Inpatient COVID-19 Lollipop Study

Last IRB Protocol Approval 4/6/2023

#NCT05801341

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Protocol Number: IRB #2023-0290
Principal Investigator: Ellen Wald, MD
Co-Principal Investigator: Joseph McBride, MD

Protocol Version History

Protocol Version	Version Date	Summary of Revisions Made	Rationale
1.0	03/01/2023	Initial version	
2.0	04/04/2023	Study samples may temporarily be stored in a designated refrigerator or freezer.	The laboratory suggested temporarily storing study samples in a refrigerator, so we needed to add flexibility in the protocol.

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1.0 STATEMENT OF COMPLIANCE

I confirm that I have read this protocol. I will comply with the IRB-approved protocol, and applicable regulations, guidelines, laws, and institutional policies.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitment.

Name	Signature	Date
_____	_____	_____
Principal investigator		

2.0 LIST OF ABBREVIATIONS

AE	Adverse Event
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease of 2019
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management Software
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DSMP	Data & Safety Monitoring Plan
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
EHR	Electronic Health Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICTR	Institute for Clinical and Translational Research
IRB	Institutional Review Board
NP	Nasal Pharyngeal
OHRP	Office for Human Research Protections
OnCore	Online Collaborative Research Environment
PCR	Polymerase Chain Reaction
PHI	Protected Health Information
PI	Principal Investigator
POC	Point of Contact
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UP	Unanticipated Problem

3.0 STUDY SUMMARY

3.1 Synopsis

Full Title	The utility of "lollipop" oral swabs in the diagnosis of COVID-19 in an inpatient setting
Short Title	Inpatient COVID-19 Lollipop Study
Protocol Number	2023-0290
ClinicalTrials.gov Identifier & Summary	NCT ID pending. This study is being done to see if collecting saliva samples with a “lollipop” collection method works as well as nasal samples for COVID-19 PCR testing.

Number of Site(s)	UW-Madison will be the only site enrolling subjects.
Main Inclusion Criteria	• Individuals at least 4 years of age • Admitted to a hospital • Verified COVID-19 according to positive NP PCR test criteria • Enroll within 47 hours of the diagnostic NP swab; lollipop swab collected within 48 hours of the diagnostic NP swab
Main Exclusion Criteria	• Unable to suck on a swab • Previous participation in this study • Require translation services for medical care
Objective(s)	Primary Objective • To determine the performance characteristics of oral lollipop swabs compared to NP swabs for diagnosing COVID-19 via PCR molecular testing. Secondary Objectives • To identify clinical characteristics of patients when there are discordant results for NP and oral lollipop test results.
Endpoints	Primary Endpoint • Tabulated results from NP vs. lollipop swab-based PCR COVID-19 tests. Secondary Endpoints • Correlation of clinical characteristics to participants with discordant test results
Study Design	This is a prospective quantitative study evaluating the utility of a novel method of saliva collection for COVID-19 testing.
FDA Regulatory Overview	. The investigational swab and associated COVID-19 PCR test are FDA regulated and involve an IDE-exempt in vitro diagnostic device.
Study Device	The lollipop collection swab and the lollipop swab processing procedure are both investigational.
Total Number of Subjects	Up to 225 subjects will be enrolled.
Study Population	COVID-positive patients ages 4 and above admitted to a hospital in the Madison, Wisconsin metropolitan area.
Statistical Methodology	The results of the lollipop swab will be compared to that of the known positive NP PCR to estimate the performance of the lollipop test to diagnose COVID-19. Falsely negative lollipop samples will be compared with the corresponding NP sample for cycle threshold.
Estimated Subject Duration	The duration of the study for each subject is a single study visit that will take approximately 30 minutes.
Estimated Enrollment Period & Study Duration	Study enrollment will occur over 6 months with the total expected duration of the trial to be 12 months.

3.2 Schematic of Study Design

Prior to Enrollment	Screen potential participants by inclusion and exclusion criteria. Conduct consenting process and obtain informed consent.
	
Visit 1 Time Point	Confirm and document eligibility. Administer verbal questionnaire to collect clinical and demographic information. Supervise lollipop method of collecting a saliva sample.
	
Post-Visit	Collect information from participant's electronic medical record and enter into the research database.

4.0 KEY ROLES

The following is a list of all key personnel and roles:

Principal Investigator	Ellen Wald, M.D. Professor UW-Madison Department of Pediatrics 600 Highland Ave Madison, WI 53792-4108 608-263-8543 erwald@pediatrics.wisc.edu
Participating Site(s)	University of Wisconsin-Madison 600 Highland Ave Madison, WI 53792-4108
Local Laboratory Services	Wisconsin Veterinary Diagnostic Lab (WVDL) University of Wisconsin – Madison 445 Easterday Ln Madison, WI 53706 608-262-5432
Study Regulatory Contact	Department of Pediatrics Regulatory Support University of Wisconsin – Madison 600 Highland Ave Madison, WI 53792-4108 Regulatory@pediatrics.wisc.edu

5.0 INTRODUCTION

5.1 COVID-19 Background

Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus is most commonly spread via contact with infective respiratory droplets and aerosols produced by coughing, sneezing, talking, and singing.

Common diagnostic methods of COVID-19 infection include amplification of viral nucleic acid via polymerase chain reaction (PCR) or identification of viral antigens via rapid antigen detection kits or lateral flow assays. PCR techniques are used most frequently on nasopharyngeal (NP) swabs, but PCR performed on saliva samples can also identify infection.

5.2 Current Standard of Care

Current standard of care in the medical system where this study is being conducted is NP swabs for COVID-19 testing.

5.3 Oral Lollipop Swabs and COVID-19 PCR Testing

This study will utilize flocked swabs, referred to as “Lollipop” swabs, as a method of sample collection for PCR analysis for SARS-CoV-2. An oral lollipop swab will be obtained by placing a flocked swab into the mouth and sucking on the swab for 20 seconds as one would suck on a lollipop. Investigators have used this technique for sample collection in the diagnosis of Group A Streptococcal pharyngitis by PCR (DeMuri GP, Wald ER Detection of Group A Streptococcus in the Saliva of Children Presenting with Pharyngitis Using the cobas Liat PCR System Clinical Pediatrics May 19, 2020) and in past COVID-19 lollipop pilot studies (McBride JA, DeMuri GP, Wald ER The utility of “lollipop” swabs in the diagnosis of COVID-19 Pediatric Academic Societies Abstract May 2021). This method of sample collection to test for COVID-19 is not typically available as a standard of care outside of this study.

5.4 Rationale

It has been reported that the ACE2 receptor is a main host cell receptor for SARS-CoV-2 and plays a crucial role in the viral entry into human cells. There is high expression of the ACE2 receptor in epithelial cells of the oral mucosa and tongue. PCR of saliva samples have been shown to be an alternative to NP swabs.

NP swabs are cumbersome to perform, uncomfortable for the patient, require assistance from health care providers, and are not practical for large daycare and school-aged groups that may warrant repeated testing. Salivary samples can be challenging due to volume of saliva required to run the test. An oral swab, sucked on like a lollipop is a less invasive, quicker, and an easier sample to perform that may also be obtained by the individual or parent at home without a medical provider. Therefore, oral lollipop swabs may facilitate testing in adults, younger children, greater numbers of children, and when multiple longitudinal samples may be required. The oral lollipop swab will be a much more comfortable sample to obtain and will allow for the repeated and large-scale testing of populations.

In addition, PCR is a very sensitive technique that can identify persistent viral nucleic acid following acute infection. For this reason, repeat PCR tests are not recommended to determine the end point of COVID-19 isolation. Moreover, repeat COVID-19 screening via PCR is not recommended within 90 days of past infection. These persistently positive NP PCRs can lead to diagnostic and infection prevention challenges as distinguishing which tests represent true, acute, and transmissible infection versus past, non-viable, and non-transmissible virus is frequently not possible.

If the oral lollipop swab has a similar performance to the NP swab, then a new testing option, ideal for frequent testing of large cohorts of patients, especially young children, will be possible. In addition, identifying differences between NP and oral lollipop swab positivity could determine whether oral lollipop swabs have less risk of persistent, post-infectious, positivity.

6.0 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To determine the performance characteristics of oral lollipop swabs compared to NP swabs for diagnosing COVID-19 via PCR molecular testing.	Tabulated results from NP vs. lollipop swab-based PCR COVID-19 tests.
Secondary	
To identify clinical characteristics of patients when there are discordant results for NP and oral lollipop test results.	Correlation of clinical characteristics to participants with discordant test results

7.0 STUDY DESIGN

7.1 General Design

The Inpatient COVID-19 Lollipop Study is a prospective, single-center study to determine if oral lollipop swabs provide an adequate/optimum sample for diagnosing COVID-19. A total of up to 225 COVID-positive inpatients ages 4 years and older will be enrolled at one study sites. Subject accrual will occur over 6 months with the total duration of the study expected to be 12 months.

Eligible subjects will complete 1 visit that will last approximately 30 minutes. After the study team obtains informed consent and assent, if applicable, the study team will provide verbal instructions and supervise participants as they suck on a flocked swab for 20 seconds. The sample will be labeled with the study ID code and date of sample acquisition, and the result (positive or negative) of the lollipop swab will be compared to the NP swab results in the participant's medical record. Clinical information including symptoms, duration of symptoms, known past COVID-19 infections, known COVID-19 household contacts within 90 days, and COVID-19 immunization status will be assessed via conversation with the participant and review of the electronic medical record. Laboratory information including the cycle threshold of the NP sample will be collected. Each participant will be classified as having either symptomatic or asymptomatic infection. The electronic medical record will be reviewed for medical record number, birthdate, and the above clinical information regarding COVID-19. The sample will be sent to the Wisconsin Veterinary Diagnostic Lab (WVDL) for performance of the PCR for SARS-CoV-2. The specimens will be discarded in the lab after the sample has been processed.

7.2 End of Study Definition

The end of the study is defined as the date of completion of any final follow-up activity or data collection described in the protocol.

8.0 SUBJECT SELECTION

8.1 Inclusion & Exclusion Criteria

Eligibility will be determined by inclusion and exclusion criteria below and confirmed by medical record review as necessary.

Inclusion Criteria
1. Ability to understand and the willingness to provide verbal informed consent, if 18 years or older. If 4-17 years old, ability to understand and the willingness to provide verbal assent, plus have a parent or legal guardian present who can provide verbal informed consent.
2. Willing to comply with all study procedures and be available for the duration of the study.
3. Admitted to UW Health University Hospital or UW Health Kids American Family Children's Hospital.
4. Individuals at least 4 years of age.
5. Verified COVID-19 according to positive NP PCR test criteria.
6. Enroll within 47 hours of the diagnostic NP swab; lollipop swab collected within 48 hours of the diagnostic NP swab.
7. Either personally able or have a parent or legal guardian able to verbally answer questions in English about clinical symptoms, exposures, and other health and demographic information.

Exclusion Criteria
1. Unable to suck on a swab.
2. Previous participation in this study.
3. Require translation services for medical care.
4. Not suitable for study participation due to other reasons at the discretion of the investigators or their designee.

8.2 Vulnerable Populations

This study will enroll children because the research is critical to advance the care of children with COVID-19. The study presents minimal risk to children, as there are no known or anticipated risks of the lollipop

swab collection method. Confidentiality risks are minimal, as this study does not involve collection of sensitive data. The research will help inform an important scientific question that may benefit children in the future. To further minimize risks to children, permission will be obtained from a single parent/guardian, and verbal assent will be obtained using age-appropriate language. Child dissent will always be respected.

This study will enroll pregnant persons because the diagnostic testing method being studied will present no more than minimal risk to the fetus, as the study procedures involve the pregnant subject, who is already known to be COVID-positive, sucking on a sterile swab and verbally answering questions. This study will not seek to identify the pregnancy status of subjects. Pregnant women may be enrolled, but pregnancy status will not be identified as part of study procedures or included in research records.

8.3 Lifestyle Considerations

During this study, subjects are asked to:

- Always wear a face mask, except when they are collecting the saliva sample.
- Refrain from eating or drinking directly before collecting the saliva sample.

8.4 Subject Identification

8.4.1 Best Practice Alerts

The study team will set up Best Practice Alerts in Health Link so they are notified when a potentially eligible patient is admitted for inpatient care at UW Health.

8.4.2 Identification in Clinical Practice

Potential subjects may be identified by study team members who provide clinical care to patients with COVID-19. A member of the clinical team will inform potential subjects of the research opportunity and provide an IRB-approved study flyer. Potential subjects will be pre-screened through medical record review. Potential subjects who meet all eligibility criteria will be invited to enroll in the study.

8.4.3 Reporting Workbench

Study staff with UW Health electronic health record (Health Link) access may search patient list templates made available to them as part of their research access to Health Link to help identify potential subjects for study enrollment evaluation.

8.5 Subject Recruitment

A total of 225 subjects will be recruited from 1 site in the United States. Individuals from populations who are underrepresented in clinical research (e.g., racial and ethnic minorities, women, individuals from rural and underserved communities, older individuals, federally recognized nations and tribes) will be enrolled with a goal of ensuring that all eligible patients are given the opportunity to participate in novel clinical trials and that research findings can be generalizable to the entire population.

Several recruitment strategies will be employed, and the study team will use a combination of methods. Specific recruitment strategies are as follows:

8.5.1 Recruitment through Clinical Practice

If the potential subject is agreeable, they will be provided a flyer and contact information for the study team or the research team will initiate contact.

8.5.2 Posters/Flyers

Flyers announcing that volunteers are needed for a study may be posted in UW Health Inpatient settings, as well as waiting rooms. Several key details of the study will be included in the flyer (key eligibility criteria, number and length of visits, location of study site, type of remuneration) along with a call back number for people to call in case they are interested.

8.6 Remuneration and Retention Strategies

Strategies for retention include:
- Streamline data and sample collection to make the study visit as short as possible, approximately 30 minutes.

8.7 Early Termination and Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.

The Principal Investigator (PI) may discontinue or withdraw a subject from the study for the following reasons at his/her discretion:
- Subject non-compliance with study requirements (e.g., unwilling or unable to suck on swab)
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- If the subject is no longer an appropriate candidate for participation

Subjects who provide verbal informed consent/assent but do not provide a lollipop swab that can be successfully resulted will not be replaced. Subjects who provide verbal informed consent/assent and provide a lollipop swab that can be successfully resulted, then subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

The study team will attempt to obtain the following information from subjects following early termination or withdrawal: self-reported reason for withdrawal.

9.0 STUDY AGENT (STUDY DRUG, DEVICE, BIOLOGIC, VACCINE, ETC.) AND/OR PROCEDURAL INTERVENTION AND/OR BEHAVIORAL/SOCIAL INTERVENTION

9.1 Study Agent and Control Description

Investigational Devices
Both the “lollipop” collection swab and the lollipop swab processing procedure qualify as an exempt diagnostic device/test based on the Code of Federal Regulations device exemption guidelines. The swab and test are non-invasive, do not introduce energy to a subject, do not require invasive sampling, and are not used as a diagnostic procedure without confirmation of the diagnosis by another medically established test. Neither the swab nor the test meet the definition of “significant risk,” which is a device that presents a potential for serious risk to health, safety or welfare of subjects.

9.1.1 Source

The study team is already in possession of a supply of flocked swabs. The swabs are consistent with the type of swabs used for standard-of-care NP swabs.

9.1.2 Packaging and Labeling

The study team will add labels to each packaged swab with the statement "CAUTION - Investigational Device. Limited by Federal (or United States) Law to Investigational Use." [§ 812.5(a))].

9.1.3 Preparation

9.1.3.1 Investigational Swab

A study team member will open the package of the swab and offer the end of the stick to the participant, instructing them to only touch the other end of the stick (i.e., the flocked end of the swab) to the inside of their mouth and nowhere else.

9.1.3.2 Investigational Assay

The COVID-19 PCR assay will be prepared and performed by the Wisconsin Veterinary Diagnostic Lab (WVDL), in the same way that samples are processed for standard of care.

9.1.4 Storage and Stability

Prior to use, the swabs must be stored separately from normal hospital stocks and must be stored in a securely locked area accessible only to authorized study personnel until used. Approved study team members will store, handle, and guide administration of the devices. If the package of a swab is damaged such that it is no longer sterile, the swab will be discarded.

9.1.4.1 Swab Handling After Saliva Collection

The swab will be taken to the Wisconsin Veterinary Diagnostic Lab as soon as possible. If it cannot be delivered to the lab on the same day as collection, then it may be temporarily stored in a designated refrigerator or freezer.

9.1.5 Accountability

The study team is already in possession of all swabs that will be used for the study.

9.1.6 Administration

A study team member will instruct the participant to suck on the swab for 20 seconds in the same way that they would suck on a lollipop.

9.2 Method for Assigning to Treatment Groups

Not applicable.

9.3 Study Intervention Compliance

Immediately after each study visit, the study team member will complete a Reportable Event Form that asks about protocol deviations, adverse events, participant complaints, and/or any other potentially reportable events that may have occurred. A participant's data will be included in analyses if their lollipop saliva sample is successfully resulted.

9.4 Concomitant Therapy

9.4.1 Permitted Concomitant Therapy

All concomitant therapies are permitted.

9.4.2 Prohibited Concomitant Therapy

No concomitant therapies are prohibited.

10.0 STUDY VISITS AND PROCEDURES

10.1 Study Calendar

The procedures performed at the single study visit are listed in the table below.

Procedure	Study Visit	Post-Study Visit	End of Study/Early Withdrawal
Informed Consent/Assent	X		
Demographic and Health Verbal Questionnaire	X		
Lollipop Swab Saliva Collection	X		
Adverse Event Review and Evaluation			X
Collect Information from Medical Record		X	

10.2 Screening and Enrollment

The single study visit and procedures are described in detail below.

10.2.1 Pre-screening

Pre-screening consists of examining a subject's medical records by research staff who have completed HIPAA and human subjects training.

10.2.2 Informed Consent

Preliminarily eligible subjects will be approached for informed consent/assent and formal screening. The informed consent/assent process will be conducted following all federal and institutional regulations relating to informed consent. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The Consent script will be Institutional Review Board (IRB)-approved. The participant (or legally authorized representative) will be asked to read and review the document. A copy of the informed consent document will be given to the subjects for their records. Verbal informed consent/assent will be obtained prior to conducting any study-related activities.

The informed consent process will be performed as follows:

- A research nurse or study coordinator will review the informed consent form and discuss the study in detail with the potential research participant and their parent/legal guardian, if the participant is a minor.
- A research nurse or study coordinator will explain the study, its risks and benefits, what would be required of the research subject, and alternatives to participation. An oral explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects.
- The research subject will be given the opportunity to review the informed consent form and take their time considering, so they may discuss it with family members, friends, clergy or others when possible.
- The subject will have the opportunity to ask questions and have all questions answered by the research nurse or study coordinator and/or PI.
- A research nurse or study coordinator will obtain oral consent from adult subjects. In the case of minor subjects, a parent or legal guardian will provide oral consent and the minor subject will provide oral assent. If a minor subject is incapable of reviewing the informed consent form, a research nurse or study coordinator will provide a summary of the material in terms that are age-appropriate and understandable to the subject.

This research involves no greater than minimal risk to adults or children, and it involves no procedures for which written documentation of consent is normally required outside of the research context. It may not be feasible to obtain written consent and assent from all participants. Hospitalized individuals with COVID-19 may be significantly symptomatic and ill. For younger children, writing their names may be challenging. COVID-19 is also a contagious infectious disease, so it is safest to minimize the handling of paper and pens. For consistency, we would like to have the same consent/assent process for all

participants. Therefore, we are requesting a waiver of written documentation of consent, parental permission, and assent.

10.2.3 Enrollment

A research subject will be defined as “enrolled” in the study when they meet the following criteria:

- The subject has been consented/assented by study staff.
- The PI or designee has verified that the subject meets all of the inclusion criteria.
- The PI or designee has verified that subject meets none of the exclusion criteria.
- The subject has provided a saliva sample.

10.2.4 Screen Failure and Re-enrollment

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a factor that could change over time may be rescreened. Rescreened subjects should be assigned a new subject ID number when they are re-screened.

10.3 Study Visit

After subjects have been enrolled, they will complete a single on-study visit, and the procedures performed at the visit are described in detail below.

10.3.1 Study Visit

Study visits will occur in a private location, such as the participant’s hospital room, during their inpatient stay at AFCH or University Hospital. Study team members will adhere to the University Hospital’s personal protective equipment (PPE) requirements. After verbal consent/assent is collected and documented in REDCap, the study team will collect basic information about participants, including their name, date of birth, sex, race and ethnicity. If participants are younger than 18 years old, the study team will collect their parent or guardian’s name. The study team will also collect information from participants or their parent/legal guardian verbally and from the participant’s medical record. The information will be relevant to their COVID-19 symptoms and diagnosis, as well as their vaccination status. A detailed list of data points can be found in the Data Collection Sheet. The study team will record this information directly in the study’s SMPH REDCap project. Once a study team member has collected this information, they will guide the participant through the lollipop swab collection. The lollipop swab is obtained by sucking on a swab for 20 seconds in the same way that one would suck on a lollipop. The study procedures will take approximately 15-30 minutes to complete.

A study team member will transport the lollipop swab to the WVDL as soon as possible. The WVDL will provide the study team with the COVID-19 PCR results.

10.4 Unscheduled Visits

If the single study visit is interrupted by routine clinical care or for another reason, it may be paused and restarted when the participant is available to continue.

10.5 Early Termination/Withdrawal Visit

Subjects who are either withdrawn or terminated early from the study may be asked why they chose to withdraw.

10.6 Long-Term Follow-up | Re-contacting Subjects

Not applicable.

11.0 DATA HANDLING AND RECORD KEEPING

11.1 Data Collection

11.1.1 Data Collection Forms

Standardized data collection forms (e.g., source documents, case report forms, standardized assessment forms, etc.) are used to ensure data collected are consistent and compliant with the protocol and IRB application.

Data collection is the responsibility of study team members under the supervision of the Principal Investigator (PI). The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the recorded and reported data.

All data collection forms must be completed thoroughly; any missing data will be explained. Data entry errors will be corrected within REDCap.

Data collection forms are maintained in the subject files and retained as described in Section 12.3: Records Retention.

11.1.2 Data Management Software Systems

Clinical data (including AEs, concomitant medications, and solicited events data) and clinical laboratory data will be entered into the following data management software system(s) to ensure consistent data entry and data quality. Clinical data will be entered directly from the source documents, typically Health Link.

OnCore

The Online Collaborative Research Environment (OnCore) Clinical Trial Management Software (CTMS) may be used for this study.

OnCore is a web-based data management system that: a) ensures secure, easy data entry at multiple sites; b) integrates multiple data sources; c) provides controlled, secure access to sensitive data using role-based access control; and d) provides workflow automation. This software provides protocol and subject management functions (e.g., subject scheduling; screening; data organization), maintains updated forms, addresses budget development, billing and fiscal management, generates summary reports, and provides essential links with research administration and electronic medical records systems. The OnCore system eases the burden of the individual researcher and unifies protocol management within research programs and across research sites, enhancing protocol integrity and regulatory compliance efforts.

REDCap

The SMPH Research Electronic Data Capture (REDCap) system is used to manage the data for this study.

REDCap is a largely self-service, secure, web-based application for building and managing data collection forms. REDCap provides data management functionality by allowing the development of instrument and surveys to support data capture for research studies.

11.2 Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information

concerning the study or the data will be released to any unauthorized third party without prior written approval.

All research activities will be conducted in as private a setting as possible.

All study staff engaged in the conduct of this project have completed training on the protection of human subjects and the Health Insurance Portability and Accountability (HIPAA) Privacy Rule. In addition, all key personnel (i.e., Principal Investigator, individuals involved in identifying/recruiting subjects, obtaining informed consent, or interacting and intervening with subjects) have undergone Good Clinical Practice (GCP) training.

Information about study subjects will be kept confidential and managed according to HIPAA requirements. All subjects will receive a combined informed consent and HIPAA authorization script that includes specific privacy and confidentiality rights. Study data will be maintained per federal, state, and institutional data policies.

The investigator(s) will ensure that the identities of subjects are protected by using coded subject information. Data will be maintained securely in REDCap. All paper-based study records will be maintained in locked rooms or cabinets, and access will be limited to approved study personnel. Electronic study records/files will be stored in SMPH REDCap and on the Department of Pediatrics server. Electronic data will be accessed via networked computers that are password-protected with access provided only to authorized study personnel.

Authorized representatives of the following groups may need to review this research as part of their responsibilities to protect research subjects: representatives of the IRB, and federal oversight agencies, such as the Food and Drug Administration (FDA). The clinical study site will permit access to such records.

11.3 Records Retention

At the end of this study, participant names and contact information will be destroyed. All other study data will be banked.

11.4 Retention for Future Research: Mandatory Data Banking

11.4.1 Purpose of Storage

Data is being stored for potential future research uses.

11.4.2 Data and/or Biospecimens Being Stored

There is no biospecimen banking in this study, as saliva samples will be exhausted during the PCR testing process. Only a coded Limited Data Set will be stored. Names and contact information (i.e., all direct identifiers) will be destroyed at study closure. All other data will be banked indefinitely.

11.4.3 Location of Storage

Data will be stored on Department of Pediatrics secure server.

11.4.4 Duration of Storage

Data will be stored indefinitely.

11.4.5 Access to Data and Security Measures

Only UW researchers who have completed the *Required Training for Researchers* will have access to the folder with banked data on the Department of Pediatrics secure server. Only de-identified data will be shared with external researchers, using platforms and tools approved by UW Office of Cybersecurity.

11.4.6 Procedures to Release Data

Researchers may request data by writing to the Principal Investigator or Co-Principal Investigator. Documentation of IRB approval may be required prior to releasing the data.

11.4.7 Process for Returning Results

Not applicable.

11.4.8 Process for Tracking Subject Consent and Authorization

The study team will document verbal consent from all participants or their parent/legal guardian in the study's REDCap database.

11.4.9 Withdrawal of Permission to Bank Data

Data is fully anonymized prior to banking, so participants may not withdraw their banked data from future research use after study closure.

11.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or investigational plan requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the Principal Investigator/site investigator/study staff to use continuous vigilance to identify and report deviations. The Principal Investigator is responsible for assessing whether the deviation constitutes noncompliance as defined by the reviewing IRB and if so, reporting it within the required time frame(s). The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

11.6 Publication and Data Sharing Policies

Not applicable.

12.0 STUDY ANALYSIS

12.1 Statistical Hypotheses

- **Primary Efficacy Endpoint(s):**
  - For participants who have had COVID-19 symptoms for <5 days, the sensitivity of lollipop swab-based PCR COVID-19 testing is non-inferior to the sensitivity of NP swab-based PCR COVID-19 testing.

- **Secondary Efficacy Endpoint(s):**
  - For participants who have had COVID-19 symptoms for ≥5 days, the sensitivity of lollipop swab-based PCR testing is inferior by 50% to the sensitivity of NP swab-based PCR COVID-19 testing.
  - For participants who are asymptomatic, the sensitivity of lollipop swab-based PCR testing is inferior by 50% to the sensitivity of NP swab-based PCR COVID-19 testing.

12.2 Sample Size Justification

Based on a small pilot study in 2020-2021, sensitivity of lollipop swabs compared to NP was found to be 88%. As we will now be including both asymptomatic and symptomatic individuals, we anticipate the

sensitivity of the lollipop swab to drop to approximately 80%. With a Type I error rate of 5% and a power of 90%, our calculated sample size is 206.

12.3 Subject Population(s) for Analysis

Protocol-compliant Population: all participants who provided a lollipop swab that was successfully resulted and complied with the protocol sufficiently to ensure that the data would be likely to represent the effects of the study intervention according to the underlying scientific model.

12.4 Statistical Methods

Sensitivity and specificity of the lollipop swabs will be calculated.

The primary variable is binary (positive or negative). A separate subgroup analysis of sensitivity/specificity of lollipop swabs will be calculated for asymptomatic, symptomatic (<7 days), and symptomatic (>7 days) individuals.

12.5 Planned Interim Analysis

An interim analysis will not be performed.

12.6 Handling of Missing Data

Since the analyses of this study won't involve any formal multivariate or longitudinal statistical modeling, no imputation-based analyses will be conducted.

Guidelines promulgated in the National Research Council report on handling of missing data will be followed.[2,3]

13.0 RISK/BENEFIT ASSESSMENT

13.1 Known Potential Benefits to the Subjects

There will be no direct health benefit to subjects.

13.2 Known Potential Risks

13.2.1 Known Interventional Risks

There are no known or anticipated risks of the lollipop swab collection method. Our study team implemented a similar testing method in a previous study (2017-1425) and it was tolerated well by participants.
There is a risk of breach of confidentiality.

13.2.2 Other Known Study Risks

There are no knowns procedural risks potentially related to study participation.

13.3 Risk/Benefit Analysis

The risks are minimal, and the potential benefit to society is significant.

14.0 DATA AND SAFETY MONITORING

14.1 Adverse Event (AE) Definition

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

14.2 Serious Adverse Event (SAE) Definition

An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it meets any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

14.3 Classification of an Adverse Event

14.3.1 Severity of Event

All AEs will be assessed by the clinician using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

Mild (Grade 1)	Events require minimal or no treatment and do not interfere with the subject's daily activities.
Moderate (Grade 2)	Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe (Grade 3)	Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.
Life Threatening (Grade 4)	The subject was at risk of death at the time of the event.
Fatal (Grade 5)	The event caused death.

14.3.2 Relationship to Study, Study Procedure(s) and/or Study Intervention(s)

For all collected AEs, the clinician who examines and evaluates the subject will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely Related	Clearly related to the study procedures/intervention and other possible contributing factors can be ruled out.

Probably Related	Likely related to the study procedures/intervention and the influence of other factors is unlikely.
Possibly Related	Possibly related to the study procedures/intervention and there are other factors that could be equally likely.
Unlikely to be related	Doubtfully related to the study procedures/intervention and there is another likely cause.
Unrelated	Clearly not related to the study procedures/intervention and/or evidence exists that the event is definitely related to another cause.

14.3.3 Expectedness for Study, Study Procedure(s) and/or Study Intervention(s)

The PI will be responsible for determining whether an AE is expected or unexpected in relation to the study procedures and intervention(s) (as applicable).

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the clinical protocol, device manual, investigator's brochure, the package insert(s), the IRB application, or the informed consent document. Expectedness is recorded for both study procedures and interventions.

14.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Events will be followed for outcome information until resolution, stabilization, or completion of study participation.

14.5 Reporting AEs and SAEs

14.5.1 Reporting AEs

- AEs will be recorded from enrollment until completing all study activities.
- AEs will be recorded regardless of whether or not they are considered related to the study device.
- All AEs will be recorded on the appropriate study specific REDCap Reportable Event form within the study's REDCap project.

14.5.2 Reporting SAEs

The investigator will immediately report to the sponsor any SAE, whether or not considered study intervention-related, including those listed in the protocol or investigator's brochure and must include an

assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the IRB.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the subject is stable.

14.6 Reporting of Pregnancy

Not applicable.

14.7 Unanticipated Problems

An unanticipated problem (UP), as defined by the DHHS Office for Human Research Protection (OHRP), is any incident, experience, or outcome that meets all of the following criteria:

- The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the informed consent documents, the Investigator's Drug Brochure) and the characteristics of the subject population being studied. An event may be considered unexpected if it exceeds the nature, severity, or frequency described in the study-related documents, Investigator's Drug Brochure, product labeling, or package insert.
- The incidence, experience, or outcome is related or probably related to participation in the research study. "Probably related" means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.
- The occurrence of the incidence, experience, or outcome suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

The investigator will report UPs to the reviewing IRB and to the Data Coordinating Center (DCC)/lead Principal Investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol, informed consent documents, or other corrective actions that have been taken or are proposed in response to the UP.

Report UPs within the timeframe(s) specified by the IRB(s) of record.

14.8 Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)).

A sponsor who conducts an evaluation of an UADE shall report the results of such evaluation to the FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1).]

14.9 Incidental Findings

Not applicable.

14.10 Safety Oversight

Safety oversight will be under the direction of the Principal Investigator.

14.11 Study Monitoring

Not applicable.

14.12 Study Stopping Rules

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:
- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and/or data quality are addressed and satisfy the applicable federal and institutional regulatory authorities.

15.0 STUDY FEASIBILITY

15.1 Economic Burden to Subjects

Subjects will not have to pay for study procedures (such as home blood pressure monitors, 24-hour monitoring). The subject will not be billed by the healthcare system or their health insurance company for any costs related to a study procedure.

Subjects will be responsible for any costs related to their COVID-19 follow-up as directed by their healthcare team, such as clinic visits and medication, including all out-of-pocket costs.

15.2 Facilities and Locations

UW Health Kids American Family Children’s Hospital and UW Health University Hospital inpatient units.

15.3 Feasibility of Recruiting the Required Number of Subjects

While COVID levels fluctuate in the community, in 2023 at University Hospital/AFCH there are generally 10-20 individuals hospitalized with a positive COVID test on any given day. If the COVID rates are maintained, then obtaining the sample size is possible over the next few months.

If UW/AFCH stops pre-procedural or COVID admission screening, then the amount of known COVID-positive individuals will likely decrease and it may take a longer time to identify 225.

15.4 Principal Investigator Considerations

15.4.1 Time Devoted to Conducting the Research

PI and Co-PI are interested in the results of this study have dedicated academic time to its completion.

15.4.2 Process for Informing Study Teams

Not applicable.

15.5 Availability of Medical or Psychological Resources

Not applicable.

16.0 MULTI-SITE RESEARCH

Not applicable.

17.0 REFERENCES

1. National Research Council. The Prevention and Treatment of Missing Data in Clinical Trials. Washington, DC: National Academies Press, 2010.
2. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, Frangakis C, Hogan JW, Molenberghs G, Murphy SA, Neaton JD, Rotnitzky A, Scharfstein D, Shih WJ, Siegel JP, Stern H. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012 Oct 4;367(14):1355-60.