Evaluating the Onset, Severity and Recovery from Smell and Taste Changes Associated with COVID-19 Infection in a Singaporean population; A Prospective Case Controlled Study (The COV-OSMIA-19 Trial)

Florence Sheen, Vicki Tan, Sumanto Haldar, Sharmila Sengupta, David Allen, Jyoti Somani, Hui Yee Chen, Paul Tambyah, Ciaran G. Forde

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Table of Contents

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Abstract

Background: Sudden smell and/or taste loss has been suggested to be an early marker of COVID-19 infection, with most findings based on self-report of sensory changes at a single time-point.

Objective: To understand the onset, severity, and recovery of sensory changes with COVID-19 infection, this study will longitudinally track changes in chemosensory acuity among those suspected of COVID-19 infection, using standardised test stimuli that are self-administered over 28-days.

Methods: In a prospective, case-controlled observational study, volunteers will be recruited when they present for COVID-19 screening (respiratory tract PCR; hereafter, swab test) and will initially complete a series of questionnaires to record their recent changes in smell and taste ability, followed by a brief standardized smell and taste test. Participants will receive a home-use smell and taste test kit to prospectively complete a daily self-assessment of their smell and taste acuity at their place of residence for up to 4-weeks, with all data collection submitted through online software.

Results: This study has been approved by the Domain Specific Review Board of the National Healthcare Group, Singapore, and is funded by the Biomedical Research Council Singapore COVID-19 Research Fund. Recruitment began on 23rd July 2020 and will continue through to 31st March 2021. As of 2nd October 2020, 69 participants have been recruited.

Conclusions: To our knowledge, this study will be the first to collect longitudinal data on changes to smell and taste sensitivity related to clinically diagnosed COVID-19 infection, confirmed using PCR-swab test, in a population-based cohort. Findings will provide temporal insights on the onset, severity, and recovery of sensory changes with COVID-19 infection, the consistency of symptoms, and the frequency of full smell recovery among COVID-19 patients. This self-administered and cost-effective approach has many advantages over self-report questionnaire-based methods and provides a more objective measure of smell/taste changes associated with COVID-19 infection, and will encourage otherwise asymptomatic individuals who are potential spreaders of the virus to self-isolate and seek formal medical diagnosis if they experience a sudden change in sensory acuity. This broadened case finding can potentially help to control the pandemic and reduce the emergence of clusters of infections. Clinical Trial: ClinicalTrials.gov NCT04492904. Registered on 27 July 2020, Retrospectively registered, version 1, https://clinicaltrials.gov/ct2/show/NCT04492904.

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Long title: Evaluating the Onset, Severity and Recovery from Smell and Taste Changes Associated with COVID-19 Infection in a Singaporean population; A Prospective Case Controlled Study **(**The COV-OSMIA-19 Trial)

Short title – The Singapore Smell and Taste Test (SSTT) to track Sensory Changes with COVID-19 Infection **(**The COV-OSMIA-19 Trial)

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Discussion: To our knowledge, this study will be the first to collect longitudinal data on changes to smell and taste sensitivity related to clinically diagnosed COVID-19 infection, confirmed using PCR-swab test, in a population-based cohort. Findings will provide temporal insights on the onset, severity, and recovery of sensory changes with COVID-19 infection, the consistency of symptoms, and the frequency of full smell recovery among COVID-19 patients. This self-administered and cost-effective approach has many advantages over self-report questionnaire-based methods and provides a more objective measure of smell/taste changes associated with COVID-19 infection, and will encourage otherwise asymptomatic individuals who are potential spreaders of the virus to self-isolate and seek formal medical diagnosis if they experience a sudden change in sensory acuity. This

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Trial registration: ClinicalTrials.gov NCT04492904. Registered on 27 July 2020, Retrospectively registered, version 1, https://clinicaltrials.gov/ct2/show/NCT04492904.

Key words: SARS-CoV-2, COVID-19, olfactory dysfunction, gustatory dysfunction, anosmia, ageusia.

BACKGROUND

Early identification of symptoms linked with the SARS-COV-2 (COVID-19) has been recommended to encourage early diagnostic testing, self-isolation and reduce the risk of community spread of infection. While a high temperature, continuous dry cough and fatigue are often the clinical symptoms associated with COVID-19 infection, numerous recent reports from patients and clinicians globally have consistently identified a sudden loss of smell (anosmia) and/or taste (ageusia) as a key early symptom of infection (1–6).

Recent self-report questionnaire data from many countries highlights an association between sudden onset smell and taste loss and COVID-19 infection, with reported incidences of changes in sensory acuity ranging from 11 to >60% (7–13). A recent systematic review and meta-analysis of studies investigating loss of smell and/or taste with COVID-19 infection reported a pooled prevalence of 52.7% and 43.9% of olfactory and gustatory dysfunction respectively (14). Also, Hopkins et al. (15) found that 1 in 6 patients reported new onset anosmia as an isolated symptom. The onset of smell and/or taste loss is often abrupt and, unlike other upper respiratory tract infections, often occurs in the absence of nasal obstruction (13,16). Importantly, the loss of smell and/or taste occurs early during COVID-19 infection, often before the onset of more established symptoms (8,17–20), and may be an important marker for infection. This has prompted many global public health bodies to recommend individuals who experience sudden changes in sensory acuity to

self-isolate and present for diagnostic testing (2–4,21–24).

The majority of published studies investigating smell and taste loss with COVID-19 have used subjective measurements of smell and taste, specifically self-report questionnaires. In Singapore, there have been anecdotal reports of smell and taste loss with COVID-19 infection (25,26) and one prospective cohort of COVID-19 patients that found 22.6% experienced acute olfactory loss (27). The positive predictive value of acute olfactory loss for COVID-19 was 24.1% and the negative predictive value was 96.5% (27). Data to date have been based largely on self-report questionnaire measures with a lack of objective data on measured smell and taste sensitivity. One study has used a validated smell test, (University of Pennsylvania Smell Identification Test (UPSIT)) to compare smell acuity in patients diagnosed with COVID-19 with a matched control group and shown that 98% of the patient group exhibited some smell dysfunction, scoring significantly lower on the UPSIT compared to controls (28).

In addition, to our knowledge, there has not yet been a longitudinal study to systematically track the onset, severity, and recovery of changes to sensory acuity across the pre- and post- infection periods, with emerging reports of sustained anosmia among a small proportion of those recovered from infection. To date, questionnaire measures alone have relied on self-report and may not accurately reflect the true extent of smell and taste changes during COVID-19 infection in the absence of a standardized tool for such measurements. Reliance on self-report questionnaire data and variable approaches could help to explain the wide variability in reported prevalence of olfactory dysfunction with COVID-19 infection (5-98%) (29). There is therefore a need for objective testing of smell and taste loss in COVID-19 infected patients using standardised smell and taste stimuli (29–31). Moreover, due to extensive restrictions on movement, the need to socially distance and the potential for infection spread with re-usable standardized odour and taste test materials, the collection of in-person physical data is challenging. Furthermore, while clinically validated smell and taste assessments are preferred, they are often expensive, and their re-use is not recommended

among infected patient populations. Home use sensory tests have been developed to track changes in smell and taste sensitivity using common household items as test stimuli (32,33). However, these rely on participants sourcing and preparing their own test stimuli from available household items, introducing unwanted stimulus variation which may present problems for comparability of smell loss across individuals using different stimuli.

The COVOSMIA-19 study will standardise the smell and taste stimuli used by all participants to ensure consistency and provide a disposable, rapid, self-administered home use test (the Singapore Smell and Taste Test, SSTT), to minimise the risk of cross-contamination and infection spread. The trial will enable self-testing for up to 28-consecutive days and will provide a standardised longitudinal assessment of smell and taste function to enable tracking of the onset, severity and recovery of the sensory changes reported to occur with COVID-19 infection. The standardised smell and taste test will also be compared with self-reported questionnaire measures of smell and taste changes, and measured changes to sensory acuity using common household items (an approach previously used by (32).

The primary objectives of the study are to (i) assess the prevalence of sudden changes in smell and taste sensitivity with COVID-19 infection in a population at risk for COVID-19 infection in Singapore, (ii) to establish the temporal onset, severity and recovery of changes in smell and taste sensitivity with COVID-19 infection, and (iii) evaluate the efficacy of the SSTT as a rapid, cost-effective, self-administered measure of changes to smell and taste compared to previous measures using house-hold items. The secondary objective of the current study is to investigate the effect of loss of smell and taste acuity on food enjoyment and appetite, to establish the impact of COVID-19 infection on food-related markers of quality of life. We hypothesise that loss of smell and taste acuity will be associated with COVID-19 infection, will return on recovery from infection for the majority of patients, and will result in short-term reductions in appetite, food enjoyment and food-related quality of life.

METHOD

Figure 1. Frequency of the different test measures for the Singapore Smell and Taste COVID-19 Clinical Trial

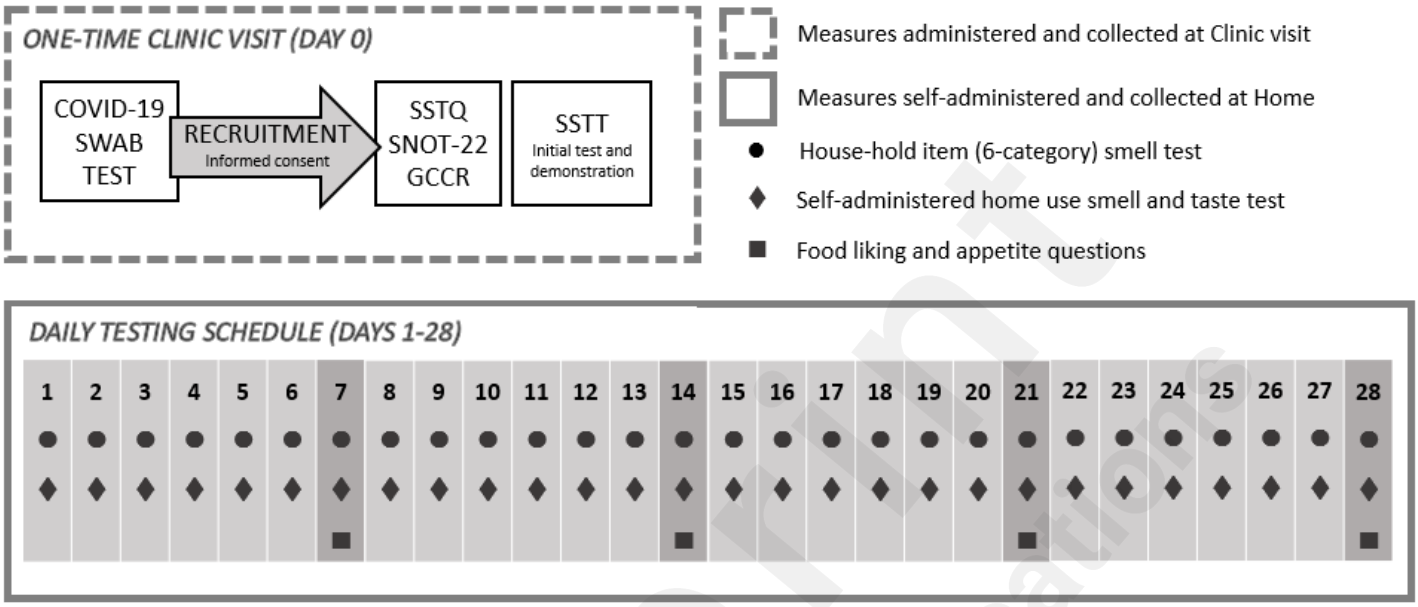

Table 1. Schedule for participant enrolment, intervention, and assessment

TIMEPOINT	Enrolment	Study Period					Close-out
		In-clinic		*At home (4 weeks)*			
	Day 0	***Day 0***	***Week 1***	***Week 2***	***Week 3***	***Week 4***	***Day 28***
ENROLMENT:							
Eligibility screen	**X**						
Informed consent	**X**						
PROCEDURE:							
Questionnaires		**X**					
SSTT testing kit demonstration		**X**					
Initial SSTT session		**X**					
SSTT (daily)							
Additional questions (once a week)			**X**	**X**	**X**	**X**	
ASSESSMENTS:							
Baseline variables: Gender, Age, Education status, Nationality, Ethnicity, employment status, smoking status, vaping status, medication, C-19 test result		**X**					
Primary outcome variables C-19 symptoms, (and onset) smell and taste acuity]		**X**					
[Secondary outcome variables: appetite, food enjoyment, eating behaviours, nausea, weight, food related QoL]		**X**	**X**	**X**	**X**	**X**	**X**

SSTT Singapore Smell and Taste Test; C-19 Coronavirus disease 2019; QoL Quality of Life.

Study Design

The study will track changes in smell and taste with COVID-19 infection using a prospective longitudinal, case-control study design. Participants will be recruited from volunteers presenting at hospital and hospital facilities across Singapore for COVID-19 screening. Following informed consent, study participants will be asked to report on changes to smell and taste sensitivity in the previous 2 weeks via a series of questionnaires, and to prospectively track daily changes in smell and taste acuity using a self-assessment test and a series of questionnaire measures to measure the onset, severity and recovery of changes in chemosensory acuity for the next 28 days. A schematic of the study procedure is shown in Figure 1, and the schedule for enrolment and assessment is shown in Table 1.

Recruitment procedure

Participants will be recruited from patients attending the hospital and its ancillary units for COVID-19 screening (Nasal Swab PCR). Following their COVID-19 screening, individuals will be approached and invited to participate in the current study and provide informed consent.

Inclusion criteria for participants

Participants are required to be above the age of 21 years, residing in Singapore for the next 28 days, to possess a mobile device with a 3G or 4G network and to know how to use mobile apps (i.e. QR scanner).

Exclusion criteria for participants

Participants will be excluded from the study if they are unable to provide informed consent, are allergic or intolerant to any of the test items (i.e. mango fragrance, jasmine fragrance, sugar, salt, coffee powder or lime powder), are currently pregnant, or do not agree to the study team having access to their medical records to obtain their COVID-19 infection status (i.e. swab test result).

Measures

On the day of their COVID-19 swab test (Day 0), once consented to participate in the trial, participants will complete three questionnaires to document recent changes in smell, taste and chemesthetic ability, and detail the frequency of a wide range of naso-pharyngeal symptoms. These questionnaires include the Singapore Smell and Taste Questionnaire, (SSTQ, Additional File 2), the 22-item Sino-Nasal Outcome test (SNOT-22 (34)) and the recently developed Global Consortium for Chemosensory Research questionnaire (GCCR, (12)). Participants will receive the Singapore Smell and Taste Test (SSTT, Additional File 3), a standardized home use testing kit to monitor their smell and taste acuity, and be given a demonstration on the self-assessment procedure that they will complete daily at their place of residence for the following 28 days. All questionnaires and instructions are available in English, Mandarin, Tamil and Bengali, and participants will complete all measures via an online data acquisition software (CompuSense Cloud, Guelph Ontario, Canada).

The Singapore Smell and Taste Questionnaire (SSTQ)

Participants will complete the Singapore Smell and Taste Questionnaire (SSTQ, Additional File 2) to record any recent changes in smell and taste, and to describe the occurrence of sino-nasal or other COVID-19 symptoms. Participants rate their current smell and taste sensitivity using the SSTQ (Day-0) to provide a baseline measure for their smell and taste sensitivity. This initial self-report questionnaire will quantify any recent changes in smell and taste acuity and includes questions on participants' basic demographics, COVID-19 related symptoms experience, the temporal onset of these symptoms, their smell and taste acuity, and questions regarding appetite-related quality of life

(e.g. enjoyment of food). See Additional File 4 for information on the sources of questionnaire items.

22-item Sino-Nasal Outcome Test (SNOT-22)

The 22-item version of the Sino-Nasal Outcome Test (SNOT-22) will be used to quantify the presence and severity of nasal disorder symptoms (34). Participants will be provided with a list of 22 symptoms and social/emotional consequences of nasal disorder, and will be asked to rate the severity of each problem on a 6-point scale from “no problem” to “problem as bad as it can be”. This measure has been included to assess symptoms that are commonly associated with nasal disorder and to make the distinction between changes in smell and taste due to nasal disorders and congestion and those associated with COVID-19 infection. Current research suggests that smell and taste loss with COVID-19 infection often occurs without nasal obstruction (13,16), therefore we expect participants with smell and taste loss to have a differential prevalence of other common nasal disorder symptoms (e.g. blocked nose).

Global Consortium for Chemosensory Research Questionnaire (GCCR)

This questionnaire was developed and implemented by the Global Consortium for Chemosensory research (https://gcchemosensr.org/) to assess whether and how COVID-19 infection affects sense of smell, taste and chemesthetic sensitivity (12). Participants are asked about their COVID-19 testing status and symptoms and complete 18 items relating to their sense of smell, taste, chemesthetic and food flavours before, during and after COVID-19 illness. Due to the potential for additional participant burden, the completion of this questionnaire is optional and will not affect their study participation. For those who complete the GCCR questionnaire, we will ascertain the extent to which measures obtained using this approach correlate with the measures in the study.

Daily Smell and Taste Testing

Participants smell and taste acuity will be prospectively measured for up to 28 days following their clinic visit for COVID-19 testing using home-based assessment tools detailed in this section. At the start of each daily test session, participants are to report on any changes in their smell and taste acuity by selecting either 'improved', 'stayed the same' or 'worsened', before rating their current sense of smell and taste, from "no sense of [smell/taste] at all' to 'extremely strong sense of [smell/taste]'. Participants are also asked to 'check all that apply' across a list of symptoms they have experienced in the last 24 hours from a list of COVID-relevant symptoms.

The Singapore Smell and Taste Test (SSTT)

Participants are provided with their own standardized home-use smell and taste test that they will complete daily for up to 28 consecutive days (Additional File 3). The questioning approach is based on that used in the Yale School of Medicine "Jiffy" test of Smell Sensitivity (35), in which respondents perform a similar procedure with Jif peanut butter.

The SSTT smell test includes two odours - a food (Mango) and a non-food (detergent) odour, both consisting of odour mixtures that have been formulated by an international fragrance manufacturer (Symrise AG). Odour mixtures have been chosen to avoid possible specific anosmia's to individual odour compounds, and the odours are dosed at the supra-threshold level in a specialised odour delivery pens (Otto Hut, Germany). Both fragrances have been tested to deliver a supra-threshold odour at a consistent intensity and stability for the duration of the home-use test period. To perform the test, participants remove the pen lid and place the pen 3 inches from their nose while breathing normally. For each smell, participants will identify the smell and rate the perceived intensity on a VAS scale from 'not strong at all' to 'extremely strong smell'.

For the daily taste test, participants are provided with small quantities of powder selected to represent the four prototypical tastes: 'sweet' (table sugar, FairPrice, NTUC, Singapore), 'salty'

(table salt FairPrice, NTUC, Singapore), ‘bitter’ (granulated coffee powder, Nescafe) and ‘sour’ (Lime-Powder, Knorr, Germany). Participants are instructed to take a small amount of each item in a sequential monadic order, on the tip of their tongue with a small spoon, identify and rate the perceived intensity on a VAS scale from ‘not strong at all’ to ‘extremely strong taste’ through an online questionnaire completed on their smart phone or device. Participants will rinse with water between each taste stimulus and are provided with sufficient taste stimuli for the 28 days of assessment.

Common house-hold item Smell Test

For comparison with the SSTT, participants will be asked to complete a daily assessment of smell using household items (see Additional File 3). To assess participant’s olfactory sensitivity, we will provide participants with 6 categories of common household items. Participants will be asked to choose one odour from a drop-down menu for each category and indicate their perception of it on a scale from ‘absent’ to ‘heightened’. This approach is based on a previously reported self-assessment measure of smell sensitivity using household items (32), with an additional category of stimuli that are particularly high in trigeminal irritation. Items for all categories were adjusted to include culturally appropriate household items that are common in Singapore.

Additional questions

Once a week, participants will complete an additional set of questions (Day 7, 14, 21 and 28) relating to their enjoyment of food, appetite, weight, and food-related quality of life (e.g. “I no longer enjoy cooking/preparing food”). The goal of this questionnaire is to assess the relative impact of changes in sensory acuity with self-reported appetite and food enjoyment, as it may be related to weight fluctuations observed during the period of infection.

COVID-19 Diagnosis

During study consent participants will provide access to the outcome of their COVID-19 diagnostic swab test which will be associated post-hoc with the unique identification number linked to participant questionnaire and daily home-use test data.

Sample size determination

The current prospective trial will compare the onset, severity and recovery of smell and taste loss as it relates to COVID-19 infection, in a case-controlled prospective clinical trial. To run our proposed cross-sectional analyses (see ***Statistical Analyses***), we require a minimum sample size of 235, based on a power calculation of the sample size required to conduct a logistic regression. This will be used to analyse our primary outcome of whether loss of smell and taste acuity predict the likelihood of testing positive for COVID-19 infection. A sample size of 235 is required to observe an effect at 95% power (with a significance level of 0.05) using Pr(Y=1|X=1) H0 = 0.20 and an odds ratio of 1.723. This odds ratio was calculated as the smallest effect size of interest (SESOI), below which results would not be practically interesting. Given that it is difficult to draw well-informed sample size estimates from the current research, and we instead opted to use the SESOI to calculate an estimated odds ratio and this minimum sample size, we will also conduct a sensitivity power analysis to demonstrate the effect sizes our final sample size is powered to detect.

Primary outcomes

The primary outcomes are (i) to measure the onset, severity, duration, and recovery of changes to smell and taste sensitivity resulting from COVID-19 infection, and (ii) to assess the efficacy of the SSTT as a simple diagnostic approach. Data will be used to test the association of smell and taste loss with a positive COVID-19 infection, measuring changes in sensory acuity from baseline (initial screening, Day-0) to the end of the 4-week monitoring period, to investigate what best predicts

recovery of smell and taste sensitivity. In addition, the primary methodological outcome is a comparison of the consistency and discriminability of self-assessment standardized home use tests compared to both common household-items home use test and the questionnaire-based measures. This will inform best practice approaches for future self-assessment of smell and taste acuity among those who suspect possible COVID-19 infection. This will be measured directly via responses on the daily home-use smell and taste test, complemented by measures from the self-reported questionnaire responses (SSTQ, SNOT-22, GCCR).

Secondary outcomes

The secondary outcomes will include assessment of experienced symptoms and changes in appetite and food-related quality of life over the duration of smell and taste loss and the 4-week follow-up period. This will be assessed via the home-use test questionnaires.

Statistical analysis

Using a case-control study design in those testing positive or negative for COVID-19 infection respectively, data will be collected on changes in smell and taste loss that have occurred in the 2 weeks prior to COVID-19 test, and measured smell and taste acuity changes on a daily basis for up to 28 days following the COVID-19 test. The data will be used for descriptive comparisons of the onset, duration and severity of smell and taste changes with COVID-19 infection, and report on the incidence of these changes among those testing positive for COVID-19 infection (and those recovering from infection).

Logistic regression analysis will be used to estimate the odds ratio for losses to smell and taste sensitivity as a predictor of testing positive for COVID-19 infection. This will also enable comparison of smell and taste loss as a predictor of COVID-19 infection compared to than other symptoms such as fever and dry cough. Pearson’s correlations will be used to investigate

relationships between smell and taste changes and other symptoms. Time-series ANOVA models will be run to investigate temporal changes in smell and taste ratings over time, with baseline rating in smell and taste acuity corrected for at an individual level. Linear Mixed Models will be used to test for significant differences in smell and taste acuity between groups, with participants stratified by their COVID-19 infection status.

Factor analyses, using oblique rotation and baseline home-use test responses (conducted in-clinic), will be conducted to assess the internal consistency of our smell test and taste test. Adjusted odds ratios will be calculated to investigate the best predictor(s) of recovery of smell and taste acuity post-infection. Linear regression will be run to examine whether responses to the smell and taste test predict responses to the household item odour test (smell) and self-reported taste acuity, respectively. Regression analyses will be conducted to investigate the association between loss of smell and taste acuity and self-reported appetite and food-related quality of life. All statistical analyses will be complete using IBM SPSS software.

Data management

Data will be collected online via the CompuSense platform, from which it will be retrieved and securely stored on a password-protected university computer. This data will be transported into an SPSS file, in which data cleaning and analyses will be conducted.

All participant data will be included in the cross-sectional comparisons provided they have at a minimum undergone COVID-19 swab testing (and we have the result) and completed the SSTQ, SNOT-22 and in-clinic smell and taste test (SSTT). All remote data collection will use online forms with forced choice response questionnaires to encourage adherence to the trial protocol, and participants will each receive daily reminders to complete their home-use smell and taste test and questionnaire. Attrition rates are difficult to estimate *a priori*, but participants who provide a low number of completed tests (<25%) will be excluded from the longitudinal analyses investigating the

home-use testing procedure. Missing data per analysis will be deleted list-wise (i.e. the individual's data is removed from the analysis in question if a single value for any included variable(s) is missing).

RESULTS

The study (ref: 2020/00810) has been approved by the Domain Specific Review Board of the National Healthcare Group, Singapore. The current study is funded by the Biomedical Research Council Singapore COVID-19 Research Fund (Project: 12Al04lg1lA04). All study-related materials, tests, stimuli, and procedures are covered by this funding. Recruitment of participants began on 23rd July 2020 and will continue through to 31st March 2021. As of 2nd October 2020, 69 participants have been recruited into the study.

DISCUSSION

Study overview

The current study will longitudinally track the onset, severity and recovery of changes in chemosensory (smell and taste) acuity among those with and without COVID-19 infection (following swab test) using standardised assessment tools that can be utilised in a residential setting. The objectives of the current study are to confirm the association between sudden changes in smell and taste sensitivity and COVID-19 infection in an at risk population in Singapore, to establish the temporal onset, severity and recovery of changes in smell and taste sensitivity with COVID-19 infection, to evaluate the efficacy of the SSTT as an early diagnostic tool, and to investigate the effect of loss of smell and taste acuity on appetite and food related quality of life.

Using the longitudinal prospective study design, we aim to establish for the onset, severity and recovery of smell and taste changes with COVID-19 infection, while also providing an initial validation of a rapid, cost-effective, self-administered and standardised approach to tracking

spontaneous changes to taste and smell sensitivity in both clinical and residential settings. These findings will enable better identification of asymptomatic or pre-symptomatic carriers of COVID-19 infection, encouraging earlier self-isolation and medical consultation. Currently a small number of studies have objectively tested smell and taste acuity in COVID-19 infected patients, with the majority of studies relying on subjective self-report measures (29). Given that one time self-report measures may underestimate the prevalence of olfactory impairment (36,37) and fail to capture temporal changes in sensory acuity, the COVISMIA-19 study provides an objective measurement of smell and taste loss in a sample of COVID-19 patients that can encourage earlier self-isolation and medical consultation. Furthermore, current household item tests of smell and taste acuity are often not standardized and heavily reliant on stimuli availability and volunteer compliance (32,33). The COVOSMIA-19 approach will provide a short easy-to-use, self-administered test approach that standardises the smell and taste stimuli and can be easily completed by participants in their own home.

Study limitations

There is potential for poor compliance by volunteer participants to complete their daily assessment throughout all 28-days of the assessment period. To mitigate this, all questionnaires and home-use test procedures are short and easy to complete, while still maintaining the scientific rigour of the test approach. Similarly, the SSTT test measures focus on detecting changes in ‘usual’ sensory perception, and stimuli have deliberately been selected to monitor changes in supra-threshold perceptual intensity. As such, the SSTT approach will not provide information of changes to smell and taste at the peri-threshold level (i.e. identification, detection discrimination thresholds), or profile odour identification across a wide range of odour stimuli to identify specific anosmia’s. Although participants will be texted daily reminders to complete their daily home-use test, their participation is entirely voluntary with potential for poor adherence and retention. Our proposed procedure for

handling potential missing data scenarios are outlined previously (see ***Data management***).

Study strengths

A strength of the COVOSMIA-19 study is longitudinal nature of the participant surveillance and the parallel application of both questionnaire self-report and standardised test measures for the assessment of loss of smell and taste acuity. Objective measurements of smell and taste acuity are likely to be more reliable (38) and have not yet been used to longitudinally assess smell and taste changes associated with COVID-19 infection. Standardised test stimuli for the home-use test (SSTT) are provided, and longitudinal data collection is completed remotely via an online platform to encourage adhere and make the procedures easier for participants to compete in their own home. All test stimuli have been pre-tested to ensure standardised concentration and stimuli stability and can be utilised by individuals regularly throughout a period of self-isolation. This will both standardise measurement for improved comparison longitudinally, while reducing the risk of cross-contamination associated with sharing test measures or attending laboratory tests.

The current study will provide new knowledge in our understanding of smell and taste losses associated with COVID-19 infection and will evaluate a simple test procedure for future tracking of these changes among individuals suspected of COVID-19 infection form their own home. Through this we aim to better identify individuals who suspect COVID-19 infection but are otherwise asymptomatic or with very mild symptoms, encouraging earlier self-isolation and medical consultation.

SUPPLEMENTARY INFORMATION

Additional File 1. **Figure 1.** Frequency of the different test measures for the Singapore Smell and Taste COVID-19 Clinical Trial (pdf).

Additional File 2. The Singapore Smell and Taste Questionnaire (pdf).

Additional File 3. Daily smell and taste testing documents (instruction, daily questionnaire, and additional questions) (pdf).

Additional File 4. Table S2. Questionnaire items and their source (pdf).

Additional File 5. Informed Consent Form (pdf).

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus disease 2019; SSTQ: The Singapore Smell and Taste Questionnaire; SNOT-22: 22-item Sino-Nasal Outcome test; GCCRQ: Global Consortium for Chemosensory Research questionnaire; SSTT: Singapore Smell and Taste Test; SESOI: Smallest effect size of interest.

DECLARATIONS

Ethics approval and consent to participate

The study (ref: 2020/00810) has been approved by the Domain Specific Review Board of the National Healthcare Group, Singapore. Written informed consent will be obtained from all eligible participants prior to entry into the study. Any adverse events or unintended effects of the study procedure will be reported to the ethics committee. This information will be given to participants both verbally and written (in the informed consent form copy) during recruitment. All data will be anonymised through use of a unique participant identification number and will be stored on password-protected computers. Participants will not receive any monetary compensation for their participation in the study.

Any changes to the above protocol will be reported to the Domain Specific Review Board, as appropriate. In addition, these changes will be documented on clinicaltrials.gov. The results of the current study will be disseminated through reports, publication of articles in scientific journals, publication of articles for public dissemination, and conference presentations.

Consent for publication

Not applicable.

Availability of data and materials

No data sets are included in this protocol (not applicable). Study materials (Additional Files 2-4) and a copy of the informed consent form (Additional File 5) are provided. According to National University of Singapore guidelines, it is not possible to grant public access to a participant-level dataset. However, in the event of publication of the trial results, a full protocol, study materials, and any relevant statistical code will be made publicly available on the Open Science Framework.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

CGF is the Principal Investigator of the current study. VT is the Study Administrator. FS, CGF, VT

and SH contributed to conceptualisation and design of the current study. Symrise AG provided advice on the home-use smell test stimuli and provided the test odours. DA, JS, and PT provided guidance and assistance regarding implementing the current study in a hospital setting. SS is responsible for recruitment, collecting informed consent data collection within the clinics. FS and CGF were responsible for manuscript preparation and all authors contributed to editing the final manuscript for publication. Only CGF, VT, SH and FS will be the team responsible for conducting the study analyses and so only these individuals will have access to the final trial data set.

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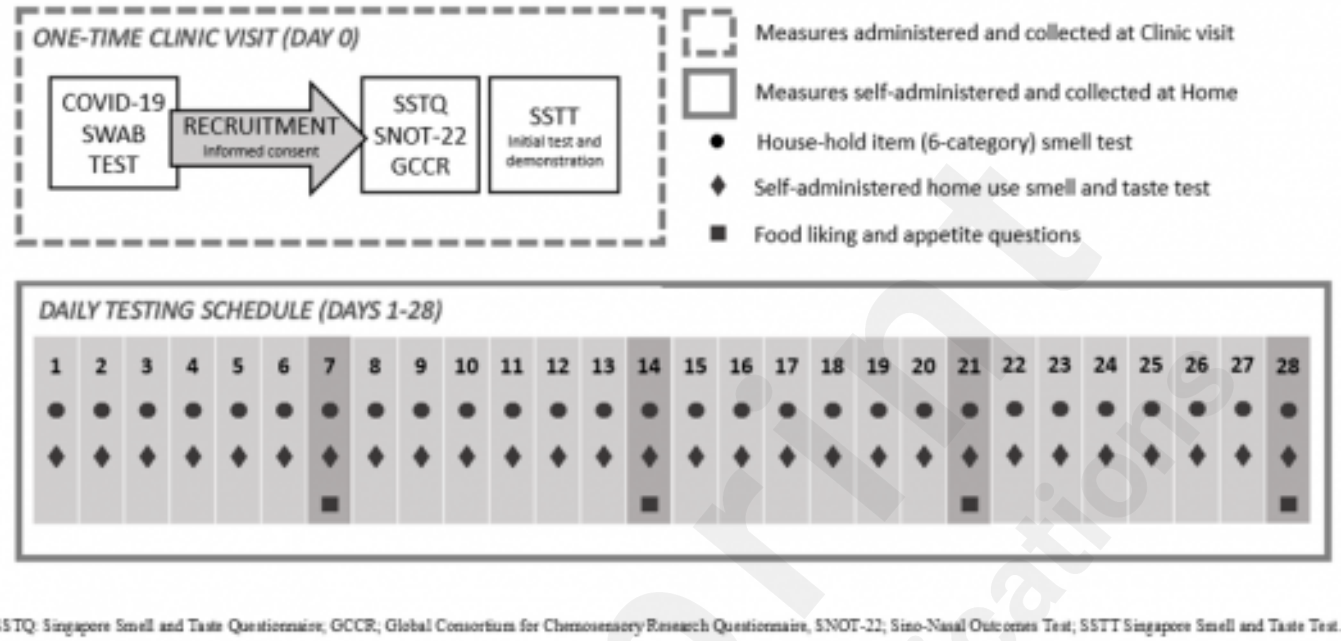
Supplementary Files

Figures

Frequency of the different test measures for the Singapore Smell and Taste COVID-19 Clinical Trial.

Figure 1. Frequency of the different test measures for the Singapore Smell and Taste COVID-19 Clinical Trial



SSTQ: Singapore Smell and Taste Questionnaire; GCCR; Global Consortium for Chemosensory Research Questionnaire, SNOT-22; Sino-Nasal Outcomes Test; SSTT Singapore Smell and Taste Test.

Multimedia Appendixes

Additional File 2. Singapore Smell and Taste Questionnaire (SSTQ).
URL: https://asset.jmir.pub/assets/eecaf84dfba611270a305ccd45d6a6f7.pdf

Additional File 3. Daily smell and taste testing documents.
URL: https://asset.jmir.pub/assets/de7ec7ed631560fb2a1e76d649489ca3.pdf

Table S2. Questionnaire items and their source.
URL: https://asset.jmir.pub/assets/bd69990ebc331c6997639e2f4c50285a.pdf