Title: Year 2 ReSET Aim 1a: Restarting Safe Education and Testing for Children with Medical Complexity - Feasibility of in-home cohort SARS-CoV-2 testing strategies, and associations with CMC parent perceptions about in-person school attendance

Short Title: Yr 2 ReSET Aim 1a (in-home cohort)

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BACKGROUND INFORMATION

The Coronavirus Disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, is a worldwide pandemic that has resulted in large-scale quarantines in cities, states, and countries throughout the world. SARS-CoV-2 is a respiratory virus that is most commonly spread via contact with infective respiratory droplets and aerosols produced by coughing, sneezing, talking, and singing.

Children with medical complexity (CMC), i.e., children with multiple severe chronic conditions, high resource use, severe functional limitations, and substantial family-identified service needs, are a *medically vulnerable population* for the development of severe COVID-19. An illustrative CMC is born months premature with quadriplegic cerebral palsy, seizures, feeding and breathing tubes, 12 medications, and 8 specialists. Our research illustrates CMC as *a socially vulnerable population* in the US with over half living in poverty, 17% in rundown housing, and 14% food insecure - all substantially higher than non-CMC. CMC are also disproportionately from communities of color. CMC account for 1-5% of children, but > 1/3rd total child health spending, the majority being for hospital care. Medical fragility puts CMC at high risk for severe COVID-19 disease, including hospitalization and death.

Deciding to send CMC to school poses a major dilemma to families wanting to minimize severe COVID-19 risk. CMC require a mean of 52 hours/week for direct care, and even three feet of physical distancing is not possible with most daily needs, e.g., enteral tube nutrition and medications, respiratory medications, diapering/toileting, and direct mobility assistance (pushing a wheelchair). Our year 1 data indicated many families opted to place CMC in virtual learning environments when offered by their school district. By the beginning of the Fall 2021 school year, many CMC returned to in-person schooling when virtual learning was discontinued. Parents' perception of risk with in-person school attendance remained high suggesting they were forced to return their CMC to in-person schooling despite concern for insufficient mitigation strategies, such as masking, physical distancing and contact tracing.

Achieving in-person school attendance is critical for CMC. In year 2 of this grant, we will continue to identify parental opinions concerning in-school attendance, track parental attitudes toward testing and vaccination, and use our findings to inform policy recommendations.

STUDY OBJECTIVE

The study objective is to promote safe in-person school attendance for CMC by 1) evaluating the feasibility of home-based testing strategies for CMC and 2) identifying parental perceptions of testing and school attendance.

STUDY DESIGN

This is a single site study taking place over 12 months (June 2022-June 2023) and involving (51) caregivers and their children who were previously enrolled in IRB #2022-0462. Year 2 study design and procedures are similar to the activities in Year 1, the primary difference being a switch to symptom and exposure only testing in Year 2 (no longer doing any surveillance testing).

COVID-19 TESTING DEVICE

BinaxNOW Rapid Antigen System (Abbott) is a point-of-care, lateral flow immunoassay intended for the qualitative detection of nucleocapsid protein antigen from SARS-CoV-2 in direct anterior nasal (nares) swabs. Internal controls are built into the testing system and results are available in 15 minutes. To collect a nasal swab sample, the entire absorbent tip of the swab (usually ½ to ¾ inch) is carefully inserted into both nostrils. Swabs are then placed in the supplied card and extraction reagent is added. After 15 minutes, the results are read as the presence or absence of a blue line as compared to the control line. Test kits will be stored in study offices and shipped to families by UPS or given in person if the family is in clinic or hospital. The test procedure itself (swabbing the nose) poses no significant safety risk. Subjects were trained on the proper administration of the test during year 1 of the study.

Abbott's ABT BinaxNOW COVID-19 Ag Self Test is covered under the FDA's Emergency Use Authorization (EUA) for over-the-counter, non-prescription, and symptomatic or asymptomatic use. The test can be used with children two years and older with sample collection performed by an adult, and can be self-administered for all people aged 15 years or more. In this study, adult caregivers will be performing the tests on their child. Use of the BinaxNOW COVID-19 Ag Self Test in this study is consistent with the FDA's EUA recommendations.

The results of BinaxNOW tests performed at home will NOT be reported to the Wisconsin Department of Health Services as this is not required per state statutes §252.05. However, any confirmatory PCR results triggered by in-home study testing will be reported to the Wisconsin Department of Health Services using the Wisconsin Electronic Disease Surveillance System (WEDSS) by the party who performed the PCR. WEDSS is a secure, web-based system designed to facilitate reporting, investigation, and surveillance of communicable diseases in Wisconsin. It is designed for public health staff, infection control practitioners, clinical laboratories, clinics, and other disease reporters.

POTENTIAL RISKS AND BENEFITS

Potential Risks

Dislike of the nasal testing procedure. There is a small risk that some caregivers and children may find the nasal swab testing procedure unpleasant, burdensome, and/or anxiety-provoking. To address this issue, participants will be reminded that study participation is completely voluntary and they may choose to refuse nasal testing. If nasal testing is refused, participants may choose to stay in study but not participate in testing. Additionally, participants may consent to all or a portion of the study (e.g., weekly study staff contact and surveys but not testing, and vice versa).

The PCR confirmatory test (performed following a positive BinaxNOW system test in a clinic or hospital) is typically done with a swab that goes deep into the nostril. The child may experience discomfort during this procedure but the test only takes a few seconds.

Distress if the test is positive. Some participants may become distressed upon hearing their child or family member has tested positive for the virus. The study team will guide families in finding the most appropriate plan of care in the event they become ill. Likewise, the study team will suggest where family members can seek care for COVID related-illness. They will also give guidance on how best to avoid spreading the illness to other members of your household and the community.

Ignoring COVID precautions with negative results. It is possible for the nasal swab test to give a false negative result. This may lead the family to stop following measures they would otherwise take to protect themselves from COVID-19 (i.e., frequent handwashing, mask-wearing, or social distancing), thus making them more likely to be exposed to COVID-19 or to expose someone else. Study staff will remind participants of the importance of following public health recommendations no matter what the results of the test show.

Distress experienced during or after completing research surveys/interviews. Some participants may find the completion of study surveys distressing. To protect against this distress, participants will be made aware that participation in the research study is entirely optional, has no effect on their children's medical care, that they may choose not to answer certain questions, and that they may end their participation at any time. If a participant expresses distress, the study staff will notify Dr. Coller. Participants will also be given the phone number (in the informed consent process) to contact Dr. Coller.

Detection of previously undisclosed dangerous or potentially dangerous situations or occurrences. It is possible that families may disclose information to our study staff that indicates they have been or may be subject to dangerous situations. Situations or occurrences that might be disclosed to or observed by the study staff and would require the staff to complete an incident report include but are not limited to child abuse, imminent threat to self, and imminent threat to others (even though our questionnaires will not specifically ask about these issues). General procedures we

will take in these situations follow. Specifically, any suspected child abuse must immediately be reported to the Wisconsin Department of Child Protective Services (CPS) and, if any immediate danger is possible to the child, family or another individual, to the local Police Department. The social worker on call will be notified immediately if a participant discloses suicidal ideation or domestic violence. In any adverse situation possibly related to the research study, Dr. Coller and the IRB will also be notified.

Accidental disclosure of confidential material. It is possible that despite careful procedures to protect private information, there could be accidental disclosure of confidential information. To protect against accidental disclosure, study staff will store all electronic data on UW-maintained servers and UW-issued computers; paper data will be kept in locked cabinets in locked staff offices with access restricted to authorized study staff. Data containing identifiable information will be deidentified as soon as possible, and staff will use ID numbers on study materials when possible. In the event of a breach of confidentiality, we will notify the participant, Dr. Coller, and the IRB.

Potential Benefits

The results of the study may help researchers advance their understanding of in-home testing strategies for children with medical complexity.

STUDY RECRUITMENT AND WITHDRAWAL

Subject Identification

The 51 caregivers and children who participated in the first year of this study will be invited to participate in Year 2. These families were recruited from the Pediatric Complex Care Program (PCCP) of the American Family Children's Hospital and Specialties Clinics. Families who drop out of the study will not be replaced.

Subject Inclusion Criteria

In order to be eligible to participate in this study, the caregiver/child must meet the following criteria:

1. The caregiver agrees to comply with all study procedures and expects to be available for the duration of the study.
2. The caregiver continues to self-identify as the *primary* caregiver (parent, foster parent, legal guardian) of the CMC enrolled in Year 1 of the study.
3. The caregiver is currently providing care on an ongoing basis to their CMC. The child may not be housed in a skilled nursing facility, an acute care or transitional facility, a rehabilitative hospital, a medical group home or in a foster home (unless the primary caregiver for the study is the foster parent).
4. Caregiver and child are residents of Wisconsin.
5. The caregiver provides a written informed consent form.

Subject Exclusion Criteria

1. Failure to meet all inclusion criteria.

NOTE: Age and school attendance status are not criteria for the year 2 study protocol. All children participating in year 1 were 16 years of age or less (so none will turn 18 in year 2), and a child may participate regardless of type of school attendance (home-schooled, in-person, or hybrid).

Subject Recruitment

Caregivers will be sent a memo by email inviting them to participate in Year 2 of the study. The memo will contain a summary of the changes from Year 1 to Year 2, as well as the informed consent form (as an attached document). In addition, caregivers will be mailed a hardcopy of the memo and consent form. The memo will be sent to current study participants in mid to late May, prior to end of Year 1 activities. It is anticipated that very few or no Year 1 participants will choose to discontinue from the study because study compliance and appreciation for access to in-home testing kits has been very high.

Subject Withdrawal

Subjects are free to withdraw from the study at any time. An investigator may terminate a study subject's participation in the study if:

- The caregiver is no longer providing care to a CMC.
- The caregiver's CMC disenrolls from Pediatric Complex Care Program.
- The caregiver or child no longer meets the study inclusion criterion and this precludes further study participation.

Study staff will attempt to contact subjects by phone to inform them they have been terminated from the study and to make arrangements for any honorarium that is due. Failure or refusal to participate in COVID-19 testing, weekly communication with the study staff, or the quarterly surveys will not result in study termination.

STUDY ENROLLMENT

Enrollment

Caregivers will be sent a memo inviting them to continue into Year 2 of the study. They will receive this material by email and United States Postal Service. They can choose to consent to participate in Year 2 in one of two ways:

1) Print the consent form from the email memo, review and sign consent form, photograph the signed document, and email back to the study staff. If they wish to speak to research staff prior to signing consent form, staff will contact them by phone to discuss questions or concerns.

2) Receive the consent form and memo in the mail, review and sign consent form, photograph the signed document, and email back to the study staff. If they wish to speak to research staff prior to signing consent form, staff will contact them by phone to discuss questions or concerns.

A week following the mailing of the memos and consent forms, study staff will begin contacting subjects who have not sent in their consent form. Staff will inquire whether they received the memo and ask if they are interested in participating in year 2 of the study. If interested in participating, staff will provide instructions on how to consent to year 2.

The caregiver providing consent will be a parent or legally authorized guardian of the child, and only a single parent/guardian signed consent will be obtained.

Like year 1, a waiver of assent will be sought based on the impairments associated with this population of children. The children in this study will be enrolled from the Pediatric Complex Care Program. To qualify for this program, children must have at least 3 organ systems affected by chronic disease, regularly see at least 3 clinical specialists, and have high utilization of the healthcare system (≥10 clinic visits or ≥5 hospital days in the prior year). The vast majority of the children in the program have moderate to severe cognitive impairment (impaired decision-making capacity) and are nonverbal. Many of the children have visual and hearing impairments. Children who express discomfort or intolerance for nasal swabbing may continue to participate even if all methods of testing are refused. Given the lack of assent capacity in the targeted subject population, and the potential for 'dissent' and excusal from nasal swabbing, assent will not be obtained.

STUDY ACTIVITIES

Year 2 participation will involve 1) quarterly surveys by REDCap survey link, 2) in-home testing, and 3) completing a weekly testing log (send photo to reset@pediatrics.wisc.edu email OR complete REDCap survey).

Quarterly surveys

Approximately every 3 months (August '22, November '22, January '23, April '23) the caregiver will be asked to complete a survey regarding their perceptions about testing and school attendance (see Quarterly Survey). This survey, administered on REDCap, will take approximately 15 minutes to complete and will be self-administered online.

In-home Testing and Weekly Testing Log

Like year 1, caregivers will be provided with BinaxNOW Rapid Antigen tests by the study team and asked to perform tests on their child when they are symptomatic or have had a known exposure to COVID-19. Unlike year 1, participants will not have the option to perform surveillance testing (testing twice weekly regardless of symptoms or exposure). This change will be clearly conveyed to participants in the invitation memo and the consent form. As they have done in Year 1, caregivers will be asked to document their testing activities, results, and any possible COVID-19 symptoms on the Weekly Testing Log. This log will be collected by email or e-survey.

Caregivers will be given the following instruction with regard to testing:

- If your child is symptomatic and the initial test is negative, test again using a Binax NOW test in 48 hours over 3 days. Report the test results in your weekly log.

- If your child is not symptomatic and the initial test is negative, test 2 more times using Binax NOW test kits at least 48 hours apart over 5 days. Report the test results in your weekly log.

- If your child is symptomatic and the initial test is positive, no need to repeat Binax Now test. Arrange to obtain a PCR test within 48 hours to confirm whether the in-home test was accurate. Report the test results on your weekly log.

- If your child is not symptomatic and the initial test is positive, no need to repeat Binax NOW testing. Arrange to obtain a PCR test within 48 hours to confirm whether the in-home test was accurate. Report the test results on your weekly log.

While false negative tests are possible with asymptomatic individuals, there will be no change in standard mitigation measures based on the test results (mandatory masks in school, social distancing, hand hygiene, etc.). If testing produces a positive result, the caregiver will be instructed to contact the study team immediately and then obtain a PCR (polymerase chain reaction) test within 48 hours. If needed, the study staff will assist the caregiver in making arrangements for this test. Study staff will not be performing PCRs. If the PCR returns as positive, the caregiver will be instructed to keep the child at home per public health guidelines and pause in-home testing for 21 days. In the event of a positive PCR, the study team will recommend that the participant not perform another PCR for 90 days. Study staff will be in close communication with Dr. Coller and Dr. DeMuri regarding families who test positive and/or are symptomatic.

Last study contact

On the day of their last weekly staff communication, caregivers will be asked to complete their last quarterly survey. Study staff will instruct them to keep any remaining testing supplies.

SUBJECT PAYMENT

Caregivers will receive a stipend of $200 five times over the course of the year-long study (approximately every 2-3 months). Participants who complete the entire study will receive a total of $1000. Payment to subjects who complete a portion of the study will be prorated. Children will not receive compensation for their participation in the study.

STUDY EVALUATIONS AND DATA TRANSFER/STORAGE

Subject ID assignment
Participants will have the same subject IDs as they had in Year 1.

Study Surveys and Trackers
Study surveys will be administered using UW-Madison REDCap. Study survey questions contain items derived from previously validated and published instruments. The year 1 Enrollment Tracker will continue to be maintained containing subject names, study IDs, addresses, telephone numbers, email addresses, and individual study activity progress across study milestones. The enrollment tracker will be housed in a secure UWBox folder, accessible to only those research staff with need to have access. Data collected on paper, such as the consent form should a participant choose not sign electronically, will be stored in a locked file cabinet in study staff locked offices until destroyed. Only study staff will have access to study data and access will be limited to only what is needed by study staff to perform their study role.

Collected data, such as test results and study surveys, will be coded to protect confidentiality. Codes to the direct identifiers, such as child and caregiver names, will be stored in a spreadsheet on the Department of Pediatrics HIPAA compliant secure file storage server with access limited to the PI and research manager.

As this is an NIH-funded study, a Certificate of Confidentiality applies, minimizing informational risks and confidentiality issues.

Following data analysis and study conclusion, server data will be de-identified and remain housed on the Department of Pediatrics server or on UW-Madison Box. Note that UW Cybersecurity will set up and approve the Box account to be used for data storage.

A summary table of the data elements, collection, transfer, and storage follow.

Collected	Entered/Transferred	Stored/Access rights	Destruction
Subject ID Master List	Spreadsheet on staff computer	Stored in secure folder on UWBox; access restricted to authorized study staff.	List with identifiable data will be destroyed once study analyses are completed. De-identified data stored on UWBox indefinitely.
Consent forms	If subject signs on paper, copy will be retained in locked staff office.	Hardcopy consents will be kept in locked cabinet in locked staff office with access restricted to authorized study staff.	Hardcopy consents will be stored and retained for at least 7 years after the completion of the study. Emailed photographs will be deleted once printed.
Study surveys	Entered on-line in REDCap	Stored in REDCap (maintained by UW-Madison IT staff on campus infrastructure). Access restricted to authorized study staff.	De-identified data set stored indefinitely
Study Staff Weekly Communication Log	Spreadsheet on staff computer	Stored on UWBox; access restricted to authorized study staff.	List with identifiable data will be destroyed once study analyses are completed. De-identified data stored on UWBox indefinitely.
Positive PCR results – verbal report from parent	Recorded on study staff log	Documented in REDCap and in enrollment tracker on secure Box.	• Study staff's Log: identifiable data will be destroyed once study analyses

			are completed. De-identified data stored on UWBox indefinitely.

RADx optional component

The funding for this grant is part of a larger NIH funding project called RADX-Up. In accepting the grant, Dr. Coller and his team agreed to ask permission of subjects for the sharing of certain data with NIH and their contracted research group, the Duke Clinical Research Institute. The researchers hope to use this data to learn more about COVID-19 and other diseases and conditions. Permission to share this data is voluntary and requires additional consent. If the caregiver does not consent to the sharing of data with the NIH, their responses to study surveys and testing data will be provided to NIH in an aggregated fashion (no identifiable data will be shared). If the caregiver consents to sharing their individual, identifiable data with the NIH, their name, date of birth, address, phone numbers, and email addresses will be shared with the NIH with their individual responses to their study surveys and testing data.

Parents will be presented with the following explanation of this data collection and asked whether they give consent to participate:

OPTIONAL STUDY ACTIVITIES - Consent to Share Your Re-SET Data with the National Institutes of Health

The following study activities are optional. You may still take part in this study if you say no to any or all of these optional activities. Participating in any of these activities will not help you or your child directly.

Dr. Coller and his research team received funding for the ReSET COVID testing study from the National Institutes of Health which funds a larger program called RADX-UP. The researchers overseeing RADX-UP are asking for your permission for us to share your Re-SET study data with NIH so they can learn more about COVID-19 and other diseases and conditions. The following consent form asks for your permission for us to share this study information. This is an optional, additional request. If you decline sharing your information with the NIH, your participation in the Re-SET study will not be affected.

What is the NIH and RADX-UP?

The NIH stands for the National Institutes of Health. The NIH is part of the United States Department of Health and Human Services. The NIH's purpose is to find new knowledge that will lead to better health for everyone. The NIH funded (provided support) for the RADx-UP program.

RADx-UP stands for Rapid Acceleration in Diagnostics (in) Underserved Populations. RADx-UP is a health research program to learn more about COVID-19 disease. If you join RADx-UP, we will gather some data (information) about you. We will combine these with data from other people who join RADx-UP. We will study the data from all who join to understand how to help more people at risk for or with COVID-19.

What will you ask of me?

If you decide to join this study, we will gather data (information) about you and your child. If you choose to participate in this data sharing, Dr. Coller and his team will share the information collected in the study surveys with the NIH/RADX-UP team. Examples of the information that we may collect from your study surveys are, but not limited to:

- basic information about you and your child such as name, date of birth, address, contact information, race, ethnicity, gender, language, health insurance status, disability, job, and household information including address history
- information about COVID-19 related to you and your child, including information about any symptoms and test results. If you had a positive COVID-19 test, we will ask information about contact tracing (people who may have come in contact with you while you had COVID-19). We will ask about your child's medical history and if they have or have not had vaccines and why.
- information about you and your child's health, education, family, home, relationships, and social life, among others.

What will you do with my data?
We will keep your data securely (which means with extra protection), along with the data from all the other people who take part in the RADx-UP program. Researchers will use the data to learn more about COVID-19 or other diseases and conditions.

The Duke Clinical Research Institute (DCRI) is a research group chosen by the National Institute of Health (NIH) to combine the data collected from everyone taking part in RADx-UP studies.

The DCRI will build two RADx-UP databases (systems that hold electronic information).

The first database will only hold information that can identify you (called identifiable information). Examples are your name, address, email, and date of birth.

- These data will be kept at the DCRI. The DCRI will not share these data with the NIH.
- Only if you agree, by initialing below, the DCRI will keep information that can identify you in order to contact you for future research studies. If you do not agree, this information will stay with your study team, as applicable.
- These data will stay in a password-protected secure electronic system and only staff responsible for maintaining the security of your data at the DCRI will be able to see this information.
- This database will contain the following identifiable information: name, date of birth, address, phone numbers, and email addresses of you and your child. This information will be paired with your responses to the study survey questions. Survey questions include information about your child's medical conditions, school attendance, health insurance type(s), vaccination status of you and your child, COVID testing history, your opinions about vaccinations and testing, household income, race, ethnicity, gender, your educational background, employment status, and marital status.

The second database will not hold information to identify you. It will hold all the nonidentifiable information you agree to give.

- You will be assigned a study code and you will only be identified in this database by this study code.
- It will not contain your name or other information that could easily identify you.
- We plan to transfer and keep these non-identifiable data in a secure database for COVID19 research at the NIH. Other researchers may use these data for studies, other than the ones stated in this consent form.
- When using the data from this second database, researchers will only have access to your non-identifiable data and cannot link the data back to you.
- Because the data cannot be linked back to you, we will not contact you to inform you or ask your permission before sharing the data with researchers.
- This database will contain the nonidentifiable information that you provide on the study surveys.

How will you protect my privacy?
Your privacy is *very* important to us. We will take great care to protect your privacy. However, there is always a chance that, even with our best efforts, your identity and/or information collected during this study may be accidentally released or seen by unauthorized persons. Here are a few steps we will take:

- Data will be stored on protected, secure computer systems. We will limit and keep track of who can see these data.
- Anyone who can see these data will have to use a password.
- We will take steps to protect your information from others that should not be able to see it.
- When your data are shared with other researchers, they will not have information that can identify you.
- This project has a Certificate of Confidentiality from the United States government. Certificates of Confidentiality protect your privacy by blocking the release of identifiable, sensitive research information to anyone not connected to the research except when you agree, or in a few other specific situations.

Optional:

I agree to let Duke Clinical Research Institute (DCRI) collect the following identifiable information: name, address, contact information, and date of birth, as stated above.

Yes, initials _____ No, initials _____

I agree to let the DCRI collect only my zip code and no other identifiable information as stated above.

Yes, initials _____ No, initials _____

I agree to be contacted for future research as stated above.

Yes, initials _____ No, initials _____

DATA ANALYSIS

In primary analyses, feasibility and school perception measures will be summarized with descriptive statistics. Differences by race/ethnicity and urban/rural category will be identified with t-tests or Wilcoxon rank-sum tests (continuous variables) and Chi-squared or Fisher's exact tests (categorical variables). Aim 1's design will allow us to conduct a couple of comparative analyses:

(1) We will evaluate whether statistically significant differences in feasibility or perceptions exist for in-home compared to school-based cohorts (see IRB ReSET Aim 1b)

(2) We will explore differences in perceptions associated with changes in community spread.

We anticipate the relatively small number of subjects and low COVID-19 rates will make sensitivity and specificity determination of BinaxNOW tests difficult; however, we will measure the number of positive and negative tests during the study period as well as the concordance of positive tests with PCR testing.

UNANTICIPATED PROBLEMS OR COMPLICATIONS

Study staff will report any unanticipated problems or complications to the principal investigator promptly. Weekly team meetings will review study issues such as any deviations from the protocol, subject complaints or questions, and positive test results. The principal investigator will provide guidance on these issues and determine whether such events are to be reported to the IRB in accordance with posted guidance. Should urgent issues arise, study staff will have access to principal investigator and/or research manager guidance at all times via email, texting and phone.

INSTITUTIONAL REVIEW BOARD

The UW-Madison Health Sciences Institutional Review Board (IRB) will serve as the IRB for this study.

PROJECT FUNDING

This project is funded by the National Institutes for Health.