Safe & Healthy Schools

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PROTOCOL TITLE:

Safe and Healthy Schools

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
2	August 2021	Change BinaxNOW interval from 3 days to 5 days, add compensation, update details about data labeling and storage	Yes
3	September 2021	Add 50 participants with positive at-school BinaxNOW, add option to consent prior to initial BinaxNOW testing, clarify process for Spanish translation, change eligibility to include all MMSD staff and students ages 4-14 with at least one symptom who are getting at-school PCR testing, clarify criteria that define	Yes

		who will be excluded from the final study sample, add questions to data collection form	
4	October 2021	Add back-up data collection method, add questions to data collection form, update follow-up guidance for positive at-home BinaxNOW	
5	December 2021	Modify recruitment method to allow participants to directly contact or approach the study team, and also to allow the study team to gently approach potential participants; describe sharing of results for at-school antigen test; explain that all study participants will receive a BinaxNOW home testing kit, not just participants with negative at-school antigen tests	Yes
6	January 2022	Add option of study team collecting at-school BinaxNOW test if it isn't already being collected, change child age range to 4-19, and add lollipop-only alternative if study team runs out of BinaxNOW tests	Yes
7	April 2022	Add Accelerated Clinical Laboratories (ACL) as a lab service provider, in addition to Exact Sciences Laboratories.	Yes
8	May 2022	Change lollipop sample labels from coded to fully identifiable. Update recruitment to explain ACL introducing the study. Make lollipop-only an option if a potential participant is unwilling or unable to do at-home BinaxNOW testing. Extending study timelines—completing enrollment in August instead of March.	Yes

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1.0 Study Summary

Study Title	Safe and Healthy Schools
Brief Summary	This study will target Madison Metropolitan School District school children ages 4-19 and staff who have not had a previous positive COVID-19 test within the past 3 months. It will enroll children and adults for 1-3 days to explore whether serial "at-home" BinaxNOW testing is feasible and non-inferior to "at school" single PCR testing for the evaluation of symptomatic individuals with a negative initial BinaxNOW. It will also explore whether lollipop swabs are more acceptable and perform as well as nasal swabs with PCR testing.
Number of study sites	1
Study Design	Community-based empirical research
Primary Objective	(1) Determine whether "at-home" BinaxNOW testing is feasible for families, (2) Evaluate whether serial "at-home" BinaxNOW testing is non-inferior to "at school" single PCR testing, (3) Compare the acceptability of lollipop swabs and nasal swabs, and (4) Compare the performance of lollipop swabs to nasal swabs with PCR-based testing.
Secondary Objective(s)	NA
Research Intervention(s)/ Investigational Agent(s)	NA
Drugs/devices used on study (including any IND/IDE #)	This study will evaluate the BinaxNOW COVID-19 Ag Card and the "lollipop" swab sample collection method
Study Population	Madison Metropolitan School District school children ages 4-19 and staff
Sample Size	400 with negative at-school BinaxNOW and 50 with positive at-school BinaxNOW. Total n=450.
Study Duration for individual participants	Up to 5 days
Study Specific Abbreviations/ Definitions	PCR: polymerase chain reaction EUA: emergency use authorization

2.0 Background

2.1 Relevant prior experience and gaps in current knowledge:

Current standards for COVID-19 diagnosis include nasopharyngeal (NP), nasal or saliva specimens to detect SARS-CoV-2 via polymerase chain reaction (PCR) test. Because NP swabs are cumbersome to perform, uncomfortable for the patient, require health providers in personal protective equipment, scare young children and are not practical for large groups or repeat testing, we have been exploring the use of "lollipop" swabs. A lollipop swab, is an oral swab, sucked on like a lollipop for 20 seconds. It is essentially a sample of saliva that is conveniently collected. A previous experience with the use of lollipop swabs for the detection of group A streptococcus in children with pharyngitis, prompted us to perform a pilot test to assess the sensitivity of the lollipop swab compared to a NP swab for the detection of SARS-CoV-2 in symptomatic individuals with PCR.

Additionally, our group has extensive experience training and implementing testing for SARS-CoV-2 in K-12 schools. During the 2020-2021 academic school year, we trained two elementary schools to perform SARS-CoV-2 reverse transcription-loop-mediated isothermal amplification (RT-LAMP) saliva-based testing in Madison, WI. More broadly, we visited more than a dozen schools and districts to train staff how to perform BinaxNOW antigen tests. We generated an online portal, complete with videos, training slides, and examples of consenting documents. Through these efforts, we provided more than 100 schools in Dane County with the tools needed to perform antigen tests in the spring of 2021.

2.2 Relevant preliminary data:
Our previous research showed that 25 symptomatic patients assessed within 7 days of onset of symptoms (and known to be infected with SARS-CoV-2) were all positive when a lollipop swab was used for collection. In addition, 5 asymptomatic patients known to be infected with SARS-CoV-2 also proved to be positive when evaluated with a lollipop swab.

2.3 **Significance**: The prevalence of SARS-CoV-2 among school-aged children in the 2021-2022 academic year is unknown. Intense vaccination campaigns will reduce the number of cases, but vaccination uptake varies widely across Wisconsin. Children under the age of 12 years will likely not be eligible for vaccination until the late fall, leaving many children still susceptible to infection during part of the school year. With the large number of children simultaneously returning to school (with many extracurricular activities), and potentially decreased attention to mitigation

strategies, there will be increased transmission of respiratory viruses among members of the school community.

We expect there will be a surge in respiratory illnesses caused by enterovirus, rhinovirus, community coronaviruses, influenza, RSV, parainfluenza, human metapneumovirus and adenovirus as well as SARS-CoV-2 in the fall and winter of next year. When schools reopened post COVID-19 shutdowns in Hong Kong and the UK, there were rapid increases in the cases of rhinovirus. This anticipated rise of symptomatic children requires a comprehensive strategy to quickly distinguish between cases of SARS-CoV-2 and non-SARS-CoV-2 infections and implement a policy to consistently enable a prompt return to school.

In order to appreciate the nuances of testing for infections with SARS-CoV-2, it is necessary to briefly discuss clinical presentation and viral replication.

Clinical presentation and viral replication: Since the beginning of the pandemic, it was recognized that children are infected with SARS-CoV-2 less often than adults and that their illness has been, in general, milder than in adults. Many children and adults are completely asymptomatic. However, when children are symptomatic, their symptoms take the form of a mild upper respiratory infection with nasal congestion, nasal discharge, sore throat or cough.

The time from when a person is exposed to the SARS-CoV-2 virus to the time that they become infectious to others is called the incubation period. Just before the onset of symptoms, virus multiplication in the nose and throat accelerates and the infected individual becomes infectious to others. Infectivity of a given individual peaks in about the next 24 hours. They remain infectious for about 5 days, during which time the amount of virus in the nose and throat gradually decreases.

Diagnostic Testing for SARS-CoV-2 – Nucleic acid detection: The gold standard for diagnostic testing has been detection of SARS-CoV-2 nucleic acids by a polymerase chain reaction (PCR). The first tests to be developed were performed on a sample obtained from the nasopharynx. Eventually, these PCR assays were modified to be performed on other samples including either nasal mucosal swabs or samples of saliva collected in small receptacles. The transition to the use of other samples has been important since acquiring the nasopharyngeal (NP) sample requires trained personnel and is uncomfortable for the patient. Repeated NP tests are dreaded. *Identifying the optimum sampling technique for children remains a challenge.*

PCR tests are generally performed in hospital or commercial laboratories. They are expensive—usually costing $75 to $150 dollars. They also take time to perform; although some tests are run in as short a time as an hour or two; others take 6 to 12 hours. Transportation from the collection site to a centralized testing facility significantly prolongs turnaround time ranging from 1-3 days. These delays limit the use of PCR as a tool for infection control.

The PCR test will be negative during the incubation period because there is not enough virus present to give a positive reaction. Just as the individual is becoming symptomatic, the PCR becomes positive. As the titer of virus peaks during the next 24 to 48 hours, the PCR test stays positive and will remain positive for quite a few more days while the patient is symptomatic and infectious to others. Of importance, the PCR may even remain positive when the patient is no longer infectious to others, because the test detects the nucleic acids even though the virus is no longer capable of replication.

Antigen testing: Instead of detecting viral nucleic acids, the target for antigen tests is the nucleoprotein (N) protein of the SARS-CoV-2 virus. Antigen tests can be performed in a shorter time than PCR tests and are much less expensive. While antigen tests are less sensitive than PCR tests, they both detect individuals who are infectious. The Abbott company developed a very simple assay that has been commercialized for use both as point-of-care as well as an in-home test called the BinaxNOW-COVID-19 Antigen test (hereinafter call BinaxNOW). The test comes packaged within a card which is the size and shape of a credit card and which opens like a small book. In addition, there is a container of reagent. The reagent is delivered into a small hole in the card. A nasal swab is obtained from the patient by swirling the swab gently in the anterior nares several times. The swab is then inserted into the space where the reagent is located and turned several times. A positive test is indicated by the presence of 2 lines, very similar to home pregnancy tests. The testing time is 15 minutes. A positive swab can be detected within 5 to 8 minutes, but the test cannot be classified as negative until 15 minutes have elapsed. In addition, this test is CLIA-waived and can be performed by school health personnel in the school setting, eliminating the need for specimen transport and dramatically reducing turn-around-time and providing immediately actionable results for determining the need for exclusion from school.

The BinaxNOW test is reported to be approximately 94% sensitive in patients with symptomatic COVID-19 infections. Accordingly, it would be anticipated that if an individual who was truly infected with SARS-CoV-2 tested negative with the BinaxNOW test, then another test would almost certainly become positive if repeated within 24 hours, as the climb in viral load is particularly steep once

symptoms have developed. On the other hand, if the symptomatic individual with a negative BinaxNOW test is not infected with SARS-CoV-2, the repeat BinaxNOW will be persistently negative.

Testing in schools: There are several instances in which testing individuals for SARS-CoV-2 infection in the school setting is useful. Children or teachers may arrive at school and suddenly notice symptoms, or they may become symptomatic during the day. For these scenarios, we want to determine if the individual is positive for SARS-CoV-2 so they can be isolated and contact tracing can be initiated. If the patient is not infected with SARS-CoV-2, then an individual will only need to remain at home until their symptoms have resolved.

BinaxNOW tests are a valuable adjunct to PCR testing in symptomatic individuals because they are available, simple, and rapid. A positive result for a student or staff member can rapidly exclude the individual from the class and begin contact tracing. However, Wisconsin Department of Health Services (DHS) requires that a negative BinaxNOW test in a symptomatic individual be followed by a PCR. This requirement reflects the imperfect sensitivity of the BinaxNOW card at 94% rather than 100%. However, PCR tests are inconvenient for families and time consuming, so many families prefer to be isolated for 10 days, creating a situation in which school will be missed unnecessarily. DHS is attempting to improve adherence to PCR follow-up testing by providing nasal swab kits directly to schools. However, transporting these swabs to the testing facility is time-consuming for staff, thereby adding cost and decreasing accessibility.

Given that mask use is likely to be less stringent in the future, the likelihood of an increase in community-acquired viral infections is very high. This will translate into a greater proportion of children and adults presenting with respiratory symptoms who will have a negative BinaxNOW because their infection is caused by a virus different from SARS-CoV-2. Accordingly, we need a less resource-intensive approach to test symptomatic individuals for SARS-CoV-2.

3.0 Study Objectives and Endpoints

3.1 **Aim 1**: We will test the hypothesis that serial at-home BinaxNOW testing will be feasible and non-inferior to the single at-school PCR testing program. To do this, we will distribute over-the-counter BinaxNOW antigen tests to volunteer families and create a protocol to ensure families can perform and report test results accurately to the school. We will address two key questions:

1. Is 'at-home' BinaxNOW testing feasible for families?

2. Is serial 'at-home' BinaxNOW testing non-inferior to 'at-school' single PCR testing?

Aim 2: We will test the hypothesis that lollipop swabs are more acceptable to individuals and PCR testing is non-inferior to performing PCR on nasal swabs. To test this hypothesis, we will work with MMSD schools to incorporate a lollipop swab for PCR at the time a symptomatic student or staff receives a nasal swab for PCR that is part of the DHS program. We will address the following two key questions:

1. Are lollipop swabs more acceptable to individuals when compared to nasal swabs?

2. Will lollipop swabs perform as well as nasal swabs with PCR-based testing?

3.2 Hypotheses to be tested:
Aim 1.1: "At-home" BinaxNOW testing will be feasible for families.

Aim 1.2: Serial "at-home" BinaxNOW testing is non-inferior to "at school" single PCR testing.

Aim 2.1: Lollipop swabs are more acceptable to individuals than nasal swabs.

Aim 2.2: Lollipop swabs will perform as well as nasal swabs with PCR-based testing.

4.0 Number of Participants

4.1 Total number of participants to be accrued:

We expect to enroll approximately 450 participants.

4.2 Number of participants needed to complete the research procedures:

To achieve adequate statistical power, 358 participants with negative at-school BinaxNOW tests need to complete the research procedures, including the at-home BinaxNOW test.

An additional 50 participants with positive at-school BinaxNOW tests need to provide lollipop swabs.

4.3 Replacing enrolled participants:

If participants with negative at-school BinaxNOW test results do not complete the procedures within the target window, i.e., do not successfully completing the at-home BinaxNOW test within 72 hours, they will be replaced. We will continue enrolling until 358

participants have completed the research procedures within the target timeframe.

We will continue enrolling participants with positive at-school BinaxNOW test results until 50 participants have nasal and lollipop PCR results.

5.0 Inclusion and Exclusion Criteria

5.1 Eligibility Screening:

This study will enroll MMSD school children ages 4-19 and MMSD staff who currently have at least one symptom of COVID-19, have not had a positive COVID test within the past 3 months, and will undergo nasal PCR testing at an MMSD elementary school.

If symptomatic MMSD school children or staff intend to have nasal swab PCR tests at school, then school-approved personnel may inform adults—staff or children's parents—of our research study. The staff will either provide a flyer or verbally let them know it involves a lollipop test at that time, and if the at-school BinaxNOW is negative, it will also involve the performance of an at-home BinaxNOW test in approximately 24 hours. If the school does not conduct a BinaxNOW test, then the study team will collect a nasal swab for the "at-school" BinaxNOW test.

If the study team does not have any BinaxNOW tests due to a supply shortage, the at-school and at-home BinaxNOW tests will be dropped and participants will be recruited for a Lollipop Only alternative. Additionally, if a potential participant expresses interest in the study but is unwilling or unable to do at-home BinaxNOW testing, then the study coordinator will offer them the Lollipop Only alternative.

School-approved personnel will also let potential participants know that they would not be eligible to participate if they have had a previous positive COVID-19 test in the past 3 months, either verbally or by providing a flyer. The staff will ask if the adult is interested in speaking to a study coordinator to learn more about the study. If yes, the staff will either direct the potential participant to the study coordinator or they will inform the study coordinator that a potential participant is interested in speaking with them, and they will connect the coordinator to the potential participant, either on the phone or in person.

Alternatively, the study team may gently approach potential participants near the at-school testing locations. Potential participants may also directly contact the study team in response to poster and flyer advertisements.

Once an interested participant is identified, the study coordinator will review eligibility criteria and explain more details about what is involved. They will let them know what the exclusion criteria are and tell them that prior to enrolling in the study, they do not need to disclose whether they have received a positive COVID-19 test. The coordinator will ask, after the potential participant has learned more about the study and had a chance to ask questions, whether they are eligible and interested in participating. If they decline, the study coordinator will not ask for more details about why they do not wish to participate. In other words, study coordinators will be careful not to probe about COVID-19 diagnoses prior to enrollment. If a potential participant indicates that they are interested in participating but are unable or unwilling to complete the at-home BinaxNOW testing, then the study coordinator will present the Lollipop Only alternative. They will also have this conversation in a setting that is as private as possible. If the potential participant says that they are eligible and interested in participating, the study coordinator will conduct verbal consent with the adult and assent with the child, when applicable. The study coordinator will record the participant's name and information after consent and assent are complete. This study will not track information or explanations from participants who decline enrollment.

5.2 Criteria that define who will be included in the final study sample:

For Aim 1, participants with a negative at-school BinaxNOW test and nasal PCR results who complete both the lollipop PCR and at-home BinaxNOW tests within 72 hours will be included in the final study sample.

Aim 2 will include participants who provide a lollipop swab that is successfully resulted at Exact Sciences or ACL.

5.3 Criteria that define who will be excluded from the final study sample:

If certain samples do not provide a result—such as if samples are missing, compromised, or invalid—the subject will not be included in analyses for one or both of the study aims. Criteria for exclusion from analyses are as follows:

Aim 1

-Missing nasal PCR result

-Do not successfully complete an at-home BinaxNOW test within 72 hours of the at-school BinaxNOW test

Aim 2

-Missing nasal PCR result

-Missing lollipop PCR result

6.0 Special Populations

6.1

☒ Children/Minors (HRP-416 - CHECKLIST - Children)
☐ Pregnant persons / fetuses (HRP-412 - CHECKLIST - Pregnant Women; HRP-413 - CHECKLIST - Non-Viable Neonates; HRP-414 - CHECKLIST - Neonates of Uncertain Viability)
☐ Prisoners (HRP-415 - CHECKLIST - Prisoners)
☐ Participants with impaired decision-making capacity (HRP-417 - CHECKLIST - Adults with Impaired Decision-Making Capacity)

This study will enroll MMSD students ages 4-19, staff and teachers. This research involves no greater than minimal risk to individuals, including children. It is necessary to enroll children in this study to determine what types of tests are optimal in school settings. Verbal assent will be obtained from all children enrolled in the study after their parent or legal guardian provides consent.

6.2 ☒ Non-English speaking participants
☐ Illiterate or Low Literacy participants
☐ Participants with visual or hearing impairments
☐ Status Relationship: Individuals with a status relationship with the PI or other study team members (e.g., employees, students, family members)

This study will enroll Spanish-speaking participants. Ideally, the study team member conducting the consent/assent process and study procedures will be fluent in Spanish. If not, they will utilize a translator employed by the school district, school-approved personnel who are fluent in Spanish, or UW-Madison or UW Health interpreter services.

6.3

☐ Individuals who are receiving inpatient or outpatient services for mental illness, developmental disability, or alcohol and other drug abuse (AODA)
☐ Individuals who are protectively placed by a court in a treatment facility
☐ Veterans/Military Personnel
☐ Emancipated minors
☐ Anyone especially vulnerable to manipulation or inducements for participation as a result of their illness or socioeconomic condition

This study will not include any of the populations listed above.

7.0 Recruitment Methods

7.1 Recruitment Source:

Participants will be recruited by nursing staff at Madison Metropolitan School District elementary schools.

7.2 Methods to Identify Potential Participants:

Potential participants may learn about the study from the school nurse, nurse's assistant, or whichever school-approved personnel are coordinating or administering COVID-19 testing. The school nursing staff may recommend at-school COVID-19 testing if staff or students become symptomatic while they are at school. Additionally, MMSD sends COVID-19 Student Screening emails to parents every weekday morning. If parents indicate that one or more of their children have symptoms, they are prompted to take a screening survey, then school nurses review the survey. Nurses may talk with parents on the phone and recommend that they bring their child(ren) to school for testing. If parents agree to at-school testing, the nursing staff may inform the parent of the study. Additionally, if a parent has a symptomatic child who attends a different MMSD school (e.g., a child who attends middle or high school), the nursing staff may also recommend at-school testing for them, as well. If parents agree to at-school testing for any of their children ages 4-19, the nursing staff may inform them about the study. The nursing staff will ask whether a potential participant is interested in talking with a study coordinator.

There will also be a sign at the schools near the location where COVID-19 testing is taking place. The sign will ask if people are symptomatic and getting tested, and if yes, they may be eligible to participate in a study. It instructs people to "call the study coordinator now" if they would like more information. When they call the number provided, the study coordinator would talk with the potential participant or parent on the phone or in person to provide more information about study details and eligibility. The study coordinator will also be wearing a UW badge, so if they are in close vicinity of the sign, participants may also walk up to them to ask about the study. Additionally, the study team may gently approach potential participants to see if they are interested in learning more about the study.

7.3 Where, When and How Participants will be Recruited:

If an MMSD student, teacher or staff member develops one or more symptoms consistent with COVID-19, either at home or at school, they may confer with the school nursing staff. The staff may recommend COVID-19 testing at the school. If a symptomatic individual (or their parent, in the case of children) agrees to a nasal

swab PCR test at the school, then staff will inform them about the opportunity to participate in research. School-approved personnel will ask if they are interested in speaking with a study coordinator, and if yes, they will connect them with a study coordinator. The study coordinator will provide more information, and if the potential participants indicate that they are eligible and interested in participating, they will complete the consenting process. When possible, this initial information discussion and the consenting process will be conducted in person. If school personnel talk to parents on the phone, then the study coordinator may also talk with parents on the phone. This may be necessary in certain situations, such as when a parent intends to have someone who is not a legal guardian pick their child up from school, such as an older sibling or grandparent. When needed, the school personnel will connect the parent and the study coordinator over the phone for the initial discussion and consenting process. There will also be a sign near the location where the COVID-19 testing is taking place that will instruct people to call the study coordinator at the time of testing.

There are times when symptomatic adults and children may come to the school for testing without first talking with school personnel. In these cases, school personnel would not be available to introduce the study. School-approved personnel, such as Accelerated Clinical Laboratories staff collecting the BinaxNOW and nasal PCR swabs, may also introduce the study to adults. Additionally, people getting tested may see the sign and call the study coordinator to learn more about the study. Or, if study team members are in the close vicinity of the sign, wearing a UW badge, then participants may walk up to the study coordinator to ask them about the study.

With the presence of a sign near the testing location, the study team members may also gently approach potential participants. For example, the study team may ask whether they have questions about the sign or are interested in learning more about the study. The study team will be careful to be respectful, rather than intrusive, in their approach.

7.4 Recruitment Materials:

Flyers describing the study are available in both English and Spanish. Schools could use the flyer, at their discretion, to inform the school community about the study that is taking place. School-approved personnel, such as ACL staff, could also use the flyer to inform potential participants about the study at the time they are eligible.

A sign describing the study will be placed near the location where COVID-19 testing is taking place. It instructs people to call the study coordinator if they are experiencing symptoms and getting tested.

If the study team does not have a supply of BinaxNOW tests, the Lollipop Only flyer and poster will be used for recruitment.

7.5 Compensation:

All participants will be offered a small prize, such as a sticker or small toy, for completing the lollipop swab. All participants who complete an at-school BinaxNOW test will also be given a BinaxNOW COVID-19 Ag Card Home Test kit, which includes two tests and instructions in both English and Spanish. These test kits cost approximately $20 at local retailers. Participants with a negative at-school antigen test will need to use one of the two tests to complete study procedures. Remaining tests may be used at participants' discretion.

For participants who have a negative at-school BinaxNOW test and therefore complete the at-home BinaxNOW test, this study will provide subjects or their parent/legal guardian, in the case of children, with a $10 gift card. The gift card will be given to adults after completing the at-home BinaxNOW test. It is possible for people to participate in this research study more than once—they may be eligible each time they get a BinaxNOW test and nasal PCR at school, if they have not had a positive COVID-19 test in the past 3 months. Therefore, participants will be re-consented and compensated each time they participate in the study. If participants do not complete the virtual/home visit, they will not receive a gift card.

8.0 Consent/Assent Process

8.1 A trained study team member will obtain informed consent from all adult participants and all parent/legal guardians of child participants. The trained study team member will also obtain assent from all children. If a parent or legal guardian chooses to enroll more than one child in the study, the consent and assent process will be completed for each child enrolled. Children ages 4-14 will be assented using the Assent Script. Children ages 15-17 will be assented using the Consent Script. There will be minor differences in assent discussions depending on children's ages, as study team members will use age-appropriate language.

If the study team does not have a supply of BinaxNOW tests, or if a potential participant is unwilling or unable to complete at-home BinaxNOW testing, the Lollipop Only consent and assent will be used.

The consent process will occur in person whenever possible. When needed, the consent may occur over the phone. The assent process will always occur in person, at the school, after the parent or legal guardian has provided consent.

The consent process will be conducted face to face whenever possible. If needed, it may be conducted with parents or legal guardians over the phone. The consent informs participants that email is generally not a secure way to communicate, as there are many ways for unauthorized users to access email. It instructs participants to avoid sending sensitive, detailed personal information by email. It also says that subjects may participate in the study even if they do not consent to email communication. At this time during the consent process, study staff will ask and record on the data collection form whether or not the parent or legal guardian consents to email communication. Consent scripts will be provided in person, by mail, or by email, per the participant or parent's preference.

There will not be any waiting period between informing the prospective participant and obtaining the consent. Study team members will ensure that parents and legal guardians will not feel pressured to participate. When initially approaching subjects about the research participation opportunity, the study team will emphasize that there is no penalty for choosing not to participate. If parents or legal guardians indicate that they feel rushed, do not have time to fully consider the decision, or they can't ask all their questions, then study team members will encourage them not to enroll. Assent will be sought after obtaining consent from a parent or legal guardian.

A trained study team member will ask questions about key elements of the consent and assent to ensure the potential participant is understanding. Based on their responses to the questions, the study team member will determine whether a potential participant understands the information.

At the beginning of the virtual or at-home study visit for BinaxNOW testing, the study team member conducting the visit will remind the participant and their parent (in the case of children) that participation in research is voluntary. Virtual visits will be conducted using a UW-approved videoconferencing platform.

We will be following HRP-090 – SOP – Informed Consent Process for Research. In accordance with the SOP, the consent script used for this study is the same as the consent form used for the long form of consent documentation, except the signature block has been removed.

Consent scripts and information sheets for adult participants and for parents or legal guardians of children participants are uploaded in ARROW. An assent script is also uploaded.

8.2 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. Therefore, we are requesting a waiver of written consent and assent documentation. We will use consent and assent scripts to obtain verbal consent and assent, and we will provide an information sheet to the consenting guardian in person and/or via email or mail. We will document in the study's secure database that verbal consent and assent occurred prior to any study procedures. We anticipate that parents or legal guardians may have someone else pick their child up from schools, such as a grandparent or older sibling. Therefore, the ability to obtain consent verbally over the telephone is essential to be able to conduct this study. To keep in-person and phone consent processes consistent by using a script, we request a waiver of written consent and assent documentation for all participants.

Non-English-Speaking Participants

We will enroll Spanish-speaking families. The consent script has been translated into Spanish by a translator employed by UW Health Translation Services. Ideally, the study coordinator will be fluent in Spanish so that they can read the consent and assent scripts, solicit and answer any questions, and directly obtain verbal consent and assent. If the study coordinator is not fluent in Spanish, they will use the services of a translator. In that case, the study coordinator would conduct the consenting discussion and solicit questions in English, and the translator would relay this information to the participant in Spanish. In other words, the questions would be translated to English for the study coordinator, and the study coordinator's responses would be translated back to Spanish. If this process is conducted with a parent or legal guardian over the phone and a translator is required, the process would occur as described above.

Participants who are not yet adults (children)

We will obtain assent from all children who enroll in this study. If they do not assent, we will not enroll them. The study coordinator conducting assent will have sufficient experience and/or training in working with children in this age range. They will use age-appropriate language to inform children that participating in research

studies is voluntary, meaning it is entirely up to them if they want to be in the study. They will be told that no one on the study team will be upset or disappointed if they do not wish to participate. The child will be asked directly if they would like to participate, and they will need to verbally answer in the affirmative. Passive resignation will not be considered assent. Study coordinators will receive training from experienced study staff in recognizing and responding to children's dissent.

Individuals under the age of 18 are considered "children" for the purposes of this study. We will enroll students 4 to 19 years old.

Since no greater than minimal risk to children is presented by this study, we will obtain permission from one parent or legal guardian, even if another parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

Permission will be obtained from legal guardians, as determined by the school.

Assent will be obtained from all children enrolled in the study.

Assent will be obtained using a verbal script. The Assent Script will be used for children ages 4-14, and the Consent Script will be used for children ages 15-17. If children choose to participate, their verbal assent will be documented in the study's secure database.

9.0 Process to Document Consent in Writing

9.1 We will not document consent in writing. However, we will document that both consent and assent, when applicable, occurred prior to study procedures in the Data Collection Form in in the ICTR version of REDCap.

9.2 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. Therefore, we are requesting a waiver of written consent and assent documentation. Consent and assent scripts have been uploaded in ARROW.

10.0 Setting

10.1 Research procedures will be performed at elementary schools and virtually. We have received approval from the Madison Metropolitan School District. If enrollment targets are not met, we will seek approval from additional area school districts. If a participant is unable to complete a virtual visit, the study procedures will take place in person, at the participants' homes. Study team members will be in private, quiet locations whenever conducting virtual study visits.

Since we are conducting research in elementary schools, we will seek approval from school districts. We will submit documentation from an appropriate authority at each school or district granting permission to conduct the human subjects research. We will contact each school or district to obtain this permission and meet the requirements each site may have for conducting human subjects research.

11.0 Study Intervention

11.1 The "lollipop" swab collection method and the BinaxNOW COVID-19 Ag Card Home Test are being evaluated. The PCR testing method, the COVID-Flu Multiplex Assay, may also be included in this study. This test provides results for COVID-19, Influenza A, and Influenza B.

11.2 Study team members will store, handle, and guide administration of the "lollipop" collection swab. They will instruct participants to suck on the swab for 20 seconds, as they would suck on a lollipop. The study team member will closely oversee that the participant is following instructions.

Study team members will provide all participants who consent to at-home antigen testing with a BinaxNOW COVID-19 Ag Card Home Test kit, which includes two tests and instructions in both English and Spanish. A trained study team member will supervise the test via video chat or in person. For Spanish-speaking participants/parents, the study team member supervising the test will either be fluent in Spanish, or they will use the services of a translator.

11.3 The "lollipop" collection swab is a non-significant risk device. It does not meet the definition of "significant risk," which is a device that presents a potential for serious risk to health, safety or welfare of subjects.

The saliva sample collected from the "lollipop" will be analyzed by Exact Sciences Laboratories using the COVID-Flu Multiplex Assay. The FDA approved this assay for use with nasal swabs under the Emergency Use Authorization (EUA) only. The saliva samples collected from the "lollipop" may also be analyzed by ACL using either their standard process for COVID-19 PCR testing or a multiplex assay.

The BinaxNOW COVID-19 Ag Card Home Test received EUA from the FDA. The test is authorized for prescription home use with self-collected observed direct anterior nasal swab samples from individuals aged 15 years or older who are suspected of COVID-19 by their healthcare provider within the first seven days of symptom onset or adult-collected nasal swab samples from individuals aged four years or older who are suspected of COVID-19 by their healthcare provider within the first seven days of symptom onset. The BinaxNOW COVID-19 Ag Card Home Test is to be performed only with the supervision of a telehealth proctor. Documentation of the EUA, including an updated Letter of Authorization, have been submitted to the IRB.

12.0 Study Timelines

12.1 Participation in the study will typically last from 12-72 hours, depending on when the at-home BinaxNOW test virtual visit is completed. When scheduling virtual visits, we will try to schedule as close as possible to 24 hours after the initial in-school test. The target window is no sooner than 12 hours and no later than 72 hours after the in-school test. If it is not completed within 72 hours, the study team will ask the participant to schedule a time to complete the at-home test as soon as possible. If the participant is not able to complete the at-home test within 5 days of enrollment, they will be withdrawn from the study.

We anticipate enrolling all study participants by August, 2022. We intend to complete primary analyses by October, 2022.

13.0 Procedures Involved

13.1 Study Design: This is a quantitative community-based study, conducted in the K-12 setting with school children 4-19 years old, teachers, and staff.

If a participant's initial at-school BinaxNOW test is **positive**, then they will only complete the lollipop swab for PCR testing. They will NOT do the at-home BinaxNOW test virtual visit.

If a participant's initial at-school BinaxNOW test is **negative**, then they will complete both the lollipop swab for PCR testing AND an at-home BinaxNOW test approximately 24 hours later.

If the study team does not have any BinaxNOW tests due to a supply shortage, or if a potential participant is unwilling or unable to complete at-home BinaxNOW testing, the BinaxNOW procedures will be dropped and only the lollipop swab will be collected.

13.2 Schedule of Study Procedures

Study Activity	At school or by phone*	At school	Virtual or Home Visit**
Informed Consent	X		
Assent		X	
Collect Basic Information	X		
BinaxNOW test	X***		
Lollipop swab		X	
BinaxNOW test			X***
Adverse Event Assessment		X	X***

*All adult study participants will provide informed consent and basic information at school. For children participants, the parent or legal guardian may provide consent and basic information either over the phone or in person.
**Only participants who have a negative at-school BinaxNOW test will be asked to do an at-home BinaxNOW test.
***If the study team runs out of BinaxNOW tests, or if a participant is unwilling or unable to complete at-home BinaxNOW testing, these study procedures will not be performed. Participants will be consented for the Lollipop-Only alternative.

13.3 Immediately after consent/assent, the study coordinator will collect information about the participant (name, date of birth, gender, race, and ethnicity), as well as the parent or legal guardian's name, in the case of children. The study coordinator will also collect the participant's physical and mailing addresses, phone number, and email address. If participants provide their email address, the study coordinator will ask if they are willing to be contacted about this study in the future. The study coordinator will verbally ask questions and record responses via real-time electronic data capture in ICTR REDCap.

If the study coordinator is unable to collect data directly in REDCap, such as if there is no internet connection or ICTR REDCap is down, then the study team will enter data according to an emergency back-up protocol. For this protocol, the study team may record answers electronically in a PDF version of the data collection form. They may temporarily store PDF files locally on an encrypted laptop computer managed by UW-Madison Department of Pediatrics Computer Services. As soon as possible, study team members would enter data and upload the PDF into REDCap, then immediately delete the file from local storage. The local laptop storage will serve as a transfer proxy, rather than a storage location. Whenever this emergency protocol for data collection is followed, the study team will also follow a sanitation protocol to ensure that the PDF is stored only in REDCap. For sanitation, the PDF will be permanently deleted by the end of the following business day, once the primary data collection method becomes available. The PDF files will be stored locally in a folder specifically set up to be excluded from

the client's backup routine. If files are accidentally backed up, they will be manually removed from the backup and deleted permanently from all locations except REDCap. Additionally, the SMPH VPN via the Palo Alto Global Protect client, configured and available for use on all DOP endpoints, will be enabled and connected by the end-user on data collection endpoints whenever study data is being accessed or transferred.

The study team will make every effort to enter data directly into REDCap in real time. The study team will use a wireless hotspot for reliable internet connectivity, rather than relying solely on the school's Wi-Fi connection, to minimize the need for this emergency data collection protocol.

After this basic information is collected, the study coordinator will begin testing. If the participant did not already receive an at-school BinaxNOW test, then the study coordinator will collect the nasal swab for and administer the BinaxNOW test. When study staff collect the nasal swab for the BinaxNOW test, they may encourage parents/legal guardians to comfort their child. Participants under the age of 18 will only receive nasal swabs when their parent or legal guardian is physically present. If a potential participant is unwilling to have the study team collect a nasal swab, they will not be enrolled in the study.

Next, the study coordinator will guide the participant through completing a "lollipop" swab at school. The lollipop swab is obtained by having the participant suck on a swab for 20 seconds in the same way that they would suck on a lollipop. The study coordinator will ask whether they prefer the PCR nasal swab or lollipop collection method. The study coordinator will provide the lollipop swab to Exact Sciences or ACL for analysis. For Exact Sciences, it will be labeled with the study ID and date of collection. For ACL, lollipop samples will have a label and accompanying requisition form that will both contain the subject's full name, date of birth, and the date and time of collection.

If the study team does not have any BinaxNOW tests due to a supply shortage, study participation will end after the lollipop swab is collected. If BinaxNOW tests are available and the participant intends to do the at-home antigen testing, then the at-school antigen testing is required.

If a participant's initial at-school BinaxNOW test was **positive**, then their study participation is complete after providing the lollipop swab for PCR testing.

If a participant's initial at-school BinaxNOW test was **negative**, then they will be asked to complete an at-home BinaxNOW test approximately 24 hours later.

If a participant is unwilling or unable to complete an at-home BinaxNOW test, then their study participation is complete after providing the lollipop swab for PCR testing.

For the at-home BinaxNOW testing, the participant will schedule a follow-up virtual visit with the study coordinator. If they are unable to complete a virtual visit, they will schedule an in-person home visit. They will also be sent home with a BinaxNOW testing kit.

The study coordinator will send participants a confirmation email with a unique link to a secure video chat platform, such as Microsoft Teams, Cisco WebEx, or HIPAA-Secure Zoom. They will also send instructions about how to join the meeting link. During the virtual visit, the study coordinator will instruct the family to read the instructions in the BinaxNOW box, do their best to do the test accurately, and ask questions as needed. The study coordinator will also ask if the participant understands and feels comfortable with the instructions, and the study coordinator will offer to demonstrate the steps of the test. The study team member will use the video to observe sample collection and offer tips or suggestions, as needed, to ensure proper collection. They will also ensure that participants take time and care to read the test results accurately, and they will answer any questions that participants may have. The participant or their parent will verbally provide the test results to the study team, and the study team will record the result in REDCap. The completed test card will be observed and the results verified by the study coordinator.

If a participant is unable or unwilling to do a virtual visit for at-home testing, such as they do not have access to technology or do not wish to provide an email address, they will be offered an in-person home visit. The procedures would be the same. If participants are not able to complete the test during the virtual visit, such as inability to collect the sample or accidental tampering with the test card, the study team member will also provide the option of a home visit. At home visits, if participants are unable or unwilling to collect the nasal swab sample themselves, the study coordinator may collect the sample.

After recording the result of the BinaxNOW test, the study coordinator will ask the participant if they think they would have been able to accurately do this test on their own or if help was necessary. The study coordinator will record their response in REDCap. They will also note what type of help was needed, if any. Furthermore, the study coordinator will ask if the adult thinks they would be able to accurately do the test on their own in the future.

The BinaxNOW test kit contains two tests. The second test will be used as a back up, in case the first test is compromised in some way.

If the second test is not used during the study, the participant may keep it and use it in the future if they feel confident doing so. If a participant says that they do *not* think that they could accurately do the test on their own, the study coordinator would advise them to seek assistance from a medical provider.

To accomplish the aims of this study, the study team will also need access to the results from the nasal swab antigen and PCR tests collected by the school. Parents will learn the results of the antigen test, and they will share the results with the study coordinator. If the samples are processed at Exact Sciences Laboratories, they will share the test results of the nasal swab and lollipop PCR tests with the study team via Exact Science's instance of HIPAA-secure Box. If the samples are processed by ACL, then the study team will share the results of the nasal swab and lollipop PCR tests with the study team via a UW-Madison Cybersecurity-approved data sharing tool.

13.4 A data collection form is uploaded in ARROW. Below is a list of data elements. Note that all data elements will be collected from participants who complete the at-home BinaxNOW test—those whose initial at-school BinaxNOW test was negative. The data elements related to at-home BinaxNOW testing will not be collected from participants whose initial at-school BinaxNOW test was positive, as they will not complete the at-home test virtual visit.

- Administrative information
    - Dates and locations (i.e., virtual or in-person) of study activities
    - Times of data collection and study activities
    - Confirmation of consent and assent
- Participant information collected verbally and recorded in REDCap
    - Participant's first and last name
    - Participant's parent or legal guardian (in the case of children)
    - Address
    - Phone Number
    - Email Address
    - Questions about participant's opinions on data collection methods
- Biosample Collection Date/Time
    - At-school BinaxNOW (collected by school or study team)
    - Nasal swab for PCR testing (collected by school)
    - Lollipop swab
    - BinaxNOW test (administered by participant/family)
- Biosample Results

- Results of at-school BinaxNOW
- Results of nasal swab PCR collected by school personnel—COVID-19 and, whenever these tests are ordered by the schools, also Influenza A, Influenza B, and cycle threshold (CT) value
- Results of lollipop swab PCR testing—COVID-19, Influenza A, Influenza B, and CT value
- At-home BinaxNOW test result

Source records that will be used to collect data about participants:

- ☐ UW Health medical or billing records via ICTR's Clinical Research Data Service (CRDS)
- ☐ UW Health HealthLink Records (study team will directly access)
- ☐ Data from departmental QA or QI database
- ☐ Data from UW Health Enterprise Data Warehouse (EDW)
- ☐ Data from PACS (Picture Archiving and Communication System);
- ☐ Data from Center for Medicare/Medicaid Services
- ☐ Data from publicly available datasets (e.g., U.S. census data)
- ☐ Data from outside institutions or organizations (specify: _____)
- X Other (specify: _Data from Exact Sciences, accessed via Exact Sciences' HIPAA-secure Box, and Data from ACL, exchanged via UW-Madison Cybersecurity-approved data sharing tool__)

13.5 The "lollipop" collection swab is a non-significant risk device. It does not meet the definition of "significant risk," which is a device that presents a potential for serious risk to health, safety or welfare of subjects.

The FDA granted Emergency Use Authorization for the BinaxNOW test.

14.0 Comparison of usual care and study procedures

14.1 If individuals want additional testing for COVID-19, they could obtain PCR testing at a variety of locations, such as a local testing center, pharmacy, or their child's PCP's office. The parent could also choose to purchase and administer their own BinaxNOW test from a supplier, such as Walgreens or CVS. They may also seek out an alternative type of testing. Cost, convenience, and parent and child willingness are all factors that influence which types of testing may or may not be selected.

14.2 UW Health guidance about COVID-19 testing is described at https://coronavirus.uwhealth.org/COVID-19-testing/. Individuals who are

experiencing symptoms of COVID-19 are encouraged to contact their health care providers. The typical guidance for symptomatic patients is to get PCR testing done.

14.3 Standard of care at UW Health for children experiencing one or more symptoms of COVID-19 is a nasal PCR test. Elementary schools are offering nasal PCR tests, so the school's procedures overlap with standard of care at UW Health. The "lollipop" and BinaxNOW testing procedures in this protocol do not overlap with standard clinical care.

14.4 Research participation would not affect standard clinical care.

15.0 Withdrawal of Participants

15.1 If a participant with a negative at-school BinaxNOW test result does not complete the BinaxNOW at-home test within 5 days (120 hours) of the initial test, they will be withdrawn from the serial antigen testing portion of the study without their consent.

15.2 For orderly termination, a study team member will notify the participant that their study participation is complete.

15.3 If a participant asked to complete the at-home BinaxNOW test fails to do so, we will still use their lollipop swab results and results of the nasal swabs collected at school to explore Aim 1.

16.0 Data Management and Confidentiality

16.1 Procedures that will be used for quality control of collected data:

A study team member will watch participants conduct the at-home BinaxNOW test to ensure quality of sample collection and test administration. The result of the test will be verified by the coordinator.

16.2 Steps the researchers will take to secure the data:

- [X] Data will be coded, and the "key" linking identities to codes will be kept separately from the data. (applies to lollipop swabs processed by Exact Sciences Laboratories)
- [ ] Data will be coded, and the "key" linking identities to codes will be kept on paper only. The study data will be stored electronically and labeled only with codes.
- [ ] Only those listed as key personnel will have access to the "key."
- [ ] Access to the "key" will be limited to the following person (e.g., Database Administrator): _____
- [ ] This study is funded by the National Institutes of Health and is covered by a Certificate of Confidentiality.

☐ This study is NOT funded by the National Institutes of Health but because it will collect sensitive information, the research team will apply for a Certificate of Confidentiality to protect data from being requested without the subject's consent as part of a legal proceeding.

X Other: _Data will be stored in REDCap, and all fields containing PHI will be labeled as such. Granting study team member's permission to export data containing PHI will be limited to a need-only basis.___

16.3 How and where data and/or specimens will be stored and maintained:

☐ Online Collaborative Research Environment (OnCore) Biospecimen Management

X Research Electronic Data Capture (REDCap) *Specify which instance you will be using (e.g., ICTR's, Department of Medicine's)*: _ICTR_____

X Other software option that will be stored on departmental server. *Specify the department*: _Pediatrics_____

X Locked filing cabinet or drawer inside a locked room. Specify the building: __800 University Bay Drive_____

X Other (describe): _Lollipop specimens will be provided to Exact Sciences Laboratories or ACL for analysis after collection by the end of the day. Lollipop test results will be provided to the study team using Exact Sciences' instance of HIPAA-Secure Box or using a UW-Madison Cybersecurity-approved data sharing tool. ACL, adult participants, or parents of child participants will verbally share the results of the at-school antigen test with the study team.

☐ Data will not be stored or accessed on portable devices.

X Portable devices will be used to access secure web-based data collection sites such as ICTR's REDCap.

☐ Data stored on portable devices will be coded with the key stored separately. No identifiers will be stored on portable devices.

X Data stored on portable devices and therefore only encrypted devices will be used.

16.4 Management of Identifiers:

☐ Identifiers will be destroyed after all data has been collected.

X Identifiers will be destroyed at study closure.

☐ Identifiers will be destroyed at study closure or at the time of publication.

16.5 Plans for sharing of data and/or specimens outside the study team / institution:

Exact Sciences or ACL will provide us with the results of the nasal swab PCR test collected by the school. The study team will provide lollipop collection swabs to Exact Sciences or ACL for analysis.

To obtain the nasal swab PCR test results from Exact Sciences, the study team will send Exact Sciences a result pull request with the participant's name, date of birth, and collection date. We will do this by uploading information to Exact Sciences' HIPAA-secure Box for sharing with Exact. The lollipop collection swabs will be labeled with the participant's study ID and date of collection.

To obtain the nasal swab PCR test results from ACL, the study team will include information on the lollipop swab label and accompanying requisition form, including the participant's name, date of birth, and date and time of collection. ACL will match this information to a nasal swab and provide PCR test results for both the lollipop and nasal swab.

The results of the nasal swab and lollipop PCR tests will be sent via Exact Sciences' HIPAA-secure Box or a UW-Madison Cybersecurity-approved data sharing tool.

A study team member will deliver the lollipop swabs from the school to Exact Sciences or ACL.

17.0 Provisions to Protect the Privacy Interests of Participants

17.1 Steps that will be taken to protect participants' privacy interests:

- ☐ Procedures will be performed in a private area where others cannot see the procedures being performed or overhear the conversation between subjects and researchers.
- X All members of the study team are up to date on their institutional HIPAA training.
- X The study is not collecting information that could pose legal or reputational risks to participants.

17.2 To conduct research on COVID-19 testing methods, it is necessary to collect participant's communicable disease status, which is considered sensitive information.

17.3 Study team members will be experienced and/or trained in how to work with children and help them feel at ease during research procedures. Study team members will explain study procedures to participants in advance using age-appropriate language, and they will take time to answer any questions that participants may have.

18.0 Sharing of Results

18.1 Since the lollipop PCR test is investigational, the results will not be shared with participants or others. If the at-home BinaxNOW test is positive, the study team member will encourage the participants to follow up with their primary care provider. The school will receive the results of the nasal PCR from Exact Sciences or ACL, and that result will govern whether the child is permitted to return to school when symptoms resolve (if PCR is negative) or is required to stay at home for 10 days (if PCR is positive). As the resulting lab, Exact Sciences and ACL are responsible for reporting the nasal PCR results to Dane County Department of Health Services. Since the lollipop swab is investigational, results do not need to be reported to health officials.

For overall care management and recommendations, the study team is deferring to the school, which conducts and receives results of the nasal swab PCR result. Since this is the clinical test, the investigators would not recommend changing care management based on the exploratory test results in this study (lollipop swab and BinaxNOW). Any time an at-home BinaxNOW test is positive, the study team will encourage participants to follow up with the school and/or their PCP for recommendations. In short, the overall care plan will be based on the nasal swab PCR and managed by the school.

18.2 The results of this study will be published and accessible to the public.

19.0 Data and Specimen Banking

19.1 The lollipop swabs and assays will be destroyed after results are recorded. Participants will be instructed to dispose of BinaxNOW test cards after the test is completed. There will be no biospecimen banking in this study. All data for this study will be stored in Exact Sciences' HIPAA-Secure Box, a UW-Madison Cybersecurity-approved data sharing tool, Department of Pediatrics Secure Server, and REDCap, and only approved study team members will have access to the REDCap project.

19.2 At the end of this study, participant names and contact information (phone, address, email) will be destroyed. All other study data will be banked.

19.3 Only de-identified data will be shared with external researchers.

19.4 Data will be fully anonymized prior to banking, so participants may not withdraw their banked data from future research use.

20.0 Study Analysis

20.1 Statistical Hypotheses:
Aim 1: The null hypothesis is that the negative predictive value of BinaxNOW is at least 91% (which is the reported rate in symptomatic

subjects after a single test) versus the alternative hypothesis that the NPV is greater than 91%.
Aim 2: The lollipop swab test will be non-inferior to the gold-standard PCR testing of nasal swabs.

20.2 Sample Size Justification:
For Aim 1, it is anticipated that the majority of initial BinaxNOW tests will be negative. It is hypothesized that the proposed two-day serial testing procedure using BinaxNOW tests in participants with an initial negative test will identify true negatives in >95% of participants. The primary diagnostic outcome measure will be the negative predictive value (NPV). The NPV of BinaxNow is ~91% in symptomatic subjects. For the proposed study, the NPV after the second test (24 hours after the first negative results), is assumed to be substantially higher than 91% since the first test was already negative. In order to detect a true NPV after the second test of at least 95% with 90% power at the one-sided 0.05 significance level, a sample size of N=358 participants with an initial negative test is required. To reach a sample size of N=358 participants with an initial negative test, BinaxNOW kits will be administrated to 400 participants. We intend to continue enrolling until we reach the target sample size of N=358 completing the at-home BinaxNOW test.

20.3 Participant Population for Analysis:
For Aim 1, we will include all participants who complete the at-home BinaxNOW test within 72 hours (N=358) and have nasal PCR results. For Aim2, we will include all participants who have both nasal and lollipop PCR results.

20.4 Statistical Methods:
Aim 1. Sensitivity, specificity, positive predictive value (PPV) and NPV of the proposed BinaxNOW testing procedure for symptomatic subjects will be calculated and reported along with the corresponding two-sided 95% confidence interval. Formal non-inferiority testing of the BinaxN0W testing procedure with PCR will be conducted with respect to sensitivity and specificity with a non-inferiority margin of δ=5% and a sensitivity/specificity of PCR of 99%.

Aim 2. Results obtained from nasal and lollipop swab-based PCR testing will be summarized in tabular format. Concordance between the PCR test results will be evaluated by calculating the Kappa statistic which will be reported along with corresponding two-sided 95% confidence interval. The nonparametric bootstrap technique will be used to construct the confidence interval. A kappa statistic of >0.95 will be considered as sufficient to define lollipop swab test non-inferior to the gold-standard PCR testing of nasal swabs. Furthermore, standard diagnostic test outcomes, i.e., sensitivity, specificity, NPV and PPV will be calculated (using the nasal swab-based

testing as gold standard), and reported along with the corresponding two-sided 95% confidence intervals. Formal non-inferiority testing of the lollipop swab test with PCR will be conducted with respect to sensitivity and specificity with a non-inferiority margin of δ=5% and a sensitivity/specificity of PCR of 99%. Statistical analyses will be conducted using SAS software (SAS Institute, Cary NC), version 9.4 or greater.

20.6 Handling of Missing Data: The primary analysis for evaluating the diagnostic utility of the BinaxNOW testing procedure will be based on the complete case principle. Since the analyses of this study won't involve any formal multivariate or longitudinal statistical modeling, no imputation-based analyses will be conducted.

21.0 Potential Benefits to Participants

21.1 For participants who only participate in the lollipop PCR portion of the study, there is no immediate benefit.

Through doing the at-home BinaxNOW testing under the observation of a trained study team member, participants and their families may learn about how to accurately conduct this type of at-home test for COVID-19. Through asking questions and/or receiving confirmation that they are conducting the test correctly, individuals and families may feel more confident conducting at-home tests in the future. If the second test in the BinaxNOW kit is not used as a back-up during the study, the participant may keep the test and use it later if they feel comfortable doing so. The BinaxNOW tests are also readily available to families at local retailers, such as Walgreens. Therefore, if a family member is symptomatic in the future, they may feel more comfortable doing at-home testing independently.

The results of the BinaxNOW test, along with other information, can help participants' healthcare providers make informed recommendations about their care. For example, in the case that the original BinaxNOW and nasal swab PCR tests were negative and the delayed, at-home BinaxNOW test is positive, that would be helpful information for a participant's primary care provider. That information will need to be integrated with the results of the nasal PCR that was also performed. The probability that the delayed, at-home BinaxNOW test will be positive is less than 5%.

If the results of the at-home BinaxNOW test are negative, that may help individuals and families feel more confident in the initial results they received.

The results of the at-home BinaxNOW test in this study, or any future at-home BinaxNOW tests that families may conduct, may help limit the spread of COVID-19 to participants' families and others in their community.

22.0 Risks to Participants

22.1 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 well tolerated by participants.

Potential risks of the BinaxNOW at-home test include possible discomfort or other complications that can happen during sample collection. Since study coordinators will observe sample collection and correct or support as needed, the probability of this risk is very small.

Another potential risk of the BinaxNOW test is a possible incorrect test result. However, the definitive test result which will govern management of care is the nasal PCR.

There is a risk of a breach of confidentiality.

22.2 The lollipop swab collection method, although investigational, has no associated risks. The performance of the BinaxNOW test will be supervised, therefore avoiding risks other than not obtaining the nasal swab correctly.

22.3 Study procedures do not pose risks to an embryo or fetus should a participant be or become pregnant.

22.4 For child participants, a parent or guardian will collect the nasal swab sample from the child. To do so, the adult will need to be in close proximity to the symptomatic child. Hand washing and masking by the parent or guardian will protect them from becoming infected.

Since this study collects the names of parents or legal guardians, there is also a risk of breach of confidentiality for them.

22.5 Consistent with guidance in the EUA, the BinaxNOW test conducted at home for purposes of this study will be performed only with the supervision of a telehealth proctor. Or if telehealth supervision is not possible, a study team member will supervise the test in person, at the participant's home.

23.0 Provisions to Monitor the Data to Ensure the Safety of Participants

23.1 The study team will build, run, and regularly review reports in REDCap to monitor study progress and identify potential problems.

Regularly reviewed reports will include data elements essential to the study's aims, as well as information about potentially reportable events.

Study team members will enter information about any potential reportable events, including adverse events, protocol deviations, and/or participant complaints into REDCap. Information will be reviewed by a principal investigator.

Information about potentially reportable events will be recorded at each participant interaction.

The principal investigators will review potentially reportable events in a timely manner.

Cumulative data will be reviewed every two months after enrollment commences.

We do not anticipate any conditions that would trigger an immediate suspension of the research.

24.0 Economic Burden to Participants

24.1 Participants will not be responsible for any costs because of participation in the research.

25.0 Resources Available

Will the research be conducted outside School of Medicine and Public Health or UW Hospitals and Clinics (e.g. the researcher does not have an SMPH research feasibility attestation for this study)?	☒ YES (complete 25.1) ☐ NO (remove text below, but retain this section)

25.1 We received approval from the Madison Metropolitan School District (MMSD) to recruit participants at local elementary schools. Based on data from schools reopening post COVID-19 shutdowns in other countries, infectious disease experts on the study team anticipate that there will be a surge in respiratory illnesses caused by enterovirus, rhinovirus, community coronaviruses, influenza, RSV, parainfluenza, human metapneumovirus and adenovirus, as well as SARS-CoV-2, in the fall and winter of 2021-2022. Therefore, we expect that several elementary school children, teachers, and/or staff will become symptomatic each school day, and we will be able to reach our target enrollment numbers. If we are unable to enroll at our target recruitment rate in MMSD schools alone, we will pursue approval with other local school districts.

At least one full-time study coordinator will be assigned to conduct and complete this project.

This study will be conducted at elementary schools, via virtual visits by staff in a private, quiet location, and at participant homes.

If participants receive a positive at-home BinaxNOW test, we will refer them to their healthcare provider. We will also verify the results of the nasal PCR which will govern the management of return to school.

Study team members will meet and/or communicate regularly to ensure that all persons assisting with the research are adequately informed throughout the study about the currently approved protocol, the research procedures, and their duties and functions. Any changes to the protocol and/or consent/assent will be communicated via email to all study team members conducting study activities.

26.0 Multi-Site Research

NA

27.0 References

NA

28.0 Appendices

NA