NCT04887129

PROTOCOL

Title: COV-IDD: Testing for COVID-19 in high risk children with intellectual and developmental disabilities

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1.3 STUDY DESIGN

Scientific Questions and Impact: School-aged children with intellectual & developmental disabilities (IDD) are at extreme risk for severe COVID-19. Many have compromised immunological and respiratory function, and their risk is compounded by high prevalence of communication disorders that can lead to impaired self-reporting of illness, as well as cognitive impairment and mobility issues that lessen compliance with safety protocols (distancing, masking, and sanitization). While some of these children are served in public schools, many are in IDD-specialized schools that provide not only educational services, but also clinical services, speech and psychological interventions, nutritional needs and physical care. For parents or guardians, the burden of homecare is enormous, such that maintaining employment is often impossible when the child is out of school. It is therefore essential that schools re-open in a manner that is safe for students with IDD. This project proposes a holistic virological and serological testing strategy, augmented by a mobile testing unit, systems modeling, educational outreach to address vaccine and testing hesitancy, and a scalable, innovative outcomes assessment that addresses multiple health domains (including anxiety, depression and social functioning), to stand up, refine and understand the best strategies for returning this vulnerable population safely to school. Our ultimate goal is to develop generalizable and scalable approaches that can be disseminated rapidly to facilitate school opening.

Participants: Rochester's Mary Cariola Center (**MCC**) serves moderate-to-severe IDD children (**N=450**) via a large professional and support staff (**N=500**). 70% of MCC students live in poverty, and 54% are from under-represented minority (URM) backgrounds. MCC is highly representative of similar settings across the nation. Here, we will build on the existing close partnership between MCC and the UR-IDDRC, to implement and evaluate innovative testing strategies in this community that will prevent, contain and mitigate virus outbreaks – and maximize safe school participation for these vulnerable students.

Scientific Goals: We will use systems simulation modeling to develop an efficient virological and serological testing regime, and to optimize tracing and isolation processes. Longitudinal virological testing will track infection rates and serological testing will quantify durability of protective immunological responses, which may be shorter-lived in IDD populations. We will deploy an innovative mobile testing-unit for optimal testing flexibility. We will also address psychological barriers to full engagement with public health policies, including anxiety about COVID-19, as well as vaccine and testing hesitancy. To do this, we will develop effective support and educational outreach tools and strategies to mitigate these concerns. We will also establish **a community-engaged leadership plan** to direct this project, assure its sustainability, disseminate findings, and engage fully with all stakeholders (including the MCC community). We will work directly with the Coordination and Data Collection Center (CDCC) to facilitate full, accurate, rapid research data acquisition, curation and standardization, and deposit in the NIH RADx Data Hub. Our five goals are:

1) Virological Testing: We will establish a nasal-swab FDA-approved testing regimen to monitor and identify disease outbreaks in a specialized school setting serving 450 children with moderate-to-severe IDD and the 500 staff supporting them**,** a setting at ultra-high risk for COVID-19 disease transmission. We will rapidly identify infections and develop approaches for isolating and contact-tracing to stem virus spread. **2) Serological Testing:** Serology will establish background immunity levels in students and staff, from infection or vaccination, and will follow those who are antibody-positive longitudinally to quantify temporal decay of IgG and neutralizing antibody levels. We will determine whether protective immunity in children with IDD, a population with prevalent immunological dysfunction, wanes at an accelerated rate compared to the population-at-large; by doing so we will address an important knowledge gap, and provide key data to inform public health policy. **3) Modeling to Optimize Testing:** We will use network models and agent-based simulation models (or hybrid approaches) to guide testing strategies and interventions at MCC. Simulations will be conducted interactively and iteratively, to assist in planning and implementation of testing procedures, exploring the dynamic interplay between school operations and personnel interactions, potential infection risks and disease dynamics (including variant strains), and implementation of control measures (e.g. quarantine, isolation, contact-tracing and vaccination rates). **4) Mobile Unit Testing:** We build on our successful mobile approach to delivering mobile dental care to the IDD students of MCC (the SMILEmobile), by staffing, equipping and deploying a customized, disability-enabled, mobile testing unit equipped with a specialized HEPA-filter enabled HVAC system (***UR Health in Testing - HIT Mobile***). We will use this to directly deliver rapid flexible testing to MCC. **5) Overcoming Testing & Vaccine**

Anxiety/Hesitancy: We will conduct focus group interviews at MCC to identify key community concerns, myths and misconceptions about vaccination, and we will then build on our success in reducing vaccine hesitancy among URMC staff, to create a multimodal educational campaign that addresses these concerns. Strategies will include a speakers' bureau, group discussions, and "table talk" conversations, combined with innovative visual approaches that communicate complex information in a readily accessible manner (via graphic medicine) and that promote vaccine uptake (via narrative portraits of trusted peers and coworkers who have chosen to be vaccinated). Finally, we will assess the impact of this program by deploying a validated, electronic patient reported outcome scale (PROMIS-29) already in widespread use across the UR health system and at Rochester's East High School, to collect longitudinal data from staff, parents/guardians and children (by proxy reporting) across multiple health domains (including anxiety, depression, sleep disturbance, and social functioning). This scalable approach will reveal the full impact of the interventions and approaches proposed, and is readily compatible with extension to other sites in the RADx network.

Table 1: URMC COVID-19 Testing Capacity and Modalities

Platform	Test	Capacity: Tests/Day	Certification
Roche 8800	Molecular	2000	FDA-EUA
Cepheid	Molecular	500	FDA-EUA
Holologic	Molecular	500-1000	FDA-EUA
Abbot Architect	Serology	1000	FDA-EUA
TF Amplitude	Molecular	3000-6000	FDA_EUA-pending

Testing Capacity: Our Clinical Microbiology laboratory began SARS-CoV-2 molecular testing on 3/16/2020, and has now tested over 500,000 specimens, with consistent turn-around times of 24-48 hrs. Current capacity is approximately 10,000 tests/day High throughput SARS-CoV-2 molecular platforms include: COBAS 8800 (Roche), Panther (Hologic), GeneXpert (Cepheid), and Amplitude (Thermo-Fisher), among others. The lab has sufficient capacity to run all testing in-house and does not currently utilize reference testing (**Table 1)**. Serological testing (IgG) has been available since 6/20 on the Abbott Architect. Available capacity greatly exceeds the needs of the present project; ***the project testing engine will be ready to start on day one of the project (i.e., as soon as the first participant is enrolled***).

1.4 CENTRAL AIMS

Scientific Goal 1: Establish a molecular testing program to monitor and identify COVID-19 infections within a school community of individuals with IDD

Overview and rationale: This program will focus on the students (n=450) and staff (n=500) of the MCC, who collectively form a community that is highly representative of other IDD school communities across the nation. We will establish testing across this difficult-to-test population, using a tailored and flexible approach to foster test uptake and to prevent and/or mitigate COVID-19 outbreaks.

Establish a clinical molecular and serological COVID-19 testing program for the Mary Cariola Center: The dynamics of viral spread are unknown in a school serving individuals with IDD such as the MCC. Questions to be answered with *molecular* testing include: What is the incidence of asymptomatic COVID-19 infection, and how is this affected by rising vaccination rates? How do activities within the school alter risk? *Serological* testing will assess baseline prevalence of prior infection (anti-NP IgG), and changes over time, in response to infection (anti-NP IgG+) and vaccination (anti-S IgG+, anti-NP IgG-).

Molecular Testing: RT-PCR tests for SARS-CoV-2 with FDA EUA will deliver highly sensitive and specific clinical-grade results. Respiratory samples will be obtained by mid-turbinate or nasal swabs, collected in a dedicated area with proper ventilation and PPE (see Mobile Unit testing plan below), and delivered to the URMC Central Laboratory for testing in a CLIA environment with 24-72h turnaround times. The testing plan includes two groups: those tested as part of scheduled surveillance and those tested for symptoms or exposure.

Surveillance Screening and Exposure/Symptomatic Testing: Participants will be tested every 5-14 days to increase likelihood of detecting infected but asymptomatic individuals. Enrolled students and staff who report symptoms in the on-site screening will be tested on-site. Symptomatic individuals will be tested separately from asymptomatic participants every 3 days for up to 10 days. *Reported* test results will be qualitative, although Ct (cycle threshold) values will also be captured for modeling purposes.

***Clinical** Serological Testing:* Tests with FDA-EUA will be used to assess the presence of IgG antibodies to SARS-CoV-2 (Table 1) every 6 months. Our current Abbott Architect assay qualitatively assesses IgG binding to the SARS-CoV-2 nucleocapsid (NP) protein and we intend to offer the Architect anti-spike (S) semi-quantitative assay when it is granted EUA (expected shortly). Serum will be collected upon enrollment and then every 6 months for the duration of the study period. Assuming 70% study enrollment, this will result in 1,680 staff and 1,330 student serological tests.

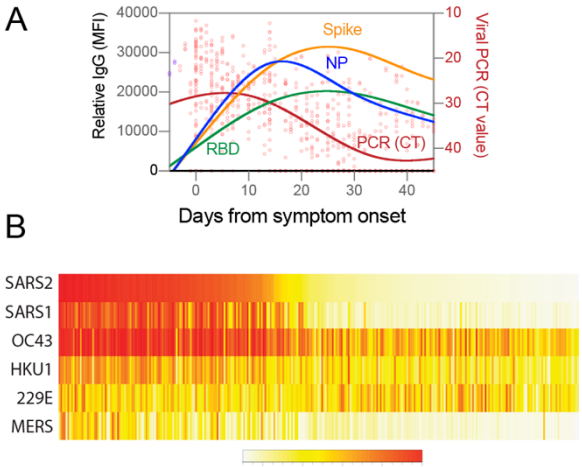


Figure 1 – Serological Testing. (A) Clinical analysis of persistence of anti-S, anti-NP, and anti-RBD binding IgG and PCR results from the URMC Clinical Laboratory. Note the early decline of anti-NP IgG. (B) Multiplex testing for IgG directed against S proteins for common circulating coronaviruses, including SARS-CoV-2 (SARS2), and prior SARS-CoV-1 and MERS (Middle East Respiratory Virus)

Reporting and Result Handling: The ordering provider (Dr. Anne Francis) at the MCC and nursing staff will receive test results. Positive results will be reported to public health agencies via standard clinical protocols. Both molecular and serological *clinical* results will be qualitative (Positive, Negative, Inconclusive). *Upon the communication of a positive molecular test result*, students and staff will be referred to their primary care providers (PCPs) or urgent care if lacking a PCP. Enrolled study subjects who have been in close proximity to the positive individual will be immediately PCR tested. Unenrolled, exposed individuals will be offered study enrollment or else referred to their PCP/urgent care for testing. RT-PCR positive students will be re-tested every two weeks to assess viral load kinetics.

Research Serological Testing: Modeling requires continuous, quantitative data to estimate antibody persistence, and as a correlate of immunity. We will test 200 subjects every 4 weeks for up to 36 months using a multiplex research assay that simultaneously measures IgG levels against the spike (S) and nucleocapsid (N) proteins of SARS-CoV-2 and human seasonal strains (OC43, HKU1, NL63, 229E); we will also measure antibodies directed against the receptor binding domain (RBD) of the S protein. This assay provides absolute measures of serum IgG (ng/ml), and is currently in use in several NIH funded studies (see Fig 1). We are also adding emerging SARS-CoV-2 variants (e.g. UK, South African). Samples will be collected by fingerstick and volumetric micro-sampling (VAMS) to collect 40µl of capillary blood. A topical anesthetic cream can be used prior to collection. Samples will be analyzed by batch in Dr. Zand's lab.

Scientific Goal 2: Serological Testing and Modeling

The dynamics of the immune response to SARS-CoV-2 are as yet unknown in children with IDD, a population with prevalent immunological dysfunction, who may show different COVID-related immunological profiles and latencies to those of the general population. Here, we longitudinally follow those with IDD identified as antibody-positive, from either infection or vaccination, to quantify the timing of reductions in IgG and neutralizing antibody levels. We will use a combination of the SARS-CoV-2 clinical serological assay (described above), and a research multiplex assay for anti-spike and nucleocapsid protein IgG and receptor binding domain (RBS) antibodies, against SARS CoV-2 (including emerging virus variants), and a panel of commonly circulating human coronaviruses. *This will provide serological data uniquely focused on the IDD population with clear implications for public health immunity strategies.*

Experimental Approach. IgG responses to individual SARS-CoV-2 antigens (S, NP, RBD) in enrolled students and staff will be measured initially by clinical testing and fingerstick at baseline, and then every four weeks by fingerstick for up to 36 months. Any large increase in anti-SARS-CoV-2 levels will be confirmed by clinical serology. Dynamics of anti-SARS-CoV-2 IgG will be assessed by fitting the anti-S, NP and RBD quantitative results to a modified power law model that accounts for long-term antibody persistence: $f(t) = k + \log\left[(1-\lambda)(c+t)^{-\alpha} + \lambda\right]$, where k is the peak log IgG level, α is the decay rate, c is a constant, and λ is the steady-state long-term IgG level. We will fit the model using a mixed effects

method, where k and α are subject specific random effects drawn from a bivariate normal distribution. This will allow comparison of decay rates (α) and steady state anti-SARS-CoV-2 IgG levels (λ) across subjects.

Scientific Goal 3: Systems modeling to direct testing strategies

Our aim here is (A) to model potential transmission routes of COVID-19 at MCC using a network approach which can then be used to guide testing, and (B) to develop agent-based simulations to aid in developing and testing strategies to reduce risk of COVID-19 spread. We will pay particular attention to modeling how changes in vaccination rates and asymptomatic infection with low viral load (PCR cycle threshold – Ct) affect risk of transmission. These models will be used to define testing strategies and interventions to reduce the risk of COVID-19 spread in the Fall semester, and to explore the dynamic interplay between school operations, infection risks and control measures. *Successful completion of this work will result in development and deployment of generalizable simulation models to guide COVID-19 testing.*

Network modeling is ideally suited for analysis of risk of disease transmission in complex systems (1), and can account for symptom latency, changes in classroom group composition, and student mobility. Agent based models (ABMs) developed from network models can be used to study time varying outcomes arising from changes in behavior (e.g. vaccine acceptance), immunity, and asymptomatic infection among students, teachers and staff. This approach enables *in silico* evaluation of hypothetical testing strategies, simulation of infection dynamics, and assessment of alternative mitigation strategies. Dr. Zand has developed network models and analytics for risk of transmitted infection in a complex, high contact hospital environment (1), and Dr. Seplaki is currently creating ABMs that assess strategies to decrease COVID-19 infection risk on the UR Undergraduate Campus. Analytic approaches based on our prior work (1-6), will be used to construct (1) a network model of who is in contact with whom, for how long and (2) a mobility model of individual's travel between school locations and (3) agent based models of behavior, given data about anxiety, vaccine status, and adherence to guidelines. The ***contact network,*** will model testing strategies for surveillance for new infections in a mix of individuals with varying levels of immunity, vaccine acceptance, exposure, and new emerging viral strains. The ***mobility network*** will be used to model prevention strategies of changing staff and student classes/movement/interaction to decrease the risk COVID-19 transmission. ***Agent based models*** will test the effects of behaviors on school operations. The number of students and staff who remain on-site and in-school, will be key outcomes. Questions will include: How does the mixture of immunity, class/student scheduling, and vaccine acceptance create opportunities for COVID-19 spread (and control)? Do asymptomatic individuals with positive PCR tests spread virus?

<u>*Network modeling*</u> – We will contrast both a **contact network** and a **mobility network model (Fig 2)**. Data used for modeling will include the instruction schedules of IDD-students, staff and class locations. Each data record will contain the subject ID, activity, location, time, and duration. Student and staff attributes will be stored in the secure BLIS informatics database system (see Facilities and Resources), which will also hold the COVID-19 PCR and serology testing results. We will also incorporate anxiety data from the PROMIS survey (Goal 5 below), and rates of prior infection/vaccination (derived from serology data). We will use the schedule database to construct directed, bipartite graphs where the nodes represent two categories of individuals (students, staff), and the edges are weighted by the duration of contact (4, 6). *A mobility network model (1, 2)* (**Fig. 2B**) will capture the movement of students and staff between physical locations within the building. For both network models, we will characterize measures of network structure (density, diameter) (1, 4, 6), and identify individuals with high contagion centrality. We will simulate various testing frequencies of asymptomatic individuals (1). For example, we will model outcomes for increasing testing for: (1) staff who contact many students to decrease transmission risk, (2) staff who connect groups of students to decrease between-group spread. Sensitivity analysis will assess how modification of parameters (e.g. vaccination proportion, asymptomatic viral load) affects the ability to detect infection.

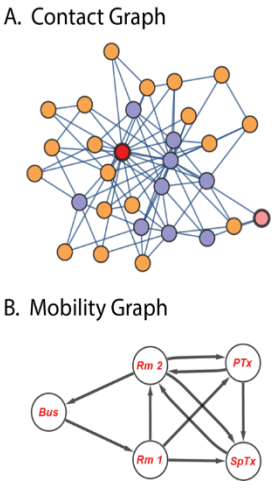


Figure 2

Agent-based modeling **-** ABMs are well-suited to dynamically characterize complex and difficult-to-measure mechanisms driving infectious disease transmission (7, 8). They are also used to design and evaluate interventions to reduce infection risks by simulation of "what-if" scenarios. MCC is an ideal setting for agent-based modeling as it is a circumscribed physical location with well-defined populations (i.e. students, staff), movement and interaction patterns. It is worth emphasizing that MCC is highly characteristic of the many similar school settings that provide services to children with IDD nationwide, and as such, provides an excellent test population form which to derive generalizable models. Agents will be individually characterized with fundamental attributes (e.g., movement rules, contacts with other agents, infection-susceptibility) that are abstract reflections of key variables (e.g. contact time, asymptomatic viral load, vaccine status). A wide range of use cases will be simulated including support for planning and deployment of testing procedures, exploring hypothetical testing or screening strategies, simulation of virus transmission dynamics, and assessment of alternative prevention or mitigation strategies. We will leverage guidance from administrators on student and staff activity schedules to study density and space in order to understand how they relate to possible patterns of infection. Simulations will examine the numbers of people in given rooms contemporaneously and the potential mixing of vulnerable and asymptomatically infected subjects. These efforts can inform the network models (see above) to guide decisions about when and who to test. The ABM models will be used to identify strategies to prevent negative impact of asymptomatic infected individuals, with logistical and/or financial constraints.

Contingency Plans: During COVID, MCC has had to respond to immediate changes in requirements from DOH and the NYS Governor. The process to "pivot" will be replicated, as it has worked well within the organization structure. Upon notification of a change, this will be broadly communicated to the project team, with same day conference established to evaluate and implement required changes. We anticipate during the course of this study that vaccinations will be approved for children under 16. This opportunity will be incorporated into educational initiatives, and will be recorded for study participants. Our scientific goals as outlined herein have built in contingencies around the expected introduction of vaccines in this population. We will also work with NIH program to revise the research and testing program in response to major changes in policy. The modeling goal described above is specifically designed to react to changing infection/vaccination landscapes.

Community Partnerships and Engagement: Our goal is to enroll 70% of eligible students and staff at MCC. This enrollment projection is based on past local experience of Dr. Foxe and the MCC leadership, and the high motivation level of MCC parents/guardians and staff. To increase participant engagement and interest in the project we will modify our proposed student recruitment and retention approaches based on key input and feedback from MCC leaders and a convenience sample of parents/guardians (9, 10). Our approach will start with an Introduction Phase followed by an Engagement phase, concluding with a Consent phase that includes baseline (and follow-up) surveys to characterize the participants, their households and community of residence. The UR Clinical and Translational Science Institute (directed by MPI Zand) will assist, and has extensive experience in community engagement, recruitment and retention of special populations. The IDDRC Human Phenotyping and Recruitment (HPR) Core will also be leveraged for their expertise including recruiter training and retention strategies.

Involvement of Community Stakeholders: We will develop a full partnership with the MCC community that results in sustained community engagement across project activities, and also after the current project ends. In this context, the term 'community' includes: all students, their family members (including guardians), and all staff, affiliated with MCC. To do this, we have established the **Community Advisory Board (CAB)** to provide broad input on project design, implementation and iteration (see **Goal 1**).

Strategies to Improve Testing and Vaccine Uptake; Communication Approach: See **Goal 5**.

Scientific Goal 4: Mobile Unit Testing: We will staff, equip and deploy a customized, disability-enabled, mobile unit (*UR Health in Testing - HIT Mobile*) to bring testing directly to the MCC community.

Overview and Rationale: We have built a robust and trusting relationship with MCC, its leadership, staff, parents and students. A flagship component of this relationship is our UR-SMILEmobile, which provides specialized dental services to the IDD community. In 2020, the *SMILEmobile provided 280 visits and 927 treatments* to MCC children – thereby providing greater access to needed care.

The same considerations behind the creation of the *SMILEmobile* also apply to testing for COVID-19 (including access/mobility issues, limited agency and intellectual disability). The innovation of bringing care directly to MCC students has proven to be efficient, effective, and appreciated by MCC students, their parents, and the MCC staff. *A mobile COVID testing unit will add flexibility and scalability to testing at MCC, and will also enable testing at other remote locations.* For instance, if there were several positive test results in a nearby school or town, the mobile unit could be deployed to quickly test large numbers of students and staff *in situ*. This rapid response 'hotspot' testing will help identify people who are positive and reduce spread allowing schools to remain open without risking additional contamination. Positive subjects will be offered enrollment into the study to track dynamics and immunity.

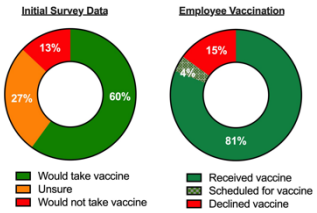
Approach: We will staff, equip and deploy a customized, disability-enabled, mobile testing unit equipped with a specialized HEPA-filter enabled HVAC system (***UR Health in Testing - HIT Mobile***) that will directly deliver virological and serological testing to MCC students and staff on their campus. To do this, we will procure a customized van, designed to incorporate a wheel chair lift and seating for the driver, a nurse practitioner and a research assistant. The *HIT Mobile* will be smaller, simpler and more agile than the already successfully deployed SMILEmobile, since it does not require dental chairs or complex equipment, but will be designed for sufficient space to carry out testing. We have already sourced a number of vendors and solicited initial designs. A simpler design using a standard van and a pop-up medical tent (E-Z UP EMC100) will be implemented at study startup. This will permit initiation of the mobile testing unit approach within the first month after project approval. The custom van conversion will require several months to complete (anticipated in August 2021). The process will be initiated immediately upon project approval, in order to put a sustainable approach in place for the fall and winter months.

Testing strategy: We will use a blended approach to testing start-up, setting up initial testing in a dedicated room within the MCC building complex, but we will transition to outdoor testing using the on-site van and pop-up tent as available. We project that the mobile unit should be able to administer tests every 5-10 minutes for staff, and every 10-15 minutes for students, allowing between 40-80 tests/day.

Evaluation: *The goal of the mobile testing strategy is to demonstrate the generalizable value and utility of bringing testing directly to the IDD community, using an innovative, mobile approach. We hypothesize that this approach will increase engagement and uptake by the IDD community and school staff.* We will assess attitudes towards testing, use of the bus, and differences in testing turn-around/adoption between the in-school testing and the mobile unit as part of our program evaluation efforts.

Dissemination of Findings: Mobile units will expand services beyond MCC and can be replicated in other locations. They are sustainable and easy to maintain compared to on-site footprints which are often difficult to acquire, expensive and disruptive to existing workflows/classrooms. We will disseminate our findings in a methods paper and will also present them to the NYS 853 and 4410 Coalition of Schools.

Scientific Goal 5: Overcoming Testing & Vaccine Hesitancy; Measuring Impact: Major barriers to return-to-school efforts are driven by (mis)perceptions of risks related to virus infection, testing and vaccination by parents, guardians, and staff. Anxiety, stress and medical mistrust further add to testing and vaccine hesitancy, which is a particular concern in a setting where many of our at-risk children meet diagnostic criteria for autism spectrum disease (ASD). To address these issues, we will leverage our recent success in reducing vaccine hesitancy in our URMC staff, to design and implement educational and intervention strategies that mitigate these issues in the MCC community by addressing common myths, misconceptions and concerns about vaccination, testing and virus infection. Initial surveys of URMC staff in late 2020 (reflecting over 10,000 responses) revealed a disappointing 40% level of vaccine hesitancy. We addressed this with a major targeted educational outreach effort, tailored to specific staff populations. The result was an 85% uptake rate of the vaccine among the 20,000 plus URMC staff eligible to receive it in early 2021 – i.e., ***a***



60% reduction in the rate of vaccine hesitancy. We will take a similar approach in the MCC community, as follows:

1) Conduct focus group interviews via zoom with priority populations to understand the nuances of COVID-related anxiety and vaccine hesitancy, and the locations/context that encourage greater vaccine acceptance.
2) Develop and deploy targeted strategies to increase understanding of the COVID-19 vaccine, that help individuals and communities make informed decisions about whether or not to receive the vaccine. This will require building and mobilizing a network of community partners, leaders and influencers, maximizing opportunities to build trust and share information.
3) Develop effective communication tools and platforms, including the preparation of materials in multiple languages, and the development of specifically targeted messaging for the MCC sub-communities and populations most impacted by COVID. Examples of these tools are: educational videos, testimonials, posters, digital and social media, web pages and public relations efforts.
4) Deliver on-the-ground education, including an educational speakers' bureau, accessible by online request, which will send speakers to community groups (via Zoom or other virtual platforms). Even more targeted activities in the form of individualized "table talk" conversations will be developed for families and other small groups to discuss the vaccine in trusted settings.
5) Create innovative visual media and art, in collaboration with the URMC's Artist in Residence. Specifically, we will use graphic medicine to address common myths, misconceptions and concerns about vaccines, as well as humanizing portraiture that creates visual narratives in which trusted peers and coworkers share their reasons for choosing to become vaccinated.

Measuring Impact: We will assess the impact of this program by deploying a validated, electronic outcome reporting scale that is already in widespread use across the UR health system (11), and at Rochester's East High School (12), to collect longitudinal data from staff, children (by proxy reporting) and parents/guardians across multiple health domains - including anxiety, depression, sleep disturbance, and social functioning (13). Specifically, we will customize the standard, short form Patient-Reported Outcomes Measurement Information System (PROMIS®-29) survey, by adding an additional domain to evaluate COVID-specific anxiety and vaccine hesitancy in our parent and school worker communities, based on concerns identified in our URMC staff baseline survey (see above) and in our initial MCC focus group interviews. We will then deploy the enhanced PROMIS-29 scale in electronic form within the MCC community, via two user-friendly approaches: (1) iPad/tablets at MCC (our standard approach in UR's ambulatory health clinics), and (2) mobile devices. We expect the latter approach to substantially increase survey participation, particularly among parents/children who have elected not to attend school, due to severe underlying health concerns, high levels of anxiety or other considerations.

Data collection takes < 5 mins with these approaches. All data will be stored on a secure, redundant, HIPPA-compliant server located behind the URMC's firewall. Participants will be sampled monthly using methods from our prior work at East High School (12) and the UR medical system (11). Each participant will receive a survey invitation unique to their email address or cell phone number, and surveys will be delivered in a self-report format (for MCC staff and parents) or in a proxy-report format (for children with IDD). In addition to the custom COVID-related survey domain, PROMIS-29 domains that we expect to be most informative will include the following: A) Anxiety, B) Depression, C) Sleep Disturbance and D) Social Functioning. We are especially interested in the relationship between generalized anxiety, COVID-specific anxiety and vaccine hesitancy – and how these parameters are influenced by the educational, interpersonal and art-based interventions that we will deploy. We are also interested in measuring the impact of in-person school attendance by MCC school children, on all of these domain areas (this will be analyzed by comparing the two cohorts of MCC school children who are currently attending the school in person, to the cohort who are participating in school programs on a 100% virtual/distance basis).

Our goal is to use the enhanced PROMIS-29 scale to determine if a highly effective COVID testing and containment/prevention program, based on cutting-edge data-driven modeling approaches, and combined with innovative educational outreach efforts, not only enables sustainable in-person school attendance, but also results in broad improvements in health outcomes for children and their families. Finally, in proposing to adapt and enhance the PROMIS-29 scale to this specific use case, and to develop generalizable models and educational interventions, we also intend to develop a scalable approach that can be readily disseminated and adapted to schools across the country.

Confidentiality of Testing and other Data: Identified data will be reported from the laboratory to the ordering provider (Dr. Francis at MCC) via secure fax. MCC will report results clinically, to the State via secure electronic channels, and to the county DOH for the purposes of guiding contact tracing and post-exposure testing. Individuals who are selected for post-exposure testing will NOT be informed of the identity of the individual to whom they may have been exposed. At UR, individual-level data will be made available only to a very limited number of persons in the modeling and intervention team, who will use the information exclusively to inform their modeling and infection control efforts.

2. CHARACTERISTICS OF THE RESEARCH POPULATION

2.1 Subject Characteristics

All staff and students at Mary Cariola Center (MCC) are eligible for this study

a) Number of Subjects – There are 500 on-site staff and 450 students. Up to 950 people may enroll, although we expect around 70% enrollment

b) Gender and age of subjects – Among MCC **employees**, approximately 75% are female. We expect at least 50% to consent to testing and another 30% to complete the baseline survey. **Among students under age 18**, approximately 30% are female, consistent with the national IDD population. We expect 70% to enroll. Unless our enrollment trends show otherwise we do not anticipate any unique messaging or additional outreach to achieve our enrollment target. There are also Mary Cariola students age 18-21 approximately 30% female.

There are no exclusions by age however we are limited by the ages of those attending or residing in MCC and the age range of employees.

MCC students are included in this study as the main participants as the study seeks to understand testing and transmission patterns among individuals with IDD in school and residential settings including modeling. Most of the students in the school setting are under age 18; The youngest student is age 3. There are also about 60 students at the school between the ages of 18-21. Approximately one third of these students have legally authorized representatives (guardians).

Age distribution of students is:

3-5	20%
6-10	28%
11-14	25%
15-17	19%
18-21	8%

We will track early enrollment to determine if rates are lower than expected or if there are under-represented age groups (based on the age distribution of MCC students). This will warrant revising of recruitment strategies and tactics within the research team and the CAB.

MCC Staff range in age from 18 to 75.

Efforts to enroll employees will be informed by the CAB. We will track early enrollment to determine if rates are lower than expected or if there are under-represented age groups. Lower than anticipated enrollment will warrant revising of recruitment strategies and tactics within the research team and informed by the CAB.

c) Racial and Ethnic Origins

Underrepresented minorities in the local community are Black and Hispanic. The minority participation in this research among students is based on the distribution of races and ethnicities at Mary Cariola. Thus approximately 43% will be a racial minority (Blacks representing 76%) and 11% will be Hispanic. Materials will be available in Spanish. As part of our vetting process we will assure that the messaging, photos and other representations include minority images and language that reflect health equity.

Among MCC Staff, approximately 30% are Black and 3% are Hispanic.

d) Vulnerable Subjects

This study, by design, involves a vulnerable population, children under age 18. The importance of this study is provided in the application and in the NOSI itself given the risks associated with COVID-19 among this population. The benefits of undergoing testing and the proposed modeling in this group of children considered at high risk for illness and hospitalization due to COVID-19 exposure will be both direct and indirect. First, children will have access to testing not readily available to them. Second, indirect benefits would be the information provided to MCC to modify procedures to mitigate or minimize transmission at the children's residential and school facilities. The proposed testing regime will also help define what pattern of testing is warranted for individuals with IDD. Given the high risk nature of COVID-19 among this population, and the potential for local and national impact, the risks to subjects (primarily discomfort with testing) are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

e) Spanish-speaking Staff and Parents of students

There are staff at Mary Cariola whose primary language is Spanish. To enroll these participants we will use consent documents and questionnaires translated into Spanish. Additionally, Spanish-speaking members of the study team will consent these participants in Spanish or if necessary we will have translators on-site to facilitate consent in Spanish. Some parents of Mary Cariola students may also have Spanish as their primary language and we will get permission using Spanish and permission and questionnaires translated into Spanish.

2.2 Inclusion and Exclusion Criteria

Criteria are presented below in a table for each of the three groups involved in the study: MCC students, MCC Staff and parent/guardian decision makers.

Inclusion and Exclusion Criteria

Cohort	Study Procedure	Inclusion Criteria	Exclusion Criteria
IDD Students	• COVID-19 RT-PCR Testing	• IDD Student of the Mary Cariola Center • Age 3 – 21	• Contraindication to nasal swab

	• Anti-SARS-CoV-2 Antibody Testing	• Have a parent/guardian who can give informed consent • In the judgement of the Mary Cariola Medical Staff will be able to safely participate in the study procedures (nasal swab, phlebotomy)	• Contraindication to phlebotomy (e.g. anticoagulated, bleeding diathesis)
Mary Cariola Center Staff	• COVID-19 RT-PCR Testing • Anti-SARS-CoV-2 Antibody Testing	• Age 18 – 72 • Able give informed consent • Anticipated duration of remaining employment less than 1 month (e.g. retiring) • Must be willing to participate in RT-PCR and antibody testing	• Contraindication to nasal swab • Contraindication to phlebotomy (e.g. anticoagulated, bleeding diathesis)

3. SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT

3.1 Method of Subject Identification and Recruitment

Participants will be assigned de-identified code numbers to maintain confidentiality. This code will be used to label all de-identified documents and data files relating to the subject.

Selection will occur as a function of the criteria above.

3.2 Process of Consent

Consent is an on-going process that starts when you first inform potential subjects about the study and ends when the subject's study participation is completed.

a) Written informed consent will be obtained by standard procedures approved by the University of Rochester Medical Center Research Subjects Review Board (RSRB). Consent form will be e-mailed or sent via letter or fax to the subject (if an adult) or to the subject's parent/guardian for their review at least 24 hours before their scheduled appointment. Informed consent will be obtained in person by one of the study investigators prior to any study-related activities, typically as the first line of action when a subject comes in for the experiment they are participating in. The consent form will be reviewed and the participant or guardian will be given as much time as they desire to decide. If they would like to take more time to seek input from other individuals before deciding about participation, this will be allowed and the visit rescheduled. The participant or guardian will again be given the opportunity to ask any questions before signing the consent form. The study will again be explained in detail by a study investigator and the participant or guardian will be given the opportunity to ask questions and will be reminded of their right to discontinue the study at any time. Participants or guardians will be given copies of

their written consent to participate. The original signed consent form will be stored in a locked file cabinet in the study coordinator's office for future reference.

b) This study includes children, a vulnerable population, and these MCC students have moderate to severe IDDs. We will administer an age/ developmentally-appropriate assent form in conjunction with guardian permission. There may be participants with IDDs that are unable to be assented due to cognitive and language limitations. We will consult MCC personnel when determining the cognitive abilities of the students. The study staff will still explain the procedures to the individual and attempt to determine their level of understanding. If determined that they cannot provide informed assent we will document this on an assent form (there is a check box on the assent forms to indicate subject's ability to provide informed assent) and proceed only with parent/guardian permission. For these participants, the staff will also use a low threshold for any indication a participant wishes to stop their participation.

c) Consent for participants with Spanish as a primary or sole or preferred language. Mary Cariola Staff whose primary and preferred language is Spanish will be consented using our Spanish Consent forms, by study personnel who speak fluent Spanish or by translators from the URMC. Two study team members are fluent in Spanish. Questionnaires have been translated into Spanish and are built into RedCap forms sent to participants based on the language used to consent them. Email contact with the link to surveys is also in Spanish. All questionnaire data on both English and Spanish forms are coded and transmitted to the data team as coded information without information about the language of the data collection form – this prevents identification of participants based on language of consent. Parents of students whose primary/preferred language is Spanish will be given the Spanish permission forms and work with one of the Spanish speaking study team members. Students at Mary Cariola are fluent English speakers and all classes are taught in English. We will use English Assent forms with students.

d) Alternately, the patient will be given the choice to utilize the Electronic Informed Consent (eConsent) process to provide consent remotely. This platform involves a computer based consent form accessed on personal electronic devices (e.g., computers, portable tablets, smart telephone), rather than traditional paper documentation created using a REDCap-based electronic consent form. The IRB-approved consent form will be developed in REDCap, a secure, web-based, HIPAA compliant, data collection platform with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data (e.g. read only, de-identified-only data views) for other users.

If the patient chooses to eConsent, a member of research team will request verbal permission to send the eConsent via email or text. The request will state: "Because URMC can't control the security of email or text messages once we send them, we need your permission to text or email you. Do you want to receive the link to the eConsent via email or text?" The permission will be documented. The email or text will not include PHI.

- The patient will be contacted by the research coordinator via telephone and/or video conference to ensure that the subject or legally authorized representative has full understanding of the study and has had ample opportunity to ask questions.

- In order to authenticate the identity of the subject or legally authorized representative signing the consent, an agreed passcode is communicated between the subject and the research coordinator. This passcode is saved as part of the subject's record for verification use later. The subject or legally authorized representative, at the

time of accessing the survey/eConsent, must then enter the passcode which is compared with the stored version entered by the research coordinator.

- Subject or legally authorized representative signatures will be obtained using a typed signature.

- Once the consent form is signed and submitted, subjects will be able to receive a print out of the paper copy, download a PDF, and/or receive an email with a PDF attachment of the signed document. The original consent form will be placed in the research record. Prospective subjects will be given the opportunity to consent to future use of information and consent to re-contact in the future.

e) Some students at Mary Cariola School are age 18 or older (up to 21) and have legally authorized representatives (LARs). We will use our adult consent documents and have the LAR consent to participation of the student in the study. We will also get signed assent directly from the student when they are developmentally capable of providing informed assent. There may be participants with IDDs that are unable to be assented due to cognitive and language limitations. We will consult Mary Cariola personnel when determining the cognitive abilities of the students. If determined that they cannot provide informed assent we will document this on an assent form (there is a check box on the assent forms to indicate subject's ability to provide informed assent) and proceed only with consent of the LAR. For these participants, the staff will also use a low threshold for any indication a participant wishes to stop their participation.

4. METHODS AND STUDY PROCEDURES

4.1 Study Procedures and Assessments

Funding of study elements: A grant to the University of Rochester from the National Institutes of Health RADx-UP program is providing funding for all aspects of the study procedures with the exception of the fingerstick blood draw and analysis of these blood samples. The fingerstick test for COVID-19 antigens is not an FDA approved test – it is solely for research purposes. Funding for this aspect of the project comes from a separate grant from the National Institutes of Health as a supplement to the University of Rochester Intellectual and Developmental Disabilities research Center.

***Questionnaire*:** Staff or parents of students will be sent a unique link to a RedCap form for them to fill out. We will arrange to send this to them via email or provide them with an opportunity to fill this out on-site using a study iPad. The questionnaires are designed to collect information about the household of the subject, demographics information, attitudes and opinions regarding COVID-19 risk and testing, and vaccines. Also asked are questions about medical history, health status, drug/alcohol use.

A second link to the questionnaire will be sent all current participants to collect a cross-section of responses at a single time point – beginning mid May 2022. The questionnaires will be identical to the initial questions presented to each participant at the time of their enrollment.

Asymptomatic Testing –

Nasal Swab: Participating individuals (students and employees) will be tested for COVID-19 (RT-PCR) using a specimen collected using a mid-turbinate swab. This asymptomatic testing

regime starts on or after (if scheduling testing requires this to begin on a different day) enrollment and is repeated every 5-14 days for up to 36 months. Anyone testing positive is followed up as described below for symptomatic individuals.

Saliva Sample: For those participants (students only) that are unable to tolerate the nasal swab (mid-turbinate) test, we will use the Spectrum Solutions™ SDNA-1000 Molecular Diagnostic Saliva Collection Device. This is a self-contained, **EUA authorized** saliva collection system. It requires filling a small tube with saliva.

Blood Samples: Participating asymptomatic individuals (students and employees) will be tested for antibodies using the fingerstick upon scheduling first sampling visit and monthly thereafter for up to 36 months. This first blood sampling will be using a fingerstick and 1-2 drops of blood will be collected in a curette for serology testing. Possible complications include pain from the fingerstick, and a low risk of infection. The rationale for this intervention is to measure serum antibodies against SARS-CoV-2 using standard FDA approved testing methods.

A second method for blood sampling using venipuncture will be carried upon enrollment or upon scheduling the first sampling visit and subsequently, every six months for up to 36 months. In addition this method will be used for additional blood collection for MBC and DNA analyses. This second method will use venipuncture to collect ~6-10 cc of whole blood (except in students younger than 5 years in whom we will collect between 3-5cc). The possible complications of phlebotomy/venipuncture include pain, small local hematoma formation, bleeding and infection. However, this method of blood collection and testing is widely used by millions individuals daily in the United States with minimal complications, including IDD subjects. Phlebotomy will be conducted by a team specially trained in working with IDD subjects to minimize risk.

***Symptomatic Testing*.** Those presenting with symptoms will be also tested for COVID-19 (RT-PCR). Those with negative test results will return to the asymptomatic testing protocol. Those with positive tests will follow NY State guidelines for quarantine/isolation. Upon return to work/school they will continue with PCR and antibody testing as described above

Additional Study Procedures

The below are **not** accomplished using FDA approved tests and are for research use only.

Blood Sample - Analysis of memory B cell recall responses. Memory B-cell (mBC) recall responses are key to generating new antibodies against highly homologous antigenic epitopes after vaccination. Dr. Zand and Wang have demonstrated that IgG secreted by in vitro mBC after SARS-CoV-2 infection and vaccination contain IgG recall reactivity that includes new pathogen-specific epitope specificities2, 3, 6. We will compare the mBC recall specificities for SARS-CoV-2 in vaccinated and unvaccinated subjects. Peripheral blood mBC in one tube (one tube – 6-10ml) of heparinized blood will be stimulated to form antibody secreting cells (ASCs) by 6 days *in vitro* culture with a combination of pokeweed mitogen, Staphylococcus aureus protein A, CpG ODN-2006, and IL-10. IgG secreted by ASCs in vitro will be analyzed by mPLEX-CoV3, 4, 6. Antigen-specific and total IgG ASCs in the cell pellet will be enumerated by ELISpot. Antigen-specific IgG ASCs as a percentage of total IgG ASCs will quantify antigen-specific IgG mBC as a proportion of total IgG mBC 8.

Genetic Research Procedures

Banking of DNA samples for mRNA vaccine response and IgG level decay targeted genotyping:

Blood Sample - One tube (one tube – 6-10ml) of blood will be collected from up to 200 neurotypical staff and 50 IDD students and stored for later DNA isolation and targeted genomic analysis. This is genomic research and NOT genetic testing. It will be carried out for research purposes only and no information about genetics will be disseminated to participants. After all testing is completed samples will be destroyed.

Population *(Minor vs. Adults)*	**Blood Draw Procedure** *(COVID antibodies, MBC, or DNA)*	**Amount of Blood**	**Frequency of Blood Draw**	**Fingerstick or Venipuncture**
Adults	COVID anti	1-2 drops	monthly	fingerstick
Minors	COVID anti	1-2 drops	monthly	fingerstick
Adults	COVID	6-10 cc	Every 6 months (completed)	Veni.
Minors	COVID	6-10cc (unless under age 5 (then 3-5cc)	Every 6 months (completed)	Veni.
Adults	MBC	6-10 cc	Once only	Veni.
Minors	MBC	6-10cc (unless under age 5 (then 3-5cc)	Once only	Veni.
Adults	DNA	6-10cc	Once only	Veni.
Minors	DNA	6-10cc (unless under age 5 (then 3-5cc)	Once only	Veni.

Mandated COVID-19 testing for Mary Cariola Staff: In response to the New York State vaccine mandate Mary Cariola Center policy requires **staff who are not vaccinated** to be tested weekly for COVID-19. One method for meeting this policy requirement is enrollment in this study. Staff who are enrolled will be tested weekly and results reported to Mary Cariola personnel. **For all unvaccinated staff enrolled in the study** missing the scheduled weekly COVID test will be reported to Mary Cariola administrative personnel in accordance with Mary Cariola Center policy.

Other data. MCC will also provide student and staff schedules (i.e. what room they are in) for use in the modeling

Multisite collection procedures:
All data will be collected by the URMC team in the Rochester area. The primary data collection location will be the Mary Cariola Center. Some home visits for testing of MCC students or staff will also be accomplished using our mobile test unit.

4.2 Future Use Data/Samples

We provide subjects with the option of participating in future research studies on all our consent forms. If they consent, we store their data in a de-identified fashion indefinitely. We offer to destroy their records at any time upon their request to withdraw from future studies. If this request is made, we will permanently delete all stored data recorded with that participant during the study.
Data will be encrypted and electronically sent to Duke Clinical Research Institute at Duke University. They are serving as the NIH-funded Coordination and Data Collection Center (CDCC). Data sent to DCRI include all questionnaire data, results of COVID-19 tests and results of serology tests. Biosamples will NOT be sent. Results of the tests WILL be transmitted electronically to the CDCC. Blood samples will be securely stored until the end of the study when they will be destroyed.

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 The first database will only hold identifiable information

These data will be kept at the DCRI. The DCRI will not share these data with the NIH.

These data can be linked with information from other sources, such as the Centers for Medicare and Medicaid Services and electronic health record, among others if parent permission or participant consent is provided

The DCRI will keep identifiable information to contact participants for future research studies only if parents/participants provide permission/consent to be contacted.

Identifiable data will be password-protected and only staff responsible for maintaining the security of the data at the DCRI have access.

The second database will contain de-identified data. Only data that parent has given permission or participant has consented to maintain.

De-identified data will be kept 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.

Blood drawn for B-cell analysis and for future genomic testing will be maintained solely at the University of Rochester. These samples and data derived from them will NOT be transmitted to DCRI. Data will be integrated and managed in REDCap and CABIN servers. All biological samples will be obtained specifically and solely for research purposes. De-identified residual blood and extracted DNA will be stored in locked -80C freezers and saved for future analysis.

4.3 Costs to the Subject

There are no costs for participation

4.4 Payment for Participation

Mary Cariola staff will be paid $25 gift card after the first visit and $10 at their monthly visits that involve fingerstick for the duration of their enrollment.

Mary Cariola students (children ages 3-17) will get $25 for enrolling in the study and an additional $10 at each monthly fingerstick visit,

Mary Cariola students (age 18 and over) will be paid $25 gift card after the first visit and $10 at their monthly visits that involve fingerstick for the duration of their enrollment.

Students and Staff participants will get an additional payment of $25 for completing the second set of questionnaires (CDE/PROMIS)

4.5 Return of Individual Research Results

Subjects (and/or their parent/guardian) will be informed if there is a positive COVID-19 test.

5. SUBJECT WITHDRAWALS

If a subject wishes to self-withdraw from this study, there are no impediments or consequences. The participant will be paid what is owed for participation to that point. This is outlined in the consent form. A minor or vulnerable participant may be withdrawn by the researcher if they are identified as distressed by study procedures. Minor subjects can withdrawal by withdrawing assent either explicitly or implicitly (by being non-compliant during study procedures). The parent/guardian can withdrawal permission at any time without consequences. The participant will be paid what is owed for participation to that point. This is outlined in the consent form.

6. RISK/BENEFIT ASSESSMENT

6.1 Risks to Subjects

Potential Risks and Benefits for Participants

This study, by design, involves a vulnerable population, children under age 18. The importance of this study is provided in the application and in the NOSI itself given the risks associated with COVID-19 among this population. The benefits of undergoing testing and the proposed modeling in this group of children considered at high risk for illness and hospitalization due to COVID-19 exposure will be both direct and indirect. First, children will have access to testing not readily available to them. Second, indirect benefits would be the information provided to MCC to modify procedures to mitigate or minimize transmission at the children's residential and school facilities. The proposed testing regime will also help define what pattern of testing is warranted

for individuals with IDD. Given the high risk nature of COVID-19 among this population, and the potential for local and national impact, the risks to subjects (primarily discomfort with testing) are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

Potential Risks:

Nasal Swab: The nasal swab will be used to collect the samples for FDA approved RT-PCR. Potential risks include slight discomfort or irritation of the nasal area being swabbed, anxiety and agitation in an IDD child. While unlikely since a mid-turbinate (rather than a nasal pharyngeal) swab is used, it is possible that the nasal mucosa could be damaged while obtaining the specimen. Those collecting specimens will have special training that is specific to specimen collection in an IDD population This is generally a minimal risk procedure, and we have specifically chosen to use nasal swabs, and not deep nasal pharyngeal swab method sample collection, for this reason.

Saliva test: The saliva test (ThermoFisher SDNA-1000 Saliva Collection Device) uses a small tube to collect a saliva sample for testing for presence of COVID-19. This tube contains a viral stabilization fluid to prevent deterioration of the sample until testing can occur. This test will be offered for use when your child refuses to have the nasal swab test. There are risks of this new test. The tube itself is a choking hazard. The fluid inside the tube can cause harm if ingested. The fluid in the tube should not get on skin or in eyes. To prevent these risks the collection tube is designed to prevent any of this fluid from exiting the tube using a 'spill-proof' design. In addition, the study coordinators will securely hold the tube at all times and your child will not be able to ingest either the tube or the fluid.

Phlebotomy: Two methods will be used to collect blood samples. The first will be using a fngerstick and 1-2 drops of blood will be collected in a curette for serology testing. Possible complications include pain from the fingerstick, and a low risk of infection. The rationale for this intervention is to measure serum antibodies against SARS-CoV-2 using standard FDA approved testing methods. In the second method phlebotomy will collect ~4-8 cc of whole blood (except in students younger than 5 years in whom we will collect between 3-5cc). The possible complications of phlebotomy include pain, small local hematoma formation, bleeding and infection. However, this method of blood collection and testing is widely used by millions individuals daily in the United States with minimal complications, including IDD subjects. Phlebotomy will be conducted by a team specially trained in working with IDD subjects to minimize risk.

Monitoring Risk: Data from the virological and serological surveillance testing will be used to inform models of how surveillance testing in a school for IDD children, with parent/guardian consent, can be used to improve surveillance and minimize infection, given the scarce resource of COVID-19 testing reagents currently in the US. First, there is currently no NYS DOH or CDC recommended or mandated COVID-19 testing surveillance plan for such schools, and thus we do not know what the optimal testing plan is. Given this clinical/epidemiological equipoise, it is possible that the changes in testing patterns will improve detection of COVID-19 in this community. It may also be possible that such changes will not improve detection or, although we think that this possibility is very small, worsen detection rates. Given that surveillance testing is currently not standard of care for students, it is hard to conceive of how regular surveillance testing would worsen COVID-19 detection rates, especially in asymptomatic individuals.

Genetic Information Risk: While the controlled-access databases used to store data from this project will not contain information that is traditionally used to identify participants, such as name, address, and telephone number, people may develop ways in the future that would allow someone to link genetic or medical information in these databases back to. For example, someone could compare information in our databases with information from participants (or a blood relative) in another database and be able to identify them (or a blood relative). Individuals who request access to these data will have to agree not to try to identify participants or any relatives, or to contact participants or relatives. However, there is a small possibility that in the future an unauthorized attempt to identify a participant in the study could succeed. Some genetic variations can help predict the future health problems participants or their relatives. Patterns of genetic variation can be used by law enforcement agencies to identify a person or their blood relatives. Therefore, participant's genetic information potentially could be used in ways that could cause them or their family distress, such as by revealing that a participant (or a blood relative) carries a genetic disease. There also may be other privacy risks that we have not foreseen.

A Federal law, called the **Genetic Information Nondiscrimination Act (GINA)**, makes it illegal for health insurance companies, group health plans, and most employers to discriminate based on genetic information. This law generally will protect participants in the following ways:

• Health insurance companies and group health plans may not request your genetic information that we get from this research.
• Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
• This Federal law ***does not*** protect participants against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

6.2 Benefits to Subjects

Potential benefits to the subjects. This research seeks to develop new methods of adjusting surveillance testing for SARS-CoV-2 infection the prevalence of antibodies against SARS2 in a high risk and vulnerable population using FDA approved clinical tests. There are several direct benefits to research subjects and their families, including regular monitoring for asymptomatic COVID-19 infection at no charge, potential prevention of spread or infection to the Mary Cariola School and community and participants families.

Another possible benefit is the increased sense of well-being and psychological satisfaction of altruistic participation in a study to further the our understanding of, and potentially improving our understanding of COVID-19. Such motivation, and the personal satisfaction that comes with contributing altruistically to medical research, which does not directly benefit the participant, has been described in cancer and HIV trials, with similar descriptions for bone marrow donation. We will also provide each subject and their parent/guardian with their test results (if positive), and an explanation of what this means.

Definition, Collection and Reporting of Adverse Events (AEs), Serious Adverse Events (SAEs) and Unanticipated Problems (UPs)

Identification of Adverse Events and Serious Adverse Events

Athough this study is not testing a drug, device or biologic, and all testing methods are NYS and/or FDA approved, we will adhere to the Food and Drug Administration definition of adverse

events, serious adverse events, and unanticipated problems. In addition, we will adhere to the Office of Human Subjects Research Protections (OHRP) reporting requirements.
 Adverse Event Definition: An AE will be defined as “Any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the study intervention.” Examples of adverse events in this study could include bruising or bleeding at a phlebotomy site, phlebotomy site infection, bleeding from a nasal swab, mild injury due to subject agitation during the study procedures (e.g. bruise on a leg from increased agitation). In addition, in our experience during previous studies, the use of specially trained personnel to perform such minimal risk procedures results in phlebotomy and similar minimal risk procedures being extremely well tolerated by IDD children.

 Serious Adverse Event Definition: An SAE will be defined as “Any adverse event that results in death, immediately life threatening conditions, hospitalization, persistent or significant disability or incapacity.” The study procedures in this proposal are generally classified as *minimal risk , and thus we do not anticipate serious adverse events.* In the IDD population, examples of possible SAEs could include unexpected death or hospitalization in a study participant.

 COVID events – This is a surveillance study, and it is expected that some subjects will become COVID-19 positive. This rate may be high depending on the local indicence of new COVID-19 cases. Thus, we will use the following schema for defining COVID-19 AEs and SAEs
- *COVID-19 PCR positive No Adverse Event* – asymptomatic, resulting in only quarantine. This will not be reported as an AE or SAE.

- *COVID-19 PCR positive Adverse Event* – resulting in changes in medical therapy, COVID-19 specific outpatient therapy, prolonged interval with positive test results (>30 days after initial test or symptoms).

- *COVID-19 PCR positive Serious Adverse Event* – resulting in hospitalization, life threating conditions (e.g. hypoxia, intubation), significant new disability or incapacity (e.g. new lower functional status with no recovery, new oxygen requirement), or death.

- *Unanticipated Problems Definition:* We define UPs as any event that meets *all* of the following criteria: **(1) It is *unexpected*** (in terms of nature, severity, or frequency) given (a) the research procedures in the protocol documents, such as the RSRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; **(2) It is related or possibly related to participation in the research** (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and **(3) suggests that the research protocol places subjects or others at a greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

Reporting of Adverse Events:
Adverse Events and Unanticipated Problems will be reported as follows:
 Responsibility for Reporting Events: The PIs will be responsible for reporting any AE, SAE, or UP to the University of Rochester Humans Subjects Review Board and the COV-IDD Data Safety Monitoring Board within 5 days of the event. They will be assisted by the study coordinators. Any SAE must be reported to the RSRB within 24 hours.

 Reporting to the NIH Study Sponsor: Dr. Foxe, as the Communicating PI, will be responsible for timely reporting of any AE, SAE or UP to the National Institutes of Health through the Program Officer, and any other required governmental reporting

 COVID-19 Infection Reporting: Dr. Nicole Pecora will report any positive COVID-19 RT-PCR testing to the NYS Department of Health. As these tests are clinical tests, this reporting is mandated and occurs automatically 4 time daily.

6.3 Alternatives to Participation

7. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

There is a well-established secure data management approach using LabKey that links to REDCap as described in the application. Access to identifiable data will be limited to selected members of the study team

Participant identities will be kept confidential unless safety concerns necessitate unmasking some or all data.

We employ a state-of-the-art data management system (BLIS) (Figure 1) that is ideally suited to managing and integrating clinical study data with biospecimen records and customized modules for high-throughput assays data (primary and derived results). BLIS is a customized instance of the open-source LabKey Server an application developed to integrate, analyze, and share biomedical research data, including Luminex®, ELISpot, rt-PCR and specimen inventory. Specific scientific applications and workflows are added on top of the basic platform and leverage a data processing pipeline, managing raw experiment files and derived datasets generated from computational tools.

REDCap (Research Electronic Data Capture): REDCap is a secure, web-based platform for structured data capture providing real time validation rules (with automated data type and range checks) at the time of data entry with complete transaction audit logs.[6] It has tools for sending notifications to study team members when a patient has completed a study visit which improves communication between the clinical site and the labs. The proposed COV-IDD data management team has in depth experience utilizing REDCap to design and implement customized electronic data capture (EDC) solutions. REDCap servers are housed in the University's Primary Data Center and all web-based information transmission is encrypted. REDCap is available free of charge to the UR CTSI through the REDCap Consortium and is widely used for research studies and trials. Currently, over 3100 institutional consortium partners from 126 countries use REDCap.

Ripple (RippleScience.com): Ripple is a participant recruitment and management software initially developed at the University of Michigan to serve the needs of academic investigators. It closes a gap left by existing tools by providing investigators a centralized web interface to manage all aspect of recruitment and post-enrollment tracking of participants for clinical, translational, and social science studies. Its toolset includes multi-study calendaring and protocol event tracking, automated reminders and recruitment metrics. Ripple is HIPAA-compliant through a BAA with the University of Rochester.

Data Analysis and High-Performance Computing

In order to enable High Performance Computing (HPC) and Data Analysis, the COV-IDD systems and researchers integrate with the Center for Integrated Research Computing (CIRC)

BHWARD. BHWARD is a specialized, FISMA compliant, HIPAA secure, high-performance computing environment designed and built to work with legally restricted data. All research data is kept quarantined from different projects through controlled resource allocation methods. All project data are kept segregated through independent tablespace allocations, appropriate access rights, and encryption.

Long-term Data Storage and Archival

To enable the long-term storage and archival of large-file data, the COV-IDD has partnered with the Research & Academic IT group for use and expansion of SMD-NAS, a Dell-EMC Isilon scale-out storage system which is detailed in the Administrative Core DMP.

Research & Academic IT provides a broad range of IT services and is committed to meeting the technology needs of the University of Rochester community including desktop support, application management, and Information Security for the University of Rochester School of Medicine and Dentistry including other affiliated organizations.

Due to the provision of these systems, no long-term data storage or archival is necessary within individual cores or labs. This provides additional safeguards from the need for diverging management procedures and ensures proper backup, encryption and security methods are inherited without additional effort.

Data will be encrypted and electronically sent to Duke Clinical Research Institute at Duke University. They are serving as the NIH-funded Coordination and Data Collection Center (CDCC).

Data Security and Safety

All systems across the University, including instruments, require user authentication against the URMC-managed Active Directory. External users, including sponsors gain access to these systems via creation of URMC guest accounts obtained from University IT. The COV-IDD Data Management Committee, will setup templates for study team user roles and permissions which can then be implemented by the Protocol PI and the study delegation log as detailed in the Administrative Core DMP.

The University also has an extensive intrusion detection, firewall and centralized logging system. External collaborators that require access to specific data paths have their access and systems assessed to ensure the encryption both in-transit and at-rest and safe handling of any data they may have access to.

8. RESEARCH INFORMATION IN MEDICAL RECORDS

No research data will be included in the subject's medical record for this study.

9. DATA ANALYSIS AND DATA MONITORING

Data Safety Monitoring

The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis and for reporting Serious Adverse Events and Unanticipated Problems to his or her Institutional Review Board (IRB), the NIH Program Officer and the Data Safety Monitoring Board

as required. The study coordinator and the statistician (Dr. Dongmei Li) prepares reports that list adverse events, serious adverse events, deaths, and disease- specific events required for monitoring body review in order to ensure good clinical care and identify any emerging trends. The Data Safety Monitoring Board (DSMB) will act in an advisory capacity to to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

Frequency of Data and Safety Monitoring
The PI will be informed of serious adverse events as soon as they occur by the study coordinator and will notify the RSRB, NIH Program Officer, and the Data Safety Monitoring Board (DSMB) within 48 hours of becoming aware of the event. The PI will report the Serious Adverse Events and Unanticipated Problems the RSRB within 5 business days of becoming aware of the event, according to local RSRB requirement. Specific triggers for an ad hoc review or initiation of the process of an ad hoc review will occur if there are unforeseen deaths or the threshold for SAE has been met.
Safety reports are sent to the Data Safety Monitoring Board twice a year and will include a detailed analysis of study progress, data and safety issues.

Content of Data and Safety Monitoring Report
The study report will contain the following documents and tables:
 Actual versus expected enrollment table, including a CONSORT diagram.

 Table of testing results, including number of tests per student or staff member, testing outcome (positive, negative) for both Serology and RT-PCR

 Table of aggregate adverse events, deaths, and unanticipated problems

 Demographic data will include sex, ethnicity, race, education and age and will be stratified by site.

 Table of expected and missing visits, time points, and tests

 Table of protocol deviations

Monitoring Body Membership and Affiliation
The following individual(s) has/have accepted position(s) as part of the Data Safety Monitoring Body (DSMB). DSMB membership will be reviewed and approved by the University of Rochester Research Subjects Review Board (RSRB). Should there be any questions regarding the independence of the DSMB it will be addressed and corrected if necessary.
Michael Keefer MD (Chair)
Chief – Division of Infectious Diseases
University of Rochester Medical Center
Ann Francis MD
Chief Medical Officer
Mary Cariola Center
Nancy Bennett MD MPH
Director – Center for Community Health and Prevention
University of Rochester Medical Center
Brenda Tesini MD
Associate Hospital Epidemiologist - URMC Adult and Pediatric Division of Infectious Diseases
University of Rochester Medical Center

The Independent Monitors for this study, Dr. Michael Keefer (Infectious diseases, clinical trials, vaccine studies), Dr. Ann Francis (pediatrics), and Dr. Nancy Bennett (epidemiology infectious diseases expertise) are not associated with this research project and thus work independently of the PIs, Dr. Foxe, Dr. Pecora, and Dr. Dewhurst. They not a part of the key personnel involved in this grant, and are qualified to review the patient safety data generated by this study because their unique expertise in the area of infectious diseases, epidemiology, and pediatrics. Dr. Tesini is the hospital epidemiologist and will be advising on infection control issues.

Conflict of Interest for the DSMB Members
Monitoring body members should have no direct involvement with the study investigators or intervention. Each member will sign a University of Rochester Conflict of Interest Statement which includes current affiliations, if any, with any steering committees or advisory councils associated with the study, pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial or non-commercial interests pertinent to study objectives.

Protection of Confidentiality
Only deidentified and/or masked data will be presented during the open sessions of the DSMB. All data, whether in a report or discussed during a DSMB meeting are confidential. Participant identities will be kept confidential unless safety concerns necessitate unmasking some or all data.

Monitoring Entity Responsibilities
The responsibility of the Monitoring Board will include:
 Reviewing the research protocol, Data and Safety Monitoring Plan (DSMP), and informed consent documents, proposed revisions.

 Evaluating the progress of the study on an ongoing basis including periodic assessments of data quality, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect the outcome.
 Considering the impact of factors external to the study when new information, such as scientific or diagnostic developments becomes available that may affect safety of participants, their willingness to participate in the study or the ethics and conduct of the study.

 Reviewing Unanticipated Problems, Serious Adverse Event.

 Reporting any problems with study conduct or performance to the UR Research Study Review Board.

 Ensuring the measures to ensure the confidentiality of study data and results are appropriate.

 Reviewing and evaluating requests for protocol modifications/amendments.

 Reviewing before study initiation the stopping rules and plans for interim analyses presented in the protocol. These plans outline the conditions under which a study may be stopped (e.g., difficulties in recruitment, retention, obtaining outcome measures or other issues).

 Reviewing the interim analyses and/or accumulating data at the specified interval(s), and as appropriate and make a recommendation to continue, terminate or modify the study based on observed benefit or harm in accordance with the planned stopping rules.

10. REFERENCES

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