Self-care Decision-making: Feasibility of the BREATHE Asthma Intervention Trial - Phase II (Part 2 - a Pilot Randomized Trial Phase)

NCT03300752

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## STUDY PURPOSE AND RATIONALE

### Study Purpose

The **overall goal** of this study is to develop and to preliminarily validate a novel intervention delivered by primary care providers (PCPs) to their Black adult patients with uncontrolled asthma in federally qualified health centers (FQHCs). We recently developed and rigorously tested a brief questionnaire, the Conventional and Alternative Management for Asthma (CAM-A) tool[1,2], that screens patients for beliefs about asthma self-care and inhaled corticosteroid (ICS) treatment and prompts PCPs to discuss ICS adherence at office visits based on patient CAM-A responses[3]. In over 300 adults (80% Black; 67% uninsured or government-insured) with high rates of uncontrolled asthma (69%), the validated CAM-A identified that erroneous personal health beliefs and negative ICS beliefs were commonly endorsed (93% and 68%, respectively)[1]. Importantly, erroneous personal health beliefs were significantly associated with uncontrolled asthma, likely driven by ICS non-adherence. In the first phase of this trial we held six focus groups (AAR0605) with adult asthma patients and their loved ones to inform the intervention by adapting an evidence-based brief shared decision-making strategy with proven efficacy[4-6], delivered by PCPs, for use with our validated CAM-A tool. As such, this project has three **specific aims**:

**Specific Aims:**

1. **To develop an intervention to improve asthma control in Black adults receiving care in FQHCs (completed);**
2. **To evaluate the feasibility and acceptability of the intervention procedures; and**
3. **To assess the preliminary evidence of intervention effects on asthma control (primary outcome), ICS adherence, forced expiratory volume in one second ($FEV_1$) – an objective lung function measure – and asthma quality of life (secondary outcomes) over a 3-month follow-up period.**

**Please note, we already have IRB approval for Phase I (focus group and PCP review only). Focus groups are completed and independent PCP review is about to begin (AAR0605).**

**In this application we are seeking approval of Aims #2 and #3 (Phase II-pilot intervention).**

### Background / Rationale

**Uncontrolled asthma due to ICS non-adherence is common among Black adults.** Nearly every asthma-related hospitalization and death could be prevented with appropriate self-management that achieves and maintains disease control[7-10]. However, as many as 64% of adults have uncontrolled asthma[11]; minorities are disproportionately represented within that population[12]. While inhaled corticosteroids (ICS) are a safe and effective treatment for uncontrolled asthma, relative to Whites, Blacks have lower rates of ICS adherence (74% vs. 29%)[13-17].

**Health beliefs are associated with ICS non-adherence.** Erroneous personal beliefs about asthma and its pharmacologic treatment are among the most significant factors contributing to ICS non-adherence[18-21]. ICS non-adherence, a primary cause of uncontrolled and/or fatal asthma[7], is more common in Blacks relative to Whites[13-17] due, in part, to higher rates of endorsement of non-pharmacologic approaches to asthma self-care[1] (e.g., coffee is a safe, effective asthma treatment) and negative ICS beliefs[13-15,22-29] (e.g., ICS is addicting)

These beliefs have been shown to be associated with ICS non-adherence[22,23,27], more asthma attacks[22,30] and delays in seeking care[23].

**There are unique challenges to achieving asthma control in FQHCs.** PCPs deliver up to 80% of asthma care. However, compared to specialists, uncontrolled asthma is more common in their patients[31]. There are unique challenges to achieving asthma control in FQHCs, a particular type of primary care setting designated to receive enhanced Medicaid reimbursement because their clientele are underserved, underinsured, and uninsured Americans who receive more episodic primary care[32]. In these settings PCPs have limited time to evaluate asthma control, to assess ICS non-adherence, and to identify beliefs associated with ICS non-adherence[33]. This speaks to the pressing need for novel brief interventions that facilitate evidence-based guideline-directed asthma self-management.

**Shared decision-making interventions to promote asthma control in this vulnerable population are lacking.** The study is guided by the theoretical model of Shared Decision-Making in evidence-based practice[34], which posits that the best treatment decisions are informed by patient's preferences, the best available evidence, and practitioner expertise. The PCPs role is to facilitate discussion of the risks and merits associated with specific options in the context of patients' goals and preferences, and in a manner that activates patients to engage in self-management. PCPs offer options to consider jointly[35] with the goal of reconciling differences and reaching mutually agreed upon higher quality decisions that align patients' needs with evidence-based guideline-directed care[36,37]. Prior research has demonstrated that with repeated lengthy engagement (1+ hour), highly-trained interventionists in settings other than primary care can increase medication adherence[38-40]; this intervention model improves disease control[39,41-43], identifies health beliefs that conflict with evidence-based care[44] and reduces risky behaviors[4-6]. The framework's application to asthma has been limited to children[39,47] and to White privately insured adults[40]. Sustained implementation of effective shared decision-making interventions has been restricted, in part, by burdensome protocols requiring multiple visits, lengthy engagement, highly-trained interventionists, and by protocols inappropriate for populations like those served in FQHCs.

**Implementation research is underutilized in asthma intervention research.** Evidence-based interventions may be difficult to sustain[8-10], in part, because factors associated with implementation are overlooked. To close this gap between research and practice, researchers should conduct formative assessments with the target audience and program providers during development, and evaluate the program features that enhance a program's reach. Further, FQHCs are overlooked in asthma intervention research.

**Impact.** Black adults with uncontrolled asthma experience profound health disparities. Despite data that point to the critical need for enhanced asthma self-management, we continue to see rates of controlled asthma well below Healthy People 2020 targets[48], particularly among vulnerable populations[49]. Our **Brief Evaluation of Asthma Therapy (BREATHE)** intervention has the potential to offer a new avenue to asthma control via shared decision-making that supports ICS adherence.

## STUDY DESIGN AND PROCEDURES

This R21 proposal will proceed in two major phases: (1) a development phase (Year 1) where **BREATHE** was developed using iterative community-based participatory research (CBPR) approaches with feedback from PCPs (focus groups completed; independent PCP review about to commence); and (2) a pilot randomized trial phase that will allow estimation of parameters crucial for a larger randomized control trial (RCT) including final content specification, participant recruitment rates, and potential intervention effect sizes (the focus of this application).

**PHASE II ONLY**

**Study Procedures**

**Pilot Randomized Clinical Trial Phase**

**Study Procedures: PCP Recruitment, Consent and Randomization.** Randomization will be at the level of the PCP. This is a two-group randomized trial with outcomes analyzed at the patient level. We will randomize 8 PCPs (4 / FQHC site) into **BREATHE** and attention control conditions stratified for provider type (physician vs. nurse practitioners [NPs]/physician assistant [PAs]) to insure equal numbers of PCPs within each PCP type are assigned to each condition. Randomization lists will be computer generated in advance by our data manager (allowing the biostatistician to remain blinded during analysis). We do not anticipate difficulty in recruiting 4 PCPs/FQHC since one FQHC has ~15 PCPs (10 physicians and 5 NPs/PAs) and the other has 35 (20 physicians and 10 NPs/PAs).

**Provider Consent**. After reading the informed consent and having questions addressed, PCPs will be asked to sign informed consent indicating they are entering the study voluntarily. Declinations to enroll, if any occur, will be a metric that we will track. Consent will be obtained by either the PI or the Project Manager as these individuals are unblended.

**Inclusion Criteria:** PCPs (MDs and NPs/PAs) working in family, primary or internal medicine care services who have at least 40 adult patients with persistent asthma (defined as having been prescribed ICS) on their patient panel will be considered eligible for enrollment.

**Exclusion Criteria:** PCPs whose primary focus is outside of adult health services (family, primary or internal medicine), such as behavioral health, pediatrics and OB-GYN.

**Patient Recruitment.** We will recruit patients using methods we have used successfully in prior studies[7,16,18,32,33,55]. The FQHC administrator will create a potential list of subjects using a combination of ICD-10 (Asthma 493)-specific queries of electronic membership records and searching of scheduled patient visits for the FQHC PCPs to review. The research team will receive only the names and contact information of those the FQHC clinicians have contacted and who agree to receive a call from the research team. We will also accept subjects who respond to posted recruitment flyers.

**Patient Participants & Consent**. We will enroll 80 Black adults with uncontrolled asthma (10 / PCP). The study team will read the informed consent and when subjects have had all questions addressed, they will be asked to sign indicating they are entering the study voluntarily. Consent will be obtained the RA who is blinded.

**Inclusion Criteria:** Patients must be 1) adults (≥ 18 years of age) who self-report race as Black or African American; 2) with PCP-diagnosed persistent asthma; 3) prescribed ICS; 4) receiving asthma care at participating FQHCs; 5) who have uncontrolled asthma (defined below) ; and 6) have erroneous personal health and/or negative ICS beliefs (defined below)**.**

Interested participants who meet the first 4 criteria will be screened for uncontrolled asthma by administering the Asthma Control Questionnaire (ACQ) by phone (phone administration is both reliable and valid) [73-75]. The ACQ includes 6 self-reported items about asthma symptoms and an objective measure of pulmonary function:

the forced expiratory volume in one second ($FEV_1$). The ACQ has demonstrated validity and reliability with and without the use of the $FEV_1$. ACQ scores $\geq$1.5 have a positive predictive value of 88% in identifying uncontrolled asthma in clinical trials[73]. PCPs will be notified of all patients with ACQ scores $\geq$1.5 and patients will be scheduled for a follow-up visit with their PCP as these scores indicate that asthma is not in good control. At that visit, if they remain interested in enrolling in the trial, they will be screened for beliefs associated with ICS non-adherence using the CAM-A instrument, administered on customized tablet that allows for immediate scoring. patients will complete the 17-item CAM-A[18] which will self-score. Any one endorsement of a non-prescription asthma management preference or negative ICS belief is considered a positive screen and the patient is eligible for enrollment in this two-step screening process (+ ACQ screen by phone and + CAM-A screen at visit). At this visit, trained study staff will also obtain the $FEV_1$ using a hand held spirometer calibrated daily, as well as additional surveys (see Table 1).

**Exclusion Criteria:** 1) participation in Phase 1 of the **BREATHE** trial (focus groups); 2) non-English speaking; 3) serious mental health conditions (e.g., psychosis) that preclude completion of study procedures or confound analyses.

**Enrollment feasibility.** The two FQHCs provide primary care to over 100,000 unique patients a year, who are cared for by 50 providers. Each provider sees approximately 2,000 asthma patients. Using a conservative estimate of 8% asthma prevalence, 160 unique patients with asthma are served per provider. Based on our preliminary studies[6, 55,58,599] we expect ~69% of subjects screened will have uncontrolled asthma (n=110 patients / PCP); of these, 97% will screen positive on the CAM-A[16] yielding 107 eligible patients / PCP. Thus, we have an adequate patient pool from which to draw 10 patient subjects / PCP.

**Blinding.** Patient codes, tied to PCP assignment (active vs. control), will be entered into a tablet prior to the completion of the CAM-A by the RA**.** The meaning of these codes will not be known to the RA. Using these codes, the software will trigger the tablet to load either the **BREATHE** intervention steps or the attention control timer (described below) after the CAM-A has been completed. These screens will be hidden from the patient and the RA by two "hold" screens warning the RA/patient subject not to advance further. We will assess the adequacy of blinding of the subject and the RA as a process outcome at the end of the study. Both active and control PCPs will receive the tablet from the RA and the results of the lung function testing ($FEV_1$). The RA will set up two digital recorders to capture the audio of the office visit and then leave the room. The RA will be instructed to stay close by to monitor the end of visit but not close enough to overhear the conversation. The statistician (Jia) will be blinded. The PI , Project Manager and database manager will not be blinded.

**Survey Administration.**
The PI and/or Project manager (unblinded) will administer the following surveys after the clinician has signed informed consent: Demographic and professional history; PCMI.
The RA (blinded) will be responsible for all patient data collection.

| Surveys, Diaries, Testing, Interviews and Fidelity Checks | Type of Data; how collected | Who will collect | Data source | Pre-visit 1 (V1) | Visit 1 Baseline | Within 24 hours of V1 | Visit 2 ~ 4 weeks after V1 | Visit 3 ~ 4 weeks after V2 | Visit 4 ~ 4 weeks after V1 | Post-trial |
|---|---|---|---|---|---|---|---|---|---|---|
| **Asthma Control Questionnaire – 6 items (ACQ6) without item 7 (FEV1)** | Survey; Collected by phone | RA or PM | Patient | X | | | | | | |
| **Demographics** | Survey: Collected by phone | RA or PM | Patient | X | | | | | | |
| **Conventional and Alternative Management for Asthma (CAM-A)** | Survey; Collected on tablet | RA | Patient | X | | | | | X | |
| **Asthma history** | Survey; Paper and pencil | RA | Patient | | X | | | | | |
| **Forced Expiratory Volume in One Second ($FEV_1$) alone – item & on the ACQ** | Non-invasive measure of airflow obstruction; hand-held spirometer | RA | Patient; hand-held spirometer | | X | | | | | |
| **Newest Vita Sign (NVS)** | Survey; Paper and pencil survey | RA | Patient | | X | | | | | |
| **Shared Decision Making Questionnaire- 9 items (SDMQ9)** | Survey; Paper and pencil | RA | Patient | | X | | | | | |
| **Medication Adherence Record Scale-Asthma (MARS-A)** | Survey; Paper and pencil survey | RA | Patient | | X | | X | X | X | |
| **Patient reported Outcome Measurement Information System- 29 items (PROMIS-29)** | Survey; Paper and pencil survey | RA | Patient | | X | | X | X | X | |
| **Asthma Quality of Life Questionnaire (AQLQ)** | Survey; Paper and pencil survey | RA | Patient | | X | | X | X | X | |
| **Patient Immediate post-visit debriefing and blinding assessment** | Survey; Paper and pencil | RA | Patient | | X | | | | | |
| **Asthma Control Questionnaire – 7 items (ACQ7) with FEV1** | Survey and non-invasive measure of airflow obstruction; Paper and pencil and hand-held spirometer | RA | Patient; hand-held spirometer | | | | X | X | X | |
| **Asthma daily diary** | Diary; Paper and pencil | Patient | Patient | | DISPENSED | | X | X | X | |
| **Doser electronic dose counter** | Electronic dose counter | RA will download by hand | Patient; Doser electronic counter | | DISPENSED | | X | X | X | |
| **Client Satisfaction Questionnaire 8 items (CSQ8)** | Survey; Paper and pencil | RA | Patient | | | | | | X | |
| **Post-trial interviews** | Interviews, Audio recorded | PI | Patients, loved ones and providers | | | | | | | X |
| **Provider Data Collection Form** | Survey; Paper and pencil | PM or PI | Providers | X | | | | | | |
| **Provider Co-Management Index (PCMI)** | Survey; Paper and pencil | PM or PI | Providers | X | | | | | | |
| **Readiness Ruler** | Scale; Collected on tablet | Provider | Patient | | X | | | | | |
| **Provider Immediate post-visit debriefing** | Survey; Paper and pencil | RA | Providers | | X | | | | | |
| **Brief Negotiated Intervention (BNI) Adherence Scale (Active condition)** | Fidelity Checklist | Coder (TBD) | Audio files of patient-provider visits | | | X | | | | |
| **Fidelity Check Attention control condition** | Fidelity Check | Coder (TBD) | Audio files of patient-provider visits | | | X | | | | |

**Intervention Condition.** PCPs randomized to **BREATHE** will receive the tablet which, when the screen is advanced by the PCP, will prompt the PCP through a 7-minute, 4-step brief intervention tailored to respond to the patient's specific beliefs endorsed on the CAM-A using content identified in our CBPR development phase (focus groups). See the Brief Negotiated Intervention (BNI) for the full intervention details.

Step 1: Raise the subject (1½ minute). PCP establishes rapport using persuasive communication techniques and assesses the patient's disease knowledge, perception of asthma control, quality of life (QoL), self-care preferences, and motivation for enhanced asthma control, exploring specific beliefs that may affect adherence.

Step 2: Provide feedback (1½ minutes)**.** PCP provides feedback to the patient based on assessments made in the prior step. The PCP candidly discusses the patient's uncontrolled asthma and specific beliefs in the context of ICS non-adherence, drawing a connection between current symptoms and ICS non-adherence.

Step 3. Enhance motivation (2 minutes). The PCP attempts to enhance the patient's motivation to increase ICS adherence using motivational interviewing techniques such as collaboration, empathy, concern, and acceptance of ambivalence about self-management. In this step, the PCP may elicit the patient's beliefs regarding the benefits, and negative sequelae, of their current self-management approach (pro/con).

Step 4: Shared decision-making (2 minutes). The PCP and patient jointly consider treatment options. The PCP will actively attempt to build consensus around ICS adherence, reconciling conflicts to better align beliefs with evidence-based guideline-directed ICS treatment. For example, if the patient uses ICS intermittently (rather than the required twice-daily dosing) because of an erroneous belief that tolerance to ICS develops with daily dosing, then the PCP will attempt to counter that belief using responses gleaned from the CBPR development phase (focus groups) and information from national guidelines. This will likely include encouraging the patient to use ICS once a day (50% adherence) as an initial short-term plan to be followed by a return visit and re-evaluation of asthma control. If the patient declines to engage in shared decision-making or declines attempts at negotiating ICS use, then the PCP and the patient agree to disagree. This is a one-time intervention.

**Usual care with an attention control condition.** Patient codes associated with PCPs randomized to the attention control condition will trigger the tablet to load a 7-minute timer for the PCP to use to track the length of the attention control condition (discussion of healthy lifestyles). Control PCPs will have access to all the data that the active intervention PCPs have: the ACQ score, CAM-A results, and lung function results. To control for contact, they will be instructed to engage in a 7-minute diet and exercise discussion as this will not confound results and it was a common topic in our prior study; ICS adherence was not discussed[18].

**Intervention Training for BREATHE PCPs.** We will train PCPs randomized to the **BREATHE** condition using procedures we have used before[26-28,60-62] with content gleaned from our CBPR development phase (focus groups and PCP review) as described previously. The core training for PCPs delivering the **BREATHE** intervention will be conducted by our consultant, Dr. Pantalon, and will consist of one, 2-hour instructional session: 30 minutes of didactic instruction addressing the delivery of the 4 steps of the brief intervention; 10 minutes of role-playing of commonly encountered scenarios and; a 50 minute skills workshop in which PCPs role play creating a trusting environment, relinquishing sole decision-making, motivating and empowering patients to engage in self-management decisions. A question and answer period will conclude the training. PCPs will receive a laminated action card that fits in a lab coat pocket summarizing the intervention steps as a resource although the steps of the intervention will be available to the PCP on a tablet during the visit.

Immediately after training, PCPs will be tested using a standardized patient scenario to demonstrate that he/she can deliver the intervention in 7 minutes or less. All testing will be audiotaped and a trained rater will determine

whether the critical elements of the brief intervention were completed in 7 minutes using the validated Brief Negotiation Interventions Adherence Scale (BAS)[76] adapted to asthma (see draft BNI protocol and BAS). If the PCP fails testing, she/he will receive additional instruction and retested. Prior studies have shown that such remediation re-training results in 100% proficiency[76]. PCPs will be encouraged to informally try out some of these techniques before the study goes live. The Consultant will follow-up with each PCP to answer questions from this "dry run" before the first subject is enrolled.

**Intervention Fidelity.** To evaluate adherence to the treatment protocol, all **BREATHE** visits will be audiotaped. The Project Manager (who is not blinded) will review all audio files within 24 hours of the visits at which time she will complete the Brief Negotiated Intervention Adherence Scale (BAS) to evaluate drift, when in the visit (beginning, middle, end) the intervention is delivered, as well as the length of the **BREATHE** sessions. The Consultant Pantalon will conduct additional training to enhance intervention fidelity and brevity if problems are identified. PCPs will not be excluded from the study if they fail to deliver all elements or require more than 7 minutes to deliver **BREATHE**; this feasibility metric will be tracked.

**Fidelity to the attention control condition.** PCPs randomized to the control intervention will not receive any specific training but audio files will be reviewed by the Project Manager (who is not blinded) within 24 hours of the visit to ascertain the content and length of the healthy lifestyles discussion (the attention control condition), as well as to listen for any evidence of contamination (use of the 4-step shared decision making intervention using motivation interviewing techniques). Feedback to improve fidelity to the attention control condition, if needed, will be made promptly after reviewing the audio files.

**Anticipated Problems and Strategies.** If time does not allow for rapid review of all audio files, 20% will be randomly selected to be rated by the Project Manager: all 1st visits will be rated, and at least one additional file per PCP will be reviewed prior to enrollment of their 5th patient subject. We will minimize contamination within FQHCs by (1) training only **BREATHE** PCPs to deliver the active intervention and (2) encouraging PCP confidentiality regarding training and intervention content. We will also review audio files of the attention control condition to assess for contamination.

**Final assessment and refinement of the intervention**. We will conduct nested cohort interviews with five patient subjects and five family/support person of enrolled subjects post-trial to ascertain their reactions to the intervention. An additional five patients will be interviewed who were lost to follow-up to better understand what it was that prevented their continued participation. A purposive sample of ~ 6 PCPs (2-4 who participated in the **BREATHE** intervention and two who declined participation, should we have any) will also be interviewed to better understand their perspectives about the intervention or their clinical settings that facilitated or prevented study participation. The PI will conduct the interviews and data will be analyzed as described in the methods section.

## STATISTICAL PROCEDURES

**Patient data collection.** While we recognize the need for longer follow-up in a full-scale RCT, trained RAs, blind to treatment status, will collect data four times: baseline and 1-month, 2-month, and 3-month follow-up. To address the risk of assessment reactivity, both groups will receive an equal number of assessments.

**Patient subject measures (see Table 1).** The **primary outcome** measure is patient-reported asthma control over 3 months as measured with the ACQ[73-75]. We will collect the ACQ and **secondary outcomes** including objective measures of airflow obstruction ($FEV_1$), asthma QoL using the Asthma Quality of Life Questionnaire - AQLQ[77,78] and ICS adherence using the Medication Adherence Record Scale-Asthma (MARS-A) [79-89]. The MARS-A correlates with objective ICS adherence as measured by electronic monitoring and ICS fill/refill claims data[79-89]. Other surveys that will be used to characterize the subjects include the asthma history, Newest Vital Sign, the PROMIS-29 and the Shared Decision Making Questionnaire- 9 items. All patient subjects will

also be asked to complete the Patient Debriefing and Blinding Assessment survey immediately after V1. The blinded RA will dispense a 30-day asthma diary (4th grade reading level) to all subjects after each data collection visit. The Doser™, an electronic monitor capable of recording 30-days ICS use, will be attached to compatible ICS. Due to unique delivery systems for ICS, there is no single electronic device to monitor all ICS types. No change in ICS is required to participate in the Doser tracking log. Finally, we will collect patient satisfaction using the Client Satisfaction Questionnaire-8 (CSQ-8)[90] at 3-months..

**CP measures.** PCPs will be asked to complete a demographic and professional history form and one survey at the time they sign informed consent: the Provider Co-Management Index (PCMI). The PCMI is a measure of PCP shared management. All PCPs will also be asked to complete the Provider Debriefing survey immediately after V1.

**Data Management & Statistical Analysis**. Double data entry will be made into a secure database with regular integrity checks. Data analysis in the context of an R21 must balance two primary agendas: (1) effect size estimation and (2) statistical significance testing. Our primary goal is to examine intervention feasibility, which will guide modifications of design elements for a future RCT, if warranted. Descriptive data analysis will proceed with formal hypothesis testing and model building in order to understand the data distribution and to check for outliers. Linear mixed models will be used to adjust for the heterogeneity of the sites and subjects by including PCP- and patient-specific random effects. The linear mixed model is used to adjust for clustering of data due to the repeated measurement of the same patient and due to association within a PCP with both PCP-level and patient-level random effects. We will examine the patterns of missing data; linear mixed models provide unbiased estimates for data with missing values. Intention-to-treat analyses will be conducted.

**Hypotheses 1: Intervention Feasibility.** We will document **BREATHE'**s penetration using PCP recruitment data. The process evaluation will include descriptive statistics on PCPs intervention proficiency and fidelity (e.g., session length) and will assess proficiency and fidelity differences by sites. If we find variability, we will explore potential causes (e.g., FQHC size).

**Hypotheses 2: Intervention Effects**. Intervention effects will be assessed using mixed effects regression models[90]. All hypothesis tests will be two-sided at level $\alpha$=0.05. The key outcome will be asthma control; ICS adherence, $FEV_1$ and QoL will be examined to inform the future RCT. Separate models will be fitted for different outcome measures. If $y_{ijt}$ is the outcome for patient j of provider i at time t, without loss generality then the following linear mixed model will be used: $y_{ijt} = \beta_0 + \beta_1 Group + \beta_2 X_i + \beta_3 X_{ij} + v_{1i} + v_{2ij} + \varepsilon_{ijt}$, where $X_i$ and $X_{ij}$ are vectors of possible PCP- and patient-level confounders, respectively. The random term $v_{1i}$ $iid \sim N(0, \sigma_1)$ is a PCP-specific random effect and $v_{2ij}$ $idd \sim N(0, \sigma_2)$ is a patient-specific random effect; $\varepsilon_{ijt}$ $iid \sim N(0, \sigma^2)$ is the model random error. We assume that $v_{1i}$, $v_{2ij}$ and $\varepsilon_{ijt}$ are mutually independent. To test for a time and group interaction, we will add the time*group term to the model.

**Power & Sample Size.** With a sample size of 10 patients/PCP and 4 PCPs in both intervention groups (total n=10*4*2=80), and a conservative estimate of 10% attrition at 12 weeks, we calculated the reliability of estimated mean score differences between the two groups. Power calculations were based on: (1) 4 repeated observations / patient over the 3-month follow-up with a correlation of $\rho$=0.8 between repeated measures; (2) intra-cluster correlation among PCPs=0.2 to account for clustering of patients from the same PCP; and (3) linear mixed models to estimate mean score differences. For the ACQ, the half-width of 95% CI for the estimated mean score difference between the 2 groups is 0.32 (assuming SD=0.76). This is equivalent to having 91% power to detect a medium effect size (Cohen's d=0.5). We are powered to detect a clinically meaningful difference on ACQ[74] and AQLQ[78].

**Qualitative analysis.** Qualitative descriptive data analysis will focus on refining the intervention (see draft of sample questions for PCPs and patient/loved ones). De-identified transcripts will be entered into NVivo 11.0 for coding and analysis. Three coders working independently of each other will systematically read the transcripts to identify emerging themes; the Patient Advocate consultant will serve as one coder. Themes will be compared between coders and disagreements will be reconciled by consensus. As we have done in the past, we will employ an iterative process in which themes in earlier interviews will be presented to subsequent interviewees to ascertain if they resonate with them; unendorsed themes will be discarded. Typically, this iterative process continues until no new essential information is obtained, an endpoint known as data saturation. Data saturation usually occurs after in-depth interviews with 20-30 individuals per category (e.g., patient, loved one, PCP) [55]. However, the focus of these more limited interviews are simply to assess acceptability and identify categorical level findings. We will use interview data to triangulate with the 8-item Client Satisfaction Questionnaire (CSQ-8) that is completed by all 80 subjects. All retained responses that are similar will be grouped together by code words to form the final thematic categories. Transcripts, field notes and codes will serve as points of triangulation.

**DSMP**

The proposed study includes (1) a development phase where we will develop the intervention using focus groups with patients and patients' family/support persons (N = 60) with primary care provider (PCP) review, and (2) a pilot validation phase where we will conduct a pilot randomized controlled trial with 8 PCPs from Philadelphia primary care clinics randomized to one of two study arms: (1) the **BREATHE** intervention, or (2) usual care. We will follow 10 Black adult patients with uncontrolled asthma per PCP (N = 80) for three months post-intervention. Post-study refinement will include additional interviews with patients, family/support persons and PCPs who did and did not participate.
This Human Subjects Research meets the NIH definition of "Clinical Research." Institutional review board (IRB) permission for the study will be obtained from the Columbia University (IRB of record) and will be reviewed annually. Although the NIH requires data and safety monitoring for any clinical trials, having an Safety Monitoring Committee (SMC) – a small group of 3 experts who are independent of the protocol who review data from a particular study including independent investigators and biostatisticians - may be appropriate if the study includes multiple sites and a vulnerable population. Because the application includes a feasibility trial in urban minority adults from different clinical sites, and because inclusion criteria require that participants have uncontrolled asthma, we will establish an SMC.
**a. Monitoring entity or who will monitor the study.** While the behavioral intervention itself is a low risk intervention, participants must have uncontrolled asthma to be eligible for enrollment. Because of this, we will appoint an SMC to establish a threshold for asthma exacerbations (defined below) with the PI's input. The SMC will be appropriate experts who are independent of the study and available in real time to review and recommend appropriate action regarding adverse events and other safety issues.

The SMC, appointed by the PI and approved by the Program Officer include:
**Physician knowledgeable about the disease and treatment:** Emily Dimango, MD is a pulmonologist and Associate Professor of Medicine, Columbia University Medical Center. She is the Director of the John Edsall-John Wood Asthma Center and the Columbia University Asthma Coalition. She has been a PI or Co I for multi-center clinical research trials since 2002, helping design and/or execute nearly two dozen clinical research studies in lung disease, including a $9 million study of the role of environmental intervention in asthma. Through her work in asthma, she has interacted with the local inner city community, and has been successful in recruitment and retention of inner city minority subjects into clinical trials. Dr. Dimango will have primary responsibility for defining a plan for monitoring safety, minimizing risk to subjects, and adherence to protocol requirements; defining expected adverse events (AEs) and approving the definition of AEs, including serious adverse events (SAE).
**Statistician:** Bruce Levin, Ph.D., Professor and Past Chair, Department of Biostatistics at Columbia University Mailman School of Public Health will serve as the statistician on the SMC. Dr. Levin has a great deal of experience with small SMCs, including serving as a SMC chair for an anesthesiology study. He has served as a senior design and analysis statistician on many projects in diverse areas of clinical trials, HIV/AIDS, reproductive epidemiology, and statistics in the law. He is the senior living co-author of the classic textbook, *Statistical Methods for Rates and Proportions*, 3rd Edition, which devotes entire chapters to the randomized clinical trial and methods for analyzing trial data. He specializes in

innovative designs for early phase clinical trials. Of additional importance to the current proposal, he is currently a co-investigator of a clinical trial which aims to test the effectiveness of an asthma intervention with proven efficacy in urban high school students with a new sample of rural adolescents and was the statistician for the R01 that tested the efficacy of *Asthma Self-Management for Adolescents* (ASMA) with urban adolescents in NYC (R01 HL67268). He (Levin) will have primary responsibility for statistical monitoring of AEs reported to the SMC and, through the SMC chair, notifying the team if such events meet the stop rules. Prior to the start of the study, and in coordination with the other SMC members and the study team, he will review and approve a proposed plan for monitoring completeness and quality of the measurements and the statistical analysis of the data. Mr. Jesse Chittams, the study's database manager, will assume responsibility for statistical tabulations and reports to the SMC.

**Clinician knowledgeable about the disease and treatment**: David Evans, PhD has over 30 years of research experience in intervention to enhance asthma control. He was one of the developers of *Open Airways for Schools* (OAS), a school-based program for children with asthma that has been shown to reduce the frequency of asthma symptoms in participating children; OAS is now delivered by the American Lung Association in more than 24,000 public elementary schools nationwide. He also participated in the development of the *Physician Asthma Care Education* (PACE) program, a four-hour program to improve pediatricians' medical management and patient communication and teaching skills that showed pediatricians could be trained to deliver the program. The PACE program is now being disseminated through the NHLBI website. Dr. Evans was a Co-Investigator on a recent R01 testing the efficacy of PACE Plus, a version of PACE that included cultural competence training. Currently, he is part of a team (as is the PI) working on a Direct-to-Phase II SBIR grant from NHLBI to develop and to pilot test *Camp Air*, a dynamic, e-learning intervention for adolescents with uncontrolled asthma. He serves as Director of Community Outreach and Education for two environmental health research centers at Columbia University, the Center for Environmental Health in Northern Manhattan and the Center for Children's Environmental Health. He has served on several NIH panels to improve the quality of asthma care, including the Data and Safety Monitoring Board of the NHLBI Children's Asthma Management Program clinical trial (1992-2008), and the NHLBI Expert Panel (Report 3) on the Guidelines for the Diagnosis and Management of Asthma (2006-2007). Dr. Evans will have primary responsibility for reviewing the study protocol including benefit/risk ratio of procedures and participant burden, selection, recruitment, and retention of participants and informed consent procedures. He will also review any amendments to the study protocol and consent forms, including whether any new data from other sources affect the equipoise of the study being monitored.

Although not members of the SMC, the research team has a responsibility to the SMC. These include the **Principal Investigator** (PI) who is responsible for ensuring participants' safety on a daily basis for the protocol that will be overseen by the same SMC. The SMC will act in an advisory capacity to the PI and to NINR to monitor participant safety, evaluate the progress of the study, and review procedures for maintaining the confidentiality of data and the quality of data collection, management and analyses. The PI will be responsible for timely communication of safety data to the appointed SMC, appropriate response to any safety concern identified by the SMC, and compliance with any actions that the SMC identifies as being needed. The PI will also be responsible for all reporting requirements. Lastly, the PI will train all project staff to recognize and report any adverse event immediately to her. The **project manager** and/or the data manager will review all data collected by the research assistant (RA) and communicate data and/or safety concerns in real time to the PI. The **RA** will notify the project manager and/or the PI in real-time when data collection indicates a possible data/safety concern. Details are provided in (d) below.

**b. Procedures for 1) monitoring study safety to include monitoring schedule, auditing selected cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents, and investigator compliance; 2) minimizing research-associated risk, and 3) protecting the confidentiality of participant data.** For the pilot test, we will use the following strategies to monitor and deal with possible adverse impacts. Research participants will be told to contact research staff (who will return calls within 72 hours) at any point during the entire project if they have any questions or concerns about their participation. The PI and researchers will meet daily to review adverse or unexpected events data and weekly to review data reports generated by the data management team regarding all study-related activities. This will include case detection, consent, intervention activities, and surveys/interviews. The SMC will act in an advisory capacity to the PI and NINR to monitor participant safety, evaluate the progress of the study, and to review procedures for maintaining the confidentiality of data and the quality of data collection, management and analyses.

Recruitment. We will recruit patients using methods we have used successfully in prior studies. The federally-qualified health center (FQHC) administrator will create a potential list of subjects using a combination of ICD-10 (Asthma 493)-

specific queries of the electronic membership records and searching of scheduled patient visits for the FQHC PCPs to review. The research team will receive only the names and contact information of those the PCP permits the team to contact. We will also accept subjects who respond to posted recruitment flyers.
Informed Consent. The study team will read the informed consent and HIPAA to the subject and will discuss it section by section. When subjects have had all questions and concerns addressed, they will be asked to sign the consent indicating they are entering into the study voluntarily. Participants will be given a copy of the HIPAA and the signed informed consent document; a copy of the informed consent and HIPAA will be maintained with the study team.
Auditing Selected Cases. Fidelity to consenting, data collection and the intervention will be evaluated in the following manner. Twenty percent of all visits will be randomly selected for auditing of the informed consent and data collection protocols. In addition, intervention fidelity will be assessed by reviewing audiotapes of 20% of randomly selected visits (with the exception of the first visit; all first visits be reviewed) to be rated by three independent blinded raters. At least one additional file per PCP will be reviewed prior to enrollment of their 5th patient subject, to evaluate drift and the length of BREATHE sessions, and length, content and contamination, if any, of control sessions. Consultant Pantalon will conduct additional training to enhance intervention fidelity and brevity if problems are identified.
Minimizing research –associated risk. While the behavioral intervention itself is a low risk intervention, participants must have uncontrolled asthma to be eligible for enrollment. Because of this, we will ask the SMC to use the established threshold for asthma exacerbations (defined below) with the team's input (see details below).
The risk associated with the focus group procedures and intervention may include psychological distress due to sharing of personal information and the loss of confidentiality (see below). To minimize the risk of loss of confidentiality, participants will be told that whatever they say in these group settings or report in the study surveys is confidential.

We will not be collecting any sensitive patient data, such as experiences with asthma death or asthma-related depression. However, we will be asking about previous asthma attacks that may have been life-threatening which may be a traumatic memory. Subjects will be allowed to skip any questions that they find troubling and should there be any indication of imminent medical or psychological risk associated with any aspect of the study, participants will be referred to previously identified resources in the study catchment areas. In concert with our partners, we will establish specific medical and counseling protocols prior to study onset. To that end we have established the following procedure: all study visits will take place at the FQHCs which have urgent medical and psychological services available on-site for evaluation and have set procedures for the timely and safe transfers of acute medical and psychological conditions to appropriate services.

To the best of our knowledge, the risks of obtaining spirometry (a measure of obstructive airflow) is minimal as this procedure is typically performed in community-based health screenings.
Study participants will be informed that they have a right to withdraw from the study at any stage.
Patient confidentiality.
Paper and electronic case report forms and transcripts. Patients' confidentiality will be protected in multiple ways. First, all study subjects will be assigned a code that cannot be tied to personal identifiers and this code will appear on all study-related materials. The personal identifiers tied to these codes will be known only to study personnel and will be stored in a password-protected program. All other deidentified materials will remain in a locked office in a locked cabinet. All electronic documents will be password-protected.
As part of the consent process, the procedures for obtaining outcome data as well as the safeguards for maintaining confidentiality and minimizing invasion of privacy will be fully described to potential participants. Participants will not have to answer any question they do not want to answer. Participants will be given the contact information for the research staff to answer any questions they might have about the study and consent process. To further minimize risk, the PI will train the RA on potential breach of confidentiality specific to this study and study environment and will assure that all study personnel complete and maintain Human Subjects Protection certificates. The PI will periodically monitor adherence of these principles during a random sample of visits.
Audio files. Digital audio files (focus groups, audio recorded office visits and interviews) will be downloaded as a media file and stored on the PIs password-protected personal computer. Digital audio files will be assigned a code tied to personal identifiers. The personal identifiers tied to these codes will be known only to study personnel and will be stored in a separate password-protected program. We will transcribe all focus groups and individual interviews and some/all office visits. The transcriptionist is an approved Columbia vendor and has provided services in support of Phase I of this trial. The same standards will apply this this second phase: Audio files of the interviews and office visits will be deposited to the Columbia-approved transcription vendor's

dropbox. The vendor has a confidentiality agreement that all employees sign stating that they may not share anything about any of the work that they transcribe with anyone. The vendor will then deposit the transcript in a word document in the drop box for the PIs retrieval. When it has been ascertained that the transcript is a verbatim representation of the interview/office visit the PI will notify the vendor to destroy all files. A copy of the transcript will be maintained by the PI as described in the protocol.

Equipment. After downloading digital audio files, the digital recorder's memory will be cleared. The memory of the spirometer will be cleared of lung function results after a copy has been printed and entered into the electronic data base. Subjects who have the Doser™ electronic ICS monitor will have the dose counter cleared monthly after a record of its use has been transcribed to spread sheets that will be stored in a password-protected program.
Data management, data entry and integrity. An electronic study database (REDCap) will be created and maintained on the password-protected research server at Columbia University. Data entry personnel will receive standardized training on data entry. The Project Manager and RA will be trained and monitored by the PI with periodic checks for drift in standardized practices. If drift is observed they will be re-trained. The study's statistician (Jia) will receive deidentified data transferred via secured communication.
Data entry into desktop computers will be equipped with password lockout and screen savers which activate if the computer is on but not in use for 15 minutes. All study personnel will have their own unique usernames and passwords. All servers are located in a secure datacenter, with necessary redundancies. The server is behind a firewall and is registered as a "Critical Host" by the University. This means Columbia follows all University polices regarding critical hosts: firewalls, access controls, timely patch management and anti viral scans and software updates, and an enterprise system monitoring solution (allowing us to detect and address intrusion attempts). All servers have HIPAA compliant

security. School of Nursing computers operate under a managed desktop solution which is locked down, including hard drive and thumb drive encryption. The base image includes, but is not limited to, Windows 7 with current patches and Antivirus software (which is updated every 4 hours).
Publication or presentation of study findings. Aggregate group data will be used, free of identifiable features, in any publication or presentations that arise from this research.

**c. Procedures for identifying, reviewing, and reporting adverse events and unanticipated problems to the IRB and NINR, the type and number of events that would halt accrual and would generate a review of eligibility, monitoring, assessments, intervention, and how the resumption of accrual would occur.**

All study personnel will report any study-related adverse reactions and/or unanticipated problems involving risks to the PIs as soon as they occur. The PI and/or study researchers will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance.
During the trial, subjects will be instructed to notify the study team within 48 hours of any Emergency Department (ED) visit or hospitalization, regardless of its cause, and to notify the study team within 48 hours of initiating oral corticosteroids (OCS), each event representing the standard definition of asthma exacerbation. Because not all exacerbations cause individuals to seek acute care, we will track OCS use as those who manage an exacerbation outside of the ED or hospital will manage their exacerbation with OCS. In this manner we will not miss any exacerbations. To that end, we will also ask subjects to report these at monthly data collection points in an attempt to capture any exacerbations that might otherwise go unreported. Subjects' answers will then be compared to the medical record and/or claims data, as available.
Because there are 1.75 million ED visits annually (7%) among 24 million individuals with asthma we could anticipate a rate of 1.7% ED visits in a 3 month trial. However, only individuals with uncontrolled asthma will be eligible for enrollment so we will plan for 5% of our subjects to have an ED visit for asthma at some time during the 3 month trial. Therefore, data on adverse events, including serious adverse events (SAEs) that meet the standard definition of asthma exacerbation (ED visits, hospitalizations, and OCS initiation), will be reviewed. Exacerbation rates as meeting any of the three standard definitions of asthma exacerbation (ED visits, hospitalizations, and OCS initiation) in excess of the threshold set by the SMC will trigger an immediate study shutdown (see below). AEs and SAEs will be systematically assessed at all data collection points via review of the medical record and/or patient interview. Subjects will be instructed to report AEs and SAEs to the study team within 48 hours of their occurrence. This information will then be shared with the SMC in real-time, as well as additional information about the event that the study team can obtain from the PCP or from the medical record, as available. The SMC will then determine how an AE is to be categorized using standard taxonomy: Unrelated (clearly not related to the research), Unlikely (doubtfully related to the research), Possible (may be related to the research), Probable (likely related to the research) and Definite (clearly related to the research).
The SMC will use the following definitions:
Adverse events are defined as unanticipated problems involving risks to study participants or others, or as any untoward medical occurrence that may present itself during the study time period which may or may not have a causal relationship with the treatment.
Serious adverse events result in any of the following outcomes: death, a life threatening experience, inpatient hospitalization, or a significant disability/incapacity. Such events also include breeches of confidentiality.
Moderate adverse events are those discomforts severe enough to cause interference with usual activities or requiring treatment by a health care provider. Such events also include the loss of participants from the study for reasons related in any way to a deviation from procedures for ensuring confidentiality.
Mild adverse events are those events that are easily tolerated signs or symptoms of discomfort; minor irritants that cause no loss of time from normal activities; symptoms that require no medication or a medical evaluation; and transient signs and symptoms.
Unexpected adverse events are those events, the specificity or severity of which is not consistent with the risk information described in the general investigative plan or the IRB proposal. "Unexpected" refers to an adverse event that has not been previously observed.
Expected adverse events are those events, the specificity or severity of which is consistent with the risk information described in the general investigative plan or IRB proposal.
Any ED visit or hospitalization associated with primary ICD-10-CM Diagnosis Code 493. Asthma (493.00 asthma atopic unspecified; 493.01 asthma atopic asthmaticus; 493.02 asthma atopic acute exacerbation; 493.10 intrinsic asthma unspecified; 493.11 intrinsic asthma asthmaticus; 493.12 intrinsic asthma acute exacerbation;493.20 asthma chronic

obstructive pulmonary disease copd; 493.21 asthma chronic obstructive pulmonary disease copd; 493.22 asthma chronic obstructive pulmonary disease copd; 493.81 exercise induced bronchospasm; 493.82 cough variant asthma; 493.91 asthma bronchial allergic nos asthmaticus; 493.92 asthma bronchial allergic nos acute exacerbation) will be characterized as a Probable or Definite SAE.

SAE reporting.

Any SAE, whether or not related to study intervention, will be reported to the IRB and the SMC. The PI will inform the IRB and SMC immediately and jointly make a decision whether the reported event is a SAE that must be reported to NINR due to the unexpectedness and/or the severity of the event. The initial SAE report will be followed by submission of a completed SAE report to NINR within two days (refer to Table 1. Adverse Events Form, Table 2. Adverse Events Coding, and Table 3. Matrix for Adverse Events Reporting).
In the event that a patient either withdraws from the study or the investigator decides to discontinue a patient due to SAE, the patient will be monitored by the investigator via ongoing status assessment until 1) a resolution is reached, i.e., the problem requiring hospitalization has resolved or stabilized with no further changes expected; 2) the SAE is determined to be clearly unrelated to the study intervention; or 3) the SAE results in death. Outcome of SAEs will be periodically reported to the IRB and to the funding agency. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to the IRB and the SMC. The report will include the participants' sociodemographic characteristics, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of AEs and SAEs, and any actions or changes with respect to the protocol.

Table 1. Adverse Events Form

| Participant number | AE | Onset Date | Ending Date | *Severity | *Relatedness to Study | *Action | *Outcome | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |

Table 2. Adverse Events Coding

| Severity | Relatedness | Action Taken | Outcome |
|---|---|---|---|
| 1=mild<br>2=moderate<br>3=severe<br>4=life threatening | 0=Definitely unrelated<br>1=Unlikely<br>2=Possibly related<br>3=Probably related<br>4=Definitely related | 0 = None<br>1 = Referral to Health Center for evaluation<br>2 = Referral to Emergency Evaluation | 1=Resolved<br>2=Recovered<br>3=Condition still present and under treatment<br>4=Condition continues to worsen<br>5= Participant died |

Stop rules. If the PI, IRB and/or SMC determines that serious adverse events meeting the standard definition of an asthma exacerbation (ED visit; Hospitalization and/or OCS initiation) have occurred in excess of the 5% threshold set for the study, then data collection and study enrollment will be stopped. The SMC and the IRB will be asked to review the study and suggest modifications of the protocol, the threshold limit or other changes. If the SMC and the Chairperson of the IRB believe that these modifications are adequate for resumption of the study, then the study will resume. NINR will receive a written report within three days of any such suspension and/or resumption of data collection.

Content of Data and Safety Monitoring Report
The Data and Safety Monitoring Report will include the following items:
1. Narrative/Trial Summary including study status; minutes of SMC consultations (action items, resolution of action items), and summary of any protocol changes.

2. Study Administration Recruitment and Participant Status including tables reporting overall study status, actual vs. expected enrollment, participant enrollment status by condition, overall reasons for eligibility

screen failures, overall protocol deviations, protocol deviations by condition, demographic and key baseline characteristics, participant attrition by condition, and study duration for all participants.

3. Study Administration Data including tables reporting overall summary of assessment measures collected, assessment measures collected by condition, overall summary of missing outcome measures, missing outcome measures by condition.

4. Safety Assessments for All Participants including tables reporting incidence of adverse events and severity of adverse events overall, as well as incidence of adverse events and severity of adverse events by condition.

Table 3. AE Reporting Timeline

| What Event is Reported | When is the Event Reported | By Whom is Event Reported | To Whom is Event Reported |
|---|---|---|---|
| Fatal or life-threatening unexpected, suspected SAE | Within 2 calendar days of initial receipt of information | PI | • SMC<br>• Institutional IRB<br>• NINR Program Officer |
| Non-fatal, non-life-threatening unexpected, suspected SAE | Within 7 calendar days of initial receipt of information | PI | • SMC<br>• Institutional IRB<br>• NINR Program Officer |
| Unanticipated problem (UP) that is not a SAE | Within 10 calendar days of the investigator becoming aware of the problem | PI | • SMC<br>• Institutional IRB |
| All UPs<br><br>Within 15 calendar days of the IRB's receipt of the report of the UP from the investigator | | IRB | • OHRP |
| | | PI | • SMC |

**d. For multi-site studies, procedures to ensure compliance with the monitoring plan and reporting requirements across study sites.** As described above we offer a robust plan for Auditing Selected Cases. In addition, consenting and data collection will be conducted by the same research assistant.

**e. An assessment of external factors or relevant information (e.g., developments in the literature, results of related studies) that may have an impact on the safety of participants or on the ethics for the research study.** Since our submission no new literature has been published that impacts the safety of participants. Uncontrolled asthma due to poor patient- and provider-recognition of uncontrolled disease with subsequent underuse of ICS therapy remains a major cause of excess asthma morbidity and mortality. Our study specifically seeks to improve recognition and treatment of uncontrolled asthma and therefore decrease risk of poor asthma outcomes. We will follow the literature during the trial and notify our participants and NINR if a change in the standard of care poses a safety risk or creates an ethical dilemma. If that were to occur the PI would consult with the SMC, the IRB and NINR to either stop the study or modify the protocol to address safety or ethical concerns. All participants would be notified and participants would be re-consented.

**f. The advanced plans for interim and/or futility analysis as appropriate.** Not applicable; this is a feasibility trial and is not powered for statistical significance.

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