ANCILLARY REVIEWS

DO NOT DELETE. Submit the completed checklist below with your protocol.

Which ancillary reviews do I need and when do I need them? **Refer to HRP-309 for more information about these ancillary reviews.**			
Select yes or no	**Does your study…**	***If yes…***	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette Children's Specialty Healthcare resources, staff or locations?	*Gillette Scientific Review and Gillette Research Administration approval is required.* *Contact: research@gillettechildrens.com*	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☒ **Yes** ☐ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*Fairview approval is required.* *Contact: ancillaryreview@Fairview.org*	
☒ **Yes** ☐ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*If required, the regulatory ancillary review will be assigned by IRB staff. Contact: medreg@umn.edu* *See: https://policy.umn.edu/research/indide*	
☐ **Yes** ☒ **No**	Require Scientific Review? Not sure? See "Does my research require scientific assessment?" in the Investigator Manual (HRP-103).	*Scientific merit must be documented prior to full committee review. HRPP-facilitated scientific review may be assigned.* *Contact: hrpp@umn.edu*	
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Completion of the CPRC application process may be required.* *Contact: ccprc@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The COI ancillary review will be assigned by IRB staff.* *Contact: becca002@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals,	*Complete the AURPC Human Use Application.*	**Approval from these committees**

	external beam or brachytherapy)	*See Submission Resources for additional guidance.* *Contact: barmstro@umn.edu*	**must be received prior to IRB approval;** **These groups each have their own application process.**
☐ **Yes** ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) as a study location or MR at Masonic Institute for the Developing Brain (MIDB) as a study location?	*Complete the CMRR pre-IRB ancillary review.* *Contact: ande2445@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu.*	
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance.*	
☒ **Yes** ☐ **No**	Include use of protected health information (PHI)? OR Include international collaborators and involves the collection, transmission, and storage of health data?	*If yes, HIPCO may conduct a review of this protocol. This review will be assigned by IRB staff.* *Contact: privacy@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☐ **Yes** ☒ **No**	Include the use of a controlled substance?	*If yes, University Health and Safety Compliance for controlled substances will review the protocol.* *Contact: cshelp@umn.edu*	
☐ **Yes** ☒ **No**	Use data from CTSI Best Practices Integrated Informatics Core (BPIC), formerly the AHC Information Exchange (IE)?	*The CTSI Best Practices Integrated Informatics Core ancillary review will be assigned by IRB staff.* *Contact: bpic@umn.edu*	
☒ **Yes** ☐ **No**	Plan to use CTSI Monitoring services, and/or have an IND, IDE, or designated NSR-IDE by the UMN IRB?	*The CTSI monitoring ancillary review will be assigned by IRB staff.* *Please note eligibility criteria here.* *Contact: fencl003@umn.edu*	

☐ **Yes** ☐ **No**	Use histology or procurement support from Biospecimen Support, formerly Biorepository and Laboratory Services (BLS) or Bionet?	*The Biospecimen Support ancillary review will be assigned to your study by IRB staff.* *Contact: bionet@umn.edu*	
☐ **Yes** ☒ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned.* *For assistance with registration or record updates, contact ctgovumn@umn.edu for non-oncology studies or dsg1@umn.edu for oncology studies.* *Contact: fencl003@umn.edu*	
☐ **Yes** ☒ **No**	Use of student education records?	*The FERPA ancillary review will be assigned.* *Contact: ande8670@umn.edu*	
☐ **Yes** ☒ **No**	Include collaborations with Tribal partners, Tribal communities, Tribal-serving institutions, or include focused recruitment of Indigenous Peoples?	*The Office of Native American Affairs ancillary review will be assigned.* *Complete the Form for Ancillary Indigenous Research (Must Download).*	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned by IRB staff.* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**
☐ **Yes** ☒ **No**	Propose use of eConsent process that captures electronic signatures of participants?	*The REDCap Ancillary Review will be assigned to confirm IRB approval status prior to moving your eConsent to production in REDCap.* *Contact: redcap@umn.edu*	
☐ **Yes** ☒ **No**	Propose to use Community-University Health Care Center (CUHCC) resources or include access to patients or their data?	*The CUHCC ancillary review will be assigned.* *Contact: hlogren@uumn.edu*	

PROTOCOL COVER PAGE

Protocol Title	Vocxi Breath Analyzer Study
Principal Investigator/Faculty Advisor	Name: Gwen Fischer
	Affiliation: ☒UMN ☐ Fairview ☐ Gillette
	UMN Home Department: Pediatric Critical Care
	UMN Home Dept ID: 11845
	Telephone Number: 612-625-6678
	Email Address: fisch662@umn.edu
Scientific Assessment	I believe Scientific Assessment is not required.
IND/IDE # (if applicable)	N/A
IND/IDE Holder	N/A
Sponsor-Investigator: Please check box	☒ This study will comply with ICH GCP requirements for drugs, biologics, and devices.
Investigational Drug Services # (if applicable)	N/A
Version Number/Date:	Version 1, 02Jun2026

REVISION HISTORY

Describe changes made to the protocol after initial approval.

Revision #	Version Date	Summary of Changes	Consent Change?

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ABBREVIATIONS/DEFINITIONS

- ARI = Acute Respiratory Illness
- CDC = Centers for Disease Control and Prevention
- DNA = Deoxyribonucleic acid
- ED = Emergency Department
- ESI = Emergency Severity Index
- IDDL = Infectious Disease Diagnostic Lab
- PGCoE = Pathogen Genomics Center of Excellence
- POC = Point of Care
- VOC = Volatile Organic Compound
- UMMCH = University of Minnesota Masonic Children's Hospital
- MBP® = MyBreathPrint
- rRNA = Ribosomal ribonucleic acid

1.0 Objectives

1.1 Purpose:

The purpose of this pilot his study is to assess if the My Breath Print (MBP®) System can distinguish between pediatric participants with upper or lower respiratory tract infections and healthy controls.

MBP uses graphene-based nano sensors and machine learning based algorithms to detect volatile organic compounds (VOCs) produced by the body in a person's breath that correspond with specific diseases. The device is a handheld breath sensor (see figure 1) attached to a mask that the patient can breathe into. The MBP system has been initially designed to detect cancer cells, but early research shows it may also be able to distinguish VOC patterns between different infectious diseases. The University of Minnesota is currently studying this device to determine if it can help diagnose adult sepsis *(IRB STUDY00020721)* through breath VOCs. This pilot study will focus on pediatric respiratory infections.

2.0 Background:

2.1 Significance of Research Question/Purpose:

Pathologic conditions such as cancer or infections induce localized changes in the metabolism of diseased tissue. This changes the levels and composition of volatile organic compounds (VOCs) that are released from tissues and removed from the body during gas exchange in the lungs1. The totality of these metabolic changes is disease specific; in other words, different infections and different diseases will generate distinct patterns of VOCs2. The challenge is having a detector that is sensitive enough to identify these VOCs in parts-per-million to parts-per-billion scale.

There is evidence to support that the mixture of gases in exhaled breath can be related to a disease state (3). However, most of the work related to breath sampling has been done by collecting samples that require analysis in centralized laboratories using mass spectrometers that are not well suited to POC testing(4). In addition, the various methods used for sample collection, preservation, and transportation can impact accuracy and reproducibility, and centralized testing can take several days to complete. The MBP® System has solved each of these issues by using novel nanomaterial sensors that allow real-time POC analysis. This breakthrough technology integrates 40 sensors tuned to several different families of VOCs, creating a cross-reactive array that can sense small concentrations of VOCs in exhaled breath in real time. More specifically, the MBP® System provides a complete picture of the families of VOCs that are present in a breath sample, generating unique patterns or "breath prints" that are assigned to particular disease states, achieving clinically meaningful sensitivity, specificity, and predictive values through evaluation of these patterns using artificial intelligence. Overall, the MBP® System has the potential to deliver accurate and reproducible results in less than 5-10 minutes once an infrastructure of data flow and analysis has been constructed.

2.2 Preliminary Data:

Two independent studies have established performance metrics for the MBP® System. The first study used the earliest prototype to evaluate the potential of breath sensing to classify 23 pet dogs into "unaffected" and "heart failure" groups. The sensitivity and specificity of canine breath prints to achieve this classification was >83% and >90%, respectively.

A second study (*STUDY00001834, PI Roy Cho MD, approved 05/07/2018*) used the current and improved MBP® System to categorize two independent cohorts of 40 human subjects each (total sample size = 80) into "unaffected" and "lung cancer" (stages I-IV, small cell and non-small cell) groups. The MBP® System successfully captured breath and output useful data in 79/80 subjects (one failed due to a power loss to the system during the test). Distinct signal patterns were observed for the lung cancer and unaffected groups in both cohorts, which could be trained to achieve classification accuracies approximating 100%. Altogether, our data indicate that the MBP® System can detect distinct breath prints associated with diseases within and outside the lungs. This supports its potential for broad diagnostic applications and provides confidence for the use of breath prints as a rapid screening test for subjects with sepsis.

An adult human study is underway at UMMCH to determine whether MBP® System can identify patterns of sepsis in adult patients (*Early Detection of Volatile Compounds for Rapid Detection of Sepsis: Pilot Study, PI Dr. Sameh Hozayen (IRB STUDY00020721).*

In addition, a bench test of a variety of fungal and bacterial ex vivo samples were completed at Dr. Thielen's lab using the MBP® System showed promise in identifying varying VOC patterns between controls and different pathologic species.

2.3 Existing Literature:

Bacterial species are identified in the clinical laboratory by morphological traits and biochemical and cultural tests and more recently through a specific gene, rRNA fingerprinting, and whole DNA sequence (5). The chemical release of metabolites and VOCs represent a good alternative for the analysis of bacterial species from the clinical specimen and application in different areas. A disease is characterized by dysfunction of one or multiple organs and systems in response to impartment of host immune response to microbial infection and can be caused by various pathogens that escaped from local sites and entered the blood, causing a systemic infection (6). Diverse and dynamic bacterial communities live in the upper and lower respiratory tracts (7,8). The expected partial overlap is a critical determinant of why rapid POC tests evaluating early profiles of infection and response must consider multiple parameters, or "disease signatures," rather than single analytes.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

Aim 1:

Primary Hypothesis:

The MBP® System can reliably collect breath samples containing measurable VOC profiles from pediatric participants with acute upper or lower respiratory infections and from healthy pediatric controls demonstrating acceptable performance and functionality in a pediatric clinical setting.

Endpoints:

1) Successful collection of breath samples from pediatric patients using the MBP collection device.
2) Breath samples collected via MBP device will have measurable VOC signals

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

Aim 2:

Secondary Hypothesis:

Breath samples collected from the MBP system from pediatric participants with signs or symptoms of respiratory infection contain unique VOC signatures that are not present in healthy controls

Endpoint:

Comparison of VOC chemical signals from pediatric patients in the healthy controls vs pediatric patients with respiratory infection

Exploratory Hypothesis:

Breath samples from pediatric participants with bacterial or viral respiratory infection contain unique VOC signatures that differentiate different types of respiratory infection, and can be identified using the MBP® System.

Endpoint: Identification of different VOC chemical signals collected from patients with the MBP® system associated with specific infectious agents confirmed by testing done in the course of clinical care, such as RSV, influenza, strep pneumonia. VOC signatures collected with the MBP system will be compared to any positive samples patients have in the course of their care that indicates a specific infection. VOC signals will be compared to patient bacterial or viral nasal or oral swabs, sputum cultures and gram stains, blood cultures, pulmonary imaging results completed as part of clinical care in the Emergency Department.

4.0 Study Intervention(s)/Investigational Agent(s):

4.1 Description:

The breath sensor-complex integrated device (BSCID) system consists of a single use MBP® Breath Analyzer connected to a secure and dedicated study mobile phone with the Vocxi app. A mask is directly connected to the MBP® Breath Analyzer (Figure 3). The array is electrically connected to the reader with an isolated surface that is not exposed to the breath sample (Figure 1). The subject applies the mask and breaths normally for 1 minute to provide the necessary data (Figure 2). The process is simple and very easy to train health care providers to use. The mask is disposed of after the test. The MBP® Breath Analyzer will be returned to Vocxi Health if not used within 90 days. The MBP® Breath Analyzer is small and highly mobile.

Figure 1 MyBreathPrint® System



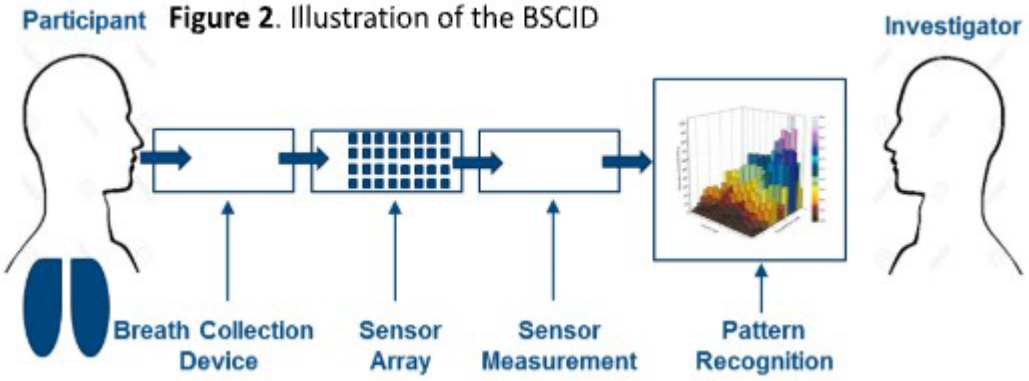
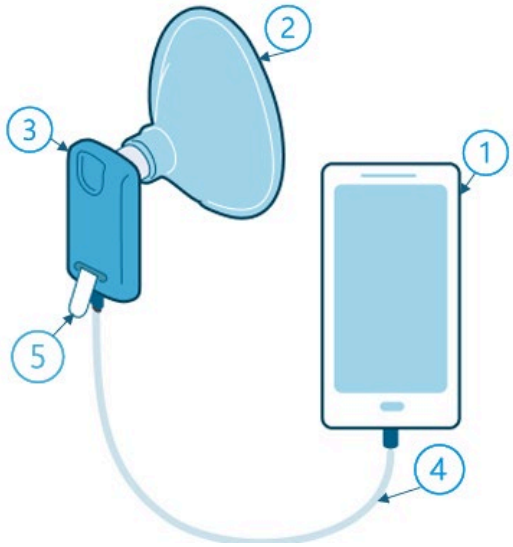


Figure 3. Device-participant setup. 1. secure dedicated mobile phone. 2. Breathing mask. 3. MBP device 4. USB-C cable 5. Pull tab that covers sensor until use



The use of the MBP® Breath Analyzer in the proposed protocol is non-significant risk (NSR) as it does not meet any criteria to be considered significant risk per 21CFR812.3(m), based on that the device:

1. is not intended as an implant
2. is not for supporting or sustaining human life,
3. does not otherwise present a potential for serious risk to the health, safety, or welfare of subjects.

In addition,

1. The device is not banned by the FDA
2. The study will comply with abbreviated IDE regulations for monitoring of device studies, as well as for recordkeeping and reporting and the device(s) used in the study will be labeled in accordance with 21 CFR 812.5. See ETHOS form HRP-1899 for further information on sponsor-investigator requirements and compliance.
3. The investigator will not market or promote the device
4. It's use will be used for research only and not used to determine clinical care outcomes, such as diagnosing, curing, mitigating, or treating disease
5. The device is non-invasive and will not administer any drug, biologic, or other substance to participants.

More information on mitigation of risk to the use of the device may be found under section 12.0. Along with that the study team will ensure that consent for use of the device will be conducted in accordance with protocol section 22.0.

4.2 Drug/Device Handling:

The MBP® System is a class II medical device and meets the conditions for an abbreviated IDE as a non-significant risk device (NSR). The study device will be clearly marked as "Research Only" with study staff contact information. The research team will store investigational devices in a locked cabinet in our administrative offices and transport the devices during all recruitment and enrollment time periods. The devices will be returned to the company if not used within 90 days due to sensor expiration.

4.3 Biosafety:

The research does not involve recombinant or synthetic nucleic acid molecules (r/sNA; RNA, DNA) or biologically derived toxins. Specimens, which may contain infectious agents, will be handled according to standard protocols for human specimens.

4.4 Stem Cells: N/A

4.5 Fetal Tissue: N/A

5.0 Procedures Involved

5.1 Study Design:

This is a prospective observational pilot study, evaluating VOC signals collected with the MBP device. VOC signals from pediatric patients with signs and symptoms of respiratory infections being seen in the Emergency Room will be compared to VOC signals from healthy pediatric controls being seen in the Emergency Room for minor injuries.

5.2 Study Procedures:

Study staff will obtain informed consent and assent from pediatric study participants aged 7-17 who are in the Masonic Children's Hospital Pediatric Emergency Department.

Up to 20 pediatric participants will be enrolled: 10 pediatric participants with clear clinical signs of respiratory infectious disease and up to 10 pediatric participants being seen for non-infectious concerns (minor traumas such as sprained ankles). For this study, we will use the Centers for Disease Control and Prevention's (CDC's) case definition of an acute respiratory illness (ARI), which is two or more of the following signs or symptoms: fever, cough, runny nose, nasal congestion, or sore throat.

Study staff will assist the participant with holding the MBP® Breath Analyzer mask in place to collect data. The device will notify the user that a baseline air sample is being taken. After the baseline data has been collected, the user will be instructed to practice exhaling into the device. Once the user feels comfortable to perform the official exhale, the mobile app will prompt the user to remove the pull tab from the device. If needed, the mask can be temporarily removed while pulling the tab, before replacing the mask and resuming breathing as instructed. The user will place and hold the mask tightly over their nose and mouth and breathe normally. Participants will be advised to inhale normally through the nose and exhale through the mouth, if possible. The participant will breathe into the

collection device for 1 minute at normal resting respirations, exposing the sensors to the breath gas mixture.

Data from the sensors is sent directly from the MBP device to a dedicated, secure study phone that contains Vocxi's proprietary app. After breathing into the device, the study visit will be complete. Participants will be given a parking voucher for as a thank you for their time. The VOC signals are then uploaded from the phone to Vocxi's secure web portal using a unique UMN team login and password. Patient VOC signals only will be uploaded to Vocxi's web portal will be accompanied only by a study patient ID (ex. UMN-001). VOC signals will be analyzed with proprietary software that uses artificial intelligence to recognize unique patterns in the VOC signals. Comparison of VOC signals to clinical data will occur in concert with the UMN study team. All patient data other than patient study number will remain with the UMN study team and non-phi data will be shared under a data use agreement with Vocxi.

Viral swabs and other infectious samples collected during the ED visit or within 72 hours of a subsequent hospital admission will be submitted to the Infectious Diseases Diagnostic Laboratory (IDDL). Once routine clinical testing has been completed, IDDL staff will transfer any residual specimen into a collection tube with the participant study ID and the date of collection. IDDL staff will notify Dr. Thielen's lab that specimens are available for research testing. Specimens will undergo subsequent next-generation sequencing in the Thielen lab to identify potential respiratory pathogens using procedures similar to those employed for pathway D specimen collection (*STUDY00019522: PGCoE Respiratory and Antimicrobial Resistance Surveillance*).

Research staff will conduct a chart review to collect information from participant's medical record on demographics and clinically relevant data. These data will include, symptoms, onset of symptoms, chest x-ray findings related to possible infections, sputum/other culture results, hospital length of stay (LOS), age, sex, BMI, ethnicity, home medications, medications given in the ED, home medications, primary diagnosis in the ED. This information from the participants medical record will be entered into a REDCap database. The healthy control group will consist of pediatric patients who are being seen in the Emergency Department for a minor injury such as a sprained ankle, with no respiratory symptoms. Initial chart review for study screening will be the same. Age, sex and BMI will be recorded as well as primary ED diagnosis. They will undergo the same MBP device procedure. No clinical specimens will be tracked. Patients who are getting admitted to the hospital for any reason will be excluded as controls from the study.

5.3 Study Duration:

Each individual's participation will only be about 45 minutes, including time for consenting and obtaining the breath sample. We anticipate it will take up to 6 months to enroll all study participants.

5.4 Follow-Up: N/A

5.5 Use of radiation: N/A

5.6 Use of Center for Magnetic Resonance Research: N/A

5.7 Development, Testing, or Deployment of Artificial Intelligence:

The MBP® System provides a complete picture of the families of VOCs that are present in a breath sample, generating unique patterns or "breath prints" that are assigned to particular disease states, achieving clinically meaningful sensitivity, specificity, and predictive values through evaluation of these patterns using artificial intelligence (AI). VOC signal data will be analyzed using Vocxi Health's proprietary AI pattern recognition software. Exploratory analyses will be performed to identify VOC patterns that may distinguish participants with acute respiratory infections from healthy controls. AI is being used for pattern recognition and is not connected to any network.

6.0 Sharing of Results with Participants

6.1 Sharing Results: No research data or results will be shared with participants

6.2 Sharing Genetic Results: N/A

7.0 Study Population

7.1 Inclusion Criteria:

Acute Respiratory Illness (ARI) Group:

- Age 7-17
- Able to participate in study procedures including breathing comfortably into the MBP® Breath Analyzer for 1 minute
- Meets case definition of an acute respiratory illness (ARI), which is two or more of the following signs or symptoms: fever, cough, runny nose, nasal congestion, or sore throat.

<u>Control Group:</u>

- Age 7-17
- Able to participate in study procedures including breathing comfortably into the MBP® Breath Analyzer for 1 minute
- Does not have symptoms of an acute respiratory illness (ARI)
- Has not had symptoms of an ARI within the past month per parent or patient report

- Being seen for a minor injury (example: ankle sprain, laceration) with plan to discharge from Emergency Room.

7.2 Exclusion Criteria:

Acute Respiratory Illness (ARI) Group:

- Unable to comfortably breathe normally into the MBP® Breath Analyzer for 1 minute
- Has eaten in the 30 minutes prior to use
- Has smoked in the 2 hours prior to use
- Primary diagnosis or parent concern in the Emergency Department is asthma or reactive airway disease
- History of or current cancer of any kind
- Current smoke inhalation injury
- Current concern for a drowning event
- Current concern for a drug overdose
- Requiring oxygen in the Emergency Department
- Current Tracheostomy in place

Control group:

- Unable to comfortably breathe normally into the MBP® Breath Analyzer for 1 minute
- Has eaten in the 30 minutes prior to use
- Has smoked in the 2 hours prior to use
- Primary diagnosis or parent concern in the Emergency Department is asthma or reactive airway disease
- History of or current cancer of any kind
- Current smoke inhalation injury
- Current concern for a drowning event
- Current concern for a drug overdose
- Requiring oxygen in the Emergency Department
- Current Tracheostomy in place

7.3 Screening:

Pre-screening will occur by the study staff through review of clinical care records of the unit, based on the relationship of the investigator team as a treating clinicians of this patient population. Only minimal information will be reviewed in order to determine necessary approach for consent. The study PI or co-investigator will confirm eligibility prior to enrollment. Any patient chart indicting research opt-out will not be approached.

Patients presenting to the emergency department are triaged and assigned a score called an emergency severity index (ESI). Scores of 1 or 2 indicate life threatening emergencies or high risk medical conditions. Scores of 3, 4, and 5 indicate that patients are stable, needing care with varying levels of urgency. ESI is charted in the medical records, and will be reviewed as part of prescreening. We will not approach patients with ESI scores of 1 or 2.

8.0 Vulnerable Populations

8.1 Vulnerable Populations:

Population / Group	**Identify whether any of the following populations will be focus of the research (targeted), included, but not necessarily the focus or excluded from participation in the study.**
Children	Primary focus of the research
Pregnant women/persons	included but not the focus
Fetuses	Excluded
Neonates	Excluded
Prisoners	Excluded.
Adults lacking capacity to consent and/or adults with diminished or fluctuating capacity to consent	Excluded
Non-English speakers	Excluded
Those unable to read (illiterate)	included but not the focus
Employees of the researcher	included but not the focus
Students of the researcher	included but not the focus
Undervalued or disenfranchised social group	included but not the focus.
Active members of the military (service members), DoD personnel (including civilian employees)	Excluded.

Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	included but not the focus
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	included but not the focus
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	included but not the focus
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Excluded
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Excluded

8.2 Additional Safeguards, if any, to ensure inclusion is appropriate:
Children: Children aged 7 to 17 are the included population to meet the objectives of this protocol. Refer to section 22.5 of this protocol for information on the obtaining of child assent (if applicable) and parental permission. Dissent will be honored. Child Life Services may be offered and used during visits to aid the child is care during study procedures.

Pregnant women/persons: Based on eligibility criteria, pregnant women/persons may participate in this study. If at any time during recruitment or consent the parent/guardian and/or study team believes there is undue stress or concerns for continuation of the discussion, it will be ceased at that time. The parent/guardian will be offered an opportunity to have the study team return at a more appropriate time (if able, per eligibility time requirements) or may decline of participation.

Those unable to read (illiterate): If it is made known to us that the parent or guardian is illiterate, we will take extra care to go through the consent form and read it to the potential participant. An unbiased witness (non- study team member) will be present during the consent process and at signing to attest that the consent form was described accurately and consent was given. The parent may make their “mark” on the consent document, along with obtaining the witness signature on the form in order to have

documented compliance with the consent for child's participation. If future visits require completion of study materials (e.g. questionnaire), the study team will read the questions to the parent/guardian, having them make their mark on the appropriate question. An unbiased witness may be present to attest that the questions were read to the parent/guardian and accurately documented.

Employees of the researcher: If the participant is an employee of the researcher is eligible for the study, a member of the study team who does not have an employment relationship with the participant will obtain consent. They will be reminded at the time of consent that study participation is voluntary and whether or not they participate will not affect their employment or relationship with the PI.

Students of the researcher: If the participant is a student of the researcher is eligible for the study, a member of the study team who does not have an relationship with the student will obtain consent. They will be reminded at the time of consent that study participation is voluntary and whether or not they participate will not affect their employment or relationship with the PI.

Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.:

Due to the critical nature of the patient's condition, and therefore eligibility in the study, the child/family may need be approached during a stressful time, e.g. in the emergency department. All precautions for approaching the parent(s) will be taken, ensuring that communication with the clinical care team is in place to ensure that the current condition is appropriate for meeting with the child/family. A private location will be offered for the family to speak with the research team. All appropriate measures for consent will be taken, as outlined in section 22 of this protocol. If at any time during recruitment or consent the parent/guardian and/or study team believes there is undue stress or concerns for continuation of the discussion, it will be ceased at that time. The parent/guardian will be offered an opportunity to have the study team return at a more appropriate time (if able, per eligibility time requirements) or may decline of participation.

For all other "included by not the focus" population/groups listed above: The vulnerability of the individual participant/parent/guardian/LAR may not be known when approaching for participation. In addition, no direct questions will be asked that would reveal such status. Therefore, parents/children may meet this vulnerable population but may not be known to the research staff. The study team will follow all appropriate procedures from obtain consent, which includes the assurance that participation is voluntary and will not have any impact on the care they/their child receives."

8.3 Rationale for exclusions in the table above if the research has the potential for direct benefit: There is no potential for direct benefit to participants.

9.0 Number of Participants at this Site

9.1 Number of Participants to be Consented by Researchers at this Site: Up to 20

10.0 Local Recruitment Methods

10.1 Recruitment Process:

Participants will be recruited through the UMMCH ED. Initial contact with potential participants will be made by the PI, Co-I, or study coordinator. We will refrain from approaching patients who have opted out of research.

10.2 Recruitment Materials: N/A

10.3 Payments: Participants will receive a parking voucher valued at $15

10.4 Recruitment Barriers and Challenges:

Recruitment in a pediatric emergency department setting presents inherent challenges due to variability in patient volume and eligibility, which limits the ability to conduct targeted outreach. Enrollment is dependent on real-time identification of eligible patients during their ED visit. Additional barriers include the need to ensure patients are medically stable and able to participate in study procedures, as well as time-sensitive clinical care priorities that may limit recruitment opportunities. Families may also experience increased burden during acute care visits, which could influence willingness to participate.

10.5 Recruitment Monitoring and Mitigations plans:

No explicit monitoring and mitigation plans are expected. Participant recruitment and demographic details (e.g., race, ethnicity, gender, socioeconomic status) will be monitored through REDCap. These metrics will be evaluated through regular reviews. If recruitment differs significantly from anticipated goals, the study team will evaluate potential barriers such as eligibility constraints, outreach limitations, or workflow challenges in the ED setting. Adjustments may be made as needed, such as refining screening procedures, modifying recruitment workflows, or engaging additional clinical staff to support identification of eligible participants. Recruitment strategies will be reviewed to ensure equitable engagement of all eligible participants.

11.0 Withdrawal of Participants

11.1 Withdrawal Circumstances: Participants can voluntarily withdraw from the study at any time. An investigator may discontinue a participant from the study for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- If they behave inappropriately toward study staff;
- or it is in their best interest, as determined by the PI.

11.2 Withdrawal Procedures: To withdraw from the study, patient and/or parent can notify the study team based on contact information listed on the consent form. If a patient wishes to withdraw or we determine that the participant should be withdrawn, we will stop any future data collection but will keep the data that has already been collected.

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

11.4 Identify Potential Barriers to Ongoing Participation – Retention Monitoring and Mitigation Plans: N/A

12.0 Risks to Participants

12.1 Foreseeable Risks:

Forseeable risks include minor discomfort from wearing and breathing into the mask; possible lightheadedness or fatigue; emotional discomfort or stress (especially given the ED setting). There is a risk that data security could be compromised and loss of confidentiality could occur. Our team will mitigate this risk by using UMN Box secure storage and limiting data access to only members of the approved study team

12.2 Reproduction Risks: N/A

12.3 Risks to Others: N/A

13.0 Potential Benefits to Participants:

There is no direct benefit to participating in this research study.

14.0 Statistical Considerations

14.1 Data Analysis Plan:

Data Analysis Plan

This pilot study is designed to evaluate the feasibility and performance of the MBP® System for collection and analysis of breath volatile organic compounds (VOCs) specifically in pediatric participants. Because this is an exploratory pilot study, analyses will be primarily descriptive and hypothesis-generating.

MBP® System performance will be evaluated by examining sensor responses, including minimum and maximum capacitance values and changes in capacitance and voltage following

exposure to participant breath samples. Data visualization techniques, including graphical displays of sensor output, will be used to assess signal quality and consistency across samples.

Feasibility will be assessed by determining the proportion of participants who successfully complete breath sample collection and diagnostic testing. Feasibility outcomes will be summarized overall and by participant age and weight categories to identify factors that may influence successful completion of the procedure.

VOC signal data will be analyzed using Vocxi Health's proprietary artificial intelligence and pattern recognition software. Exploratory analyses will be performed to identify VOC patterns that may distinguish participants with acute respiratory infections from healthy controls. AI is being used for pattern recognition and is not connected to any network.

Additional exploratory analyses will evaluate relationships between VOC signal patterns and microbiologic findings obtained from clinical specimens. VOC profiles will be examined across pathogen groups to identify potential associations and generate hypotheses regarding pathogen-specific VOC signatures.

Results from this pilot study will be used to assess device performance in a pediatric population, establish feasibility for children old enough to follow directions, and inform the design, endpoints, and statistical methods of future larger-scale validation studies and identify changes to software or hardware that may need to happen for a future pediatric infectious use case.

14.2 Power Analysis:

A formal power analysis will not be performed as this is a pilot descriptive study of the feasibility of VOC breath testing the diagnosis of ARI.

14.3 Statistical Analysis:

As this is a pilot feasibility study, analyses will be primarily descriptive and exploratory. No formal hypothesis testing or sample size-based power calculations are planned.

Participant characteristics will be summarized using descriptive statistics. Continuous variables will be reported as means and standard deviations or medians and interquartile ranges, as appropriate. Categorical variables will be summarized using frequencies and percentages.

To assess performance of the MBP® System, minimum and maximum capacitance values and changes in capacitance and voltage following exposure to breath samples will be summarized descriptively and displayed graphically. Data plots will be used to visualize sensor responses across participants and study groups.

Feasibility will be assessed by the proportion of participants who successfully complete breath sample collection and diagnostic testing. Completion rates will be summarized descriptively overall and across age and weight categories to evaluate potential associations between participant characteristics and procedural feasibility.

VOC signal data generated by the MBP® System will be analyzed using Vocxi Health's proprietary artificial intelligence and pattern recognition software. Exploratory analyses will be conducted to evaluate whether VOC signal patterns differ between participants with acute respiratory infection (ARI) and healthy controls. Results will be used to identify candidate VOC signatures associated with respiratory infection.

Additional exploratory analyses will assess relationships between VOC signal patterns and microbiologic findings obtained from clinical specimens. VOC features will be evaluated across pathogen groups to identify potential pathogen-specific signatures and discriminatory patterns. Given the pilot nature of the study, these analyses will be considered hypothesis-generating and intended to inform the design and statistical methods of future validation studies.

14.4 Data Integrity:

Data will be periodically reviewed by study staff for accuracy and quality control.

15.0 Health Information and Privacy Compliance

15.1 Health Care Component:

Are any research personnel working on this study part of the Health Care Component (HCC)?

☒ Yes

☐ No

15.2 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

☒ I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research: NA

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of

M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

15.3 Preparatory to Research. Please attest to one of the following statements:

☐I will only be accessing participant medical information/records for the purpose of Preparatory to Research Activities

☒ I will be accessing participant medical information/records beyond the purposes of Preparatory to Research Activities

☐ I am unsure and require HIPCO guidance to determine if the activities I am proposing are considered Preparatory to Research Activities

☐ Not applicable to this study

15.4 Identify the source of Private Health Information you will be using for your research (check all that apply):

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me.

☒ I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☒ I will pull records directly from EPIC.

The research investigators or appropriate study team member will conduct a manual review of charts in EPIC of enrolled participants (n=20). Abstracted data will include: demographics and clinically relevant data. These data will include, symptoms, onset of symptoms, chest x-ray findings related to possible infections, sputum/other culture results, hospital length of stay (LOS), age, sex, BMI, ethnicity, home medications, medications given in the ED, home medications, primary diagnosis in the ED. Patient charts indicating research-opt out will not be approached for research, nor will any data be collected.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution.

☐ I will receive a de-identified data set from another institution.

☐ Other. Describe:

15.5 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed: Prior to enrolling participants, all hospital patient records will be screened for research opt out status.

15.6 Approximate number of records required for review: Up to 200 records may be prescreened for eligibility.

15.7 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes:

☐ This research involves record review only. There will be no communication with research participants.

☒ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

☐ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

☐ Communication may require the use of interpreter service(s) or translation service(s).

15.8 Explain how the research team has legitimate access to patients/potential participants: Potential participants/patients are known to the study team based on the legitimate access of the patient to the physician-investigators through the patient's clinical care. Access to patient's medical record information and data collection is through voluntary consent and signing of HIPAA authorization by a participant or participant's parent/guardian. This is to ensure that understanding of the study and release of PHI is approved by the patient's parent/guardian.

16.0 Health Science Technology (HST) HIPAA Compliant Devices and Data Storage

16.1 HST Device Number:

Gwenyth Fischer – 20222110
Beth Thielen - 20251719
Ethan Beltrand - 20232087

Other non-HST managed devices:

☐ UMP Computer(s)

☐ Store ☐ Analyze ☐ Share

☐ Fairview Computer(s)

☐ Store ☐ Analyze ☐ Share

☒ Other non-HST managed device(s):
Vocxi secure and dedicated mobile phone with Vocxi app

16.2 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply):

☐ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☒ In REDCap (recap.ahc.umn.edu)

☒Store ☒ Analyze ☒ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☒ In OnCore (oncore.umn.edu)

☒ Store ☐ Analyze ☐ Share

☒ In the University's Box Secure Storage (box.umn.edu)

☒Store ☒ Analyze ☒ Share

☒ Sponsor Electronic Data Capture Tool (i.e. Advarra or other)

☒ Store ☒ Analyze ☒ Share

☐ In UMP devices/servers

☐ Store ☐ Analyze ☐ Share

☐ In Fairview devices/servers

☐ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

☐ Store ☐ Analyze ☐ Share

☐ Other. I will use a server not previously listed. Describe:

16.3 Consultants. Vendors. Third Parties:

The MyBreathPrint VOC signals are uploaded from the phone to Vocxi's secure web portal using a unique UMN team login and password. Participant VOC signals only will be uploaded to Vocxi's web portal will be accompanied only by a study ID (ex. UMN-001).

16.4 Data Ownership:

☒ UMN
☐ UMP
☐ Fairview
☐ Sponsor:
☐ Third-party university:
☒ Other (specify): Vocxi Health

16.5 Links to identifiable data: We will have a link between study ID and patient name/MRN saved in UMN Box.

16.6 Sharing of Data with Research Team Members: Data (including identifiable links) will be shared to study team members delegated & IRB approved through OnCore/Box/REDCap supported server as noted above, in addition to paper documents collected during the trial

16.7 Storage of Documents: Paper copies of the consent and HIPAA forms will be stored in the research coordinators' office in a locked filing cabinet

16.8 Disposal of Documents: We will retain research documents for a minimum of 3 years following completion of the study. HIPAA forms will be retained for 6 years from the date the document was created or the date it was last in effect, whichever is later. We will then dispose of paper documents in a secure UMN shredding/document destruction box. All electronic documents will be permanently deleted from REDCap and UMN Box.

17.0 Confidentiality

17.1 Data Security: Data will be securely stored in Box storage or REDCap. A copy of the consent will not be stored in the patient's medical record.

18.0 Provisions to Monitor the Study to Ensure the Safety of Participants

18.1 Safety Plan: We do not anticipate needing a specific safety plan. Any clinical concerns will be addressed during the ED visit.

18.2 Data Integrity Monitoring: Independent monitoring of the study will be conducted by the University of Minnesota's Clinical and Translational Science Institute (CTSI) clinical trial monitoring service. The CTSI monitors will confirm that study activities are in compliance with the approved protocol and applicable regulatory authorities (FDA, IRB, local and state regulations). The investigator will give the study monitors direct access to source documentation, study data, and relevant regulatory documentation.

18.3 Data Safety Monitoring: It will be the responsibility of the PI to oversee the safety of the study. The PI will review cumulative trends in adverse events, serious adverse events, and UPIRTSOs on an ongoing basis. Any safety event meeting the IRB's urgent reporting criteria will be reported to the IRB within its published timelines.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy: Confidentiality of the research participants will be maintained. All data will be stored in locked offices and will not be released without consent of participants. Data to be used in scientific presentations or publications will not contain participant identifiers. All material will be used exclusively for research. Pre-existing chart (electronic medical record) information may also be used. Data obtained will be stored in a confidential database without direct identifiers. The principal investigator and designated study staff will have access to the linkages, which will be stored in a separate, secured location. Hard copies of data, including source documents with identifiers, will be kept in locked file cabinets in a locked office until the completion and publication of the study, at which time any identifiers will be removed and data will be stored at a secure storage facility. Access to the locked file cabinet will be given to the study coordinators and principal investigator only. Any study files that will be shared with the University of Minnesota will remove participant identifying information.

19.2 Access to Participants: Participants will be fully informed of the ways in which their data will/may be used during the informed consent process. The research team has been trained in conducting these conversations and the participants are also assessed for their understanding of consent prior to initiating any study procedures.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury: In the event that a participant sustains an injury while in this study, treatment will be provided to the participant (e.g., first aid, emergency treatment, and follow-up care as needed). Care for such injuries will be billed in the ordinary manner to the participant or the participant's insurance company.

20.2 Contract Language: N/A

21.0 Storing Data for Future Use

21.1 Storage and Access: N/A

21.2 Data: N/A

21.3 Release/Sharing: N/A

22.0 Consent Process

22.1 Consent Process (when consent will be obtained):

- If the patient/parent/guardian is approached by the treating provider the parent/guardian will be informed that participation remains voluntary and that

treatment by the provider will not be impacted by any decision made on participation.

- A one parent signature is felt to be justified for this study based on risk.If the child has a second parent, the study team will encourage that participation is reviewed with all caregivers even if one parental signature is required.
- No study procedures will occur prior to obtaining a valid signed consent & authorization by the participant and study team member.
- The study team will ensure that the potential participant is given enough time for consideration of the study participation by allowing them to consult with others and take the form home for consideration. If willing to sign the day of the consent conversation, the participant may do so. Understanding of the study and nature of participating in research will be assessed, through methods such as the teach-back method, prior to signing the consent form.
- Consent may be conducted in-person in a private space by delegated members of the study team.
- If it is made known to us that the parent or guardian is illiterate, we will take extra care to go through the consent form and read it to the potential participant. An unbiased witness (non- study team member) will be present during the consent process and at signing to attest that the consent form was described accurately and consent was given. The parent may make their "mark" on the consent document, along with obtaining the witness signature on the form in order to have documented compliance with the consent for child's participation. This will be documented in the participant's study records the reason for lack of signature and date, along with noting the person's name and date of the consent obtained.

22.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

22.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): N/A

22.4 Non-English Speaking Participants: Given the small number of patients in this pilot study and lack of potential for direct benefit, we will exclude participants who do not speak English.

22.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

- The child will be approached with parental/guardian permission and the study discussed in a manner appropriate for age and understanding. A parent/guardian must be present during assent process and signing. Time will be given for the child to discuss with their parent/guardian and any other individual (e.g. primary care physician) regarding their study participation. They may take the form home and think about participation, of if willing, they may sign the same day.
- Dissent will be honored at time during assent and at any point during the trial.
- If the child is agreeable, a written assent will be given on the age-appropriate assent form. A signed copy will be given.

- As there is no direct benefit to the potential participant, if a child is found to be eligible but is in foster care or has a court appointed guardian, the child will not be enrolled in the study unless appropriate court and legal (OGC) approval is granted, with notification to the IRB.
- Even if the child has capability to assent, but unable to print/sign their name, verbal assent may be obtained. This will be documented on the assent form by the assenting study team member and in the participant's study records. Parental permission/consent will still be required to be signed in order for the child to participate.

22.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

22.7 Adults Unable to Consent: N/A

22.7.1 Permission: N/A

22.7.2 Assent: N/A

22.7.3 Dissent: N/A

23.0 Setting

23.1 Research Sites: UMMCH Masonic Children's Hospital ED

23.2 International Research: N/A

23.3 Community Participatory Research: N/A

24.0 Multi-Site Research: N/A

25.0 Coordinating Center Research: N/A

26.0 Resources Available

26.1 Resources Available:

This study team includes:

- PI Dr. Gwen Fischer, a pediatric critical care physician with significant experience leading studies of investigational devices. Dr. Fischer is the founder and Director of the Pediatric Device Innovation Consortium (PDIC)
- co-investigator, Dr. Jonathan Strutt, a pediatric emergency department physician,
- co-investigator, Dr. Beth Thielen a pediatric infectious diseases physician with a bench lab to conduct testing on the residual specimen
- Dr. Evann Hilt, Assistant Medical Director, Infectious Diseases Diagnostic Laboratory
- Research staff from Peds Clinical Research Services, including a project manager, study coordinators, and regulatory specialists. Research coordinators have significant experience and expertise in pediatric human research in acute settings.

All staff will be trained on research procedures before being allowed access to participants or data. All training will be documented within the regulatory binder and reviewed by the PI and project coordinator.

27.0 References

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