saliva, throat wash (gargle lavage), and oropharyngeal swab samples, they will be asked to rinse and gargle with 10-20ml (2-4 teaspoons) of the assigned mouthwash 4 times per day, for 30-60 seconds, for 4 weeks. Post-baseline samples will be collected on days 7, and 28 to compare the viral load.

Discussion: This pilot trial will build on *in vitro* studies and small, limited clinical studies of antiseptic mouth rinses to inactivate the SARS-CoV-2 virus. Considering the many benefits of prevention over treatment, reducing incident cases and decreasing disease severity will be crucial in providing a safe and healthy environment for communities, including HCWs during a pandemic of a novel respiratory coronavirus.

Trial registration: This clinical trial was registered on clinicaltrials.gov on June 1, 2020. The Clinical Trial Identifier is NCT04409873.

Objectives: The objectives of the study are as follows:

- To determine the ability of four over-the-counter (OTC) antiseptic mouthwashes on inactivating SARS-CoV-2 versus distilled water as control.
- To assess changes in self-reported clinical symptom onset or worsening (e.g. healthcare utilization and hospitalization).
- To examine tobacco use, marijuana smoking, or electronic cigarette vaping as possible modifiers of the effect of OTC antiseptic mouthwash on SARS-CoV-2.

- To follow-up with participants after the 1 month of assigned study mouthwash for the next 11 months to evaluate acceptability of the assigned mouthwash after one month, clinical symptoms, and continued mouthwash use.

Keywords: Mouthwashes; SARS CoV-2; Randomized Clinical trial; Saliva; Real-Time Polymerase Chain Reaction

{Note: Numbering in curly brackets refers to items in the SPIRIT guidelines for clinical trial protocols. https://www.spirit-statement.org/}

Title {1}	Effect of Antiseptic Mouthwash/Gargling Solutions and Pre-procedural Rinse on SARS-CoV-2 Load (COVID-19): A structured summary of a study protocol for a randomized controlled trial
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Role of sponsor {5c}	Principal Investigator

Introduction

Background and rationale {6a}

As of July 20, 2021, about a year and half after the onset of coronavirus disease 2019 (COVID-19) pandemic in 2020, about 34 million COVID positive cases and 607,000 deaths have been reported in the United States (US)[1]. Practicing public health safety measures during this period, along with the initiation of COVID-19 vaccination in January 2020 in the US has decreased daily cases to about 8,000 cases[1], however, there are pre-symptomatic, asymptomatic, and symptomatic cases that could transmit virus through respirable and inspirable particles that can be inhaled into the oronasopharynx and colonized in the upper respiratory tract (URT) causing clinical symptoms such as fever, dry cough, sore throat, and nasal congestion. Colonizing in the lower respiratory tract (LRT) causes serious conditions such as severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and death if the disease is not managed properly[3–5]. Therefore, practicing preventive measures seems to help mitigating the risk of transmission and clinical manifestations.

The COVID-19 risk, hospitalization, and death have been reported to be higher among American Indian or Alaska Native (AI/AN), Black or African American, and Hispanic or Latinos[6] with higher percentage among AI/AN than White[2]. Additionally, people with comorbidities such as diabetes, cardiovascular diseases, and chronic renal diseases suffer drastically by COVID-19. Frontline health care workers (HCWs) are at higher risk for exposure to infectious particles' spread when in contact with COVID-19 infected individuals. According to the United States (US) Centers for Disease Control and Prevention, the trend of new cases among HCP shows a decrease from about 13,000 in April 2020 to 190 cases in July 2021. Additionally, as of July 20, 2021, of 517,341 cases of COVID-19 among HCP, about 1700

deaths (0.33%) have been reported (CDC) which has increased compared to April 2020 death cases 27 of 9282 (0.29%)[3], however, it has decreased since vaccination started. Considering the staffing shortages, losing one HCP in this period could increase pressure on the health care system and reduce the workforce, hence, in addition to the vaccination as a primary prevention method, finding methods to decrease COVID-19 transmission via infectious particles can save lives among HCWs and in the community.

The World Health Organization (WHO) has presented comprehensive guidelines underscoring personal hygiene measures including respiratory hygiene against SARS, MERS, influenza, and now COVID-19[8]. While personal protection equipment (PPE), personal hygiene measures, and environmental infection control are crucial in mitigating disease transmission, the current recommended respiratory hygiene measures has not prevented SARS-CoV-2 colonization in URTs and LRTs of infected individuals, or reducing the severity of clinical symptoms. Experimental and clinical research studies on diseases similar to COVID-19 such as SARS, MERS, and H5N1 have shown that using antiseptic mouthwash or gargling solutions, such as products containing chlorhexidine gluconate (CHG), polyvinylpyrrolidone iodine (PVP-I), chlorine dioxide (ClO_2), cetylpyridinium chloride (CPC), and hydrogen peroxide (H_2O_2) could reduce viral load[9–11]. A randomized controlled trial (N=387) showed efficacy and cost-effectiveness of gargling with water or a product containing PVP-I (3X/day, 20 seconds) on URT infections in healthy volunteers (18-65 years) over 60 days from a societal perspective[12]; An *in vitro* study has shown that CloSYS Ultra Sensitive oral rinse could reduce the viral load of SARS CoV 2, SARS CoV and Influenza A H3N2 to varying extent; the viral load reduction of SARS CoV 2 by CloSYS Ultra Sensitive oral rinse was 10-fold more than reduction of SARS CoV in 30s[13]. In another *in vitro* study, three of eight OTC antiseptic mouth rinses were able to

inactivate three strains of SARS-CoV2 in 30s, however, the other five rinses partially inactivated the virus. The active ingredients of those three effective rinses were benzalkonium chloride, chlorhexidine, and povidone iodine[14]. A recent clinical trial has shown that using 1% PVP-I as mouthwash, gargle, and eye or nose drop could significantly reduce COVID-19 related morbidity, mortality, and hospitalization[15].

The CDC's initial interim guidelines for dental settings during COVID-19 suggested that using a pre-procedural rinse with an antimicrobial product (such as chlorhexidine gluconate, essential oils, hydrogen peroxide, povidone-iodine, or cetylpyridinium chloride) could have a potential effect in reducing the level of oral microorganisms in aerosols and spatter generated during dental procedures[7]. In April 2020, the CDC and the American Dental Association (ADA) recommended using a mouthwash containing 1.0-1.5% H_2O_2 as a pre-procedural rinse before dental treatment to reduce SARS-CoV-2 load potentially; however, no US clinical studies have been conducted to support this claim.

This study aims to assess the effect of four over-the-counter (OTC) antiseptic mouthwash/gargling solutions compared to a distilled water control on the SARS-CoV-2 load in unstimulated saliva, throat wash (gargle lavage), and oropharyngeal swab samples. Also, study participants will be assessed for the severity of their clinical symptoms during the study period. The 4-week protocol was selected as studies show people with COVID can continue to shed the virus and potentially transmit to the others for a 2- to 4-week period. This study will also examine tobacco use, marijuana smoking, or vaping as possible effect modifiers of antiseptic mouthwash on SARS-CoV-2. Study participants will be followed up daily via a very short daily questionnaire and every 3 months for the next 11 months after the study is finished for longer-term follow-up via text messaging.

The null hypothesis of the study is that there is no difference between any OTC antiseptic mouthwash solution (Chlorine Dioxide (ClO_2), Hydrogen Peroxide (H_2O_2), Cetylprydinium Chloride (CPC), Essential Oils (EO), and distilled water (H_2O) in reducing SARS-CoV-2 load in unstimulated saliva, throat wash (gargle lavage), and oropharyngeal swab samples (baseline to 4 week follow-up).

Objectives {7}

1a. To assess and compare the SARS-CoV-2 viral load in unstimulated saliva and throat wash (gargle lavage) samples before and after rinse at baseline in Chlorine Dioxide (ClO_2), Hydrogen Peroxide (H_2O_2), Cetylprydinium Chloride (CPC), and Essential Oils (EO) groups versus distilled water (H_2O) group (pre-procedural rinse primary outcome measure).1b. To assess the SARS-CoV-2 viral load reduction of throat wash (gargle lavage) samples from baseline to 4 weeks in Chlorine Dioxide (ClO_2), Hydrogen Peroxide (H_2O_2), Cetylprydinium Chloride (CPC), and Essential Oils (EO) groups versus distilled water (H_2O) group (homecare reduction primary outcome measure).

2. To assess the clinical symptom onset progression and health care utilization (e.g. hospitalization) from baseline to 4 weeks comparing Chlorine Dioxide (ClO_2), Hydrogen Peroxide (H_2O_2), Cetylprydinium Chloride (CPC), Essential Oils (EO) to distilled water (secondary outcome measures).

3. To assess if tobacco use, marijuana smoking, or vaping are effect modifiers of primary outcome measures.

4. To evaluate study participants' in a 12-month follow up.

Trial design {8}

This is a single center, 5-arm, parallel groups, double-blinded (participant, outcomes assessor),

randomized controlled trial of adults who are COVID-19 positive using over-the-counter (OTC) mouthwash/gargling solutions: Chlorine Dioxide (ClO_2) (CloSYS Ultra Sensitive, Rowpar Pharmaceutical Inc., USA); Hydrogen Peroxide (H_2O_2) (Oral-B Mouth Sore, Proctor & Gamble, USA); Cetylprydinium Chloride (CPC) (Crest Pro-Health Multi-Protection, Proctor & Gamble, USA); Essential Oils (EO) (Listerine Zero, Johnson & Johnson, USA) versus distilled water as a control.

Methods: Participants, interventions and outcomes

Study setting {9}

Consenting community-dwelling San Francisco Bay Area (California, USA) participants positive for COVID-19.

Eligibility criteria {10}

Inclusion criteria

- Adults 18 years and older
- Tested positive for COVID-19 with a sample collected in the prior 7 days
- Ability to read and speak in English or Spanish
- Ability to participate in the study for 4 weeks
- Ability to gargle
- Not having any oral condition that might worsen with gargling solutions
- Not having an allergy to a mouthwash ingredient that has been used before
- Not using another mouthwash/gargling solution
- Not taking antimicrobial medications (antibacterial, antiviral (e.g., Truvada), antibiotics including off-label FDA-approved medications such as Remdesivir)

- Have a cellphone and agree to receive text messages for reminders to use mouthwash during the day and for follow-up visits
- Ability to meet with study staff via videoconference (e.g., Zoom, FaceTime, WhatsApp)

Exclusion criteria

- Those who experience severe clinical symptoms which require hospitalization
- Individuals who receive antiviral medications that could potentially affect viral load in their saliva samples
- Pregnancy or lactation for women due to potential aversions to mouthwash solution taste/smell

Who will take informed consent? {26a}

Study Co-PI or a trained bilingual study staff member will confirm the study participants' eligibility based on inclusion/exclusion criteria before obtaining informed consent and the required waiver/authorization form included in supplemental IRB documents.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

The informed consent form (ICF) explains the participant sample collection procedure, lab test, and potential future studies on samples. The ICF explains test results being kept confidential and participants' ability to discontinue the study at any time, without any interference in their COVID-19 related or other health care.

Interventions

Explanation for the choice of comparators {6b}

The comparator control group is distilled water (H_2O) which may help clear microbes from the oral cavity and throat without deactivating SARS-CoV-2 virus. A published randomized clinical

trial and cost-benefit analysis has shown gargling with plain water to be cost effective in reducing URT infections (Sakai et al. 2008). Participants in the control group will be asked to rinse and gargle for 60 seconds with 20ml (4 teaspoons) 4 times per day (including after each meal and before bedtime), for 4 weeks.

Intervention description {11a}

The four OTC alcohol-free, fluoride-free, gluten-free mouthwash intervention groups are as follows: Chlorine Dioxide (ClO_2) (CloSYS Ultra Sensitive, Rowpar Pharmaceutical Inc., USA); Hydrogen Peroxide (H_2O_2) (Oral-B Mouth Sore, Proctor & Gamble, USA); Cetylprydinium Chloride (CPC) (Crest Pro-Health Multi-Protection, Proctor & Gamble, USA); Essential Oils (EO) (Listerine Zero, Johnson & Johnson, USA), which were selected based on being OTC alcohol-free and fluoride-free products legally marketed in the US, each with a different main active ingredient. Participants will be asked to rinse and gargle for 30-60 seconds with 10-20 ml (2-4 teaspoons) of the assigned mouthwash 4 times per day (including after each meal and before bedtime), for 4 weeks.

Criteria for discontinuing or modifying allocated interventions {11b}

In the rare case that a study participant has an adverse experience possibly, probably, or definitely related to the assigned oral rinse, he or she will be instructed to discontinue using the rinse to see if the problem resolves. At the discretion of the participant and investigators, after a problem resolves, the participant may resume using the rinse. If the problem does not resolve, the participant will be instructed to not resume using the rinse; if possible, the participant will be encouraged to still provide the follow-up samples and report symptoms. If a participant's clinical symptoms worsen, he or she will be instructed to contact his or her primary care physician to get

the required medical care for his or her health. A participant can withdraw him- or herself at any time without concern for repercussions about their health care.

Strategies to improve adherence to interventions {11c}

During the study, adherence data will be collected through a daily REDCap questionnaire distributed via SMS text message, asking about the frequency and duration of mouthwash use, as well as clinical symptoms and healthcare utilization.

Relevant concomitant care permitted or prohibited during the trial {11d}

The study participants should not use any other mouthwashes or take any antimicrobial medication (antibacterial, antiviral, antibiotics including off-label usage such as Remdesivir) during the study. They can continue practicing their usual home oral hygiene care (tooth brushing with a toothpaste, and flossing). If they have a dental emergency (e.g. dental infection such as abscess or pulp infection) they should contact their regular dentist for dental treatments according to their dentist's COVID protocols.

Provisions for post-trial care {30}

The antiseptic mouthwash solutions to be used by study participants are safe over-the-counter solutions that are available without requiring dentist's prescriptions, to improve oral health conditions. Unless individuals might be allergic to the ingredients of the study mouthwashes, they will not face any harm and risks when using the solutions. However, research team will provide their phone numbers and emails if participants confront any problems during the study period. If study participants feel any stress and discomfort due to their COVID-19 status, they will be advised to contact their physician and COVID-19 hotlines as soon as possible to receive required health services. After the study is finished, participants will be asked a few questions by texting a link to an online questionnaire designed in REDCap in about every 3 months over the

next 11 months to see how they are doing, their clinical symptoms, acceptability of using the assigned mouthwash during the trial, and their potential use after the trial.

Outcomes {12}

Primary outcome Measure:

- Change in SARS-Cov-2 viral load: Change in RT-PCR SARS-Cov-2 viral load in unstimulated saliva and throat wash (gargle lavage) samples (Time Frame: Baseline to 4 weeks)

Secondary Outcomes Measures:

- Change in self-reported (questionnaire) clinical symptom onset. A symptom checklist will include: cough, runny nose, scratchy/sore throat, fever, chills, fatigue, muscle ache, shortness of breath, diarrhea/nausea/vomiting, loss of taste/smell, and red /painful eye (Time Frame: Baseline to 4 weeks)
- Change in healthcare utilization and hospitalization (Time Frame: Baseline to 4 weeks)

Other Pre-specified Outcome Measures:

- Change in SARS-Cov-2 viral load in tobacco users, marijuana smokers, or vapers (Time Frame: Baseline to 4 weeks)
- Change in self-reported (questionnaire) clinical symptom onset in tobacco users, marijuana smokers, or vapers. A symptom checklist will include: cough, runny nose, scratchy/sore throat, fever, chills, fatigue, muscle ache, shortness of breath, diarrhea/nausea/vomiting, loss of taste/smell, and red /painful eye (Time Frame: Baseline to 4 weeks)
- Change in healthcare utilization and hospitalization in tobacco users, marijuana smokers, or vapers (Time Frame: Baseline to 4 weeks)

Participant timeline {13}

Study participants will remain in the trial for 4 weeks. After completing the intervention, they will be followed up for the next 11 months via text messaging to ask about clinical symptoms and healthcare utilization, experience using mouthwash, and their interest in using mouthwash after the trial.

Sample size {14}

A total of 150 eligible individuals will be enrolled in the trial after providing informed consent and randomly assigned to 1 of 5 groups. This trial is sized to provide precise estimates of effect size for a future definitive trial with at-risk individuals. However, this trial would be able to detect a rather large effect: a sample size of 24 for a mouthwash group and 24 for the distilled water control group is estimated to have 80% power to detect a 2-fold difference in mean values between the 2 groups with a 2-sided alpha=0.05. Assuming 80% retention through 28 days, 30 participants per group at baseline (150 total) will be enrolled.

Recruitment {15}

Two recruitment routes have been planned for this trial:

1- Upon referring to testing centers at UCSF individuals will receive the trial details via a letter or flyer, and if tested positive for COVID-19, they will contact study staff and enroll into the trial.

2- The UCSF Clinical and Translational Science Institute (CTSI) Participant Recruitment Program (PRP) provides new COVID+ patient lists enabling us to contact COVID+ patient who are interested in participating in research studies.

After study staff confirm their eligibility, participants will receive the sample collection package and written instructions at their home along with scheduling a videoconference to collect saliva samples and use the assigned mouthwash during the 4-week period.

Assignment of interventions: allocation

Sequence generation {16a}

The permuted block allocation sequence stratified on language (English/Spanish) will be generated in SAS and uploaded to REDCap to randomly assign participants to one of the five mouthwash groups.

Concealment mechanism {16b}

The randomization will be concealed in REDCap; once participant's eligibility is confirmed, consent form is signed, and the baseline questionnaire completed, then the assignment is revealed. No study staff involved in recruitment or procedures with participants or participants know the allocation sequence since it is revealed via REDCap after qualifying steps.

Implementation {16c}

Following release of the REDCap allocation sequence for an individual participant, study staff will obtain the relevant kit and deliver to participants.

Assignment of interventions: Blinding

Who will be blinded {17a}

Participants will be blinded/masked to the extent possible by covering product labels, but the solutions have different colors, flavors, and smells so they may guess which group they have been assigned. Lab staff performing assays (outcome assessors) and data analysts will be blinded/masked to intervention group.

Lab staff will receive participants' samples with barcode stickers with only the study ID number. The data analyst will receive data set with coded group identifier.

Procedure for unblinding if needed {17b}

We will not unblind the study groups for outcome assessors unless subsequent actions to assure participants' safety would be affected.

Data collection and management

Data will be collected via various questionnaires (eligibility, baseline, daily and long-term follow ups) designed in REDCap. The data collection will be supervised and assessed regularly for completeness and inconsistencies.

Plans for assessment and collection of outcomes {18a}

We have designed questionnaires (eligibility, baseline, daily and long-term follow ups, sample collection, and RT-PCR results) in REDCap to collect data from participants and assess outcomes. We will train research and lab staff regarding each related steps and data collection. We have pilot tested assessments. The data collection will be supervised and assessed regularly for discrepancies.

Plans to promote participant retention and complete follow-up {18b}

We have planned to send daily reminders to participants to use their assigned mouthwashes and follow-up the next day to see if they have used it and if there were problems.

At any time during the trial, if a participant discontinues from the study or deviates from intervention protocols, we will record the information.

Data management {19}

We have planned to use unique barcodes on sample collection kits and participants' packages to be scanned during the trial and automatically recorded in an Excel file on a UCSF secured laptop and the Cloud. Only PIs know about the codes. Sepideh Banava (SB) will supervise data entry and its quality on a regular basis. Data will be linked to a REDCap form.

Confidentiality {27}

Email address and telephone number are the only personal identifying information which will be kept confidential in REDCap on UCSF secured servers. Participant information will be kept confidential. After the study and its follow-up in 12 months is finished, email address and phone number will be deleted.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

The study procedures include collecting saliva and oropharyngeal samples from participants on 3 study days (day 1, 7, 28), assaying them, and storing them for future potential research use.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Primary outcome measure: To assess and compare the SARS-CoV-2 viral load in unstimulated saliva and throat wash (gargle lavage) samples at baseline, days 7 and 28, we will compare the viral load (cycle threshold, Ct) among active groups versus the control (water) and within groups on day 28 using proportional hazards regression models with right censoring for undetermined Ct, stratifying on replicate for a marginal repeated measures survival model.

We follow the intention-to-treat (ITT) approach for efficacy analyzing participant data as-randomized; a safety analysis will tabulate any adverse experiences. The ITT group will include participants who are randomized after meeting the eligibility criteria and receive at least one study mouthwash dose and have PCR data from collected samples. A safety analysis group will include participants who received study mouthwashes and have safety evaluation data after using the mouthwash at least once.

Interim analyses {21b}

We plan to conduct an interim analysis after 10 participants in each group (N=50) have finished the 28-day period (using mouthwash). The alpha-spending approach with an O'Brien-Fleming stopping rule will be used.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Similar proportional hazards regression analyses will be conducted for baseline (after rinse) and day 7. We will assess the relationship between study results and baseline variables (demographics, clinical symptoms, tobacco use, etc.).

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Since PCR Ct data (inversely proportional to viral load) are expected to include right censored data when the assay is stopped before sufficient amplified viral genetic material is detected, we plan to use statistical analyses which can accommodate right censoring. Alternatively, we may use multiple imputation for Ct values above the detection level (e.g. 32, 35, or 40) and combine the estimates and variability across multiple imputations.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

We will make the protocol available as per ClinicalTrials.Gov requirements. We do not plan to provide access to participant-level data. We may make statistical code available with publications.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

SG, study PI and supervisor, and SB, co-PI form the steering committee. They will have regular weekly meetings to review and supervise various study steps and train/lead study staff. They will work with different study staff groups (e.g. recruitment, data management, and lab staff) on a

regular basis to assess trial steps and solve any problems/errors that might rise.

Composition of the data monitoring committee, its role and reporting structure {21a}

SG, the PI, is a biostatistician and clinical trialist who will instruct and supervise study staff on designing questionnaires, data collection, and data analyses. SB, the co-PI, is a dental clinician who will work closely with and report to SG.

Adverse event reporting and harms {22}

REDCap will be configured with Twilio to send a daily text message to participants with a link to a very short REDCap questionnaire asking about previous day mouthwash use and possible adverse experiences.

Frequency and plans for auditing trial conduct {23}

Study PIs will audit trial conduct and trial procedures weekly to resolve possible errors and make decisions about required modifications, staff re-training, etc.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Study PIs will communicate with the UCSF ethics committee (institutional review board) before making any modifications during the study.

Dissemination plans {31a}

We plan to disseminate study results via publications. (If the interim analysis shows important early findings, we will share that information with the health research community via preprint such as MedRxiv.) We will report aggregate study results to ClinicalTrials.gov for the public.

Discussion

This clinical trial was originally designed to be conducted in-person at the UCSF School of Dentistry to collect saliva samples, but since specific settings and supplies are required to

examine COVID positive patients in-person, we were instructed to modify the study protocol so participants could receive sample collection kits in their homes and staff instruct them via videoconference software, telephone, and written instructions to guide them through the process.

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome- CoronaVirus-2

COVID-19: Corona Virus Disease-2019

Declarations

- **Acknowledgments**

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- **Authors' contributions**

  SB conceived and conceptualized the idea, designed the study, prepared the UCSF IRB and ClinicalTrials.Gov application and developed study documents, contributed in preparing the budget, applied for funding, developed study logistics, prepared presentations, and drafted the protocol. SG contributed to conceptualization and study design, the UCSF IRB and ClinicalTrials.Gov application and developing study documents, prepared the budget, applied for funding and prepared contracts to receive the funding, contributed to study logistics, and edited this protocol. They both read and approved the final protocol.

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- **Availability of data and material**

  Study PIs will review requests for study data on a case by case basis.

- **Ethics approval and consent to participate**

  This clinical trial has been approved by the Institutional Review Board at the University of California San Francisco (UCSF) (IRB number: 20-30874) on March 17, 2021. The reference number is 284660.

  The informed consent forms for study participants have been approved by the UCSF IRB. Study staff will obtain consent from participants after confirming their eligibility and before sending the testing package. The participants or their legal guardian will sign an electronic consent after their eligibility is confirmed prior to inclusion into the study. Information from all participants will be kept confidential, and those who do not wish to continue being in the trial can withdraw from the study at any time.

- **Consent for publication**

  Not applicable.

- **Competing interests**

  The authors declare that they have no competing interests.

- **Authors' information (optional)**

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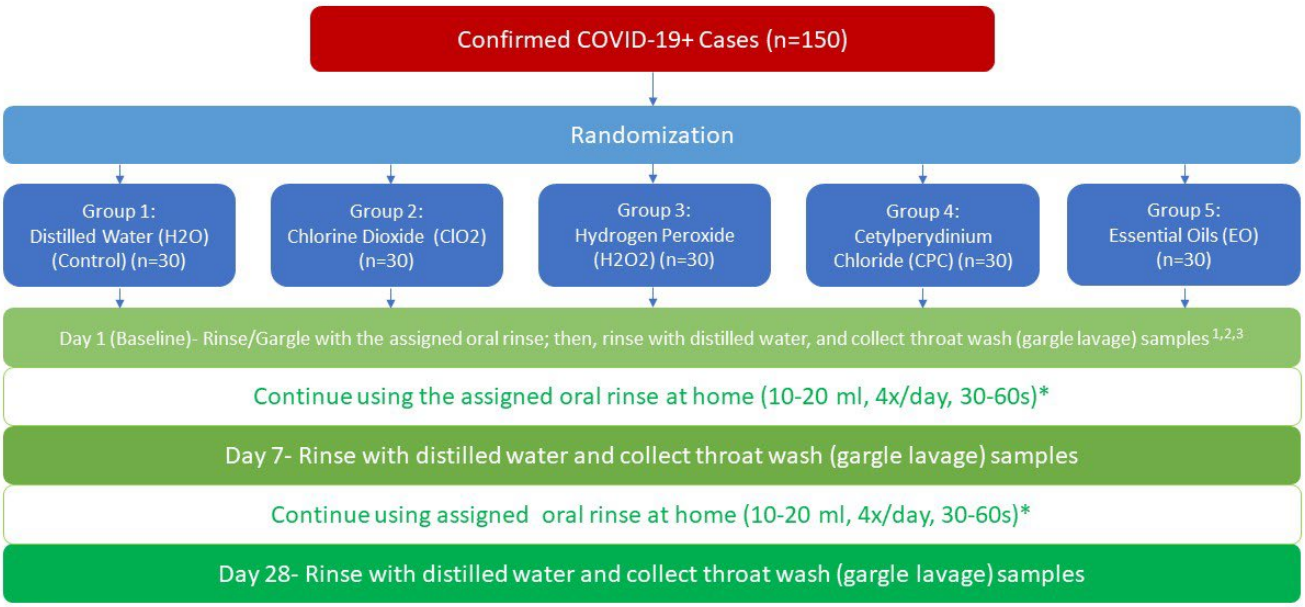

Note:

1 All study mouth rinses are alcohol-free, fluoride-free, and gluten-free.
2 At baseline, the first 75 participants will be tested with oropharyngeal (OP) swabs as well.
3 At baseline, a few participants, will be asked to provide unstimulated saliva to be compared with gargle lavage and oropharyngeal swab samples.

* The rinse volume and time range is related to various rinses use instructions.