INVESTIGATOR STUDY PLAN

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NCT number:	NCT04942379
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Official Title of Study:	Asthma Link: School Supervised Therapy to Improve Medication Adherence in Children with Poorly Controlled Asthma
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INVESTIGATOR STUDY PLAN

1. TITLE

Examination of the Effectiveness and Implementation of Asthma Link™: A Real World Application of Supervised Asthma Therapy

2. EXTERNAL IRB REVIEW HISTORY*

N/A

3. PRIOR APPROVALS:

N/A

4. OBJECTIVES*

The objective of this pilot study is to evaluate the feasibility of an implementation study of Asthma Link as an effective method of evidenced-based practice of school-supervised asthma therapy in a real-world setting. If Asthma Link is found to be an acceptable practice with appropriate adoption and sustainability, it can serve as a scalable public health model for improving asthma medication adherence and combating the significant morbidity associated with pediatric asthma in the real world, rather than just research settings.

Aim 1: We will analyze process outcomes (acceptability, adoption, costs, sustainability) of Asthma Link™ in two pediatric practices.

Aim 2: Evaluate feasibility of a cluster RCT of Asthma Link™. The *primary trial outcomes* will be participant recruitment, retention, and intervention fidelity. The *secondary trial outcomes* will be differences in the frequency of asthma symptoms, emergency department visits, hospital admissions, courses of oral corticosteroids, spirometry values and school absences between Asthma Link™ and Enhanced Usual Care sites.

As each stage of Asthma Link™ evaluation builds upon the previous stage, we will submit separate IRB amendments and proposals for each stage of this project. The data collected from the proposed study will inform a large-scale cluster RCT to test the effectiveness and implementation of Asthma Link™.

5. BACKGROUND*

Countless pediatric asthma interventions have been successful in improving asthma outcomes in research settings, yet few are adopted into clinical practice to produce noticeable public health impact. Despite aggressive efforts to address remediable causes, childhood asthma still affects 12-15% of children in the urban United States, causes over 14 million missed school days annually and costs billions of dollars in healthcare expenditures.[1-3] Most of childhood asthma morbidity is attributable to non-adherence to a daily preventive medication, an inhaled corticosteroid (ICS).[4-7] The highest asthma morbidity and the lowest ICS medication adherence rates occur in low income and minority children.[8-10] These populations fall through the cracks as a result of failure to supervise and support adherence to preventive ICS medication. Recognizing this, the National Asthma Education and Prevention Program and the American Academy of Asthma, Allergy, and Immunology have urged that providers and researchers develop more effective adherence programs.[11,12]

School-supervised administration of asthma therapy has helped improve medication adherence and improves asthma symptoms among children enrolled in research studies. There have been multiple studies that have shown that school-supervised asthma therapy not only improves medication adherence in children with asthma but also that this practice is safe, with no adverse effects seen.[13-15] School-supervised asthma therapy has been established as safe and efficacious, and therefore asthma experts (including the American Academy of Pediatrics, American Academy of Allergy Asthma and Immunology, and the National Association of School Nurses) endorse school-supervised asthma therapy as the evidenced-based standard of care.[16]

However, despite the compelling evidence from studies and endorsement from experts, these tested school-supervised asthma interventions have not been widely adopted in practice. This is likely due to reliance on research staff for implementation and operations that are costly and highly resource intense, making them infeasible to adopt and sustain in the real world after research funding ends.

In response to this critical public health issue, we propose to study Asthma Link, which is a low-cost, low-intensity community-clinical based model of supervised asthma therapy in schools. Asthma Link is an established, ongoing clinical program that promotes the adoption of the evidenced-based practice of school-supervised asthma therapy in real world settings.

Asthma Link connects the three groups that play vital roles in the health of school-aged children with asthma: pediatric practices, school nurses, and families. Pediatricians identify and enroll children with poorly controlled asthma and medication non-adherence as part of their routine practice. They send the school nurse an order for daily, supervised inhaled steroid administration at school. Families bring the prescribed inhaler to school. The school nurse supervises the child's inhaler administration and provides adherence education, as part of her daily routine, to ensure adherence and proper inhaler/spacer technique. Ongoing communication occurs between the pediatric practice, the school nurse and families throughout the school year. Asthma Link is based on prior research studies that demonstrate the safety and efficacy of school-supervised asthma therapy. The goal of Asthma Link is for school-supervised asthma therapy to operate in a real-world setting, delivered by pediatricians, school nurses and families within their current routines and relying on minimal resources and no research staff.

The goal of the proposed study is to examine the effectiveness and implementation of Asthma Link™ in sustainable real-world practice.

Preliminary Data:

The current proposed study builds from our prior research, which has informed the proposed study. To initially test Asthma Link™, we performed a small pre/post study (SEE IRB DOCKET # H00010546_2) of 84 children enrolled in Asthma Link™ (mean age 10 years, 95% Medicaid insurance, 67% Latino, 19% Black). We observed that children enrolled in Asthma Link™ experienced a 54% decline in emergency room visits, a 95% decline in hospital admissions and a 46% decline in rescue medication use over a one-year follow-up period ($p<0.001$),[17] demonstrating that Asthma Link™ merits further rigorous evaluation. Additionally, in order to examine the barriers and facilitators to Asthma Link™ real-world implementation, (SEE IRB DOCKET # H00012920_1), we are interviewing program stakeholders which include school

nurses, parent-child dyads, and medical providers who were participating in the program in addition to public health and insurance officials. Specifically, in our interviews with 12 school nurses, we found that they perceive Asthma Link™ to be an acceptable program given the brief (<5min) time required and ease of incorporation into their existing routine.

Despite our promising results, Asthma Link™ needs to be tested against a comparison group, using a cluster randomized controlled trial (RCT). The first step is to perform a pilot cluster RCT to assess feasibility outcomes and health outcomes (Aim 2). Additionally, it is imperative to assess process outcomes (acceptability, adoption, costs, sustainability) of Asthma Link™ in new pediatric practices to ensure that school-supervised asthma therapy can be successfully scaled up and utilized in real world practice (Aim 1). We propose to test Asthma Link™ using a pilot cluster RCT of 4 pediatric primary care sites in Massachusetts.

6. INCLUSION AND EXCLUSION CRITERIA*

Child eligibility criteria for enrollment in Asthma Link™ (established clinical program):
(1) children aged 6-17 years (enrolled in grade 1-12)
(2) prescribed daily inhaled corticosteroid (ICS) for asthma;
(3) 1 or more courses of oral steroids in the past 2 years OR 1 or more hospitalizations or ED visits for asthma in the past 2 years OR Asthma Control Test (ACT) score <19 OR 1 or more sick or urgent care visits for asthma (including telehealth) in the last year
(4) parent/child report of poor ICS adherence on adherence checklist- i.e. child or parent says "Yes" when provider asks if they have difficulty remembering to take their medication or if they regularly take medication holidays or breaks;
(5) able and willing to assent;
(6) parental permission
(7) English or Spanish speaking.

STUDY INCLUSION/EXCLUSION Criteria:

Child Inclusion criteria:
1) Meet the eligibility criteria for Asthma Link (as described above) with exception to (7)
2) Enrolled in Asthma Link™ (if randomized to the Asthma Link™ Condition)
3) Able and willing to provide informed assent
4) Must be English or Spanish speaking

Child Exclusion criteria:
(1) Unable or unwilling to provide informed assent
(2) Diagnosis of a serious co-morbid illness during the past 5 years
(3) Developmental delay that would prevent study participation.
(4) Planning on moving from primary residence or moving outside of the school district in the next 1 year
(5) A sibling to a child participating in this study

Parent Inclusion criteria are:
1) Parent/guardian to patient
2) 18 years or older
3) Able to understand and communicate in English or Spanish

4) Able and willing to provide informed consent.
5) May or may not be or become pregnant

Medical Provider Inclusion criteria are:
1) Able and willing to provide informed consent

Medical Provider Exclusion criteria are:
1) Unable or unwilling to provide informed consent

School Nurse Inclusion criteria are:
1) Able and willing to provide informed consent

School Nurse Exclusion criteria are:
1) Unable or unwilling to provide informed consent

Asthma Champion Inclusion criteria are:
1) Able and willing to provide informed consent

Asthma Champion Exclusion criteria are:
1) Unable or unwilling to provide informed consent

Adults lacking capacity and prisoners are also excluded

7. STUDY-WIDE NUMBER OF SUBJECTS*
N/A

8. STUDY-WIDE RECRUITMENT METHODS*
N/A

9. STUDY TIMELINES*
Describe:

- *The duration of an individual subject's participation in the study:* 6 months
- *The duration anticipated to enroll all study subjects:* 1.5 years
- *The estimated date for the investigators to complete this study (complete primary analyses)*: 3 years

10. STUDY ENDPOINTS*
Please see below table describing the primary and secondary outcome measures
SN=School Nurse
MP=Medical Provider
AC=Asthma Champion

Study Assessments, Measures and Data Collection Timing

Variable	Measure/Instrument
Designed for and Delivered to pediatric practice staff, school staff, and parent-child dyads Administered by Research coordinator	
AIM 1: Primary Feasibility Outcomes for Asthma Link™ research protocol (cluster RCT)	

Participation/Recruitment	# of screened and eligible participants; # refusing to participate; reason(s) for refusal
Retention	# of dropouts; subjects lost to follow-up; reason(s) for dropping out
Program usage/Intervention Fidelity (degree to which using program)	• Checklist for pediatric practice staff to assess % of eligible children enrolled (see Pedi Practice checklist) • School nurse report of % enrolled students receiving supervised therapy (see SN checklist) • School nurse checklist of each enrolled child attending daily school nurse sessions and his/her family bringing medicine to school (see SN checklist)
AIM 1: Secondary Asthma Health Outcomes	
Asthma symptoms	• Asthma Control Test (see Parent surveys), validated • maximum symptom days, validated
ED visits, Admissions, Oral steroids, Medication Adherence	• Parent report (see Parent surveys) and electronic medical record review • Pharmacy refill data
Spirometry	• Portable Spirometer (PIKO), validated[57] to assess Forced Expiratory Volume in 1sec
School absences	• Parent and school nurse report (see Parent surveys and SN checklist)
AIM 2: Process Outcomes for Asthma Link™ Intervention Protocol	
Acceptability	• Acceptability rating scale (5 point Likert scale) to rate each component of the Asthma Link™ intervention (see Parent, SN, MP, AC surveys)
Adoption	• Pedi practice log to track number of providers offering Asthma Link™ (See Pedi Practice Intervention Fidelity Checklist) • School nurse log to track frequency of child coming to nurses office to receive med (see SN checklist) • School nurse log to track family bringing in medicine to school (see SN checklist) • Survey to family to assess ability to obtain 2 inhalers (one for home and one for school) and deliver medicine to school (see Parent 3 mo, 6mo survey)
Costs	• Survey to assess time and costs for: pediatric practice to train in and implement program, School nurse to deliver intervention, Family to pick up medicine and bring to school (transportation), above and beyond their daily routines (see MP, AC, SN, Parent surveys)
Sustainability	Brief Sustainability Rating (5 point Likert scale) to assess pediatric practice, School nurses, and Families perception that Asthma Link™ could be continued over time (see MP, AC, SN, Parent surveys)

11. PROCEDURES INVOLVED*

Randomization. Two groups of two practices (4 practices in total) will be matched based on comparable size and percent of minority patients. Within each pair, practices will be randomly allocated to Asthma Link or the comparison condition, using a computerized function. This will result in two practices randomized to the Asthma Link condition and two practices randomized to the Enhanced Usual Care comparison condition.

Recruitment will be performed from each practice site until the target n=72 parent-child dyads (18 per site) are recruited. (see section 13 on "Sample size calculation") Recruitment will begin during the 2021-2022 academic school year.

Procedure Steps:

1. Research coordinator (RC) identifies potentially eligible patients (children aged 6-17 years (enrolled in grade 1-12) years and prescribed a daily inhaled corticosteroid per medical record from most recent visit scheduled for a clinic visit) through the practice's office scheduling and medical record system (e.g., Epic). RC will also collect that patient's name, DOB, mailing and email addresses, phone number, insurance type (as a proxy for socioeconomic status), list of

medications, number of emergency room visits, number of hospital admissions and number of oral steroid courses for asthma relief.
2. RC creates a Lilac Form for any potentially eligible patients as described above. (Lilac form is an indicator to the medical provider seeing the patient that this patient is potentially eligible for study.)
3. Asthma Link condition: As part of clinical practice, medical provider will determine if patient is struggling with taking daily asthma medicine. If YES, then will introduce Asthma Link by saying "There is a clinical program that allows for your child to receive their daily asthma medicine at school supervised by the school nurse." Child can be enrolled in Asthma Link per the usual clinical steps (see Asthma Link steps).

- After they are enrolled in Asthma Link, medical provider will give family one-page description of study (see Flyer) and state "Researchers at UMass are performing a study of children who are participating in Asthma Link, would you be interested in hearing more?"

3a. Enhanced Usual Care comparison condition: Medical provider will determine if patient is struggling with taking daily asthma medicine, if YES, the provider will give family a one-page description of study (see Flyer) and state "Researchers at UMass are performing a study of children with asthma to learn about how to support them in taking their every day asthma medicine, would you be interested in hearing more?"

- Attached to the "Flyer" will be the Authorization to Contact form. (see Authorization to Contact form)
- If the parent agrees, the Lilac form with the family's information is faxed to the Research Coordinator. The pediatric office will fax this form with a confidential cover form.
- The fact sheet will be mailed to the parent with a letter saying that the Research Coordinator will call or text them (see Fact Sheet).
- The Research Coordinator will only call the parent five times. The first and third time a message will not be left, but a text message will be sent stating "This is X from Asthma Link, can I call you at TIME?" The second, fourth, and fifth time a message will be left saying "This is X from the University of Massachusetts Medical School. I am calling about the material on Asthma Link I sent you. Please call me back at X."
- A phone screen will be conducted to ensure study inclusion criteria (see phone script).
- The Research Coordinator will obtain informed consent from eligible participants, including parental permission for their child to participate, child assent to participate, and parental consent to participate. (see sections 30, 31 on Consent)
- After all questions are answered regarding the study by the parent, the Research Coordinator will send the baseline survey via email to the participant to be completed by the parent and child together or will complete the survey over the phone with the child and parent.
- The Research Coordinator will then access the child's medical record and obtain the discharge summaries, the emergency service records, the office/clinic notes, the problem list, the pulmonary studies, the child's list of medications, and the child's height and weight (to help interpret the spirometry data).
- The Research Coordinator will then call the child's pharmacy to obtain refill history for their daily ICS inhaler.

We anticipate that recruitment of n=72 dyads will take 18 months based on Dr. Pbert's FITLINE study [18]. We do not anticipate issues with this recruitment based on prior recruitment of families for Asthma Link™ from the Worcester community in our pre/post study and based on prior recruitment from these same pediatric practices in the FITLINE study. (also see page 19 which describes estimated number of asthmatics in proposed Pediatric practices, demonstrating feasibility of recruitment). The Institutional Review Board will review all research procedures and protocols. All instruments will be submitted to the IRB for review and approval prior to use.

We will not enroll any participants in the study prior to receiving IRB approval.

SURVEY – PARENT AND CHILD – 20 MINUTES _See uploaded parent baseline, parent 3 month, parent 6 month, and parent 12 month surveys.
The 4 parent surveys will include the following constructs: Patient Health Outcome questions including the Asthma Control Test (ACT; measure of severity of asthma symptoms) and the Maximum Asthma Symptom Days (MSD), Emergency Department visits, hospital admissions, school absences, oral steroid usage and pharmacy refill data. The Baseline survey will include demographic questions that ask about the parent's age, sex, race/ethnicity, relation to the child participating in the study, education, marital status, tobacco usage, health insurance, contact information, family functioning, comorbidities, income, and average monthly as a proxy for socioeconomic status. The 3 month, 6 month, and 12 month follow up surveys for the Asthma Link™ condition will also include the following constructs: acceptability, cost, and sustainability. All surveys will be completed either on-line using RedCap (Please see data management) or over the phone with the Research Coordinator. We are using emails and/or phone calls to deliver/collect these surveys. As soon as the baseline survey has been completed, those completing the survey via email will be automatically sent out future surveys.

SURVEY – SCHOOL NURSE – 10 MINUTES _See uploaded school nurse baseline and end-of -intervention surveys.
The school nurse survey will include the following constructs: acceptability, cost, and sustainability. All surveys will be completed either on-line using RedCap (Please see data management section) or over the phone with the research coordinator. We are using emails and/or phone calls to deliver and collect these surveys.

SURVEY – MEDICAL PROVIDER – 5 MINUTES _See uploaded medical provider baseline and end-of-intervention surveys. The medical provider survey will include the following constructs: acceptability, cost, and sustainability. All surveys will be completed either on-line using RedCap (please see data management section) or over the phone with the research coordinator. We are using emails and/or phone calls to deliver and collect these surveys.

SURVEY- ASTHMA CHAMPION- 5 MINUTES_See uploaded asthma champion baseline and end-of-intervention surveys. This will include the same constructs of acceptability, cost and sustainability. Surveys will be completed either on-line using RedCap (please see data management section) or over the phone with the research coordinator. We are using emails and/or phone calls to deliver and collect these surveys.

We will be accessing the practice's medical record system (same system as above, e.g., Epic) to obtain documentation of the child's emergency room visits, hospital admissions, and oral steroid courses at the baseline time point (recording the number of events for the 6 months prior), 3 month, 6 month, and 12 month time points (recording the number of each of these events for the 3 or 6 months prior.). This data will also be collected 12 months following the completion of the 12 month survey in order to observe for sustained impact on health outcomes and to see if engagement in Asthma Link continues beyond one year. This data will be directly put into the RedCap database without any downloading of information. (please see data management section)

We will be contacting the child's pharmacy to obtain refill history of their daily ICS medication at baseline (obtaining the number of refills for the prior 6 months), 3, 6, and 12 months, and 12 months following the completion of the 12 month survey to assess for medication adherence. This data will be entered directly into the REDCap database.

Portable Spirometry: At baseline, 3, 6, and 12 months the child will perform spirometry in the school nurse's office. The Research Coordinator will perform portable spirometry in the school at the time that the student normally reports to the nurse for their daily asthma medication so as not to disrupt the child's school activities. Given that the spirometry test takes less than 3 minutes to complete for each child, we are confident that it will not pose a disruption to the child's school activities. The Research Coordinator will enter the spirometry data into RedCap for each participant without downloading any data.

School absence data will be collected through school nurse report and will be recorded from the school nurse on the School Nurse checklist and faxed to the Research Coordinator.

Asthma Link Condition: Those practices that are randomized to the Asthma Link group will receive pediatric pulmonologist delivered trainings for pediatric practices on behavioral strategies to help promote asthma medication adherence and a 1 hour training on the Asthma Link clinical program and how to enroll children in Asthma Link (reviewing the steps of this clinical program- see "Asthma Link Clinical Program Steps") and carry out this evidenced-based program in the context of their clinical practice (reviewing the steps to Asthma Link and answering any questions they may have).

Comparison Condition: Those practices that are randomized to the Enhanced Usual Care Comparison Group will receive pediatric pulmonologist delivered trainings for pediatric practices on behavioral strategies to help promote asthma medication adherence. These include training to counsel patients on the strategies such as the placement of cell phone alarms to remember to take their daily medicine and placement of an elastic band around the inhaler and the toothbrush so that a child always remembers to take their daily inhaler before brushing their teeth. We thought it ethically important to provide more than just usual care to the 2 pediatric practices assigned to the comparison condition.

Families who agree to participate in the study from either the Asthma Link or Enhanced Usual Care practices will receive a mailed "Asthma Workbook" to aid in their understanding of asthma, support their asthma care and help with daily medicine adherence (See Asthma Workbook)

12. DATA AND SPECIMEN BANKING*
N/A

13. Data Analysis and Management*

Sample size calculation

In order to obtain a sample size of 72 parent-child dyads to complete the research, we will potentially enroll up to 100 parent-child dyads. Because pilot studies do not provide meaningful estimates of effect sizes for between-condition comparisons, due to the imprecision inherent in data from small samples [19,20] we base our proposed sample size of 72 parent-child dyads (36 per condition, 18 per practice) on pragmatics of recruitment, retention and the necessities for examining feasibility, providing important information for design and recruitment for the future R01 study to test the impact of Asthma Link™ in a large cluster RCT. We will identify refinements required to implement the large cluster RCT by obtaining data about several process outcomes as well as feasibility of recruitment, retention, engagement, fidelity and assessment procedures of Asthma Link™.

Taking estimation of retention rate as an illustrative outcome, and applying an intra-class (pediatric practice) correlation of 0.01, similar to the value of 0.006 from Dr. Pbert's prior studies of school-based teen smoking, the resulting design effect=$1.19 = 1 + [1 + 0.01 \times 9]$[21] yields an effective sample size of 20/1.09 ≈18 dyads/condition. For a conservatively low retention rate of 80%, lower than the 97% observed in Dr. Pbert's previous FITLINE study,[18] we can estimate a 95% confidence interval for retention percent of (51.9%, 95.7%) for each practice separately or (68.9%, 88.5%) combining all 4 practices. A sample of 18 dyads per practice (36 per condition) yields 95% confidence intervals for practice ICC of (0.018, 0.094) for a conservatively large true ICC=0.05.[22] Because estimates from pilot studies alone tend to be underpowered due to the variability in estimated standard errors,[19,20] we will combine our results (including the ICC) with clinically meaningful effect and results of previous adequately powered interventions to calculate sample size requirements for our large cluster RCT. Data from the recruited pediatric practices show that 5-7 very poorly controlled asthmatics are seen per month.

Statistical Analysis: To assess feasibility outcomes in Aim 1, we will estimate parameters relevant for planning a larger study, including standard deviations of outcomes and ICC. We will also conduct preliminary analyses of the impact of Asthma Link™ on asthma outcomes. We will compare participants in the two arms (Asthma Link™ and comparison group), using methods such as parametric or nonparametric t-test or Poisson regression, depending on the observed outcome distribution. Some outcomes may have a Poisson distribution, such as hospital admissions, while spirometry values may be continuous. Intent-to-treat and completer analyses will be performed. The data collected in this proposal will provide estimates of trial retention, ICC, standard deviation, and effect size. We will use these and data published in the literature to estimate sample size for a larger trial. The secondary outcomes analyses of asthma health outcomes will be exploratory by necessity given the pilot nature of this study.

Data will be collected at baseline (study entry), and at 3-, 6-, and 12-month follow-up in the privacy of the parent/child's home as the parent/child survey will be sent through email, in the pediatric practice staff's office or home (for pediatric provider and asthma champion surveys which will be sent through email), in the school nurse office of home (for school nurse surveys which will be sent through email). Assessments will be pre-tested to ensure the time burden does not exceed 30 minutes. The parent/student survey and assessment tools for this study will be adapted from Dr. Pbert's prior adolescent smoking cessation trials and our pre/post study [14,18]. Data confidentiality will be emphasized on the surveys and verbally by Research Coordinator, and by the use of a unique study identification number.

Data Management: The surveys will be conducted either over the phone or by using the REDCap™ system, a nationally used secure, web-based database application (http://project-redcap.org) that provides: 1) an intuitive interface, 2) audit trails for tracking data manipulation and export, 3) procedures for importing data from external sources, 4) easy development of web survey tools and 5) automated export procedures to various statistical packages.

14. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS*

Potential Risks and Adequacy of Protection Against Risks. The interventions (both Asthma Link™ and Enhanced Usual Care) in this proposal are state-of-the-art, developed by a Pediatric Pulmonologist and represent good standards of care as recommended by the National Asthma Education and Prevention Program and the American Academy of Pediatrics and the American Academy of Asthma, Allergy, and Immunology. Asthma Link™ practices are evidenced-based and have not shown any adverse events in multiple prior studies.[13,14] The potential risks of the evaluative research component of this project are minimal. Some participants may have concerns about the confidentiality of their surveys and study records. The Research Coordinator and Primary Investigator will emphasize the confidentiality of all data collected and reassure and address any participant with concerns. Participant confidentiality will be maintained through a number of strategies. Each participant will be assigned a unique study identification (ID) number. Any link between the unique study ID and participant identifiers such as demographics, asthma health data, and questionnaire data will only be accessible to the Primary Investigator and Research Coordinator responsible for data collection and will be maintained in a secure, encrypted, password-protected, HIPAA compliant research drive. Other UMMS personnel will not be privy to identifying information about the individual participants and the link between study ID and identifiers will otherwise be destroyed. Given the minimal risk nature of this study, a data monitoring committee would not be necessary.

All data stored within computer files will be password protected behind a firewall to ensure that access is available only to those directly involved in the study analysis. Only data that has been stripped of all personal identifying information is made available to the data management (e.g. RedCap) systems;

At study completion, the link between the identifying information and their data will be destroyed, as will be contact information.

Finally, all study staff will complete the CITI Course in the Protection of Human Research

Subjects and Good Clinical Practices online training in research ethics to ensure that all staff are compliant with confidentiality training.

Monitoring Adverse Events.

The principal investigator and research coordinator will be responsible for monitoring adverse events during the study, with Dr Pbert assuming this responsibility if these individuals are unavailable. The role of the responsible person is 1) to identify the concern through assessing for health changes at each survey; 2) develop an appropriate response that involves consultation whenever possible to alleviate or minimize any adverse event (AE); and 3) to ensure that the adverse event is reported in a timely manner to the responsible authority. We will collect adverse events that are volunteered spontaneously during interactions with participants. Participants will be monitored for occurrence of events defined as any undesirable experience or unanticipated benefit. Events may occur during recruitment, intervention deployment, and follow-up assessments. Based upon previous research in school-supervised asthma therapy, we anticipate that adverse events or experiences will be rare. The Principal Investigator will assess whether an undesirable experience or unanticipated problem occurred (adverse event) and will record details of all adverse events on an adverse event case report form.

Although our study poses minimal risk to subjects and no adverse events are expected due to the nature of the study, we will follow the adverse event procedure of the University of Massachusetts Medical School. The current policy for reporting unanticipated problems and adverse events for the protection of human subjects in research at the University of Massachusetts Medical School is as follows:

"All adverse events involving risk to subjects or others that are serious and unanticipated and related to the study procedures must be reported, using the applicable Prompt Reporting Form, within 48 hours of the investigator becoming aware of the event.

All unanticipated problems which are unexpected and suggest that the research places subjects or others at a greater risk of harm and are related to the research must be reported, using the applicable Prompt Reporting Form, within 48 hours of the investigator becoming aware of the event.

In certain situations, this requirement for prompt reporting may necessitate the submission of a report before all information has been collected. In these situations, a preliminary report may be submitted with a follow-up report submitted at a later date when more information is available.

Events/problems which are not serious, are anticipated and not related to the study procedures must be reported in summary format at the time of continuing review."

Adverse events that do not meet the requirements of prompt reporting will be provided at the time continuing review is submitted. The continuing review form in the UMMS eIRB will request this information.

We do not anticipate that any serious adverse events (death, life threatening illness, new serious or permanent disability) will occur. However, should such an event occur, the Principal Investigator will report the event within 24 hours of initial receipt of information to the University of Massachusetts IRB and NHLBI program officer. Other serious and unexpected AEs related to the study will be reported to the Program Officer within 5 days. Unanticipated

problems (that are not serious AEs) will be reported to the UMass IRB and the NHLBI Program Officer within 14 days of becoming aware of the problem. Any reports sent to the funding agency about the event will be included in the report to the IRB.

The adverse event case report form will include a description of all undesirable experiences, required interventions, and an assessment of the subject after the event if possible. An estimate of the extent of injury, and prevention strategies will be reported. The Principal Investigator will classify the relationship of the study protocol to the event as follows:
• Not related: The event is clearly related to factors such as the participant's clinical state, not with the study protocol.
• Remote: The event was most likely related to factors such as the participant's clinical state, not with the study protocol.
• Possible: The event follows a reasonable temporal sequence associated with participating in the study and/or is consistent with events related to receiving the intervention but is possibly related to factors such as the subject's clinical state.
• Probable: The event follows a reasonable temporal sequence associated with participating in the study and/or is consistent with receiving the intervention and cannot be reasonably explained by factors such as the subject's clinical state. The severity of an adverse event in both groups is defined as a qualitative assessment of the degree or intensity of an adverse event as determined by the principal investigator as follows:
• Mild: No impact (in anyway) on the participant.
• Moderate: Impacts on the participant but is not life-threatening or incapacitating.
• Severe: Fatal, life threatening, permanently disabling; severely incapacitating; requires immediate medical evaluation.
All adverse events will simultaneously be reported to institutional officials. The report will summarize the facts of the case, including the date and a description of the participant; whether the event is related to the study's protocols; the steps that have been taken to address the issue; whether the event provides emerging knowledge about the risks of the study that should be conveyed to respondents; and whether the consent form should be revised.

Anticipated Adverse Events.
Given that this is a minimal risk study, a data monitoring committee and/or a data safety monitoring board is not required for this study. An adverse events log is inappropriate for this type of study. Alternatively, the PI will periodically examine the data and should any research-related unexpected events arise, the PI will evaluate the event per the procedure listed above and will adhere to the institution's prompt reporting requirements. We do not anticipate any adverse events from this study as the primary procedures involve minimal risk surveys, checklists and routine clinical spirometry.

In this research, the risks that result from study participation are considered minimal as the research is primarily evaluative with the use of surveys and performance of spirometry. The major risks are:
• Risk of loss of confidentiality: The protections against confidentiality loss have been described The PI is principally responsible for ensuring that there is no loss of confidentiality during the course of the study. Any loss that occurs despite these protections will be evaluated on an individual basis.

• Risk of Spirometry: Spirometry is a routine, non-invasive clinical test that is commonly performed in children with asthma. This test has been used both clinically and in research without any adverse events.[23,24] There are no risks associated with spirometry except for the potential for a slight dizzy feeling and/or temporary cough. These symptoms are not always present and are temporary. In order to minimize risks, the participant will be in a seated position with adult supervision and a trained technician will perform spirometry, with physician available by phone for concerns or questions. We will follow institutional policies for prevention of Covid transmission, which includes the technician wearing a surgical mask with eye protection and using a new disposable mouthpiece for each participant. For this study the test is performed without the intent of yielding direct health benefit.
• Risk of discomfort while answering questions: Some subjects may feel uncomfortable answering certain survey questions (e.g., questions about family income) however subjects will be notified that they are welcome to skip questions or withdraw from the study at any time without penalty.

Given that this is a minimal risk study, the only foreseeable risks to the subjects include the possible loss of confidentiality. To address this, all participants will be given information on ways to contact Dr. Trivedi and the University of Massachusetts Medical School IRB

Data and Safety Monitoring Board (DSMB)
Given that this is a minimal risk study (wherein participants agree to enroll in the study after they become part of the Asthma Link program if they are in the Asthma Link practices or after they fit study inclusion criteria if in the Enhanced Usual Care practices), participants will primarily be evaluated through surveys, interviews, and spirometry, and therefore a data monitoring committee and/or a data safety monitoring board is not appropriate for this study. Alternatively, the PI will periodically examine the data and should any research-related unexpected events arise, the PI will evaluate the event per the procedure listed above and will adhere to the institution's prompt reporting requirements. We do not anticipate any adverse events from this study as the primary procedures involve minimal risk surveys, checklists and routine clinical spirometry.

This research is not designed to discover incidental findings and therefore we do not plan to follow up on incidental findings

15. WITHDRAWAL OF SUBJECTS WITHOUT THEIR CONSENT*
Subjects will be withdrawn from the research if they appear to be unduly distressed

16. RISKS TO SUBJECTS*
In this research, the risks that result from study participation are considered minimal and primarily involve the risk of loss of confidentiality.

• **Risk of loss of confidentiality:** Dr. Trivedi is principally responsible for ensuring that there is no loss of confidentiality during the course of the study. Any loss that occurs despite these protections will be evaluated on an individual basis.

• **Risk of spirometry:** Spirometry is a routine, non-invasive clinical test that is commonly performed in children with asthma. This test has been used both clinically and in research without any adverse events.[23,24] There are no risks associated with spirometry except for the potential for a slight dizzy feeling and/or temporary cough. These symptoms are not always present and are temporary. For this study the test is performed without the intent of yielding direct health benefit.

• **Risk of feeling uncomfortable answering questions:** Some subjects may feel uncomfortable answering certain questions (e.g., questions about family income) however subjects will be notified of this in the fact sheet (see fact sheet) and will be told that they are welcome to withdraw from the study at any time without penalty.

Given that this is a minimal risk study, the only foreseeable risks to the subjects include the possible loss of confidentiality. To address this, all participants will be given information on ways to contact Dr. Trivedi and the University of Massachusetts Medical School IRB.

17. POTENTIAL DIRECT BENEFITS TO SUBJECTS*

The potential benefit gained by study participants is the improvement of their personal health status through the prevention of asthma-related health risks for those with improved adherence to their preventive medication. In addition, each individual participant is contributing to the evaluation of childhood asthma interventions for school-aged children. Potential benefits to society and the larger community include the implementation of effective evidenced- based asthma interventions for school-aged children and increased capability to deliver intervention programs to children and families. These benefits are substantial in comparison to the minimal risk possible.

18. VULNERABLE POPULATIONS*

This research will involve children. The description below explains the importance of including children to perform this research and the safeguards, which will protect their rights and welfare.

Childhood asthma affects 12-15% of children in the urban United States with considerable morbidity and healthcare costs, despite aggressive efforts to address remediable causes.
There exists extremely effective therapy for childhood asthma: inhaled corticosteroids (ICS). However, ICS are grossly underutilized with adherence rates at less than 20%, particularly in low-income, minority patients. Racial and socioeconomic disparities in childhood asthma are grave, with the highest rates of emergency room visits and hospitalizations for asthma occurring in low income and minority children. In spite of increasing recognition of the profound negative effects on children and families, which are mitigated by effective preventive therapy, including daily use of ICS, childhood asthma remains undertreated. Recognizing this gap, the NHLBI Expert Panel on Asthma emphasizes that asthma self-management is essential and there have been three successfully conducted trials of school-supervised ICS therapy in school-aged children.

Despite their success at improving ICS adherence rates and asthma symptoms, these research-tested interventions have not been adopted in real-world practice. This is due in part to high cost and high intensity approaches that are not feasible in the real world. This study seeks to

investigate a practical strategy (the Asthma Link™ program) to promote the uptake of school-supervised asthma therapy, which has been found to be safe and efficacious, into regular practice. This study will directly inform a large-scale cluster randomized controlled trial trial to test the effectiveness and implementation of Asthma Link with the goal of improving childhood asthma outcomes on a large public health scale.

- The parent/legal guardian will provide verbal consent for both the child to participate in the study and for them to participate in the study.
  - Research staff will mail interested families the fact sheet and contact them by phone to explain the study and describe the parent/legal guardian and child's potential role. The confidentiality of all collected information will be emphasized, and it will be explained that the child's care in the pediatric practice will in no way be affected by whether or not they participate in the study. The parent/legal guardian and child will be provided the opportunity to have questions answered by the research staff. If interested, parental/legal guardian consent and child assent will be requested and provided verbally during the call.
  - All questions will be answered before a parent gives verbal consent and child gives verbal assent, which will serve as the overt agreement to participate.
  - We will not enroll an individual if there is any sign of unwillingness to participate.
  - If a person is not eligible for the study or not willing to participate, they will not be consented or assented.
- Subjects will be withdrawn from the research if they appear to be unduly distressed.

We will obtain permission from one parent/legal guardian who will be joining the study with the child given that this is a minimal risk study.

Research staff will mail interested families the fact sheet and HIPAA authorization and contact them by phone to explain the study and describe the parent/legal guardian and child's potential role using a standardized information sheet. The confidentiality of all collected information will be emphasized, and it will be explained that the child's care in the pediatric practice will in no way be affected by whether or not they participate in the study. The parent/legal guardian and child will be provided the opportunity to have questions answered by the research staff. If interested, parental/legal guardian consent and child assent will be requested and provided verbally if the adult and child are both available at the time of the phone call.

We will answer all questions the child and parent/legal guardian may have prior to the child giving verbal assent.

- We will not enroll a child if there is any sign of unwillingness.
- We will not obtain verbal consent or assent for anyone who is not eligible or not willing to participate.

This research may also involve women who are or may become pregnant. No inducements, monetary or otherwise will be given to any pregnant woman participating in this study to terminate her pregnancy. The PI and the RC will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy. Also, the PI and the RC will have no part in determining the viability of a neonate in this study. Given that this is a minimal risk study, we believe that this study poses no risk to a pregnant woman or the fetus and does not require any additional safeguards.

19. MULTI-SITE RESEARCH*

We will be recruiting patients from 4 pediatric offices. The physicians and staff in these practices will not:

a. Obtain data about subjects through interaction for research purposes
b. Obtain informed consent or assent of subjects to take part in the research
c. Obtain identifiable private information about subjects for research purposes.

The practices performed by the physicians and office staff for enrollment in Asthma Link are considered good clinical practice based on the evidence described previously for school-supervised asthma therapy.[13-15]

20. COMMUNITY-BASED PARTICIPATORY RESEARCH*

N/A

21. SHARING OF RESEARCH RESULTS WITH SUBJECTS*

We will ask participants if they are interested in receiving a summary of the study findings. If they are, they will be added to an email list (a mailing address will be obtained for anyone who prefers this to an email address). Once the study has been completed, we will send a lay summary of the results to participants who indicated interest

22. SETTING

This pilot feasibility study will take place in 4 Pediatric Primary Care practices in Worcester MA: Benedict Pediatrics, Worcester Pediatrics, Quality Kids and Harding Pediatrics. These particular sites were selected due to their high rates of asthma and matching for relevant demographics. We have worked with these sites in Dr. Pbert's prior FITLINE study. If there are logistical issues with any of these practices after commencement of funding, we have identified 4 alternative practices in Worcester as backups.

23. RESOURCES AVAILABLE

This study includes the PI, research coordinator, research assistants, statistician and senior mentor. Collectively the staff has over 40 years of clinical research experience at UMMS. The roles of each research staff member is listed below:

Principal Investigator (PI) (0.75 FTE): This position requires advanced training in Pediatric Pulmonology, research design and methods. The PI is responsible for ensuring that all team members have current CITI training, appropriate training for their respective

roles, including knowledge of the study protocol and procedures for maintaining confidentiality. This person will oversee all aspects of the study, data acquisition, and data analysis.

Research Coordinator (0.6 FTE): This position is a specialized research professional working with and under the direction of the clinical Principal Investigator (PI). The Research Coordinator supports, facilitate and coordinate the daily clinical trial activities and plays a critical role in the conduct of the study. The responsibilities include: maintaining records, handling IRB submissions, data management, and performing any other study related procedures that fall within their scope of practice only after receiving the appropriate training required to perform the procedures.

Research Assistants (0.2 FTE): Responsibilities include support of study recruitment, data management, data analysis, and other study related activities deemed appropriate by the PI.

Statistician (0.01 FTE): This position requires training in statistics. The statistician will be responsible for data analysis and performing any other study related procedures that fall within their scope of practice only after receiving the appropriate training required to perform the procedures.

Senior Mentor (0.01 FTE): A Ph.D, Senior level investigator who will dedicate her time in-kind to oversight of this project

All study staff will be supervised by the PI and will have completed CITI/GCP certification. All persons assisting with the research will be trained and monitored by either the PI or the Research Coordinator and will be given copies of the procedures for performing this research.

24. LOCAL RECRUITMENT METHODS

Justify the feasibility of recruiting the required number of suitable subjects within the given recruitment period. For example, how many potential subjects do you have access to? What percentage of them do you need to recruit?

Feasibility of Recruitment: Rates of asthma approximately range from 15%-25% among the practices' patients, with a mean of 18.5%. Given this rate and number of patients, we are very confident that we will be able to recruit 13 families per practice over the course of the one and a half-year recruitment period.

Describe when, where, and how potential subjects will be identified and recruited. If recruiting in a clinical setting, will clinical staff ask potential subjects if it's ok for study staff to approach? If recruiting by mail, will letters come from the subject's clinician or clinic head?

For the sites that are randomized into the intervention arm of the study, a one page flyer for the clinical Asthma Link™ program will be placed in each of the exam rooms in the clinics and will encourage families to ask their providers about Asthma Link™ if they have a child who has asthma. The flyer will only advertise the clinical Asthma Link™ program. Additionally, triage nurses at these sites may remind providers to screen potentially eligible patients for the clinical Asthma Link™ program when scheduling sick visits related to Asthma or breathing

problems. During the clinic visit, the pediatric provider will give the family a one-page description of the study and, if interested, will send a referral to the study. Research staff will mail the family the fact sheet and HIPAA authorization, contact them by phone to explain the study, and obtain verbal consent for those interested. Research staff will send an email link to access the survey to families who provide verbal consent. The 4 pediatric practices participating in the trial estimate 7,462 children total in their practices between children in grades 1-6; with a conservative estimate of 15% with asthma symptoms, this provides approximately 1,119 children from which to recruit 40 children into the trial, making recruitment highly feasible.

Describe how individuals will be screened for eligibility. Will any identifiers be recorded? If so, when will identifiers be de-linked from the data and when will identifiers be completely destroyed? Be sure to address individuals who enroll and individuals who turn out to be ineligible or who decline to participate.

The fact sheets and the HIPAA authorization form will be mailed to the potential participants with a letter saying that the Research Coordinator will call them. The Research Coordinator will contact the parent by phone to explain the study and describe the parent/legal guardian and child's potential role using a standardized information sheet. The Research Coordinator will answer any questions about the study and **obtain** verbal consent. Once the parent provides consent, the Research Coordinator will obtain verbal assent from the child. The Research Coordinator will then email the link to sign the HIPAA authorization. Once the HIPAA authorization is signed, the Research Coordinator will then email the link to complete the survey via REDCap. The Research Coordinator will only call the family five times. The first time a message will not be left. The second, fourth and fifth time a message will be left saying "This is X from the University of Massachusetts Medical School. I am calling about the material I sent you. Please call me back at X. (please see uploaded flyer and phone script). Enrollment will not begin until IRB has approved these materials. Individuals who decline to be contacted or who decline to participate in the study will not be contacted.

Describe the amount, method, and timing of any payments to subjects.
To compensate participants for their time, and to incentivize participation in the completion of all assessments, we will provide compensation to each parent-child dyad in the form of gift cards to a local retailer (i.e., Target or Wal-Mart). Compensation will be divided through the study period (a $30 gift card for each parent-child dyad on enrollment and completion of baseline assessment, another $30 gift card at 3-month assessment, a $30 gift card at 6-month assessment, and a $40 gift card at the 12 month assessment). We will also be mailing families with a short hand-written thank you note and 'prize' after the 3 month survey (stickers), 6 month survey (small toy prize), at the 9 month time point (magnet or postcard with reminder for 12 mo survey), and after the completion of the 12 month survey (completion certificate). All mailings will be in a sealed envelope to protect confidentiality. Pediatric practice sites will be provided lunch during their information session for the research study which will be funded by the NIH KL2TR001454 award and will be considered separate from the subject compensation.

School nurses participating in the study will receive a $35 honorarium for their help with completing the School Nurse checklist and for completing the brief surveys.

Asthma Champions will receive $15 for completing the baseline survey and $20 for completing the follow-up AC survey for a total honorarium of $35.

We will provide coffee and donuts to the medical provider's practice if all participating providers complete both the baseline and follow-up surveys.

Upload copies of recruitment materials, including flyers, emails, letters, phone scripts, etc., to eIRB. For advertisements, upload the final copy of printed advertisements. When advertisements are taped for broadcast, provide a link to the final production of the audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording; however, the IRB must review and approve the final audio/video tape.

See flyer and phone screen

25. LOCAL NUMBER OF SUBJECTS

200 parents and children in grades 1-12 (aged 6-17 years) (i.e. 100 parent-child dyads total) with asthma will be recruited from the practices (25 parent-child dyads/practice) to achieve a retention of N=144 parents and children (i.e. 72 parent-child dyads) at the end of the study (from the 4 practices) at 12 month follow-up.

If two siblings are eligible for Asthma Link and this study, both children may participate in Asthma Link clinical program but only one child per family may be allowed to participate in the research study. We will grant the parent/guardian permission to choose which child they would like to participate in the research arm of the study.

Up to 16 Pediatric providers participating in Asthma Link™ will be recruited from the participating practices to participate in this study.

Up to 50 School nurses participating in Asthma Link™ will be recruited from the schools that the children participating in the study attend to participate in this study.

Up to 4 Asthma Champions participating in Asthma Link™ will be recruited from the participating practices to participate in this study.

26. CONFIDENTIALITY

Protection of study data will be assured by the use of locked files and password-protected computer databases with access available only to the principal study personnel. The data files will also be encrypted. Besides UMMS IRB, the NIH, research, and compliance offices, the only individuals to have access to these identifiers are the PI and the Research Coordinator. The data will be stored for at least seven years unless directed otherwise by the research organization.

Study participants will be provided with a unique de-identified research ID code. We will create a database with ONLY the de-identified separate research ID for each subject and then

associated collected survey data. The Name and DOB will be hidden and protected through REDCap database privacy settings. (see Data Management section)

Any link between the de-identified research ID code and the patient's protected information (such as name, dob) will be only accessible to Principal Investigator, study staff for this project and will be maintained in a secure, HIPAA compliant research drive. The link between the two will otherwise be destroyed.

We will not download any information. The Research Assistant or Research Coordinator will place all data collected directly into the secure protected REDCap database and the survey information is performed directly within REDCap through REDCap surveys.

Data for analysis will be completely de-identified.

27. Provisions to Protect the Privacy Interests of Subjects

Potential subjects will have ample time to read the consent and assent and ask any questions. It will be explained that the family's overall care at the clinic will in no way be affected by whether or not the child participates in the study and that confidentiality will be maintained. Children and parents/legal guardians will be informed that they can stop participating at any time without reason, if they so request.

We are accessing records before they enter the study and we are requesting a HIPPA waiver in order to identify potential subjects for this. We will obtain HIPAA authorization via electronic signature for the PHI that will be collected during the study. (see HIPAA waiver and HIPAA Authorization).
After the family interacts with the medical provider and consents to be contacted, they will provide their name, address, phone number, and email to be contacted.

The fact sheet (which will be mailed to the house and then reviewed over the phone in addition to the HIPAA authorization) will describe that we will be accessing the child's medical record and communicating with their school nurse and pharmacist to obtain information about emergency room visits, hospital admissions, oral steroid bursts, spirometry results, and pharmacy refill data.

28. Compensation for Research-Related Injury

Given that this is a minimal risk study no funds have been set aside.

29. Economic Burden to Subjects

Based on prior research experience, this study will not generate economic burden as a result of participating in this study to the families of the participating children with asthma, the participating pediatric practices, the practices' providers, the schools, or the schools' participating nurses.

30. Consent Process

We are following SOP: Informed Consent Process for Research. Potential participants will be provided a mailed fact sheet prior to receiving a phone call from the Research Coordinator.

The study will be described in full detail and all of the potential subject's questions will be answered. Subjects will be informed about all of the risks described above and all aspects of the study. The consent/assent process is expected to take 20-30 min. We will minimize the possibility of coercion or influence by providing subjects the opportunity to call back. They will have the opportunity to opt out at the initial phone contact or at any point including while the study is underway. The Research Coordinator conducting the process will determine that the subject understands the information provided and is capable of making and communicating an informed consent or assent and will document this. After the informed consent and assent are obtained subjects will be emailed the baseline survey assessment.

31. Process to Document Consent in Writing

We are asking for a waiver of written consent for the provider survey as this poses minimal risk and the research involves no procedures for which written consent is normally required outside of the research context.

We are asking for a waiver of written consent for the parent and written assent for the child as this poses minimal risk and the research involves no procedures for which written consent is normally required outside of the research context.

32. Drugs or Devices

N/A

eIRB Section 7.0 Attachments Upload Checklist

Follow How to Manage Files in eIRB and upload the following items as applicable to your submission. This checklist is provided for your convenience and is not a requirement for review.

	Investigator Study Plan
	Sponsor protocol
	Research portion of the grant
	Human subjects portion of the grant
	Written approvals from ancillary reviews (Clinical Engineering, COI, IBC, PRC, RSC, Students as Subjects, etc.)
	Recruitment materials such as flyers, brochures, posters, scripts of radio ads, etc.
	Data collection sheets, case report forms, etc.
	Surveys, measures, instruments, etc.
	Measures to assess capacity to consent
	DMC or DSMB charter
	Data safety monitoring plan
	Adverse event log
	Investigator brochure or package insert for drugs
	Instructions for use or approved FDA labeling for devices
	Sponsor justification or FDA documentation for non-significant risk device study
	IND or IDE documentation
	Patient information sheet for Humanitarian Use Device

	Approval order for Humanitarian Use Device
	Product labeling for Humanitarian Use Device
	HIPAA waiver
	HIPAA authorization
	Authorization to contact form
	Consent form(s)
	Assent forms(s)
	Fact sheet(s)
	Multi-site communication plan
	Study staff training plan
	SOPs or Manuals of Operations
	Screening log
	Compensation log
	Certificates of translation or translator attestations
	Data use agreements, memoranda of understanding,
	Documentation of data/specimen anonymity (i.e., provider will never break the code)

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