# CLINICAL VALIDATION OF NEW INJECTION MOLDED FLOCKED NASOPHARYNGEAL SWABS IN RESPONSE TO THE COVID-19 PANDEMIC

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05-21-2020

# PROTOCOL

## Background

**1. Provide the scientific background, rationale and relevance of this project.**

**INSTRUCTIONS**

- This should include a referenced systematic evidenced-based review when possible.
- If this study involves qualitative research explain the major constructs of your study.
- Do not state in this section what you plan to do in this study. This information should be entered later under "What will be done in this protocol?"
- Do not include the bibliography in this section.
- For studies submitted under the Expedited review criteria, this section need not be more than a few paragraphs.
- For those studies where data will be analyzed collaboratively by multiple sites doing a similar study for which there is no common protocol (Collaborative Site Analysis Study) include a description of the common scientific goals/ procedures/data points.
- If this is an update to current templates from Protocol Builder make sure the information throughout the protocol includes the most current information.

Answer/Response: The SARS-CoV-2 coronavirus is the cause of the Covid-19 pandemic. This novel coronavirus infection was first described in 2019 in China and testing in the United States first became available in early 2020. A linchpin of fighting the pandemic is diagnostic testing for the virus that causes Covid-19. Unfortunately, flocked nasopharyngeal (NP) swabs are in limited supply due to the explosive spread of the virus, including in Italy, home to Copan, a leading manufacturer of NP swabs. Control swabs consist of a plastic shaft with a thin neck and a head (or tip) coated with flock, a filamentous material most often made of rayon, nylon, or Dacron. The swab is inserted into the nasopharynx, swirled around, removed, and the tip broken off into a vial containing viral transport media (VTM). The vial is sealed and sent for testing, for which an aliquot of VTM is taken and used as per testing protocol.(1)

A multidisciplinary team of University of Virginia researchers, including biomedical engineers from the UVa School of Engineering and the School of Medicine, have worked with manufacturers to design and develop a prototype based on the current standard of care. This prototype has been tested according to a two-step protocol: (1) expert evaluation by representatives from clinical pathology, infectious disease, respiratory therapy, and biomedical engineering for features such as stiffness; pliancy of the head, neck, and shaft; and smoothness of material; and (2) PCR compatibility by incubating the swab tip in VTM overnight to soak up or leech out any potential PCR inhibitory substances, in known positive patient samples running our standard test, and confirming positivity.

In addition, UVA Medical Center's Sterile Processing group assessed the ability of prototypes to be sterilized via gas sterilization using an 18 hour run of ethylene oxide

with prototypes in individual permeable pouches, each with an indicator to demonstrate successful sterilization. We have also done sterility checks following sterile processing by placing the swabs in viral transport media and holding at room temp for 48 hours to confirm no contamination. The study team has worked with UVA Medical Center Supply Chain management to procure supplies for production at a rate of up to 15,000 swabs per day in short order and establish procedures for individual packaging of swabs labeled with the lot number and expiration date, which are requirements for addressing the pandemic at scale.

Prototypes that passed these tests and assessments were prioritized for the current study.

## Objectives/Hypothesis

**INSTRUCTIONS:**
If this study involves biomedical research clearly state the objectives and hypotheses and clearly define the primary and any secondary outcome measures. If this study involves qualitative research clearly state your research hypothesis or question.

This section should not include information already included in other sections such as background information or information from the procedures section.

Answer/Response: The SARS-CoV-2 pandemic has resulted in an international shortage of the nasopharyngeal (NP) swabs used to collect sample for virological testing. This shortage has become a crisis as testing capacity is growing, and threatens to become the bottleneck at University of Virginia Health System and in the Commonwealth of Virginia, as it already is in other testing centers. To resolve this crisis, a team in the Clinical Microbiology Laboratories at University of Virginia Medical Center has been working closely with biomedical engineers in the University of Virginia, School of Engineering and with high volume domestic manufacturers developing injection molded polypropylene flocked nylon NP swab. This process has resulted in a promising prototype.

We will test this prototype for non-inferiority relative to existing, already validated NP swabs produced by Copan and/or Puritan ("control swab") for purposes of molecular microbiology: i.e. the PCR tests used for virological testing for SARS-CoV-2. Specifically, we will swab the nasopharynx of patients with Covid-19 and patients under investigation (PUI) for Covid-19, the disease caused by SARS-CoV-2, using a prototype swab and a using a control swab (the standard of care swab), and test for concordance of SARS-CoV-2. In all cases we will transport the swab in validated FDA cleared viral transport medium (VTM) as per standard operating procedure at UVA Medical Center.

The primary objective is to determine whether the newly designed and manufactured NP swabs ("prototype swabs") perform acceptably compared to standard swabs

("control swabs") used for collection of nasopharyngeal samples for molecular microbiology, specifically Covid-19 testing by PCR.

## Study Design: Biomedical

**1. Will controls be used?**

Answer/Response: Yes

►**IF YES, explain the kind of controls to be used.**

Answer/Response: standard of care swabs will be the controls

**2. What is the study design?**

Example: case series, case control study, cohort study, randomized control study, single-blind, double-blind, met-analysis, systematic reviews, other. You may also view the IRB-HSR Learning Shot on this topic to help you answer this question. https://hrpp.irb.virginia.edu/learningshots/Writing_protocol_June09/player.html

Answer/Response: The study design is a clinical trial to determine whether newly designed and manufactured NP swabs ("prototype swabs") perform acceptably for recovery of viral RNA compared to standard swabs ("control swabs") used for collection of nasopharyngeal samples for molecular microbiology, specifically Covid-19 by PCR.

**3. Does the study involve a placebo?**

Answer/Response: No

►**IF YES, provide a justification for the use of a placebo**

Answer/Response:

## Human Participants

**Ages:** _0-99___
**Sex:** **_Male and Female___**
**Race:** **_No exclusions___**

**Subjects- see below**

**INSTRUCTIONS:** For question 1-4 below insert an exact #. Ranges or OPEN is not allowed. This # should be the maximum # you expect to need to enroll (i.e. sign consent) If you are only collecting specimens the number of participants should equate to the # of specimens you need. If you are collecting only data from a chart review the number should designate the number of subjects whose medical records you plan to review. Age/ Sex/Race criteria should designate the demographics of participants from whom you will obtain the specimen/data.

**1. Provide target # of subjects (at all sites) needed to complete protocol.**

**INSTRUCTIONS:** If this is NOT a database protocol, this number should be the same as the number of subjects needed to obtain statistically significant results.

Answer/Response: 40

**2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.**

Answer/Response: up to 50%

**3. How many subjects will be enrolled at all sites?**

**INSTRUCTIONS:** This number must be the same or higher than the # from question # 1 in order to account for the # of screen failures, dropouts, withdrawals described in question # 2.

Answer/Response: Up to 40 positive and 40 negative.

**4. How many subjects will sign a consent form under this UVA protocol?**

**INSTRUCTIONS:** If the protocol does not have a consent form- the number listed here should reflect such things as the number of subjects from whom specimens will be obtained, the number of charts to be reviewed etc.

Answer/Response: Up to 40 positive and 40 negative.

## Inclusion/Exclusion Criteria

**INSTRUCTIONS:**

4. The inclusion and exclusion criteria should be written in bullet format.
5. *This item applicable if the study will require consent (verbal or written).* Unless there is a scientific reason for not recruiting a certain type of vulnerable population(e.g. not enrolling fetuses, neonates or children in a study regarding Alzheimer's) list the following vulnerable populations under either Inclusion or Exclusion criteria below: pregnant women, fetuses, neonates, children, prisoners, cognitively impaired, educational or economically disadvantage, non- English speaking subjects .
6. If you will not enroll subjects who do not speak English because certain procedures cannot be carried out if the subject does not speak English (e.g. a survey is not validated in other languages) insert the following as an Inclusion Criteria: Willingness and ability to comply with scheduled visits and study procedures.
7. If this is a collection of only retrospective* specimens or data, the inclusion criteria must include a start and stop date for when specimens/ data will be collected.
8. The stop date must be prior to the version date of this protocol.
9. *Retrospective: all specimens are in a lab at the time this protocol is approved by the IRB. All data exists in medical records or records from previous studies at the time this protocol is approved by the IRB.

**1. List the criteria for inclusion**

Answer/Response:

- Individuals presenting to the site for clinical care will be evaluated for clinical screening for Covid-19 testing or other respiratory infection testing.
- Individuals felt identified clinically as needing Covid-19 testing may be approached for study participation.

- Individuals already under clinical care that have tested positive for Covid-19 will be approached for study participation.
- Volunteer health care workers who have approached the PI

**2. List the criteria for exclusion**

Answer/Response:

- Known thrombocytopenia of <50,000 platelets/µl (risk of mild bleeding).
- Individuals presenting with an anatomically altered nasal cavity.
- No other patients will be specifically excluded.

**3. List any restrictions on use of other drugs or treatments**.

**INSTRUCTIONS:** List only those drugs or treatments that are prohibited while on study, not those listed as an exclusion criteria.

Answer/Response: None.

## Statistical Considerations

**a. Is stratification/randomization involved?**

Answer/Response: No

**►IF YES, describe the stratification/ randomization scheme.**

INSTRUCTIONS:
The stratification factors and/or the randomization plan should be identified. If there is no randomization component or important patient characteristics that will be used in treatment allocation or data analysis, a statement to this effect should be included.

Stratification factors: These are pretreatment patient characteristics which could be balanced across treatment arms by design or may be used to determine starting dose or treatment allocation.

If randomization is going to be used, the details of the randomization plan should be described.

The description should include:
--the method and timing of randomization
--the type of randomization scheme that will be used in the study
--whether or not the randomization masked/blinded/if so, then to whom is it masked/blinded
--who has access to the randomization scheme

Answer/Response:

**►IF YES, who will generate the randomization scheme?**

_____ Sponsor

_____ UVA Statistician. Insert name Answer/Response:
_____ UVA Investigational Drug Service (IDS)
_____ Other: Specify Answer/Response:

**2. What are the statistical considerations for the protocol?**

The objectives section and the statistical section should correspond, and any objective for which analysis is unfeasible should be deleted. Also, the estimates and non-statistical assumptions of the statistical section should be supported by discussion in the background section.

The answer to this question should include:
--Study Design/Endpoints
--Recap of study objectives and endpoint definitions. An assessment of how study objectives will be assessed by identifying & defining which endpoints will be used to assess each component of the study objectives.
--The study design should include contingencies for early stopping, interim analyses, stratification factors (If applicable), and any characteristics to be incorporated in analyses.
--The power/precision of the study to address the major study endpoint(s), the assumptions involved in the determination of power/precision.
--If statistical hypothesis testing is included then specify the null and alternative hypotheses, the test statistic, and the type I and II error rates
--If precision of an estimate, then provide a definition for precision
--If other, then specify

Answer/Response:
Inferential statistics will be done to analyze the extent of agreement of the test results from the two viral collection kits. Dr. Aaron Pannone will conduct the statistical analysis. Quality control checks will be run on the data to detect data that is missing, out of expected ranges, or otherwise questionable.

We will evaluate using Cohen's kappa, the normed difference between the rate of agreement that is actually observed and the rate of agreement that would be expected purely by chance (4) With the study size of 40 total participant, the range that will be deemed acceptable is at least 0.85.

**3. Provide a justification for the sample size used in this protocol.**

Include sample size calculations or statistical power estimation. If not applicable, please provide explanation.
Also include the anticipated accrual rate, the accrual goal for the study, including accrual goals by strata if appropriate, adjustments for drop-outs etc. and study duration.

Answer/Response: We will need 40 evaluable subjects.

**4. What is your plan for primary variable analysis?**

Include primary outcome(s)/predictor variable(s), statistical methods/models/tests to be employed, or descriptive summaries as appropriate. If not applicable, please provide explanation.

Answer/Response:

The data to be collected include (1) demographic data: age, gender, MRN (information available through the electronic health record); (2) date of enrollment; (3) date of specimen collection; (4) Covid-19 positive/negative, using the control swab; (5) Covid-19 positive/negative, using the prototype swab, (6) date of original COVID-19 positive PCR (for the positive cases).

The study endpoint is confirmation or rejection of concordance between the prototype swabs vs. control swab. This will be achieved through a test of concordance for 20 positive Covid-19 tests, and 20 negatives. In clinical microbiology, it is standard practice to take this approach of identifying 10 positives and negatives to evaluate new swabs (2)

**5. What is your plan for secondary variable analysis?**

Include the following:
--Secondary outcome(s)/predictor variables, statistical methods/models/tests to be employed, or descriptive summaries as appropriate. If not applicable, please provide explanation.
--For phase III studies, the power/precision of the study to address the secondary objective(s).

Answer/Response: NA

**6. Have you been working with a statistician in designing this protocol?**

Consultation with a professional statistician is highly recommended to ensure good science of the study and facilitate the review process.

Answer/Response: Yes

**IF YES, what is their name?**
Answer/Response: Dr. Aaron Panonne

**7. Will data from multiple sites be combined during analysis?**

Answer/Response: No

INSTRUCTIONS: IF YES, answer the following questions

## Study Procedures-Biomedical Research

**1. What will be done in the study?**

Answer/Response:

The study population will consist of approximately up to 80 emergency-department, inpatient, volunteer health care workers (exclude any trainees/students) and clinic patients. The volunteer health care workers will be presumably negative and will have been screened with

the health system attestation. Potential COVID-19 positive subjects will be identified from their electronic medical record in hospital or upon arrival to the Medical Center for evaluation. Specimens will be labeled with a subject-specific unique identifier without PHI with the format "TESTSWAB_0001." Specimens will be linked to electronic medical record number (MRN), date specimen was taken, and result of Covid-19.

For research purposes, we will collect two nasopharyngeal swabs at enrollment: a control swab (standard swab) and a prototype swab (experimental swab). **please note, we will collect a control swab for research purposes regardless of when a person had a standard of care swab.

Prototype swab will be placed in a separate vial of the same UVA validated VTM solution and sent to the clinical labs for testing. Results from control and prototype swabs will be compared for concordance. This is a research study. The result of the prototype swab will not be returned to the patient or entered into the patient record and will not be used for clinical decision-making. The result of the control swab will be entered into the patient medical record if the result is an unexpected positive (e.g. taken from a volunteer health care worker presumed negative) and the study team will notify Costi Sifri or contact the highly infectious disease pager to relay the result, who will determine the next steps in relaying the result to the patient. This is for research use only. If the research swabs results (either the control or experimental) is discordant with the standard of care swab, the study team will notify Costi Sifri or contact the highly infectious disease pager to relay the result. Costi Sifri or the physician carrying the highly infectious disease pager will determine next steps.

All positive swabs must be reported to VDH as required by law and is considered outside of the scope of research.

The data to be collected include (1) demographic data: age, gender, MRN (information available through the electronic health record); (2) date of enrollment; (3) date of specimen collection; (4) Covid-19 positive/negative, using the control swab; (5) Covid-19 positive/negative, using the prototype swab, (6) date of original COVID-19 positive PCR (for the positive cases) (7) number of PCR cycles before COVID-19 RNA detection and standard PCR platform to compare viral recovery by prototype swab to control swab.

Regarding management of discordant results: if results are discordant, the discordant result will simply be recorded as such. Swabbing will not be repeated by the research team.

Participants can withdraw at any time. Participants who withdraw will continue to receive conventional care.

**2. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.**

**Example:** If the subject will be taking an investigational drug, will they need to be put back on an approved drug when they have completed the study? If yes, explain how

this will be accomplished and who will cover the cost. If the subject has a device implanted will it be removed? Again- who will cover the cost of the removal?
**Instructions:** Answer NA if this study does not involve a study treatment.

Answer/Response: NA

## Bibliography

**INSTRUCTIONS:** Provide a current bibliography supporting the hypothesis, background and methodology including references to papers and abstracts that have resulted from previous work by the investigator and references to the work of others.

1. Callahan CJ, Lee R, Zulauf K, Tamburello L, Smith KP, Previtera J, Cheng A, Green A, Abdul Azim A, Yano A, Kirby J, Arnaout R. 2020. Rapid Open Development and Clinical Validation of Multiple New 3D-Printed Nasopharyngeal Swabs in Response to the COVID-19 Pandemic. medRxiv 2020.04.14.20065094.
2. Michael Miller J, Campbell S, Loeffelholz M. 2013. Changing swabs: To validate or not to validate? J Clin Microbiol 51:3910.
3. Kwiecien R, Kopp-Schneider A, Blettner M. 2011. Concordance analysis: part 16 of a series on evaluation of scientific publications. Dtsch Arztebl Int2011/07/29. 108:515–521.
4. Steffen C, Thomas K, Huniar U, Hellweg A, Rubner O, Schroer A. 2008. Theoretical Studies on Pyridoxal 5'-Phosphate-Dependent Transamination of a-Amino Acids. J Comput Chem 31:2967–2970.