Telemedicine Enhanced Asthma Management through the Emergency Department (TEAM-ED)

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Background:

Asthma is one of the most common chronic illnesses of childhood, affecting nearly 10% of children in the US.[1,2,3] Asthma causes morbidity from recurrent symptoms, impairment of quality of life, limitation of activity, school absenteeism, and missed days of work for caretakers. In addition, asthma is the most common reason for a pediatric emergency department (ED) visit, contributing to substantial health care costs. In 2007, direct health care costs from asthma exceeded $14 billion.[4] In the US, children from impoverished and minority ethnic and racial backgrounds suffer disproportionately from asthma. In fact, Black children are approximately 2.5 times more likely to have an ED visit or hospitalization for asthma than White children, and ED recidivism is common.[5] The US has made a commitment to eliminate health disparities, yet numerous studies document disparities in medication use, health care utilization, and asthma outcomes in minority patients.[6-12]

It is increasingly recognized that asthma is a chronic disease characterized by inflammation of the airways, and that preventive anti-inflammatory medications are paramount for the management of the disease and prevention of morbidity. Inhaled corticosteroids are the most effective long-term therapy for patients with persistent asthma and the NHLBI Expert Panel guidelines recommend that all patients with persistent asthma receive daily preventive anti-inflammatory medications.[13] These medications reduce asthma symptoms, improve pulmonary function, and prevent exacerbations leading to emergency visits and hospitalizations when used as recommended.[14] In addition, once medications are prescribed, the guidelines recommend follow-up assessments in 4-6 weeks, with adjustments in therapy as needed, to assure the goals of therapy are met.

Unfortunately, inadequate therapy with preventive medications is common, and many children suffer from morbidity that is potentially preventable.[15-18] Strikingly, among children presenting to the ED for asthma, as many as 75% are not using any preventive asthma medication.[19] Missed opportunities for the delivery of preventive asthma care are common, in part due to very poor follow-up rates in primary care.[20-25,26,27] Further, while an office visit provides an opportunity for the clinician to apply asthma guidelines to clinical care, written action plans and asthma education are not provided consistently,[28, 29] and opportunities to prescribe preventive medications are often missed.[29,30] In addition, many children who are prescribed a preventive medication do not achieve optimal control, at least in part due to lack of appropriate follow-up care.[31] Asthma symptoms, ED visits, and even hospitalizations may occur without a primary care provider's knowledge.[32,33]Importantly, the greatest under-use of preventive medications occurs among poor inner-city children.[11,34,35]

To overcome several of these barriers, we developed the PAIR-UP (Prompting Asthma Intervention in Rochester – Uniting Parents and Providers) intervention which included 638 children from 12 diverse

urban primary care practices.[36] The primary intervention included a simple prompt that was created at the time of a healthcare visit and given to the provider with information regarding the child's symptom severity or level of control, preventive medication use, exposure to tobacco smoke, and specifically tailored recommendations for guideline-based preventive care. Results from this study demonstrated improved preventive care delivery at the time of the visit, as well as reduced asthma morbidity (see progress report). However, for PAIR-UP we only targeted children who presented for care in the primary care office, thus potentially missing a large population of high-risk children with very limited access to health care for whom the ED is the primary source of asthma care.[34,37,38] Thus we now aim to expand our successful intervention to high-risk children presenting for asthma care in the ED, to promote optimal preventive care treatments and reduce morbidity.

Preventive asthma care is rarely addressed in the ED setting, which has a focus primarily on acute, episodic care.[39] Thus, in order to provide optimal preventive care and prevent repeat episodes following an ED visit, the asthma guidelines recommend that all children follow up with a primary care provider within 1-4 wks.[40] During this follow-up visit the primary care provider has the opportunity to prescribe effective preventive asthma medications, step-up medications for children who demonstrate poor control, promote medication adherence, and provide education on asthma self-management and trigger control to ultimately reduce morbidity and prevent subsequent ED visits. However, studies show that only 6-46% of children attend ED follow-up visits,[20-25,26,27] and those rates are particularly low for high risk children living in urban areas. In one of Rochester's largest urban primary care clinics, only 6% of patients followed up in the office within 4 weeks of an ED visit.[41] Thus opportunities to optimize preventive care after an ED visit are frequently missed.

A significant amount of asthma morbidity could be prevented if a sustainable intervention improved the delivery of guideline-based care after an emergency visit. Other programs have attempted to facilitate primary care follow-up after an ED visit,[20-23,26,27] or even provide specialized follow-up for patients right in the ED setting.[19] These programs have had varied effectiveness and none have been disseminated broadly. We have developed the *Telemedicine Enhanced Asthma Management through the Emergency Department* (TEAM-ED) program, which utilizes telemedicine technology to link children from acute to primary care and provide *point-of-care* prompting to assure that children receive the guideline-based treatments that can effectively reduce morbidity. This study will allow us to build upon our successful office-based preventive care intervention, optimize its effectiveness, and facilitate access to treatment for high risk children seen in the ED.

The University of Rochester's existing telemedicine model includes mobile units that enable clinicians to provide assessments based on a full complement of clinically-important information. Equally important, it enables providers to engage parents in counseling through remote audiovisual technology. A Clinical Telehealth Assistant (CTA) collects medical data and images from the child at their school, daycare, or home. These data are then stored for the child's primary care provider (PCP) in a secure internet system. The PCP can complete the visit at their convenience, and communicate with the caregiver by telephone to collect additional information and discuss the treatment plan. Visits can also be done in 'real-time'; connecting all parties via teleconference. It enables children to be seen by a PCP without making a trip to the office, thus eliminating a significant barrier to care.[42,43] Well designed telemedicine models allow patients to be cared for appropriately for acute and chronic problems while the child remains at home or school, the parent remains at work and the PCP remains at their usual work place (or home). There is reimbursement for telemedicine visits by all local payers, including Medicaid Managed Care (which covers 75% of Rochester's urban children), making it a sustainable system of care. Telemedicine is an efficient, cost-effective, and safe way to facilitate access to care for patients.[44-46]

The overall goal of TEAM-ED is to extend our prior work with a novel telemedicine based program to promote appropriate primary care follow-up and optimal guideline-based preventive treatment for high-risk children presenting to the ED for an asthma exacerbation.

Over the past 15 years, we have established a strong partnership with local PCPs and the Rochester community, which has allowed us to implement several programs for urban children with asthma, including the PAIR-UP study[36] that informed this study. Similar to PAIR-UP, this current intervention uses a system change to improve the delivery of optimal, guideline-based asthma care with a focus on promoting prescribing of effective preventive medications. However, it is unique because it focuses on a new, particularly high-risk population (urban children in the ED) and uses telemedicine technology to provide facilitated access to optimal primary care services. The telemedicine template includes *point-of-care* prompting, which parallels the PAIR-UP prompt and includes information regarding the child's asthma symptom severity or level of control, preventive medication use, exposure to tobacco smoke, and specific tailored recommendations to promote the delivery of consistent, guideline-based asthma care. This current study represents an innovative extension of our work to improve preventive care for these high-risk children through the ED. We aim to establish whether:

- Telemedicine will successfully link children from acute to primary care, assuring timely primary care follow-up after an asthma-related emergency visit,
- The telemedicine visits, performed by a primary care provider and supported by templates with 'point-of-care' prompting for guideline-based care, will enhance the provision of preventive asthma treatment,
- Asthma morbidity and repeat unscheduled asthma visits are reduced for these high-risk children.

Study Objectives:

This study has the following objectives:

- To identify and recruit an urban sample of young children, aged 3-12 years, with mild persistent to severe persistent asthma from the ED setting at Strong Memorial Hospital (SMH) and Rochester General Hospital (RGH).
- To collect baseline morbidity data to characterize this group of children with asthma and determine risk factors for the frequency and severity of recurrent symptoms.
- To randomly allocate subjects into either: 1) TEAM-ED Intervention Group (facilitation of preventive asthma management through telemedicine assessment and follow-ups in addition to guideline-based provider prompting) or 2) a control condition including enhanced usual care (eUC) (report of symptoms to PCP).
- To follow subjects prospectively throughout the year for endpoints defined by clinical outcomes (symptom severity, asthma control, health care use), functional outcomes (absenteeism, quality of life), and airway inflammation (FeNO).
- To assess the effectiveness of TEAM-ED in reducing asthma morbidity and preventing repeat unscheduled asthma visits.
- To assess the effectiveness of the intervention in improving preventive asthma care.
- To establish the financial sustainability of the intervention with a specific focus on ultimate dissemination.

Study Overview:

This project aims to improve the delivery of optimal primary care services for high-risk children who present to the ED, using telemedicine to directly link from acute to primary care. This intervention is

designed to overcome key barriers to guideline-based preventive asthma care among minority, poor children in Rochester, NY. Screening will take place in the ED to identify children who present for an acute asthma exacerbation and have persistent or poorly controlled asthma. Children in the TEAM-ED group will receive a telemedicine asthma assessment in school (or other convenient location for family and telemedicine staff). Follow-up telemedicine visits will be completed to make treatment revisions to optimize guideline-based treatment. The overall aim of this study is to evaluate the use of the TEAM-ED intervention for improving guideline-based care, preventing repeat unscheduled asthma visits, and reducing morbidity among young urban children with asthma.

Study Design:

This is a randomized trial of the TEAM-ED intervention versus an enhanced usual care (eUC) comparison group with 430 urban children (and their caregivers) aged 3-12 who present to the emergency department for an asthma exacerbation. Children presenting to the ED will be systematically screened, and eligible children will be randomly assigned to either the TEAM-ED intervention (telemedicine asthma assessment and follow-up visits using a pre-developed template with guideline-based prompting) or the eUC comparison condition (asthma screening with symptom reports and guideline-based recommendations for preventive medications sent to the PCP, and systematic feedback to the PCP and caregiver to promote appropriate follow-up care). Randomization will be stratified by enrollment site and use of a preventive asthma medication at baseline. A permutated block design will be used to assure an equal balance of children in each group over time. Following randomization, children will be followed prospectively and systematically for a year.

Subjects and Setting:

There are 2 EDs (Strong Memorial Hospital (SMH), Rochester General Hospital (RGH)) that provide pediatric emergency care for children in Rochester and the surrounding areas. Children 4-12 years of age presenting to the ED at either site will be screened for eligibility. A total of 430 children and 430 caregivers will be recruited into the study over 4 consecutive years.

Inclusion Criteria (all 4 criteria must be met):

- Prior doctor report stating that the child has asthma or reactive airway disease (RAD).
- Current emergency visit for an acute asthma exacerbation.
- Age ≥3 and ≤12 years, and living in the city of Rochester (primary residence within the following zip codes: 14428, 14445, 14467, 14513, 14514, 14515, 14586, 14604, 14605, 14606, 14607, 14608, 14609, 14610, 14611, 14612, 14613, 14614, 14615, 14616, 14617, 14618, 14619, 14620, 14621, 14622, 14623, 14624, 14625, 14626).
- Persistent asthma or poor asthma control, defined by NHLBI guidelines[40] as any 1 of the following:
    - >2 days/wk with asthma symptoms in the past month,
    - >2 days/wk with rescue medication use in the past month,
    - >2 days/month with nighttime symptoms in the past month or
    - ≥2 episodes of asthma during past year that required systemic corticosteroids (including the current emergency visit).

Exclusion Criteria:

- Inability to speak and understand either English or Spanish.
- No access to a phone for follow-up surveys (either at the subject's home or an easily accessible location).
- Participation in another asthma study at the time of enrollment, or a sibling currently participating in this or another study.

- Other significant medical conditions, including congenital heart disease, cystic fibrosis, or other chronic lung disease, that could interfere with the assessment of asthma-related measures.
- Children in foster care or other situations in which consent cannot be obtained from a legal guardian.

(Parents unable to read will be eligible and all self-administered instruments will be given verbally.)

Based on our prior studies, we anticipate <10% of subjects to be excluded based on these criteria.

After the amendment for Spanish documents has been approved, all Spanish speaking families will be recruited by Spanish speaking research associates and follow-up surveys will be completed by Spanish-speaking research assistants. All research documents will be provided in Spanish for families to review. If Spanish speaking researchers are not available at the time of enrollment, the family will not be enrolled at that time, but may be eligible for enrollment at a future date. If a Spanish-speaking Telemedicine provider is not available to conduct the visit, then the Telemedicine providers will use translation services, as they normally would, in conducting telemedicine care visits.

The recruitment goal for this study is to enroll 430 children using the Inclusion/Exclusion criteria stated above. For the purposes of the University of Rochester's Research Subject's Review Board, we will also consider each child's caregiver as a subject of this study (430 subjects). Therefore, we anticipate approximately 860 'subjects' will be included in this study.

Study Procedures:

- **Flagging and Screening Procedures**

Screening and enrollment will occur prior to ED discharge. The study team will review medical charts to flag children with an asthma or reactive airway disease diagnosis who present with an acute asthma exacerbation. A study team member will then approach parents of identified children in the emergency department and complete a brief screening survey to assess eligibility (see inclusion/exclusion criteria above). Trained and experienced recruiters are already stationed at the SMH ED (RSRB #33814). Once this study is approved at RGH, we will also station trained recruitment staff at the RGH ED who will use identical screening and enrollment processes. We have experience enrolling at both sites.

- **Baseline Assessment**

At the time of the ED visit, informed consent will be obtained from the parent and assent from children ≥8 years. The baseline survey will include an assessment of asthma symptoms, standard family and health history variables, exposure to secondhand smoke, and an environmental checklist. The interview survey includes questions adapted from several validated scales. An asthma symptom diary will be given to the caregiver for tracking asthma symptoms throughout the year and to assist with recall during the telephone follow-up assessments. All families will receive an educational packet including basic asthma information, smoking cessation resources, and information about the local asthma coalition. We also will obtain saliva samples from each child to objectively measure smoke exposure using the biomarker cotinine. Lastly, we will obtain exhaled nitric oxide measurements from each child using a portable NIOX VERO machine, in order to objectively measure airway inflammation. All surveys will be available in English and Spanish, and questions will be read aloud.

In instances when the caregiver who provided consent is unavailable for follow-up, if a different legal caregiver would prefer to respond to the follow-up assessments, the study will be described in detail and verbal consent will be obtained over the telephone from the new caregiver for completion of the

follow-up survey. In rare instances where the child's legal caregiver changes written consent will be obtained from the new caregiver.

Participants will be given the option to allow for future contact for other research studies at the time of consent. All participants who provided permission will be added to a future contact database dedicated to childhood asthma research (RSRB #31010). A voluntary photo/image consent form will be signed at the 12 month final home visit and images will be used only for study related purpose of publications, conferences, handouts, pamphlets, and presentations/posters.

- **Randomization**

Following completion of the baseline assessment in the ED, each child will be randomly assigned to either the TEAM-ED or eUC group. Randomization will be stratified by enrollment site and use of a preventive asthma medication at baseline. A permutated block design will be used to assure an equal balance of children in each group over time. The randomization scheme will be independently developed by the Biostatistics Center, and will be implemented electronically via REDCap™.

- ***TEAM-ED Group:***

Once randomized, we will send a symptom report and notification of enrollment in the study to each child's PCP. This report will include an explanation of the processes of the TEAM-ED program and will advise them to continue to care for the child's healthcare needs as usual. We will also provide caregivers with a copy of the symptom report and a prompt for guideline-based care for their child. In collaboration with the existing UR Telemedicine Program, a telemedicine follow-up appointment will be scheduled within a week of discharge from the ED. As per the Telemedicine program's usual process, the visit will be prepared by a clinical telehealth assistant (CTA) and the CTA will bring the mobile telemedicine unit to the child's school where he/she will meet with the child. The CTA will compile clinical history and physical examination data (including medical images, height/weight, and breath sounds), which will either be securely stored in the telemedicine system's "virtual waiting room", or will be viewed by the PCP in real time, using videoconferencing to link the child and PCP (the caregiver is also invited to meet the child at school for the visit). We have experience with both 'store and forward' and 'real time' telemedicine assessments. In the event that the child is not expected to return to school within one week of the ED discharge or during school breaks, the telemedicine visit will be prepared in the child's home (or other agreed upon location) at a time that is convenient for the caregiver. We anticipate the majority of enrollment to occur during 'asthma season', which coincides with the school year.

The visit will be scheduled with the telemedicine provider in real time when possible, or will be performed within 48 hours using the 'store and forward' mechanism. The telemedicine provider will log into the telemedicine system from their office or home, review the recorded symptom information, view the child's images, and listen to the breath sounds. The telemedicine provider will then complete the assessment using a pre-developed template with guideline-based prompting based on our prior PAIR-UP study, with checklists of guideline-based actions for preventive care. They will communicate with the child's caregiver via teleconference (or telephone for 'store and forward' visits) to further discuss the child's asthma and develop a treatment plan. During this contact, the telemedicine provider will deliver asthma education (e.g. trigger avoidance, symptom monitoring) and provide referrals to community resources as needed. All of the children in the study will have persistent or poorly controlled asthma (per enrollment criteria), warranting the use of a daily preventive asthma medication per NHLBI guidelines. When the telemedicine provider writes a preventive medication prescription, the prescription may be sent electronically to a local

pharmacy that offers delivery services. As part of the telemedicine system, a summary of the visit assessment and plan will be sent to the parent and faxed to the child's PCP for inclusion in the medical record (if it is not automatically included in their EMR). The telemedicine visit will model care that would be delivered at an outpatient asthma follow-up visit. We view the post-ED time period as an ideal 'teachable moment' for education and self-management promotion, since the stress and inconvenience of an ED experience is likely to heighten the caregiver's attention towards preventive asthma care. Visits take approximately 20 minutes for the provider to complete. Similar to a standard asthma visit, reimbursement will be submitted to the child's health insurance.

Several PCPs perform telemedicine visits as part of the current telemedicine system, including at least 3 different practices that serve >60% of the children living in the city of Rochester. We will schedule asthma telemedicine visits with the child's primary care practice whenever possible. If there is no telemedicine provider at the child's practice or if the PCP is unavailable for the visit (or if the child does not have a PCP), several providers at Strong's Pediatric Clinic and Rochester General Pediatric Associates are routinely available to perform visits; this scheduling system is currently used, is well received, and works very efficiently. For children without a PCP, the study team will also assist the family in connecting with a PCP. While the telemedicine providers are well versed in the asthma guidelines and endorse the use of inhaled corticosteroids for all children with persistent asthma, they will receive refresher training from Dr. Perry prior to the start of the intervention. A 1-hour lunchtime session will be held at the beginning of each intervention year and will include an overview of asthma, the newest guideline recommendations (e.g.; distinction between severity and control, impairment vs. risk), recommendation for inhaled corticosteroids, adherence tips, resources, and a review of the telemedicine template for asthma care.

Follow-Up Telemedicine Asthma Control Assessments and Medication Adjustments:
In addition to the initial telemedicine assessment, each TEAM-ED subject will receive two additional telemedicine-assisted follow-up assessments during the study period. By including these additional follow-up visits, we will assure ample opportunity for the provider to tailor each child's asthma therapy to their specific needs, supporting maximum control and promoting long-term benefits. The second telemedicine assessment will occur 4-6 weeks after the initial assessment. The third assessment will occur 4-6 weeks after the second. Just as for the initial assessment, the CTA will meet with the child at school to prepare the visit for the provider, who will complete the visit either in real time or within 48 hours. These assessments will focus on level of control, ongoing triggers or co-morbid conditions that might interfere with an optimal response to treatment, and brief asthma education. The telemedicine provider will make guideline-based medication adjustments (or specialist referral, if appropriate) for children who continue to have persistent symptoms, and referrals to community-based resources will be made as needed. After the final telemedicine-facilitated follow-up assessment we will ask both providers and families to schedule the next follow-up in the primary care office. Providers will be given a summary of the guidelines for asthma management and will be directed to provide ongoing asthma management as needed. Additional telemedicine visits will be prepared only if specifically requested by the family or the provider.

Referrals to Additional Resources:
In the TEAM-ED group, the telemedicine provider may also provide referrals to an asthma specialist, American Lung Association of Western New York, and New York State Smokers' Quitline, as appropriate.

- ***<u>Enhanced Usual Care (eUC) Group:</u>***

Similar to children in the TEAM-ED group, children in the eUC group will receive a symptom assessment using NHLBI guidelines, a recommendation for appropriate treatment, and asthma education materials given at the time of the ED visit. After baseline and randomization we will send the child's PCP a symptom report with guideline-based recommendations for preventive care and recommend a follow-up visit with the PCP. We also will give all providers a summary of the current national guidelines. We will provide systematic feedback to the family and child's PCP at intervals that parallel the TEAM-ED group's telemedicine assessments (1st feedback: 4-6 weeks after ED, 2nd feedback: 4-6 weeks after 1st feedback letter). This feedback will include prompting caregivers to schedule a recommended asthma follow-up appointment with the PCP and encouraging providers to adhere to the NHLBI asthma care guidelines. While participants will not be blinded to their group allocation, they will be told that they are randomly assigned to two different ways of approaching asthma management. In all of our prior studies, children in the eUC group improved over time, creating a conservative bias.

- **Follow-Up Assessments**

We will follow subjects prospectively for 12 months. The effectiveness of the study will be assessed by interviews with caregivers, measures, and medical record review. Research assistants blinded to the subject's group allocation will collect follow-up data by telephone at 3, 6, and 9 months after the baseline assessment. We may also send reminders and schedule appointments through text messages and emails. Text messages will be formatted in a manner that provides research relevance in the absence of personal health information (PHI). We may use a limited data set when sending text messages that can include dates and times for visits or telephone call reminders. The final follow-up at 12 months will be conducted with a home visit. While the intervention will only last 12 months, we may follow subjects for up to 18 months post their enrollment into the study if there is difficulty contacting with participants. These measures may include medical chart review or additional survey assessments with the primary caregiver. If additional surveys are conducted with the caregiver, we will request verbal permission from the caregiver prior to collecting survey data.

- **Measures**

The table below summarizes the outcome measures and covariates that will be collected for this study. The table includes how the data will be collected, validated scales/instruments used, and times of administration.

Clinical Outcomes	**Measurement Strategy**	**Time of Administration**
Symptom Severity	Caregiver report of symptom free days (SFDs), NHLBI guideline-based items[47]	Baseline, each follow-up (3, 6, 9 mo.), final survey (12 mo.)
Health Care Utilization, Nights with asthma symptoms, Days needing rescue meds, Days with limited activity, and Asthma control	Health care utilization survey Asthma Control Test (ACT)[48,49] Review of medical chart	Baseline, each follow-up, final survey (12 mo.)
Airway Inflammation	Objective measurement: FeNO[50]	Baseline, final assessment
Functional Outcomes		
School Absenteeism & Caregiver missed days of work due to asthma	Caregiver interview	Baseline, each follow-up, final survey (12 mo.)

Quality of Life	Juniper Quality of Life Instrument (PACQLQ)[51]	Baseline, each follow-up, final survey (12 mo.)
Potential Mediators		
Adherence, Preventive Meds, Action Plans & Spacers, Preventive asthma education, Asthma Visits	Horne Adherence Scale[52], NHLBI guideline-based items, healthcare utilization survey	Baseline, each follow-up, final survey (12 mo.)

Communication with Providers	Perceived efficacy in Patient-physician interactions (PEPPI)[53]	Baseline, final
Satisfaction with Medical Care	Patient Satisfaction Questionnaire, Short-Form (PSQ-18)[54]	Baseline, final
Independent Variables		
Demographic, Medical Variables	Caregiver interview	Baseline
Caregiver Depression	CES-D[55]	Baseline, final
Environmental Allergens	Environmental survey	Baseline
Secondhand Smoke	Caregiver interview Objective measurement: Salivary Cotinine[56,57]	Baseline, final
Process Evaluation		
Training of CTAs, Providers, and System support needs	Time to train CTAs and providers for asthma assessments, and providers for reinforcement of guideline-based asthma care	Tracking logs for entire study period
Telemedicine Visits	Track telemedicine visit completion, resources needed to carry out intervention	Baseline, each follow-up (3,6, 9), final survey (12 mo.)

**All Families will be provided a list of local mental health resources at the beginning of this study.*

Fraction of Exhaled Nitric Oxide (FeNO):

Fraction of Exhaled Nitric Oxide (FeNO) measurement is a non-invasive measure of lung inflammation. This inflammation could be caused by many factors including colds, pollutant exposures, and asthma. FeNO will be measured using the NIOX VERO® Airway Inflammation Monitor, an easy-to-use electrochemical hand-held device that instantly analyzes exhaled air for NO concentration. The NIOX VERO® is regularly used in clinical practice to measure FeNO, and requires little training to use. Children will be asked to first fully exhale and then to take a fast and deep inhalation through a disposable mouthpiece attached to the device. Then, we will ask children to exhale slowly and steadily through the mouthpiece. If done correctly, a reading will appear on the screen which will be recorded manually. FeNO will be measured 2 times, once at the baseline visit and then again at the 12-month home visit. Some children may have difficulty with this procedure; we will only include data for children who are able to perform the procedure accurately. The NIOX VERO® assessment only requires children to simply breathe into the machine, thus risks with this procedure are minimal.

Secondary Smoke Exposure: Saliva Sample Collection for Measurement of Cotinine:

Exposure to secondhand smoke will be assessed by both interview survey and cotinine measurements. At the baseline interview and the final home visit a member of the research team will collect salivary fluid samples from each child using the SalivaBio Children's Swab, a thin (8mm diameter) polymer swab.

Collection will be made according to a standard protocol developed for use with children. Salivary samples will be stored frozen and shipped via courier to Salimetrics, LLC in State College, PA for analysis. The cotinine results will be recorded as an outcome measure, and will be available to families only by request. However, all families will receive resources on how to stop smoking and prevent smoke exposure.

- **Compensation**

Each participating caregiver will be paid $25 after completion of the baseline assessment. Subjects will also be mailed $20 after each of the telephone follow-up surveys and $50 after the final follow-up survey. Total payment will be no more than $130. Payment to participants will be in the form of a gift certificate.

There may be some cost to participate in this study. Participants in the TEAM- ED group will be responsible to purchase medications and spacers that may be prescribed by the telemedicine provider as well as any fees associated with telemedicine visits (e.g., co-pays etc.) completed through the study (these are medical processes that should occur according to the national guidelines regardless of the child's participation in the study). Based on our prior work with this population, we anticipate that most of the children will have some form of health insurance to cover the cost of visits and the medications with minimal or no co-pay fee. In our prior studies we found that approximately 70% of families in the City of Rochester were insured with Medicaid which often eliminates co-pay fees for medications and care. If a child does not have insurance, the study team will help the family secure health insurance. If a child is unable to obtain health insurance or if a family or provider expresses a financial concern, the study team will pay for the participant's asthma medication and spacer prescribed by the telemedicine provider. If there is no insurance reimbursement for the telemedicine visit, subjects will not be asked to pay any additional costs (e.g., co-pay). Participants and their insurance company will be responsible for the cost of all standard of care office visits and additional medications prescribed by their PCP.

- **Data Storage and Confidentiality**

To maintain the integrity, security, and confidentially of study data, the data will be maintained in a secure and encrypted web-based database and/or a password protected database on a secure university network drive. The majority of data will be entered through REDCap™, a secure password-protected website supported by the University of Rochester. Subject tracking information will also be entered into a secure password-protected database created with Microsoft Access, that is only accessible on a secure university network drive and research personnel must use their University NetID and password to access the databases No subject data will be stored on the internal hard drives of any computers. After data validation and analysis, subject information will be de-identified. All consent forms, paper surveys and additional correspondence will be stored in a locked filing cabinet in a locked hallway or locked office, and will only be accessible by the study staff.

- **Safety**

Potential risks related to participation in this study are minimal. No medications, investigational treatments, or devices are being tested as part of this study. The study is designed to improve guideline-based asthma care following an emergency visit. The pediatric telemedicine provider may prescribe a daily controller medication, as part of the treatment regimen, which is standard of care for children with the degree of asthma symptom severity required for enrollment into the program. The most frequently reported side effects of these types of medicines are sore throat, hoarseness, a fungal infection of the throat and mouth, and dry mouth. Rinsing the mouth after using this medicine and

always using a spacer/holding chamber (if applicable) decreases the risk of these side effects. The follow-up research assistants will routinely assess common side-effects of asthma treatments, and any significant adverse events will be flagged by the follow-up team and relayed promptly to the study coordinator, the principal investigator, and the Institutional Review Board within 24-hours, and to the NIH as per protocol. Any child (in either group) experiencing an exacerbation or persistent symptoms at the time of an assessment will be referred to their primary care provider. In addition, an asthma coordinator will review the treatment plans to help ensure guideline-based care is followed appropriately and will be available to families to answer questions about the treatment plan.

There is a risk that the study team may discover an unknown medical condition. If this is to occur, we will refer the family to their PCP or another appropriate health care professional for evaluation and treatment. There is also a risk that the study team may discover child abuse or neglect during a home visit, and will be required to report these concerns to authorities.

The study team has conducted over 1,500 home visits for families of children with asthma, and implements extensive training each study year about home visit guidelines, safety, mandatory reporting, and cultural competency. The study team also meets weekly to review concerns.

All records will be kept strictly confidential as required by the policies and procedures of the University of Rochester where data are collected, processed, or reported. We plan to hold bi-weekly research meetings with the study team to provide monitoring to ensure subject safety as well as treatment integrity. The family can discontinue their participation at any time during the study.

Data Safety Monitoring Plan (DSMP):
This study also includes a Data Safety Monitoring Plan as submitted to and approved by the study sponsor: National Institutes of Health and National Heart, Lung, and Blood Institute. The plan for safety and monitoring is as follows:

- **Data and Safety Monitoring**

Data Quality Monitoring

The research associates will be responsible for all data collected during the assessments. They will receive training from key study personnel regarding asthma terminology, symptoms, medication understanding, and environmental assessment. They also will be trained by the project coordinator on the use of equipment for cotinine measurements and the NIOX VERO® instrument for collection of exhaled nitric oxide.

The project coordinators are all experienced in asthma terminology, symptoms and other aspects of the illness and have extensive training in research methods. They will oversee the data collection methods and all data will be reviewed by the study coordinators. Data forms will be completed at each study visit or telephone interview and will be returned with a cover sheet and other source documentation support materials (informed consent, contact information, etc.). Pre-intervention training of study staff will be conducted to increase knowledge about asthma, asthma medications, and other important information in order to reduce the number of "real-time" data collection errors. Through this training, staff will note any inconsistencies in parent reported data and will discuss them with the parent at the time of the interview.

Key study personnel will perform all follow-up interviews and follow-up data management. These data will be collected by the follow-up research associates who are independent from the research associate recruiters, and thus we will be able to perform blinded assessments of outcomes. Our team, including the principal investigator, senior project coordinator, and recruitment and follow-up project

coordinators, has a prior record of high-quality data collection and management. We have tracked hundreds of children in our randomized trials, and completed follow-ups with over 90% of subjects. Treatment group assignment will not be included with any follow-up materials in order to ensure blinding of the outcome assessment.

Once surveys have been administered, errors that can be corrected over the telephone (legibility, incorrect dates, etc.) will be done using telephone interviews. Simple range checks as well as cross-form validation checks will be performed to ensure the accuracy and completeness of the data. Any errors detected will be noted on the form (including initials and date of change). In addition, data forms, valid informed consent documents for each enrolled patient, and supporting source documentation materials will be reviewed by the research associates for accuracy. Required regulatory documents (IRB approval, updates to the protocol, data monitoring documents) will be maintained by the senior study coordinator. All events during the course of the trial including study enrollments, adverse events and study terminations will be reported to the senior study coordinator.

Safety Monitoring Plan

Potential risks related to participation in this study are minimal since the goal of this study is to ensure follow-up after an emergency visit and improve guideline-based asthma care for children with persistent asthma. In our prior school-based and office-based asthma programs, which have included hundreds of children, there have been no reports of significant adverse events related to study participation. The frequency and severity of all reported adverse events will be systematically recorded at each follow-up interview. Telephone interviewers will inquire about any adverse events, and specifically ask about hospitalizations, emergency visits and common side-effects from medications (yeast infections of the mouth, facial rash). Any significant adverse events will be flagged by the follow-up research associates and relayed promptly to the senior study coordinator, the principal investigator, the child's primary care provider, the Institutional Review Board, and the NIH. We will hold bi-weekly research review meetings with the study team to provide an additional layer of monitoring to ensure subject safety as well as treatment integrity. The NIH does not require a formal Data Safety Monitoring Board (DSMB) for this study

All records will be kept strictly confidential as required by the policies and procedures of the University of Rochester where data are collected, processed, or reported.

- **Potential Benefits**

Potential benefits for participants of the randomized trial exist for both groups of children (TEAM-ED and eUC). The goal is for children in the TEAM-ED group to have improved symptom assessment, adherence to preventive medications, and appropriate tailoring of therapy, thus they may experience less morbidity from asthma. Although children in the eUC group will not be receiving follow-up telemedicine assessments, we will prompt their PCP to provide guideline-based asthma care including prescription of the appropriate preventive medications and will provide regular reminders to PCPs and caregivers to care for the child's asthma. Improved asthma management should result in reduced morbidity for these children.

- **Analysis**

Sample Size:

Based on our experience with prior studies and the number of unique asthma visits to the ED, we expect to be able to enroll 430 child participants in 4 years. There are more than 950 individual patients -12 years of age with a primary diagnosis of asthma presenting to the 2 EDs each year, (450 at Strong Memorial, >500 at Rochester General), and >45% of these children live in the city of Rochester (>430).

Conservatively assuming enrollment of 1/4 of eligible subjects, we will have no difficulty enrolling 108 subjects/year. We anticipate a maximum of 15% attrition, based on an attrition rate of <5% in our prior studies. We therefore expect complete data on at least 365 children, randomized into 2 groups (182 subjects per group). We now consider power calculations based on this sample size.

The primary hypothesis is that children in TEAM-ED will have more symptom-free days at 3, 6, 9, and 12-months compared to eUC. Previous asthma interventions have demonstrated that improvements of 0.85-0.95 SFD/2 weeks are feasible and clinically meaningful.[59,60] Based on our prior data, we estimate a pooled standard deviation (SD) of SFD to be 3.5 and within-subject correlation (ICC) of 0.3. We calculated power for the intervention effect on SFD while justifying repeated assessments for outcomes (3, 6, 9, 12 months).[61,62] A sample size of 182 subjects per group will provide >90% power to detect a difference of 0.85 in SFD at a 2-sided 5% significance level.[63] We also calculated the smallest detectable differences in secondary outcomes with 80% power based on prior data.

We also aim to test whether children in TEAM-ED will have fewer unscheduled asthma visits over 12 months compared to eUC. Based on our preliminary data and data for similar populations, we estimate the baseline unscheduled asthma visit rate ranges 0.7-1.5 per person year. A sample size of 365 subjects will provide 80% power to detect a rate ratio of 0.7 if the control group has rate of 0.7 per person year. For preventive measures such as preventive medication use, in our prior study, 59% of children used a preventive medication at baseline. With 182 subjects in each group, we will have 90% power to detect an increase of 16% in using a two-sided Z test at a significance of 5%.

Primary Analysis:
Assess the effectiveness of TEAM-ED in reducing asthma morbidity and preventing repeat unscheduled asthma visits; Assess the effectiveness of the intervention in improving preventive asthma care. We will follow subjects prospectively throughout the year for clinical outcomes (symptoms, asthma control, health care use), functional outcomes (absenteeism, quality of life), and airway inflammation (FeNO). We will use graphs and descriptive statistics to summarize the primary and secondary outcomes by intervention group at each assessment point (baseline, 3, 6, 9 and 12 months). We will assess for differences between groups at baseline despite randomization in key characteristics (i.e.; age, race, ethnicity, insurance, caregiver education, caregiver depression, smoke exposure (determined by cotinine)). These comparisons will enable the identification of covariates to be controlled when evaluating the treatment effect. If distributional assumptions associated with a particular statistical procedure are violated, appropriate transformations will be made or non-parametric alternatives will be used. In accordance with the intention-to-treat principle,[64] all randomized subjects will be analyzed within the group to which they were assigned. Minimal crossover is expected. Hypothesis-driven comparisons will be made to control the family-wise type I error rate at 0.05 (two-sided) for the primary hypothesis.

For the primary outcome analysis, the time-course of treatment effect on SFD during the follow-up period will be evaluated using a linear mixed model (LMM) accounting for repeated measures within each subject to test the intervention effect of TEAM-ED over time, with SFD as the dependent variable, and intervention group and group by time interaction as independent variables.[65] The treatment effect will be regarded as fixed and the subjects as the random effect, with appropriate variance covariance structure specified. Interaction effects between intervention and follow-up period are included to catch possible differences in how SFD changes over time between intervention groups. Post treatment effects and maintenance gain from short to long term will be assessed by specifying appropriate linear contrasts. To adjust for potential confounding, baseline SFD and factors that differentiate between

groups will be included in the model as covariates. Model fitting statistics such as Information Criteria and difference in log likelihood will be used for model selection. Standard measures such as residual plots will check goodness-of-fit of the regression model assumptions and identify outliers. We will calculate intraclass coefficient (ICC) within providers; if autocorrelation is significant, provider will be included as another level of random effect in the mixed model to account for the nested data structure. If the outcome measure violates the normal assumption required by LMM, we will evaluate the intervention effect using Generalized Estimating Equations (GEE).[66] By specifying marginal mean effects of independent variables on the outcome variable, the GEE method offers consistent and robust estimates but does not require specification of a fully parametric distribution. Other continuous outcomes (quality of life, FeNO, absenteeism) will be analyzed similarly.

Categorical outcomes such as unscheduled asthma-related healthcare utilization will be analyzed by fitting Poisson regression models (with number of visits as the dependent variable). Estimation of the regression coefficients and standard errors will be obtained using the GEE method with a log link function and Poisson error. Baseline rate and factors imbalanced between groups will be controlled in this analysis. Other discrete outcomes (such as preventive medication use and availability of written asthma action plans) will be analyzed in a similar manner with appropriate link functions and response probability distributions specified.

The primary analyses will be performed according to the intention-to-treat principle and will include all randomized subjects. Substantial attention will be invested in participant retention; reasons for any subject withdrawals that may occur will be carefully documented. Missing data patterns will be examined by comparing subjects who discontinued with those who remained in the study. Inference based on the proposed methods GEE and/or LMM is valid provided that missing data follows the missing completely at random (MCAR) assumption. However, if the occurrence of missing data depends on the observed response but is independent of unobserved data (MAR), weight GEE (WGEE) will be used. Sensitivity analysis to the MAR assumption will also be carried out by modeling the between-group difference using WGEE.[67,68] Separate secondary per protocol analyses will be performed, however, results of these analyses are potentially subject to bias and will be interpreted with appropriate caution.

Cost Effectiveness Analysis: *Establish the financial sustainability of the intervention with a specific focus on ultimate dissemination.* We will assess the health and economic benefits of TEAM-ED from both the societal and the Medicaid perspectives. We also will use Diffusion of Innovations Theory to help understand how this innovative model can be maintained in the current system of care.

We will use cost-effectiveness (CE) methodology[69,70] to assess the health and economic benefits of TEAM-ED versus eUC over 12 months. The basecase analysis will be conducted from the societal perspective which includes all identifiable costs and benefits, regardless of whom they impact. Since the majority of subjects are eligible for Medicaid (73% based on prior work[59]), a second analysis will take the Medicaid perspective. The intervention benefits will be assessed using the primary outcome (mean symptom-free days over 12 mos.).[71,72]

Three main categories of costs to be considered include programmatic costs, productivity costs, and medical costs estimated at the individual child level. Programmatic costs include costs of initiating and running the program, hiring and training staff, purchasing or leasing equipment, staff travel, and information system costs. Programmatic costs will be tracked by the UR General Pediatric Division Administrator and the UR Telemedicine Program Administrator. Research-related costs that are not associated with the intervention and would not exist beyond the duration of the study will not be

included. Per person programmatic costs will be calculated by dividing the total costs of the program by the total number of children with persistent asthma in the EDs. We will determine productivity costs based on the amount of time parents take from work to care for sick children or take them to a doctor. Time from work will be valued at the median of the Bureau of Labor Statistics pay scale estimates based on age, race and gender. We will assess the impact of the intervention on medical costs using both parent-reported health care utilization data and medical record review. We will ask parents at each follow-up about their child's visits to the ED, urgent care facility, or primary care office, as well as hospitalizations. Health care use will be converted to costs using the NYS Medicaid fee schedule and other sources. Money spent out-of-pocket by caregivers to cover the cost of medical procedures, medications, or equipment will also be included in the medical costs. Annual medical costs per person will be analyzed using a 2-part model to adjust for zero expenses in a given year.[73] All costs will be adjusted to the last year of the intervention using the appropriate component of the Consumer Price Index (CPI).

We will consider the total cost of initiating and maintaining the program as well as the incremental cost-effectiveness ratio (ICER) of TEAM-ED versus eUC. The ICER is the difference in cost between the 2 study groups relative to the difference in the number of symptom-free days (SFD) gained between the 2 groups. The main outcome for the analysis from the societal perspective will be the ICER, defined as: $(\Delta Medical+\Delta Productivity+\$Program)/\Delta SFD$, where $\Delta=(TEAM\text{-}ED)-(eUC)$. We will bootstrap[74] the ICER to estimate standard error and to evaluate the uncertainty around the point estimate. The ICER will be compared to similar estimates from the literature.[71,72] An acceptability curve, linking various values of 1 SFD to the probability of TEAM-ED being cost-effective, will be plotted.[75] The study from the Medicaid perspective will use the cost-benefit approach to economic evaluation. Benefits will be described as the net difference in medical and productivity costs between children in the TEAM-ED and eUC groups and accounts for a potential reduction in unplanned visits as well as an increase in number of preventive visits. The cost is equivalent to the cost of the program (*Net Monetary Benefit=ΔMedical-$Program)*.

COVID-19

In response to the COVID-19 crisis, we will follow the Human Subjects Research guidelines outlined by the University of Rochester to continue enrollment for this study. Please find the following link for these guidelines: https://www.urmc.rochester.edu/coronavirus/coronavirus-research/guidance-for-researchers/human-subjects-research.aspx. We will minimize in-person contacts to only those tasks necessary to conduct the research (e.g., obtaining consent, collecting breathing measurements if needed). We will ensure that team members are appropriately trained in safety measures, maintain social distancing when possible, use personal protective equipment for themselves and research subjects (and family members), and will ensure proper cleaning/sanitizing of hands, equipment and workstations. We will continue to monitor and follow the updated guidelines put forth by the UofR in the link above.

We've included a brief, optional survey to assess how the COVID-19 Crisis is affecting children with asthma and their families. We will ask the caregivers if they would be willing to answer these questions at the end of follow-up surveys that we are already conducting.

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