## PROTOCOL FACESHEET

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| **Protocol Number** | 2020-0001 ( NCT04321369) |
| **Principal Investigator** | Yuan Po Tu, MD |
| **Title** (Please include Initiative# as prefix) | Impact of Intranasal Site and Collector on Testing Sensitivity for SARS-CoV-2 Virus in Symptomatic Individuals |
| **Type of Research Description** | Operational project to compare clinician collected nasopharyngeal (NP) samples to both clinician- and patient-obtained mid-turbinate (MT) samples in the detection of SARS-CoV-2 in an outpatient clinic setting |
| **Funding Sponsor** | United Health Group Research and Development |
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| **External Sites** (if applicable) | University of Washington Virology Lab |
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## RESEARCH OVERVIEW/ABSTRACT

This work will serve both the Everett Clinic and broader UnitedHealth Group patient populations as well as advance the public health emergency (PHE) response to the community spread of SARS-CoV-2 virus, especially as the number of cases and deaths continues to rise in many geographies. Leveraging our presence in the Seattle/Puget Sound area with Everett Clinic, we intend to develop a model that can screen a large number of patients at varying levels of risk and manifestation of clinical symptoms while conserving personal protective equipment (PPE) and decreasing transmission risk to health care workers. This will also serve to support the enterprise and public health response. Towards this goal, we must first assess the equivalence between clinician-collected nasopharyngeal (NP) samples to both clinician- and patient-obtained mid-turbinate (MT) samples to detect SARS-CoV-2 across a broad cross-section of the population.

## 1 STUDY PURPOSE & OBJECTIVES

Measure the agreement between the detection of SARS-CoV-2 virus using clinician collected nasopharyngeal (NP) and clinician and patient collect mid-turbinate (MT) samples in patients seen in an outpatient clinic setting.

## 2 JUSTIFICATION & BACKGROUND

By March 13, 2020, the outbreak of coronavirus disease (COVID-19) reached pandemic levels with 1,215 confirmed cases in the United States across 43 of the 50 states[1]. As our understanding of transmission dynamics improves, there is an increasing need to reduce the risk of the spread of infection to healthcare professionals. Providing an avenue for patient- or parent-collected samples outside of the clinic would not only minimize transmission but also reduce the amount personal protective equipment (PPE), which already faces potential shortage.

On March 9, 2020, the Governor of the state of Washington, Jay Inslee, announced on national TV that all COVID-19 testing restrictions have been lifted, allowing for anyone to call their provider and obtain testing. The Governor's announcement along with the growing nationwide COVID-19 epidemic has created a high demand for SARS-CoV-2 virus testing. The current pandemic has created significant constraints in available PPE. In comparison with an NP sample, obtaining an MT sample is faster, usually better tolerated, safer, and causes less potential for sneezing, coughing and gagging, thus lowering the potential for aerosol generation during the collection process. Obtaining NP samples is technically more challenging than oropharyngeal (OP) and mid turbinate samples. Washington State Department of Health unpublished data suggests the recovery of SARS-CoV-2 virus significantly decreases after one week in OP samples but remains detectable in NP samples for a longer duration[2]. Thus, OP is not a viable option, leaving MT as the primary remaining alternative to NP.

The COVID-19 incubation period is 2-14 days with a median at 5-6 days[3] and its clinical features appear to be heterogeneous. As a result, asymptomatic and minimally symptomatic patients carrying the SARS-CoV-2 virus may pose additional significant transmission risks, especially to vulnerable populations. Moreover, the absence of clinical symptoms presents additional risks to health care workers and cohort-specific clinic models, causing further disruption and decreasing the ability of the system to care for large numbers of ill people. Early disease identification through mass screening outside of the clinic will increase rapid diagnosis of individuals carrying the SARS-CoV-2 virus across the symptomology range, mitigate infection risk to susceptible groups and facilitate outbreak containment.

For example, building a framework to support potentially infectious patients to self-collect intranasal specimens in their vehicles would decrease both nosocomial transmission within clinics and exposure risk to health care professionals and patients. This approach could allow for faster through-put than evaluating patients in a clinic. The first step in developing a drive-through testing model is to validate the ability of patient-collected MT samples to maintain an adequate level of sensitivity in comparison with clinician collected NP samples among symptomatic individuals in a clinical setting. If this assumption holds, we can then progress to a broader cross-section of patients, including asymptomatic and minimally symptomatic, self-collecting while staying in their car.

# 3 STUDY DESIGN

## 3.1 Design

The first step is to randomize sequence of collection of MT sample. Participants with even birth year will self-collect MT sample from both nostrils, followed by clinician collecting MT sample from both nostrils. Sequence will be reversed for participants with odd birth year. Finally, clinician will collect NP sample from the nostril corresponding to participants dominant hand.

## 3.2 Duration

Three days of sample collection at four sites of the Everett clinic. Sample testing will occur at the University of Washington Virology lab, which is expected to have a response time of 1-2 days. Given the fluctuations in demand for testing, there could be delays in receiving test results. Patients will be informed upon receipt of test results. For the purposes of reporting to patients, a result will be considered positive if any of the three tests (clinician NP, clinician MT, patient MT) returns a positive result.

## 3.3 Metrics and Variables

All samples collected will have SARS-CoV-2 virus testing conducted. The samples will be marked according to location of collection from the nasal cavity (i.e., MT or NP,), and who collects the sample (i.e., clinician or patient). This study is designed to confirm that sensitivity of test results from non-clinician obtained MT sample are acceptable compared to the clinician obtained NP sample among individuals presenting clinical symptoms indicative of upper respiratory infection. The results will inform future, follow-up research aimed at a constructing an operational framework to support rapid, less invasive testing of suspected infectious patients regardless of symptom manifestation outside the clinic. Th

## 3.4 Data

Three data sources will be recorded for each patient who consents to participate in the study:

- Electronic medical record (EMR), including reported clinical symptoms at time of testing;
- Results of testing from the three nasal swabs collected;
- Responses to a set of standard questions posed to each participant.

## 3.5 Materials

Primary materials that will be used in this study include:

- Flocked synthetic nasal swabs for the mid-turbinate testing;
- A thin synthetic nasal swab for the nasopharyngeal testing;
- A viral transport media tube to be utilized after collecting the sample- the end of the scored swab will be place in the viral transport media tube and broken off. The cap will be placed and secured.

All samples will be appropriately labeled with the patient identifiers and if the patient or clinician obtained the sample.

## 3.6 Devices

All swabs used for this study will be NasoSwab's from MDL. This swab was chosen due to its nylon flocked construction and a guard to ensure consistent depth. It is also an existing brand currently utilized in clinics for obtaining NP samples. More details on the NasoSwab can be found at http://www.mdlab.com/pdf/nasoswab_brochure.pdf.

# 4 STUDY POPULATIONS

## 4.1 Target Population

Patients presenting symptoms indicative of an upper respiratory infection visiting one of the four Everett Clinic sites of during the study duration while the operational project is occurring are eligible to participate in the project.

## 4.2 Number of Subjects

We will use a one-sided, one-sample test of proportions to determine whether the percentage of patients with a positive result on the NP test that were also positive for the MT test is significantly greater than 90%, assuming the true percentage is 98%. We selected 90% based on clinical expertise suggesting a test would not be practically useful below this threshold and 98% based on estimates from influenza testing[4]. Based on this hypothesis and a significance level of 0.05, we need to observe 48 positive NP test results to attain 80% power. Assuming 9% prevalence, we expect to have to test a total of 533 patients to observe 48 positive results. The same assumptions, hypothesis, and final sample sizes are applicable to both a comparison of clinician-collected NP to clinician-collected MT and a comparison of clinician-collected NP to patient-collected MT.

## 4.3 Eligibility

**Inclusion Criteria:**

- Able to consent and agree to participate in the project after discussing the project
- Coming to The Everett Clinic during the operational project duration
- Upper respiratory symptoms suggesting higher risk of testing positive for SARS-CoV-2 virus.

**Exclusion Criteria**:

- Not able to demonstrate understanding of the project
- Not willing to commit to having all three samples collected
- Medical history evidencing any of the following
    - Active nosebleed in the past 24 hours
    - Nasal surgery in the past two weeks
    - Chemotherapy treatment with low platelet and low white blood cell counts
    - Acute facial trauma

## 4.4 Potentially Vulnerable Populations (Please select all that apply to this research)

☒ UnitedHealth Group Employees
☒ Intellectually/ Cognitively / Developmentally Disabled Persons
☒ Economically Disadvantaged Persons
☒ Children
☐ Prisoners
☒ Pregnant Women

## 4.5 Subject Identification & Accrual Plan

All patients arriving to the Everett clinic during the duration of the protocol will be evaluated based on inclusion and exclusion criteria.

### 4.6 Recruitment Plan and Materials

No recruitment plan or materials needed given the nature of the project.

### 4.7 Enrollment / Consent Plan and Materials

This is an operational project. A verbal script will be used by Everett personnel to explain the project and give patients the opportunity to decline. Any patient that has the three samples collected would be considered as having willingly participated in the project as they allowed the sample collection and the use of the data produced from the sample.

### 4.8 Compensation / Remuneration / Reimbursement

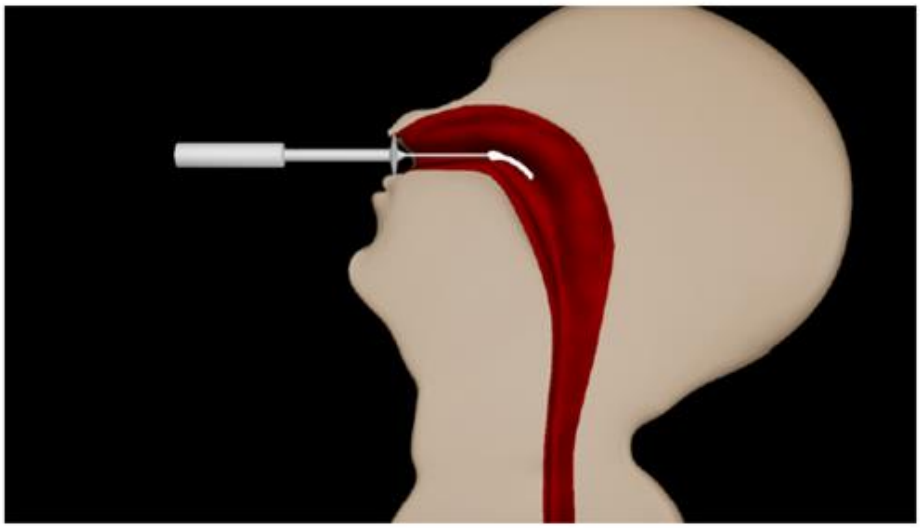
None

## 5 STUDY PROCEDURES

### 5.1 Procedures

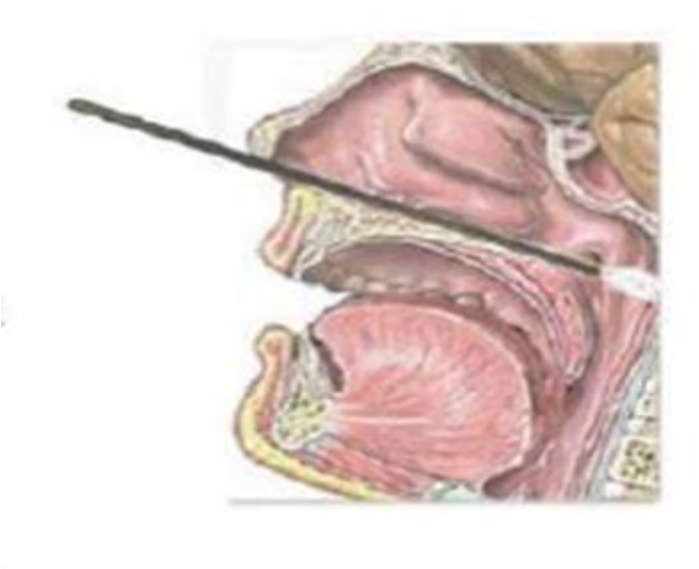
MT samples will be collected via the following steps:

- Gently insert the swab in the horizontal position until there is gentle resistance
- Leave the swab in for 10-15 seconds on each side
- Gently rotate the swab
- Repeat on the other nostril with the same swab
- Place the swab in viral transport media and break off



NP samples will be collected via the following steps:

- Use the skinny end in the horizonal position, gently pass the swab along the floor of the nose (straight back, not up the nose) until the posterior nasopharynx has been reached (distance from nostrils to external opening of ear). Hint: Place finger on the tip of the patient/resident's nose and depress slightly
- Once resistance is met (the swab should pass into the pharynx relatively easily), rotate the swab several times and withdraw the swab
- Break off top of swab (it will snap off)
- Place in transport medium.



### 5.2 Participant Engagement & Results

Patients will be notified of test results per standard clinical practice. A positive result will be reported to patients if any of the three collected samples returns a positive result.

### 5.3 Data Collection

Data collection will occur through the Epic EMR system.

### 5.4 Data Analysis

We will use the same testing procedure for both comparing clinician-collected NP to clinician-collect ed MT and comparing clinician-collected NP to patient-collected MT. We will use a one-sided, one-sample test of proportions with a significance level of 0.05 to test whether the percentage patients with a positive result on the NP test that were also positive for the MT test is significantly greater than 90%. If the NP test is considered the ground truth, then this hypothesis test can be interpreted as testing whether the MT test has a sensitivity of at least 90%.

As a secondary analysis we will also compare the percentage of patients with a positive result on the NP test that were also positive for the MT test between clinician- and patient-collected tests using a two-sided, two-sample test of proportions. Additional secondary analyses will include calculating the percentage of all patients that had a positive MT test and a negative NP test, breaking out the previous tests based on patient characteristics and symptoms, and other exploratory analyses.

## 6 RISKS AND BENEFITS

### 6.1 Risks and Risk Mitigation

The risks of the swab collection are low, and no different than usual clinical practice for MT and NP locations. The participant may experience transient mild discomfort, gagging, or slight bleeding from the nostril. The protocol will follow manufacturer collection instructions to minimize risk.

There are risks associated with the use of identifiable data for the purposes of this operational project. These risks are minimized by using appropriate confidentiality protection measures and limiting access

to data to only those authorized to do so. Any data utilized specifically for external publication would be de-identified to mitigate risk of loss of confidentiality.

### 6.2 Benefits

Patients may benefit from being screened for SARS-CoV-2 virus at the clinic, even if they had not anticipated doing so. The general benefit will be if the project confirms that the sample collection by a non-clinician from the MT location produces acceptable results compared to the more invasive collection at the NP location. This confirmation can be used to both reduce discomfort during the collection of the sample going forward and to potentially test whether patients can collect the samples themselves without having to come to a clinic and risk exposing others or being exposed to others who may have the virus.

## 7 DATA HANDLING

### 7.1 Data Protection, Storage and Transfer Plan

All patients who participate in this operational pilot will have standard COVID-19 screening information entered into their electronic medical record. The collection locations and source of collection (medical personnel versus patient) will need to be clearly distinguished for the purposes of this project. Data resulting from analysis of the samples will also be stored in the electronic medical record and any positive results will be reported accordingly to public health officials as required. The data collected due to this operational effort will be extracted from the medical record and stored for additional research analysis to demonstrate equivalence between location in the nose for the collection of the sample and similarity between sample collected by medical personnel and samples collected by the patient. Data will be shared between the participating clinics, UHG and collaborating partners performing the analysis of the samples and returning results.

### 7.2 Statistical Analysis

Described in *Section 6.4, Data Analysis*.

### 7.3 Future Utilization

If patient-collected MT samples prove capable of maintaining an adequate level of sensitivity (as defined in *Section 4.2, Number of Subjects*) in comparison with clinician collected NP samples among symptomatic individuals in a clinical setting, we intend to develop a scalable-framework supporting SARS-CoV-2 testing of potentially infectious patients via self-collection of intranasal specimens outside the clinic. This will simultaneously protect our provider workforce and slow down the spread of COVID-19 on both a national and global level.

### 7.4 Publication Plan

In an effort to minimize morbidity and mortality from COVID-19 as well as help facilitate pandemic containment, we will disseminate the findings of this study thru any means of rapid editorial review, such as peer-reviewed journal, public health institutions and/or mainstream media.

## 8 QUALITY CONTROL, MONITORING AND REPORTING

This is a minimal risk operational project. All patient oversight and use of data produced by patients will follow the standard clinical pathways.

[1] Coronavirus Disease 2019 (COVID-19) in the US. *Centers for Disease Control and Prevention*, accessed March 13, 2020. https://www.cdc.gov/coronavirus/2019-ncov/cases-in-us.html

[2] Personal communication per Dr. Scott Lindquist, MD State of Washington Epidemiologist (March 2020).

[3] Anderson, et al. (2020). How will country-based mitigation measures influence the course of the COVID-19 epidemic? *The Lancet*, https://doi.org/10.1016/S0140-6736(20)30567-5

[4] Frazee, et al. (2018). Accuracy and discomfort of different types of intranasal specimen collection methods for molecular influenza testing in emergency department patients. *Ann Emerg Med*, 71(4): 509-517.