Protocol Amendment – Summary of Changes Table

Individualizing Treatment of Asthma in Primary Care (iTREAT-PC)

BRANY File # 23-10-462 Master File

Summary of Changes from Protocol Number: 23-10-462, Version Date: 11_22_2023

to Protocol 23-10-462, Version Date: 07_23_2024

Page #, Section #, and Title	Change Description (all changes are in tracked changes)	Rationale/Justification
Page 112. Appendix 9.	1. We would like to email a follow-up message to participants that were not administered the last question(s) in their Month 3 survey to complete the remaining question(s). Message is provided in Appendix 9 (page 112).	The last questions in the IRB approved Month 3 survey were not activated in the REDCap system until July 16, 2024. This includes item #30 (pages 93-94) for the R-ICS, AZ, and AZ + R-ICS intervention groups, and items #29-#31 (page 94) for the ASM only group.
Page 113. Appendix 10.	2. We would like to email participants a message to let them know they have completed the study following the completion of their 3-month (final) survey.	End of study message informs participants that they have completed the study, thanks them, and directs them to talk with their doctor if they are taking study medications, to discuss whether to continue study medications.

STUDY (PROTOCOL) TITLE

Individualizing Treatment for Asthma in Primary Care

1) OBJECTIVES

Feasibility Aims:

Specific Aim 1: Establish the final protocol for the study, in conjunction with all stakeholder groups, including recruitment, implementation support, safety reviews, data collection/adjudication and IRB approval.

Specific Aim 2: Recruit up to 125 eligible individuals into a four-month "Vanguard" pilot study to include all data collection activities, across 5 participating sites, with qualitative feedback from participants, clinicians, staff, and research teams. Recruit up to 65 individuals at the remaining five sites to complete the active symptom monitoring activities for 4 to 6 weeks each, with qualitative feedback from up to 25 participants and up to 20 clinicians and staff.

Specific Aim 3: Adjust protocol based on the findings of specific aim 2 and feedback from all stakeholders and submit IRB protocol amendments for the full project.

Full Study Aims:

Specific Aim 1: Implement and evaluate 3 interventions, inhaled corticosteroids (ICS) as part of rescue therapy (Rescue ICS or R-ICS pronounced "RICKS"), prolonged azithromycin usage, and the combination of the two, compared to control individuals using Asthma Symptom Monitoring (ASM), in a patient-level randomized trial, among people with different asthma phenotypes, with annualized asthma exacerbation rate as the primary outcome.

Specific Aim 2: Analyze the impact on secondary outcomes of asthma control, asthma quality of life, and missed days of school or work across the 3 effector arms, and multiple asthma phenotypes, compared to control participants as well as head-to-head comparisons between arms.

Specific Aim 3: Using the PRISM (updated RE-AIM) framework evaluate the 3 different interventions for overall use with "eligible individuals," willingness of practices to engage with the interventions, fidelity of implementation by clinicians and participants, and maintenance of the interventions by participants and practices.

2) BACKGROUND

Impact of Asthma. Twenty-five million people have asthma in the US.[1] [See Appendix 3 for reference list.] Asthma exacerbations (AEX) cause the largest number of lost days from school or work for children and young adults, 1/3 of all days.[2, 3] Despite new medications,[4, 5] new drug regimens,[6-11] and evolution of treatment guidelines[12-14] the number of people with exacerbations in the previous year has decreased only slightly over the past 20 years, from 51.6% to 46%.[15, 16] Deaths from asthma have fallen by a 1/3 the past 15 years, dropping from 15 per million people with asthma to 10 per million; but asthma still accounts for over 3,500 deaths per year.[17] Asthma is also a disease with a high degree of disparities in outcomes. Blacks have exacerbation and death rates that are 2-2.5 times higher than Caucasians and Asians,[18] while Hispanics, particularly Caribbean Hispanics, have 2 times the rate of exacerbations and 1.5 times the rate of death.[19, 20] Thus, there is an ongoing need to expand and improve treatment approaches for individuals with asthma.

While asthma therapy is becoming more individualized based on asthma phenotypes,[12-14, 21-23] other than eosinophil counts for biologics, we know little about how to tailor newer therapies to individuals. Inhaled corticosteroid (ICS) medications are the foundation of care for all individuals with persistent asthma.[24] But ICS use is not without possible long term side effects, i.e., increased bone loss in pre-menopausal women,[25] transient growth retardation in children,[26] increased risk of carriage of Streptococcus pneumoniae in children,[27, 28] and pneumonia and adrenal suppression at higher doses.[29-33]

Treatment Options to be Studied:

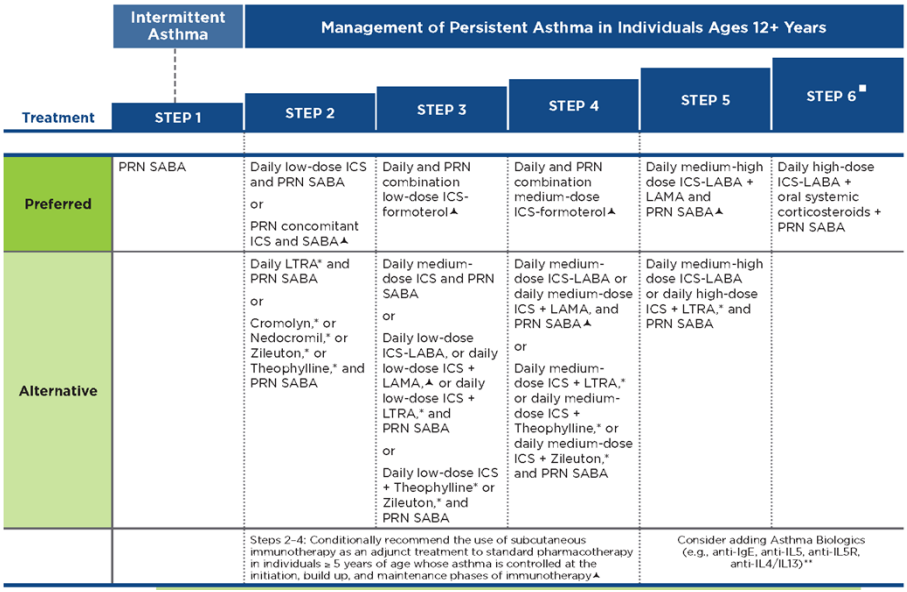
We will compare two currently available approaches to reduce AEX in primary care patients: (1) **use of inhaled corticosteroids (ICS) as part of rescue therapy, also known as SMART therapy** (Single Maintenance And Reliever Therapy) or PARTICS therapy (Patient Activated Reliever Trigger Inhaled Corticosteriods) combined referred to as R-ICS, and (2) **use of azithromycin (AZ) as a preventive therapy**, both individually and in combination.

Evidence for ICS as part of Reliever Therapy

Inhaled corticosteroids (ICS) are the mainstay for treatment of persistent asthma.[34] While the steroid molecules have been tweaked and delivery systems improved, the basic construct of use on a regular basis as a "controller" medication had not changed until recently. A number of studies have demonstrated the efficacy of ICS as part of rescue therapy. These studies enrolled tens of thousands of individuals and included both ICS plus a short acting beta agonist (ICS SABA)[32, 33, 35] as well as an ICS plus a long-acting beta agonist (ICS LABA).[36-38] Across efficacy and pragmatic trials the approaches have reduced exacerbations from 7% to 50%. Three years ago the Global Initiative for Asthma (GINA)[12] added ICS LABA therapy for rescue therapy as the preferred approach in steps 3 and 4 (see Figure 1) as did the new US guidelines released in December, 2020.[24] Based on recent studies, GINA recently expanded ICS LABA to all steps as rescue therapy.[12] Neither guideline has officially addressed ICS SABA rescue therapy, though a number of randomized controlled trials showed positive results.[32, 33, 39] Our completed pragmatic PREPARE study using ICS SABA in participants of African American/Black race or Hispanic/Latinx ethnicity [35] demonstrated a 13% reduction in exacerbations, improved ACT scores by over 3 points and ASUI scores by almost 1 point at the population level (both greater than the patient MID) and decreased lost days of school or work by 20%, all statistically significant.[40] These changes are equivalent to the combined impact of SMART therapy across the studies used by the National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC) Expert Work Group 4 in making their recommendation for SMART.[32, 33, 35-39] SMART therapy is internationally recognized as a reasonable treatment option, though currently it is only recommended in the US in two care steps, and has not been studied with nebulizer users. In talking with GINA committee members their recommendation for nebulizer users is to have them stop using nebulizers. In our PREPARE study 60% of participants used nebulizers intermittently and 40% used nebulizers weekly. In a survey conducted during the study, regular users felt their nebulizers were more effective than metered dose medications and indicated they had no interest in stopping nebulizer use. The PARTICS approach is entirely compatible with nebulizer use, in fact, nebulizer users had a greater response to PARTICS than the full population.[35] Thus, the addition of PARTICS as a treatment option alongside SMART solves the nebulizer problem without forcing people to make yet another change in their usual therapy.

Figure 1. Asthma Treatment Steps from 2020 US Asthma Guidelines Update

AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA



The full scope of whom to treat with SMART therapy, including which combinations of medications and what to use with nebulizer users is not fully elucidated.[14] Several factors complicate the dissemination of SMART therapy. First, the package insert for inhalers containing formoterol (the LABA that must be used for rescue therapy) specifically state: "not indicated for the relief of acute bronchospasm."[41] Many primary care clinicians and patient stakeholders have told us they are concerned about using a medication in direct contradiction to the package insert. Second, many insurance carriers do not cover SMART therapy in the US. Third, a large percentage of people with asthma use nebulizers (60% were nebulizer users in our PREPARE study), and integrating ICS as rescue therapy with nebulizer use has not been demonstrated until our PREPARE study. The first issue is not likely to be addressed soon as formoterol is now generic and thus no pharmaceutical company has an incentive to apply for a New Drug Indication. The second is progressing as payers are considering the new guidelines. The third requires additional study. Some of these concerns can be addressed by offering patients and clinicians another option for delivering ICS as part of rescue therapy, the PARTICS approach. PARTICS adds a stand-alone medium strength ICS to a patient's current therapy. This approach overcomes several of the concerns expressed above: 1) stand-alone ICS medications do not have language as part of their package insert indicated they should not be used during episodes of bronchospasm; 2) an additional stand-alone ICS has generally been covered by pharmacy benefits programs, furthermore these medications are typically tier 1 and thus have lower patient co-pays; 3) PARTICS is easily matched with nebulizer use. On the other hand, the current PARTICS approach requires the user to carry two different inhalers and thus does not "force" the use of ICS with the beta-agonist as the SMART approach does. A combined, single inhaler may work better for selected individuals that have difficulty in remembering their therapy and are not nebulizer users, for instance SMART may make more sense for many teenagers. Also, formoterol has a longer half-life which may have some impact on outcomes. The two approaches compare similarly in a meta-analysis performed by the PREPARE team thus, at this point both appear to be logical options where patient and clinician preferences can guide the therapy choice.

Table 1 – Equivalent ICS Preparations for PARTICS Use

Medium Dose Inhaled Corticosteroid (ICS)

Generic Name of ICS	Brand Name of ICS	Dose
Beclomethasone	QVAR	**80 mcg**
Budesonide	Pulmicort Flexhaler	**180 mcg**
Fluticasone propionate	Flovent HFA/Diskus	**110mcg/ 100 mcg**
Fluticasone propionate	ArmonAir RespiClick	**113 mcg**
Mometasone furoate	Asmanex HFA/Twisthaler	**200 mcg/ 220 mcg**
Ciclesodine	Alvesco HFA	**160 mcg**

Furthermore, dissemination of SMART or PARTICS is further complicated by another part of the US guidelines which recommends against "increasing ICS at the time of onset of an exacerbation."[24] Many clinicians report these two recommendations appear incongruent, though they are distinctly different. *The **ROUTINE** use of ICS as part of rescue therapy is a different intervention than a short-term increase in the ICS dose with worsening asthma symptoms.*[24] Additionally, not all asthma patients are steroid responsive. Patients with non-eosinophilic asthma (non-Type 2 inflammation) and smokers, among others, may respond less to increases in ICS, regardless of delivery.[42-45] Thus, our current, one size fits all guidelines are not congruent with the developing nuances of asthma treatment. **Therefore, the latest US asthma guidelines as well as GINA and others call for ongoing research into the role of ICS as part of rescue therapy.[12, 24]** This project will address these research needs by studying the extension of SMART or PARTICS treatment into steps 2 and 5 as presented by the US Asthma treatment guidelines, as well as adding options for use with nebulizers. For ease of reading from here on the use of ICS as part of rescue therapy whether as SMART or PARTICS therapy will be referred to as R-ICS, except when the two approaches are being evaluated individually.

Evidence for Long Term Use of Azithromycin

Azithromycin (AZ), an azalide macrolide antibiotic with anti-inflammatory properties, demonstrates efficacy in reducing asthma exacerbations,[46, 47] though who will respond best to treatment is not clear.[13] Some individuals treated with AZ have been able to stop ICS use for prolonged periods.[48, 49] Some individuals have remained symptom-free for years after completing 6-12 months of AZ.[48, 49]

The mechanism of action for macrolide therapy for asthma is currently unknown. Two mechanisms have been postulated: (1) macrolides have intrinsic immunomodulatory/anti-inflammatory activity that may be more specific for neutrophil-mediated inflammation;[50] and (2) macrolides have anti-microbial activity against persistent intracellular infections, particularly mycoplasma and chlamydia organisms.[51-54] Both mechanisms may be at play in reducing asthma severity across individuals.[50] While the anti-inflammatory effects are currently the most widely believed mechanism, this does not explain the long-term impact of macrolide therapy even after treatment has stopped.[55] Our primary research question (Which asthma phenotypes are helped the most with AZ treatment?) is mechanism agnostic. Our secondary heterogeneity of treatment effect (HTE) indices include *C. pneumoniae (Cp)* and *M. pneumoniae* biomarkers to explore the infectious construct and a *Challenge* sub-study after stopping AZ. A recent meta-analysis found that the population-attributable risk (PAR) of Cp-IgE for chronic asthma was 47% (39%-55%).[56] This large PAR, along with the recommendations of the recent Cochrane review[57] are strong justification for inclusion of infectious biomarkers in our study to investigate: (1) the predictive value of infectious biomarkers for positive AZ treatment responses;[58] and (2) whether infectious biomarkers predict prolonged improvements/remissions in asthma after completion of AZ treatment courses.[48, 49]

The AMAZES study,[46] an AZ-based intervention, demonstrated a 40% decrease in exacerbations using AZ. There were no sub-group differences, suggesting broad patient benefit for

AZ. A smaller study, AZISAST[59], showed an impact from AZ only in individuals with total eosinophil counts < 200/µl.[49, 55] Thus, whether the effect is more pronounced in non-Type 2 asthma is unclear. The guidelines from GINA,[60] European Respiratory Society/American Thoracic Society (ERS/ATS),[61] and British Thoracic Society (BTS)[62] all include use of AZ as a treatment option for severe asthma. A narrative review,[63] a systematic review/meta-analysis,[56] the recently released Cochrane review [57] and the GINA guidelines[12] highlight critical gaps in evidence for AZ in asthma and recommend performance of pragmatic trials such as iTREAT-PC. **The varying recommendations and current lack of research across a broad group of people affected by asthma highlight the GINA call for further head-to-head research including macrolide therapy. The Cochrane review recommends: 1) clarification of responsive phenotypes; 2) study of infectious biomarkers related to AZ responsiveness; 3) clarification of side effects from long term AZ; 4) and whether effects persist after therapy is stopped.** Should trials indicate positive results that provide clear implementation direction, adoption of AZ for uncontrolled asthma would be simple and scalable because prescribing AZ is familiar to many clinicians and AZ is a fraction of the cost of ICS/LABA or biologics.

Evidence for Asthma Symptom Monitoring for all participants

Multicomponent asthma interventions that improve asthma self-management have repeatedly been shown to decrease exacerbations and improve quality of life.[64] One component, Asthma Symptom Monitoring (ASM), is supported by dozens of RCTs showing an effect, by raising patients' awareness of worsening symptoms earlier so that treatment can be adjusted in time to avoid exacerbations.[65-69] Informed by this evidence, US asthma guidelines call for clinicians to monitor patients' asthma symptoms.[24] Driven by the COVID-19 pandemic, primary care settings have rapidly switched to remote care, and many are monitoring symptoms through apps or patient portals.[70] Various drivers, including ASM recommendations,[71, 72] pandemic "new normal" remote care, and the movement toward value-based purchasing should substantially increase ASM in the near future,[73, 74] moving towards the standard of care.

ASM can be performed with various tools, however, smart phone applications are likely the optimal solution because they can offer engaging and interactive functionality and have been demonstrated to be an effective, low-cost way to sustain engagement.[71, 75-77] Over 85% of the population uses smart phones, and there are no longer major differences in use based on income, race, or geography.[78] Our existing app successfully implemented asthma symptom monitoring between visits.[76, 77] The clinically integrated app monitors asthma weekly and allows patients communication with their clinic according to specific logic rules. Based on an iterative user-centered design process,[76] consistent with best practices,[79] the app integrates well into clinical workflows, emphasizes simplicity, and is highly scalable.[80, 81] We have demonstrated its ability to effectively implement ASM in primary[82] and specialty care.[76, 77] See Appendix 4 for details on the app.

We will require ASM in all arms of the study with the app as our preferred approach but will allow similar approaches built into EHR patient portals or a stand-alone version built in REDCap. Our patient stakeholders are very enthusiastic about the possibility of ASM minimizing steroid bursts. This approach will allow us to evaluate our asthma interventions in context of where we believe ASM will be seven years from now when this study would be completed. Our team has experience implementing all of the above ASM options.[83-85]

Summary of Treatment Options to be Studied

Table 2 – Treatment Arms

Treatment Arms	
(1) R-ICS therapy	+ Asthma Symptom Monitoring (ASM)
(2) Azithromycin (AZ)	+ ASM
(3) R-ICS + AZ	+ ASM
(4) ASM only	

The two treatment options, resulting in 3 different treatment combinations (R-ICS, AZ, R-ICS+AZ) provide alternatives to achieve control prior to starting biologics, which are only effective in ~50% of

individuals, increase the risk of life-threatening infections and perhaps some cancers, and are very costly. R-ICS therapy and AZ appear to address asthma from different mechanisms so they can be logically combined. They cover a wide spectrum of persistent asthma severity, as seen in primary care. Both appear to decrease overall steroid burden[49, 86] while reducing AEX, improving quality of life and decreasing lost days of school, work or usual activities.[36-38, 46, 59] These outcomes have been consistently endorsed by our patient stakeholders.

Research Questions

The **feasibility phase** of the project will address multiple questions: 1) Can practices implement the interventions and find eligible patients who are willing to be randomized to all four arms of the study? 2) Will data collection systems be efficient and facile? 3) What is the impact of adjusting doses of AZ on participant side effects? 4) Will clinicians be willing to prescribe azithromycin if a central prescription system is not utilized? 5) Can all sites implement Asthma Symptom Monitoring (ASM) at the minimally acceptable level? and 6) What safety activities need to be in place related to concomitant medications used by participants in either of the azithromycin (AZ) arms?

The feasibility phase will fully engage all stakeholder groups and recheck our randomization strata based on EHR queries from the participating practices. The feasibility questions are focused on implementation activities of the research cores and local research teams, on clinicians and staff in primary care practices and on participants using the therapeutic approaches, including the ASM, and reporting their outcomes. We will work closely with all stakeholder groups to refine, review, adjust, and perfect the entire research protocol during the feasibility phase. The Data Coordinating Center (DCC) will utilize information from the sites to refine their plans. We are confident that the feasibility phase will answer the implementation questions posed above.

The feasibility phase will consist of two distinct interventional activities. The primary **feasibility study will consist of a full implementation of the study protocol**, as detailed below, in five different study sites: Harvard/Brigham and Women's, Mt. Sinai, University of North Carolina, Rutgers, and Kelsey- Seybold. We will ask all five sites to recruit 24 eligible individuals to be randomized equally across the 4 study arms. These five sites will be expected to have an ASM system in place. The adequacy of the ASM systems for the five full implementation sites will be assessed per the protocol discussed below for the remaining, ASM-only, involved sites. The recruited participants will be asked to respond to monthly surveys instead of bi-monthly surveys for 3 months to shorten the overall feasibility time frame.

Protocol Amendment (April 1, 2024)

Due to delays in patient enrollment, Drs. Wilson Pace and Dave Mauger would like to add Atrium Health/Wake Forest to the group of 5 full implementation feasibility sites to enroll and consent patients. This is to ensure that the study achieves its overall enrollment target of up to 125 participants. The Harvard/BWH and Atrium Health/Wake Forest sites will enroll up to 24 participants across both sites. The minimum number of participants required of Harvard/BWH and Atrium Health/Wake Forest will be 6 participants each with a maximum of 18 each.

Interviews will be conducted with a subset of participants, at a minimum: 1) a group that responded to 100% of surveys, 2) a group that indicated medication side-effects or intervention cessation, 3) a group with low survey response rates (responded to only one month of surveys), 4) a group on traditional SMART and 5) a group on PARTICS therapy. Participants will be allowed to switch their ICS therapy approach during the feasibility and full study. In discussing this, our team is clear that having individuals continue on some ICS as rescue therapy would be preferable to having participants stop this therapy entirely. Should any individuals switch from one ICS therapy to another during the feasibility phase we will seek to talk with all of them concerning their reasons for switching. As this feasibility study is fleshed out additional sub-groups may be added. These individuals will be asked to participate in brief (approximately 10 - 20 minutes) semi-structured interviews. These interviews will be analyzed on an ongoing basis to identify concerns related to the

study protocol, which will be discussed by the Operations Committee, our core intervention teams, our sites, and our stakeholders. The two ICS groups, SMART and PARTICS, will be asked about why they chose their particular therapy, if they would have participated if only the opposite ICS therapy were offered and information on how the two therapies were presented by their prescribing clinician. Participants that have side effects to AZ that are likely to be dose dependent will be able to cut their AZ dose in half. We will include a short set of "exit" questions as part of the 3-month survey of all participants related to their participation, concerns, or problems encountered.

We will also interview four different groups of 5 clinicians each (assuming all three ICS groups exist):

1) clinicians that prescribed both SMART and PARTICS to at least one participant;
2) clinicians that prescribed only PARTICS to at least 2 participants;
3) clinicians that prescribed only SMART to at least two participants; and
4) clinicians that prescribed AZ.

These interviews will focus on the clinicians shared decision-making process with participants and for the two groups that only prescribed one option if they were willing to use the alternative or if they felt strongly about the option they had used. For the AZ group we will ask about patient or clinician concerns with this therapy for both local clinicians or central prescribing staff at the research hubs.

The remaining sites that didn't implement the protocol as described above, Reliant Health, Atrium Health, University of Washington, University of Colorado and the AAFP NRN, will be asked to **conduct a feasibility study focused on implementing Asthma Symptom Monitoring approaches.** Asthma Symptom Monitoring will be offered to study participants AND will also be available for all sites to offer to any patient with asthma. As such it is considered a "standard of care" quality improvement project. We will consent individuals who are asked to an interview related to their experience with the ASM systems at the time of their interview. We are not planning on consenting people for use of any of the ASM systems as this is not consistent with their use across asthma patients in the participating practices regardless of their study participation. We will ask that each site recruit up to 12 people that sign a HIPAA A form, or agree to be contacted when registering to use the DARTNet ASM system, so that the central research team can contact them for qualitative interviews. Verbal consent for the interviews will be obtained at the time of the interview. From the participants who signed a HIPAA A form we will ask that the operators of the ASM systems provide names of people that completed less than 3 of the 6 weeks (or the lowest reponders if everyone is > 3 weeks) and those that completed all 6 weeks. We have identified our initial "expectations" for ASM as shown in Table 3. We are in the process of interviewing all of our sites to determine their current implementation of ASM for any condition and for asthma specifically as well as any future implementation plans. We will work with existing systems or seek to support efforts that are in planning stages for all sites. The sites conducting just the ASM will focus on nuances of ASM that may be difficult for the five randomizing sites to recognize as they (the randomizing sites) will be focused on recruiting a larger number of participants and implementing the interventions.

Table 3 - Asthma Symptom Monitoring component expectations

	Required	Preferred
Standardized questions	XX	
Callback request option based on questionnaire responses	XX	
Completion reminders	XX	
Changes in frequency/number of questions based on responses through branching logic and/or dynamic question presentation		XX
Variable follow- up times based on previous response		XX
Data available in EHR with reminder to clinicians before visit to check data		XX
One data collection mode available (e.g., SMS or email link to survey)	XX	
Multiple data collection modes available (app, web, email, SMS)		XX
Prior responses available in graph/chart		XX
Educational materials		XX

Ability to enter/track peak flows		XX
Ability to enter notes/triggers		XX

Once these sites have an acceptable ASM system instantiated, either internally or by using the BWH/RAND app or a REDCap system to be set up by DARTNet if needed, we will ask them to recruit 8 participants (8 people that sign a HIPAA A form or agree to be contacted) to use ASM for 6 – 8 weeks. During this time central research staff will contact some of these individuals and ask them to request a "call back/contact" from their practice for testing purposes. We will track with them the success of this ask. Other metrics we will consider across the first 8 individuals are shown in Table 4. We will work with sites that are not able to meet these expectations to adjust their system and have them recruit an additional 4 people. We will then assess these outcomes again. We will also conduct semi-structured interviews with regular users and low users, as above defines as those that completed 3 or less assessments and those that completed 6 or 6 assessments) of ASM to determine if adjustments would have helped the low users engage with the system. Through this process we hope to develop a toolbox of ideas that can be drawn upon as sites continue to fine-tune ASM activities into the first year of the full project. Sites may offer the ASM system to other individuals they care for if they wish and may continue to use the system once testing complete as they wish.

Table 4 - ASM Success Factors and Metrics

Success Factor	**Specific Metric**
Recruitment/enrollment	8 participants recruited and completed baseline questionnaire
Questionnaire adherence	75% of participants completed 4 or more of the 6 weekly questionnaires
Participant experience	Interviews indicate the system is intuitive and easy to use
Callback request completed	All patients who requested a callback request were called back by clinician within 24 hours (test at least 3 such requests per site)

The **full intervention** is focused on individuals with asthma seen in primary care and includes individuals with moderate to severe persistent asthma who have experienced an exacerbation in the past year or remain in poor control, such that asthma is affecting their daily lives. Our comparisons will include a large portion of people with asthma (over 50% of people with asthma should be eligible in any given year)[15, 16] and provide direct information for clinicians, individuals with asthma and their parents/caregivers/guardians concerning optimal approaches to address gaps in asthma control. The kinds of questions our stakeholders are excited to better understand include: Does the level of controller compliance impact R-ICS therapy outcomes? Should everyone with a history of a lower respiratory tract infection prior to their asthma onset receive a trial of azithromycin? For people not eligible for biologics, will dual therapy make a noticeable difference in days lost from work or school? This large pragmatic trial will address these and many other stakeholder questions.

Our research questions result in 3 head-to-head primary and 12 secondary comparisons. Once heterogeneity issues and exploratory items are included, the iTREAT-PC study will include over 22 different comparisons in the final analytical plan (see Analysis section for details). Stated briefly, our research questions lead to the following **Hypotheses:** 1) All 3 intervention arms will be superior to the control approach in reducing AEX. 2) Participants with high eosinophil counts will have significantly better outcomes on R-ICS therapy than on azithromycin. 3) Individuals with lower self-reported controller adherence will respond better to R-ICS therapy than high adherence individuals. 4) Smokers and people with significant secondhand smoke exposure will have better outcomes on AZ than on R-ICS therapy. 5) Asthma control and quality of life (as measured by the Asthma Control Test (ACT) and Juniper mini-Asthma Quality of Life (mini-AQLQ) instruments, respectively) will significantly improve over baseline in all groups but will be significantly better in the 3 pharmacologic arms than in the control arm.

<u>These interventions correspond to actual healthcare options relevant to stakeholders</u>. All the interventions are currently available. Single inhaler SMART therapy with an ICS/LABA is currently available as a generic product.[41] There are multiple medium dose ICS inhalers available to use for PARTICS therapy (see Table 1 above.) such that at least one of these products should be a Tier 1 medication on all insurance plans. A combined ICS/SABA product is expected to receive FDA

approval soon (all approval materials reportedly submitted and product now under review) we are not planning on using the product at this time. AZ is recommended currently in various guidelines[13, 62] and is used across the country in a broad set of people who appear relatively steroid resistant. Chart reviews of these patients' (observational) data consistently demonstrate 50+% of people have a clinically important response.[89, 90] AZ randomized trials consistently demonstrate a >25% reduction in exacerbations.[47] The outcomes have been specifically vetted and endorsed by our patient stakeholders both for our current PREPARE study and for iTREAT.

3) INCLUSION AND EXCLUSION CRITERIA

The population for both the feasibility phase and full-scale study will be individuals ≥ 12 years of age[12] with persistent asthma requiring regular ICS or ICS + LABA, cared for in participating primary care practices. Practices will include Family Medicine, General Internal Medicine and Pediatric practices in urban, suburban and rural locations. General patient eligibility requirements are: 1) poorly controlled asthma (per the Asthma Control Test (ACT)[91, 92]) OR 2) a major exacerbation (defined in section C, Outcomes) in the past 12 months.

Inclusion Criteria:

1. A clinical asthma diagnosis for at least 1 year;
2. 12–75 years of age;
3. A current ACT total score of <20 OR an exacerbation requiring 72 hours or more of systemic steroids or a hospitalization of at least 24 hours > 30 days and < 365 days prior to enrollment;
4. Able to provide consent (adolescents: assent) in English or Spanish; (i.e., cognitively impaired individuals are deemed not to be able to provide consent and thus do not meet inclusion criteria.)
5. Patients with a coexisting clinical diagnosis of COPD are eligible if they meet any one of the following criteria:
   (i) Never smoker without secondary lung disease causing airway obstruction.
   (ii) Current or former smoker with obstruction on PFTs, but normal diffusing capacity of the lungs for carbon monoxide (DLCO) in the past 24 months.

Exclusion criteria:

1. Life expectancy <1 year (operationalized by the question to the patient's asthma care clinician "Would you be surprised if this person died in the next 12 months? If yes – include, if no – exclude);
2. No ICS prescribed for the individual (does not have to be using the ICS inhaler);
3. Active treatment for hematological or solid organ cancer other than basal cell or skin squamous cell cancer;
4. Allergy to macrolides or conditions for which macrolide administration may possibly be hazardous (e.g., acute or chronic hepatitis, cirrhosis, or other liver disease; end-stage renal disease; uncorrected hypokalemia or hypomagnesemia; clinically significant bradycardia; or history of prolonged cardiac repolarization and QT interval or *torsades de pointes*);
5. On daily or every other day oral steroids for any reason;
6. Overnight hospitalization for an asthma exacerbation in the past month (can wait and re-check eligibility after one month);
7. Currently on R-ICS or or any antibiotic therapy expected to last more than 30 days. If on antibiotics less than 30 days, enroll after they have stopped their current antibiotic for 72 hours. Individuals on biologics can be enrolled if they have been on a stable dose for ≥ 6 months and meet the ACT or exacerbation criteria as well as all other criteria.

8. On a medication with known risk (i.e., that is associated with prolonged QT and associated with *torsades de pointes* even when taken as recommended) or possible risk (i.e., can cause prolonged QT but lacks evidence for risk of *torsades de pointes* when taken as recommended) – Full lists in Appendix 1.
9. Specified medications for which close monitoring has been recommended in the setting of macrolide administration (digoxin, warfarin, theophylline, ergotamine or dihydroergotamine, cyclosporine, hexobarbital, phenytoin or nelfinavir).

4) VULNERABLE POPULATIONS

Pregnancy and Breast Feeding

Pregnancy is not a contraindication to asthma controller therapy, including ICS, azithromycin, or use of ASM. Improved asthma control has been shown to be associated with improved pregnancy outcomes. It is unknown if AZ is excreted in breastmilk but is assumed that it is. Out of an abundance of caution we will only enroll women that are pregnant or breastfeeding after their maternal or child care clinician approves of enrollment. We will not require a pregnancy test or effective birth control be used to be enrolled for women of child-bearing age but will ask that they inform us if they become pregnant. We will recommend that women on AZ who become pregnant (either arm) to stop this treatment, advise them to seek maternity care as soon as they are aware of the possibility of pregnancy and to inform their maternity care clinician of their study participation. Should the participant and her maternity care clinician feel that continued use of AZ is warranted then she may continue on therapy. If the participant is breastfeeding after delivery, the decision whether to continue azithromycin will be a shared one between the participant and the infant's care team. Whether or not the participant decides to continue azithromycin or stop it during pregnancy or breastfeeding, she will be asked to continue in the study. Pregnant or breastfeeding women in the R-ICS or control arms of the study will be allowed to continue without interruption.

Adolescents

Children ages 12 to 17 will be included. Individuals aged 12 – 17 will require both parental/guardian consent as well as participant assent to be included. Given this study involves currently approved medications for adolescents and for use with asthma only one parent or guardian will be required to provide consent.

Prisoners

No prisoners will be enrolled in the study.

Economically or Educationally Disadvantage Populations

Many of our recruitment sites care for economically or educationally disadvantaged individuals. We are not planning on screening for these factors as part of the enrollment process. We do ask about educational level attained as well as total household income and number of people in the household to be able to calculate if the individual is above or below the poverty level as part of end of study analyses. These data are collected after consent. We strive to develop consent forms that are between the 6th to 8th grade reading levels. Given the inherent complexity of some medical terms, such as azithromycin, some paragraphs may be hard to word within these parameters. While consent will mostly be conducted remotely, it will involve real time interactions with a study coordinator so that questions can be asked and answered until the person is comfortable with what they are consenting to or what they are consenting to for their adolescent. The cost of SMART therapy, if not covered by insurance, is prohibitive for many individuals, thus we have an alternative treatment approach, PARTICS, that is generally covered by insurance and much cheaper. AZ is a generic medication and generally covered by insurance. Even if paid for out of pocket the dose used in this study (500mg three times week) can be found for $12 to $20 per month at various

pharmacies. We will have staff available to assist with any appeals to pharmacy benefits managers should insurance coverage be an issue.

Cognitively Impaired

Individuals that are not able to provide consent or assent in English or Spanish will not be eligible for the study. Primarily this is due to the fact the study outcomes are entirely dependent on participants' ability to answer regularly administered surveys.

5) SETTING

Involvement of Community Advisory Board

Please see our section on community engagement, on page 40 in the community-based participatory research section.

American Academy of Family Physicians National Research Network

The AAFP NRN is one of the largest and most aggressive clinical trial-oriented practice-based research networks (PBRN) in the country. On August 16, 2023 the operations of the AAFP NRN have been assumed by the DARTNet Institute. The AAFP NRN will continue with the clinical activities as outlined in this protocol. Under Dr. Pace and now Dr. Hester, the AAFP NRN has served as the clinical coordinating center or major component of the clinical coordinating center for multiple large clinical trials including: AIM-HI,[93] Asthma APGAR,[94] TRANSLATE CKD,[95] BELT,[96] PREPARE,[40] TRIPPD[97] and numerous AHRQ task orders. The AAFP NRN works with numerous academic and private research organizations and has specific contractual arrangements with the University of Colorado, the University of Kansas and DARTNet that allows personnel and services to flow seamlessly between each organization and the AAFP NRN. The DARTNet Institute was split off from the AAFP NRN and the University of Colorado in 2011 and was initially housed at the AAFP. The AAFP NRN and DARTNet are highly committed to staff continuity across projects, and as such, the staff on this project have worked together for years, some for close to 20 years. All staff of the AAFP NRN as of August 15, 2023 were employed by the DARTNet Institute and have continued on this project. Mr. Manning, the overall project manager for the clinical coordinating center has served in this role for most of the projects listed above. He is supported by individuals involved in many of the above studies as well. The research cores and implementation sites are all experienced research units. Most are PBRNs in their own right running their own multi-site studies.

Penn State Department of Public Health Sciences:

This group will serve as the DCC for the project and has been described in detail throughout the application. It is one of the major NIH data coordinating centers in the country, with numerous large network-based clinical trials for which it has severed a similar function. For this project the DCC will focus on study methodology, data quality, and timeliness reporting, data analytics and creation and support of the DSMB. Actual management of the study data will be managed by the DARTNet Institute in keeping with the highly successful data collection processes for our current PREPARE grant. Penn State will maintain two key statisticians, Dr. Mauger, the dual PI for the project who will be blinded to all treatment assignments throughout the open phases of the project and Dr. Lan, senior biostatistician in the department who will be unblinded and deal with initial data curation, report writing, and all DSMB reports. They are supported by database and statistical analysts who will perform the day-to-day work of the project under direction from Drs. Mauger and Lan. Both Drs. Mauger and Lan have been actively involved in the study development, study outcomes, and study analytics, and have helped refine all aspects of this application.

The Department of Public Health Sciences has extensive resources that can be called upon if required to support other functions of the project including data management software and patient

directed data collection systems. The Department has a state-of-the-art data center with full suites of analytical software.

Dr. Mauger is the dual PI of the project, and how he and Dr. Pace will work together is outlined in the Leadership section. He will have full and final authority for data analytics. He will work with Dr. Pace and the clinical coordinating center to develop a detailed analytical plan for all phases and levels of analysis, and this plan will be reviewed, refined, and accepted by the Scientific Committee, the Executive Committee and finally the DSMB.

DARTNet Institute:

This organization grew out of the AAFP NRN and the University of Colorado Department of Family Medicine and has ongoing, close working relationships that span multiple projects and personnel. DARTNet will be responsible for data management for consent, randomization, participant-facing data collection, tracking ancillary study activities such as the CBC, biomarkers, or Step-up and Challenge sub-study activities, tracking all exacerbation triggers, and creating and maintaining a database to finalize and adjudicate exacerbations. DARTNet will also be responsible for the creation of the EHR data extraction, transformation and loading specifications, standardization of EHR data to OMOP Common Data Model v6 and support of any required OMOP concept ID value sets required for EHR data analytics. Dr. Amanda Ratigan, Director of Analytics, will serve as the site PI. She has supported a number of other large trials including the PREPARE trial, a large PCORI funded study, Integrated Behavioral Health in Primary Care, two NIH data coordinating centers, and numerous smaller trials. DARTNet handles ingestion of Giga Bytes of EHR data daily with automated systems for most of their transformations. DARTNet operates two patient facing data collection systems, the Patient Engaged Electronic Reporting System (PEERS) and REDCap. Both offer slightly different capabilities. The two can be linked to increase performance options. The REDCap software is planned to be used for the participant data collection and data management for iTREAT. If additional functionality is required (such as participant addressable accounts for educational purposes) PEERS can be linked to the REDCap system.

RAND:

The RAND Corporation is a research organization that develops solutions to public policy challenges to help make communities throughout the world safer and more secure, healthier, and more prosperous. RAND is nonprofit, nonpartisan, and committed to the public interest. RAND researchers have advanced degrees in more than 350 disciplines and apply state-of-the-art methods to address a broader range of issues than any other research organization. Approximately 1,800 people from 50 countries work at RAND. For this project RAND will serve as the Research Core responsible for the modifications and dissemination of the ASM systems. The smartphone app has been developed by RAND in cooperation with Brigham and Women's/Partners Health System. Dr. Rudin, the PI on the projects that have developed and tested the application, will serve as the site PI for RAND. His team, in collaboration with the Brigham team, will develop the implementation support documents, specify and oversee any modifications required for use by adolescents, and support the integration of ASM systems, including the smart phone application into all sites. DARTNet also operates ASM software that can be utilized if a site so desires. At this time, the DARTNet system will only be offered if other options are not available. Over the course of the study Dr. Rudin will serve as a key member of the clinical coordinating center research team. His team will provide ongoing support to all sites involved in the study. Dr. Rudin has been involved in all phases of the development of this project, including study design, outcomes, analytics, sample sizes, and Research Implementation site expectations.

University of North Carolina (UNC):

The University of North Carolina Division of Allergy and Department of Family Medicine (UNC DFM) are teaming up to serve as the Research Core responsible for the development and

support of the R-ICS arms of the study. Dr. Hernandez served as the site PI for the current PREPARE study and research staff in the UNC DFM served as the support staff for that project. UNC is a major research university, and the UNC DFM is recognized as one of the top research groups in that discipline in the country. The UNC DFM operates several practice-based research networks, and the one that focuses on internal primary care practices has provided a letter of support and will work with Dr. Hernandez to also serve as one of the Research Implementation centers. Under Dr. Hernandez's guidance and with support from Dr. Israel, UNC will develop the implementation tools for the use of R-ICS. They will help sites implement and support sites in the ongoing use of these intervention arms. As a Research Implementation site, the practice-based research staff will recruit, train, and assist UNC primary care sites in the recruitment of participants and the use of all study arms. UNC recruited one of the highest number of participants for the PREPARE study, mostly from primary care sites.

University of Colorado, Department of Family Medicine (CUDFM):

The University of Colorado Department of Family Medicine is another of the premier research departments in that discipline in the country. Dr. Kessler works extensively with the AAFP NRN. The CUDFM is tightly affiliated with the AAFP NRN and has worked on previous projects with the AAFP NRN and Dr. Hahn related to AZ use in asthma. The CU health system includes over 100 primary care clinical sites across three states and thus should have little trouble recruiting the 10 – 12 required for this project. The practice-based research staff at the site will work with local sites, assisting with implementation of all study arms as well as with participant recruitment.

Brigham and Women's/ Partners Health (BWH):

The Brigham and Women's/ Partners Health site will serve as a Research Implementation site. As the original research site for the smart phone application they will serve as consultants to RAND in the development of the implementation tools for the ASM options. The Internal Medicine practice-based research network will support local sites in the implementation of the arms of the study as well as with participant recruitment. The Division of Internal Medicine at BWH is one of the top research groups in the discipline in the country and is particularly known for innovative information technology tools to support and improve care.

Atrium Health:

Atrium Health is the second largest not-for-profit health care delivery system in the nation. The full system spans three states and include over 60 hospitals, thousands of ambulatory sites, and both private and academic sites. For this project the Department of Family Medicine (Atrium DFM) in the Mecklenburg County, NC, area, the home of primary care research for the organization, will serve as a Research Implementation site. The research team is expansive, and the informatics support of the organization is strong. The Atrium DFM is involved in multiple research projects at any given time and supports a research network of 30+ close by sites and many more across the entire system. The Atrium DFM will support the sites in implementing the study arms as well as in recruitment of participants. Atrium Health is a current PREPARE site and familiar with all systems to be used in this project.

Kelsey Seybold:

Kelsey-Seybold Clinic is a large multi-specialty medical organization in the Houston, TX, area with more than 500 physicians and allied health professionals representing 55 medical specialties. The Clinic provides continual care for approximately half a million Houstonians each year, with over one million clinic visits at 30+ locations throughout the greater Houston metropolitan area. Kelsey-Seybold Clinic is Houston's premier multispecialty group practice, founded in 1949 in Houston's Texas Medical Center. More than 650 physicians and allied health professionals practice at 35+ locations in the Greater Houston area. KRF actively works with Texas Medical Center institutions,

including The University of Texas M.D. Anderson Cancer Center, UTHealth's McGovern Medical School and School of Public Health, Baylor College of Medicine, Houston Methodist Hospital, CHI St. Luke's Health Baylor St. Luke's Medical Center, and the University of Houston. Medical services offered by Kelsey-Seybold include medical care in 65 medical specialties including primary care and specialty care, outpatient surgery centers, travel medicine clinics, an accredited sleep center, a radiation therapy center, laboratory services, advanced radiology services and other diagnostic services, onsite Kelsey pharmacies, and a secure web portal for patients to communicate with their Kelsey-Seybold doctors, get test results and schedule appointments.

Reliant Health Care:

Reliant Health is a private, integrated delivery system in central Massachusetts. The site includes a robust research arm and frequently works with both UMass Worcester and Harvard on NIH, AHRQ and other research projects. The research arm is a standalone group with a track record of high levels of precision in research implementation and participant recruitment. Reliant will serve as a Research Implementation site.

Rutgers/Robert Wood Johnson School of Medicine:

The Robert Wood Johnson Medical School is the academic center of a large and diverse health care system encompassing Barnabas Health as well as the Rutgers system. The Department of Pediatrics Division of Population Health, Quality and Implementation is a newer organization designed to implement and research new health care delivery interventions and models in primary care with a pediatric focus. This site will serve as a Research Implementation site and work with the Departments of Family Medicine and General Internal Medicine in implementing the project across primary care offices in the system. Dr. Kleinman, the site PI, and Dr. Pace and the AAFP NRN have worked together over the past 10+ years and are currently working together on two NIH COVID studies.

University of Washington

The University of Washington Department of Family Medicine (UWDFM) is another of the top research departments in Family Medicine in the nation. The UWDFM has close ties with DARTNet and has extensive interactions with the University of Colorado. The UWDFM operates a successful multi-state research network and works with the University of Washington community clinics. For this project the UWDFM will serve as a Research Implementation site and support both implementation of the study interventions as well as participant recruitment.

Mt. Sinai Health System

Mt. Sinai is an integrated delivery system and SafetyNet organization with the greater New York City metropolitan area. The health system and specifically the primary care division has a very active research division that supports and coordinates research of this type. Mt. Sinai is another PREPARE site and has recruited a diverse and large population of participants for that project. Mt. Sinai will serve as a Research Implementation site for this project. Dr. Wisnivesky, the site PI for iTREAT-PC, is a member of the NAEPPCC and will also serve on the Scientific Expert Panel for this project. The support staff will handle local implementation of the study arms as well as support participant recruitment.

RESOURCES

All sites have dedicated research personnel and space. Most are major, academic research organizations. Reliant and Kesley-Seybold have dedicated research staff and space and participate in industry funded pharmaceutical and device studies on a regular basis. The DARTNet Institute operates a REDCap instance that will be used for all study consent, tracking and outcome follow up. Local sites will use either their local REDCap instance or local study management software to manage recruitment prior to consent as patient names cannot be included in the central REDCap

instance until consent. The only study procedure is phlebotomy which will be performed within the clinical sites, dedicated research space and may be contracted out to a commercial laboratory for the CBCs. Therefore, there are no specific research equipment, other than standard office equipment, required to conduct this study. Extensive facility documents are available if desired.

All sites have access to Collaborative Institutional Training Initiative (CITI) training through their local IRB or through the AAFP if the site does not have a CITI account. All research staff and selected practice staff in the sites using network staff to conduct the study will complete the requisite CITI training related to their study role. All sites will rely on BRANY as a single IRB. All sites are part of SMART IRB (either through a local IRB or as part of their FWA) and will sign a reliance agreement with BRANY to be eligible to participate.

The consent rate for our PREPARE study was over 90% for eligible individuals. In looking at the number of potentially eligible individuals in a "typical" primary care office (the mean and mode for number of clinicians across the country in a physical primary care site are both between 4 and 5) each site will need a minimum of 10 clinical sites to have access to approximately 2000 potentially eligible individuals, a reasonable starting point for recruitment. All Research Implementation organizations have 3 to over 15 times this number of potential clinical sites. Since the final sites are not known exact EHR data is not available, though the information below in Table 5 is derived from the participating clinical organizations. The Feasibility potentially eligible data and the Asthma Symptom Monitoring data for potentially eligible individuals comes from EHR searches in the clinical sites to be used for 60% of the organizations at this time.

6) NUMBER OF SUBJECTS

Table 5 - Recruitment, Enrollment, and Retention Plans

Feasibility Full Study Phase	**Number**
1. Estimated number of potentially eligible study participants and a description of how this number was determined (EHR data used to estimate adolescent and adult asthma populations across the 10 networks)	Full Feasibility – 3445
2. Total number of potentially eligible study participants expected to be screened	Full Feasibility – 800
3. Total number of screened study participants expected to be found eligible	Full Feasiblity – 500
4. Target sample size	Full Feasibility – up to 125
5. If applicable, total number of practices or centers that will enroll participants	5 research hubs 5 ASM hubs will include participants for qualitative interviews
6. Projected month first participant will be enrolled (month after project initiation)	9th month
7. Projected month last participant is expected to be enrolled (month after project initiation)	12th month
8. Projected rate of enrollment (anticipated number enrolled per month of enrollment period)	31
9. Estimated percentage of participant dropout	10%

Full Study	Number
10. Estimated number of potentially eligible study participants and a description of how this number was determined (EHR data used to estimate adolescent and adult asthma populations across the 10 networks)	46,850
11. Total number of potentially eligible study participants expected to be screened	20,000
12. Total number of screened study participants expected to be found eligible	15,000
13. Target sample se same number stated in Milestones)	3,200
14. If applicable, total number of practices or centers that will enroll participants	10 centers 120 sites
15. Projected month first participant will be enrolled (month after project initiation)	2nd month full study
16. Projected month last participant is expected to be enrolled (month after project initiation)	34th month full study
17. Projected rate of enrollment (anticipated number enrolled per month of enrollment period)	95
18. Estimated percentage of participant dropout	15%
Feasibility Asthma symptom monitoring only	**Number**
19. Estimated number of potentially eligible study participants and a description of how this number was determined (EHR data used to estimate adolescent and adult asthma populations across the 10 networks)	4266
20. Total number of potentially eligible study participants expected to be screened	400
21. Total number of screened study participants expected to be found eligible	300
22. Target sample size (use same number stated in Milestones)	Up to 65
23. If applicable, total number of practices or centers that will enroll participants	5 centers 10 sites
24. Projected month first participant will be enrolled (month after project initiation)	10th month
25. Projected month last participant is expected to be enrolled (month after project initiation)	13th month
26. Projected rate of enrollment (anticipated number enrolled per month of enrollment period)	12
27. Estimated percentage of participant dropout	10%

7) MULTI-SITE RESEARCH

Most members of the Operations Committee have conducted clinical trials together over the past 15 to 20 years. Through this work a robust project and site management approach/plan has been developed and proven successful. The research team will deploy all aspects of this plan for this project. The multi-component process includes a central educational and learning meeting of all site PIs and study coordinators. At this meeting the concepts for the project are explained so that truly informed consent can be obtained. The study protocol is reviewed in detail and the site versus central responsibilities carefully delineated. During this process sites are encouraged and expected to talk with each other and the research team about how to deal with recruitment challenges, providing prescriptions to participants, helping with tracking participants and responding to possible exacerbations or adverse events. The sites provide extensive feedback to the research team and adjustments to the protocol may be made. For this project many of these activities will also include all stakeholder groups as outlined in the Engagement section. All of these groups will be expected to work together to review the current protocol and improve or adjust if they feel it is necessary.

The AAFP NRN staff will begin working with each site's study coordinator to complete any local IRB submissions that are required. Given the requirement to rely on a single IRB we will work with each local IRB, through SMART IRB, to develop a reliance agreement with the BRANY IRB, which

will be the primary IRB of record. This early work helps the local sites start to really review and understand the protocol which makes the ongoing group interactions more meaningful.

The AAFP NRN staff will have individual teaching sessions with each site along with teach backs prior to enrollment. These will include education on the REDCap study management and consent system, on web-based video consent processes, another review of enrollment criteria and how to reach a central staff or senior scientist at any time. Prior to recruitment the senior staff associated with the AAFP NRN (Drs. Pace, Hester, Westfall or Israel) will contact and talk with each site PI to be sure he or she is comfortable with all processes.

After recruitment begins the AAFP NRN staff will schedule weekly meetings with each site study coordinator and help them trouble shoot issues that arise as well as maintain communication between sites. The senior staff will touch base with the site PIs at least monthly during the Feasibility recruitment and follow-up phase. Recruitment figures are reported to the Operations Committee bi-weekly and monthly summaries are provided to the Executive Committee. The Operations Committee is tasked with assuring recruitment meets timelines. Other parts of the communication plan include the creation of a study wiki for all study coordinators and site PIs to ask questions and seek advice across sites as well as weekly tips that are sent to the study coordinators primarily.

Several months prior to beginning enrollment the AAFP NRN will schedule two recurrent meetings per month for site PI's and study coordinators for ongoing communication. The two meetings are identical and each site is expected to attend one or the other. This duplicative system allows easier coordination of schedules across multiple sites and has worked well in previous studies. This meeting is used to update people on protocol changes (which are also sent via email and posted in the Egnyte system discussed below) as well problem solve between sites and provide general communication. Should a significant protocol change be required due to safety concerns this will be emailed to all site PIs and study coordinators with a return receipt of message included. Phone calls to site PIs and study coordinators will be made of there is not clear evidence that the protocol change has been received. Study results, interim results that can be shared, protocol and IRB updates and premature study closure are handled through these meetings as well. Though final study closure typically occurs up to 18 months or more after the last participant has exited the study. Thus, final closure is sent via email to site PI and study coordinator to be communicated to the local IRB.

All sites will be provided at least two unique folders on the DARTNet Egnyte system which is HIPAA compliant and can support sharing of clinical data (one folder per site) as well as study forms or files that are site specific (the second folder.) This system will also have shared folders for all sites to access and share common documents.

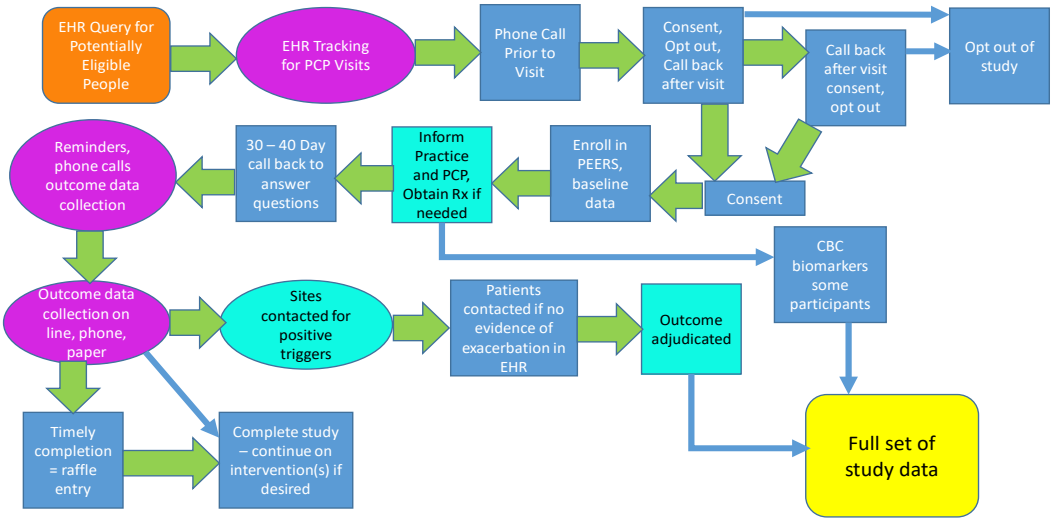
The REDCap data management system will be used to communicate ongoing project information at the participant level. The system will include study forms, such as exacerbation follow-up/confirmation forms and adverse event forms that will support direct data entry as well as attached documents. Most participant related communication will occur through this study management system.

8) RECRUITMENT METHODS

Study Population and Research Setting(s): The population for both the feasibility phase and full study will be individuals ≥ 12 years of age[12] with persistent asthma requiring regular ICS or ICS/LABA and cared for in a primary care practice participating in the study. Eligibility and exclusion criteria are stated in the named section above. During the feasibility phase each of the Research Implementation organizations recruiting for the full study feasibility arm will recruit 24 individuals who will participate for up to 3 months to test all aspects of the study. The other remaining sites will focus on testing the Asthma Symptom Monitoring systems (ASM) by recruiting 8 to 12 individuals per site to test the ASM approaches. Each individual well be asked to report symptoms at least weekly for 6 to 8 weeks. If a site has issues completing symptom reporting with the first 8 individuals (i.e. less than 100% call backs occurred within 48 hours – we will ask for 3 to start with), adjustments

will be made and an additional 4 individuals will be recruited. Semi-structured interviews with subsets of these individuals will be conducted as noted above. Likewise, several individuals at each site will be specifically asked to request a call-back from the central research staff and this will be tracked to be sure the messaging is working. These individuals will remain eligible for the full study. Note, the central research team is not asking for the actual symptom monitoring data just usage data (less than 3 weeks vs 7 to 8 weeks for qualitative interview sampling). Of the five ASM only sites three will be using the DARTNet REDCap based ASM system. At this time we will only allow adults to access the system until we finalize parental verification for adolescent use. Individuals will be provided a link to the site that is specific to the clinical organization. Upon registering the individual will complete an End User License Agreement and then be offered an option for a possible call back. The individual can accept that option or reject that option and use the system without any chance of participating in the qualitative interview described below. If an individual accepts the offer to potentially be called they will be paid $20 if they use the system for at least one week out of the 8. If they are selected for an interview and they consent and participate in the interview they will be paid an additional $25. Two sites will be operating their own ASM systems. Reliant Health Care Group has built a system into MyChart and will ask people if they are willing to have Reliant share his/her name and contact information with DARTNet for possible interviews. Up to 15 people to agree to be contacted will be paid $20 and if an individual is selected for an interview, consents and participates s/he will be paid an additional $25. Atrium/Wake Forest Health will use a version of the DARTNet REDCap system loaded into their REDCap. We will code a HIPAA A form on the DARTNet iTREAT Project Management REDCap system for this system to refer interested individuals to. Similarly to all other systems the first 15 people that agree to participate will be paid $20 and if they are selected for, consent to and participate in an interview they will be paid an additional $25.

Figure 2. Participant and Data Flow iTREAT



For the full study EHR data indicate that 100 – 120 practices can be expected to have over 35,000 potentially eligible individuals. With an 8% asthma prevalence rate, an average of 2,500 adolescent or 7,000 adult individuals per site (per EHR data), 85% of people with asthma on an ICS or ICS/LABA, approximately 45% of individuals with asthma have an exacerbation per year and at any given time approximately 50% are in poor control. Combining these estimates over the 34-month recruitment timeline, we conservatively estimate 60%+ of individuals will become eligible over the recruitment timeframe, providing a minimum of 120 eligible adolescents and over 330 adults per clinical site. With a 20% - 25% consent rate, Recruitment Implementation sites will need 10 to 12 physical sites to meet study recruitment.

The consent rate for our PREPARE study was over 90% for eligible individuals. All Research Implementation organizations have 3 to over 15 times this number of potential clinical sites. Since

the final sites are not known exact EHR data is not available, though the information above derives from the participating clinical organizations.

Participant flow is shown in Figure 2. Recruitment is expected to follow slightly different paths depending on local decisions by each Research Implementation team. In the PREPARE study, the most effective recruitment method consisted of EHR searches to find potentially eligible people coupled with EHR tracking that notified the research team when a potentially eligible individual had scheduled a visit. For sites using this approach the research team will then call the individual several days ahead of the appointment to remind the patient of the appointment and ask if the patient would be interested in hearing about a research study for which s/he may be eligible. Phone recruitment script is provided in Appendix 5. If patients expressed interest and eligibility is confirmed, the study would be described over the phone. At that point some individuals may elect to consent while others may elect to speak with their clinician first. Of course, some will opt out at this point. For those consenting over the phone, study staff will obtain consent, collect baseline data, and randomize the patient. If the randomization requires a new prescription is needed, the study clinician is notified. If the person elects to talk with their clinician first, a note about the call will be sent to the clinician including a reminder about the study within the EHR. After the visit a call back occurs to complete the same process. Our PREPARE study shows that over 90% of individuals will consent if their clinician indicates the study is safe and reasonable for the individual. At some sites a research staff member may meet the individual at the practice after assessing interest and eligibility over the phone. Some sites may use cold calls to potentially eligible individuals as well as appointment-based approaches, though the appointment-based approaches typically achieve higher consent rates among eligible individuals they are labor intensive and may not be possible for organizations with recruiting sites that cover a large geographic area. Consent can occur over the phone.

9) STUDY TIMELINES

Full Feasibility pilot – Up to 125 participants across 5 research hubs, each participant will be asked to remain in the study for 3 months. Recruitment will be over 4 months.

Asthma Symptom Monitoring pilot – up to 65 participants across 5 research hubs, each participant will be asked to complete weekly symptom reports for up to 8 weeks maximum. 4 months recruitment time period

Full study: 3200 participants recruited across 10 research hubs. Each participant will be asked to complete a questionnaire every 2 months for 16 months. Selected participants will be offered to continue in a Challenge study for an additional 12 months. Recruitment time period will be up to 32 months.

10) PROCEDURES INVOLVED

Feasibility study – at this point no procedures are included in the feasibility pilot studies.

Full Study -The only study procedure will be phlebotomy of selected individuals. All participants who do not have a total eosinophil account available in their clinical data in the past 5 years will be asked to have a CBC performed. Eight hundred of the individuals on AZ (1600 total) will be asked to have blood specimens collected and stored for testing for Mycoplasma pneumoniae RNA through highly sensitive PCR and testing for chlamydia pneumoniae IgE antibodies. Six hundred of the 800 will actually be tested. (See below.)

11) SPECIMEN BANKING

Whole blood and serum will be obtained from a subset of participants who are chosen and agree to undergo phlebotomy for study purposes. Agreeing to phlebotomy is optional and declining will not affect study status. All samples will be labelled with a study code so that lab analysis personnel will be unable to identify individuals or their treatment assignment. The sample code key allowing identification of individuals will be stored securely as described elsewhere for other iTREAT-PC study data. Specimens will be curated and stored in the laboratory of Dr. Chengming Wang, Director, Molecular Diagnostics Laboratory, Department of Pathobiology, College of Veterinary Medicine, Auburn University. Dr. Wang's laboratory will aliquot, store and distribute specimens for this study analysis to his laboratory and to two other designated laboratories described elsewhere in this protocol. Remaining samples will be stored indefinitely in Dr. Chengming's laboratory for future possible biomarker studies, at the discretion of the iTREAT-PC Executive Committee that has sole discretion to approve future studies on the samples.

12) DATA MANAGEMENT

14.1) Data Analysis

We are intentionally avoiding the factorial design framework for the purpose of analysis. This is because we are uncertain about whether the combined treatments will have an additive effect. If the combined effect is less than additive, then the standard main effects analysis based on the factorial design is not optimal. The primary analysis will consist of three hypothesis tests comparing each of the three treatment arms against the control. We will employ the maximum likelihood framework based on the Negative Binomial distribution (with offset to account for differential follow-up time due to dropout or treatment failure) to perform these tests. In addition to treatment assignment, the model will also include fixed-effect covariates sex, race, smoking history, asthma treatment step at enrollment, TEC and facility with mobile technology, as well as multi-level random-effects of organization and practice within organization. As we consider SMART and PARTICS approaches to be equivalent these will be combined for the all primary analyses, therefore individuals that switch between these approaches will not impact the primary outcome analyses.

In the presence of non-compliance, the ITT analysis may underestimate the efficacy of treatment at the patient level. Since non-compliance may be driven by confounders such as disease severity, the traditional per-protocol analysis of treatment efficacy may introduce confounding bias. We will apply causal-inference based methods to adjust for confounders. Particularly, we will perform adjusted per-protocol analysis using inverse probability weighting technique, where the probability of adherence will be estimated. We will also explore the instrumental variable approach, which does not rely on confounder adjustment, but only allows a crossover type of non-adherence. Instrumental variable approach can be used to estimate the complier average causal effect for randomized trials when certain assumptions are satisfied.

Heterogeneity of Treatment Effect: Additional analyses to examine heterogeneity of treatment effect will employ the same modeling framework, except that interaction effects between the treatment effect and pre-specified covariates will be included. These include SMART vs PARTICS, 1500mg vs 750mg AZ dosage, eHealth Literacy, compliance with treatment assignment, TEC, smoking, and lower respiratory tract infection[n (LRTI) onset of asthma. By examining these interactions, we will be able to determine which of these characteristics might contribute to heterogeneity of therapeutic interventions. We are particularly interested in the following hypotheses:

1. AZ will be more effective among those participants that smoke or have a history of LRTI onset.
2. R-ICS therapy will be more effective among those with higher eosinophil counts.

The DCC team discussed approaches to the heterogeneity analyses concerning people that may switch between the two ICS as rescue therapy options. At this point they are not prepared to commit to an approach. If the number of people who do switch is low it may not be possible to include this as an interaction variable.

Secondary Outcomes: Analyses for secondary outcomes including the ACT both as a continuous and dichotomized at 20, Quality of Life, and number of school/work days missed due to asthma will be conducting using the same framework as the primary analysis in terms of testing strategy and covariate adjustment. However, different likelihood distributions will be used as appropriate. The Normal distribution will be used for the ACT continuous and Qualify of Life outcomes, while the Binomial likelihood will be used for the ACT dichotomized outcome, and the Negative Binomial for the number or school/work days missed due to asthma. For the outcomes that are repeatedly measured, we will expand the mixed-effect models to include subject-specific random effects to account for within-subject correlations. As with the primary analysis, we will employ the Bonferroni adjustment for the three comparisons of treatment against control separately for each outcome.

Missing data: For the primary outcome, asthma exacerbations over the 16 months of follow-up, all available data will be included and an offset will be incorporated to account for differential follow-up. The mixed-effects models that will be employed can yield appropriate results in the presence of missing at random data, but we will also employ sensitivity analyses to determine the potential impact of missing not at random data, including an extreme case tipping point analysis. If covariates of interest are missing, multiple imputation methods will be applied to implement the mixed-effects models. In our previous PERPARE study overall data missingness was < 4%.

Exploratory analyses: ***Utility of Biomarkers for predicting azithromycin treatment outcome:*** Infectious biomarkers, including IgG, IgA, IgE serology and PCR, will be assessed for up to 600 participants on AZ treatment. We will define three different phenotypes depending on IgA, IgE and PCR positivity and test our hypothesis that (1) *Cp* IgA or IgE seropositivity AND a positive PCR OR *Mp* CARDS IgE seropositivity is predicted to be the most responsive to AZ; (2) seropositivity OR *Cp* PCR positivity is predicted to show less AZ response; and (3) IgG only or no positive biomarker results will demonstrate the lowest rate or degree of AZ responsiveness. The level of response will be based on ACT scores (both ACT continuous and ACT dichotomized at 20). ACT scores (> 3 point improvement) will be used to classify patients into responders versus non-responders. We will first examine the number of patients in each observed combination of biomarker results and carry out the statistical tests for the combinations with sufficient sample sizes. We will compare ACT scores across different groups based on biomarker positivity patterns and use linear or logistic regression models to evaluate the predictive values of individual biomarkers and combined biomarkers. Prediction accuracy measures, such as R-squared (coefficient of determination), will be calculated for linear prediction model; ROC (Receiver Operating Characteristic) analyses will be performed for logistic regression model to determine the prediction power and area under the ROC curve (AUC), sensitivity/specificity, and positive/negative predictive value will be calculated. Ten-fold cross-validation method will be used to assess and validate the performance of prediction models. Finally, we will evaluate if historical and demographic data, including a self-reported lower respiratory tract infection at the time an individual's asthma developed, self-reported controller use at baseline, race, and smoking status, add prediction value to the biomarkers. We may potentially have a large number of predictors (including interaction terms) to consider, so we will use penalized regression methods (e.g., LASSO) to alleviate the overfitting problem.

Azithromycin Cessation Challenge: The study will include an AZ *Cessation Challenge* sub-study among participants in the AZ monotherapy and AZ + R-ICS arms. The primary outcome will be asthma control as measured by the ACT with time to first exacerbation and mini-AQoL as secondary outcomes. This sub-study is exploratory but tracks entirely with the recommendations of the recent Cochrane AZ review[57] and the European Respiratory Society/American Thoracic Society guideline.[61] The goal of this sub-study is not to test the effect of ceasing AZ as opposed to not ceasing, but rather to identify patient characteristics associated with long term improvement or relapse after AZ is

withdrawn. For the continuous ACT and AQoL outcomes we will use mixed-effects models including effects for time (on and off AZ), patient characteristics of interest, and interactions between time and patient characteristics. The interaction effects will be of primary interest because those can be used to identify predictors of changes in asthma control resulting from AZ withdrawal. For the time to first exacerbation outcome we will use Kaplan-Meier and proportional hazards model regression analysis to identify risk factors for relapse.

Outcomes for Step-up sub-study: We expect that up to 4 - 6% of participants (N=23 – 48 per control and monotherapy arms) may step-up to the R-ICS or dual pharmacologic arms due to treatment failures. The primary and secondary outcomes will be ACT and AQoL respectively. As with the AZ cessation challenge, the goal of this portion of the study is not to test whether additional therapy is superior to continuation on the same therapy, but rather whether there are patient characteristics associated with improved outcomes when additional therapy is given. As with the AZ cessation challenge, we will use mixed-effects models with interactions between time and patient characteristics to identify characteristics associated with response to additional treatment.

14.2) Study Endpoints

Primary outcome: The annualized rate of major asthma exacerbations (a hospitalization for asthma or 72+ hours of oral/parenteral steroids). Major asthma exacerbations are a core asthma outcome for asthma clinical research[99] and a major health risk (including death) that causes distress to people with asthma and their families.[100] Our patient and parent/caregiver stakeholders overwhelmingly endorse *asthma exacerbations that require changes in their daily lives* (consistent with major exacerbations) as the most important event related to their asthma. Clinicians focus on ongoing exacerbations as a marker of poor control (over standardized asthma control instruments), and thus endorse this outcome as their most important metric. Policy stakeholders indicate that from both an overall society cost, individual's costs and quality of life perspectives they consider exacerbations as the main driver of all three concerns. Our definition of "major exacerbation" is aligned with US Guideline Expert Review Panel 4 definition and NIH Asthma Outcome workshop.[24, 99]

Secondary outcomes: Asthma control is consistently mentioned by clinicians and supported by research as the ***intermediate*** outcome that best predicts ongoing exacerbations.[101, 102] The National Asthma Education and Prevention Program's Expert Panel Report 3[103] (NAEPP 2007) and Report 4,[87] of which Drs. Pace, Israel, Yawn, Elward, Wisnivesky and Bryant-Stephens were members or reviewers (Panel 3 or 4), emphasizes the importance of asthma control as a goal of therapy because of its relevance to patients and providers in the ongoing assessment of asthma. Based on the input of our stakeholders we will use the Asthma Control Test (ACT) to measure asthma control.

Exploratory outcomes: Data, including demographic, historical, and biological data, will be collected to define sub-groups of individuals with asthma. The following sub-groups will be considered exploratory using the same primary and secondary outcomes: Black race, positive *v.* intermediate *v.* negative infectious biomarkers, and overlap syndrome (both an asthma and COPD diagnosis). The infectious biomarkers are a highly sensitive PCR for *Chlamydia pneumoniae* and *s*pecific serologic tests (including IgA, IgG and IgE) for *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* to guide AZ therapy.

Outcome Collection

Participants will complete online surveys that include all outcomes instruments (see Table 6). Patients will receive survey reminders via automated voice, text, and email messages as well as via follow up phone calls. Text and email survey reminder messages are in Appendices 6 and 7, respectively. Surveys are designed to account for a missing previous survey using dynamic questions related to the timing of possible exacerbations. The data systems include daily reporting for study staff to inform them of participants with missing surveys and tracking actions to collect these data. As in PREPARE, we will collect outcomes directly from participants using standardized instruments (ACT,[92] mini-AQLQ,[98, 104] missed days of work/school[105]) and the Asthma Exacerbation Questionnaire[96] for exacerbation trigger questions. This questionnaire is sensitive but not specific,

meaning it will overestimate exacerbations, thus requiring confirmation. But it does not miss potential exacerbations. Participants will be asked to complete their surveys every two months using various methods. Exacerbations will then be adjudicated through a multi-step process that includes the site's review of EHR or health information exchange data, communication with the patient, and occasionally requests for outside medical records. Once the data have been assembled, an initial blinded two-clinician review will occur. If there are any concerns or non-agreement at this level, an independent adjudication committee will blindly review and make a final determination. The standard operating procedures for these activities are well worked out as our team reviewed approximately 3000 such events during our PREPARE study. For the full set of analytical groups see the Power Analysis/Analysis plans.

Table 6 - Primary and Secondary Outcomes (All Power Analyses adjusted for multiple outcomes using Bonferroni adjustment)

Primary or Secondary	Name of Outcome	Specific measure to be used	Time-points	Estimated power (if applicable)
Primary	Annualized rate of major AEXs	Hospitalization for asthma or 72+ hours of oral/parenteral steroids	Every two months	.90 (α .016)
Secondary	Asthma Control	Asthma Control Test (ACT) score.[98, 106-111] Validated for patient report, developed to have low patient burden and available in multiple languages.[92] Has been evaluated in multiple populations and can be self-administered,[112] administered by telephone[91] or by mail.[113] Recommended by the NAEPP and the NIH Asthma outcome workshop[103, 114] for research use due to extensive validation data, across a range of criterion and construct measures, including demonstration of responsiveness to therapy and a minimal important difference (MID - the smallest difference in a score of interest which patients perceive as beneficial and which would support a change in the patient's management.[115]) The ACT MID is 3 for individuals[116] and cut-off values are ≤ 19 for "uncontrolled asthma" [92] and ≤15 "very poorly controlled" asthma.[92, 112]	Every two months (q 2 mo)	ACT Dichotomized .96 ACT continuous .99
Secondary	Quality of Life	Mini-Asthma Quality of Life Questionnaire (mini-AQLQ). An ideal outcome measure for comparative effectiveness analysis would capture the risks and benefits for the interventions from the patient's point of view. The mini-AQLQ captures this information.[98, 117] The full measure was developed **entirely from patient experiences. Patients were asked to assign a relative value to different health states.** The original instruments (adult and pediatric[109, 118, 119]) have undergone validation across multiple languages and constructs for all severities of asthma. Test-retest reliability is very high (intraclass correlation of 0.95). The instruments are responsive to change[117, 120] and have a well-established MID of 0.5.[110] Both instruments have shortened versions that correlate very well with the longer versions and will be used for this study. The AQLQ and its variants are frequently used in asthma studies including large multicenter clinical trials.[121-127]	q 2 mo	Mini-AQLQ continuous .99
Secondary	Days Lost from Work or School	Validated and utilized as part of the National Health Interview Survey.[105]	q 2mo	.99

14.3) Data Quality

The processes of ensuring data quality being with the build of the data collection processes. In building our data collection and study management project into REDCap we consistently assess how we can assure high initial data capture. For instance, patient facing questionnaires are all designed such that every question must be answered with prefer not to answer or similar options available when logical. This assures that all completed questionnaires do not have null data that cannot be distinguished between unintentional missingness or purposeful missingness. Reports are constructed that track partially completed questionnaires as well as questionnaires that are due to be completed. Central research staff then reach to participants to complete these questionnaires. We also build in logical data skip patterns such that data collected by study coordinators at enrollment are not missing. Finally, for patient collected data we run logic checks on responses and send out correction notices for illogical responses.

For the exacerbation and adverse event data reporting we will develop REDCap data collection forms for sites and central staff to work together to complete data collection. Forms that are not complete are in a report for central staff to track. Once completed the exacerbation forms are reviewed by two clinicians on the central team for data missingness and final determination of the outcome. This two-person review identifies any missing data that is not discretely captured. Finally, if there are discrepancies between the two initial reviewers on the outcome assignment the information is reviewed by a second level committee. This committee may ask for additional information as well.

Adverse events that are tracked are initially sent to the site so coordinators can add information they are aware of and so the PI or senior staff can determine the scales to be applied to the AE event. If there is insufficient information for these judgements, then the form will be returned to the central study team to contact the patient and obtain additional information. Medical records may be requested for SAEs that may be related to the study medications. Once a full data set is compiled the AE form is returned to the site to add the relevant assessments as to causation and severity. These forms are then reviewed internally using the same process as described above for the exacerbations.

Finally, the DCC will download the full data set on at least a quarterly basis and run their own quality and logic checks for the full population without any study arms being identified. These reports will be reviewed by the Operations Committee and any data quality concerns will require the development of a resolution plan to be implemented and tracked.

14.4) Confidentiality

Patient level data collected for this study will be housed in DARTNet's REDCap system, which is operated out of a HIPAA compliant AWS data center in Portland, Oregon. Personal identifying information will be stored in one database linked to study data via a study ID. Data downloaded by the DCC will utilize only the study ID and specific required demographic data such as date of birth, race and ethnicity. Data collection forms, such as for exacerbations, will only list the study ID requiring users to access patient information from the system. Access to the REDCap system will be based on site level permissions. Each research site will only be able to see their own participants while the central research team will be able to see all participants. Sites may develop tracking systems for study recruitment. Site specific data handling is described below.

Data elements for participants will include name, date of birth, gender, race, ethnicity, address, phone number, back up contact name and phone number. Data for the research project are in the questionnaires that are attached as separate documents. Research data will be retained for 7 years. Participant data, if a participant agrees to be contacted for future studies, will be retained for 5 years. If a participant does not allow future contact that participant's PHI will be deleted when the data is locked for the study.

Access to the full data set will be allowed for central research team members and the DCC (excluding PHI for the DCC). Local research team members will have access to their own sites data. Data will be entered directly into REDCap where it will be stored. Files that are attached to a REDCap

form are encrypted at the time of transmission. The DCC will download data directly from REDCap or from files created out of REDCap using sFTP. Files that are not attached to a REDCap form will be posted to a site's Egnyte folder to be picked up by central research staff. In general, we expect files to be attached to REDCap forms.

Data management for this project will be shared between DARTNet, and the DCC. The project will use DARTNet's HIPAA compliant, secure computing and file sharing resources, Egnyte, for sharing files between sites if necessary. Most files will be attached to the correct REDCap form that is being completed and stored within the DARTNet REDCap environment in AWS. DARTNet operates HIPAA compliant AWS services housed in the Portland, OR, data center. The systems within these organizations for this project include file transfer systems, patient-facing data collection systems, study management systems, data transformation systems, and data analytical systems. All of these systems exist in secure, locked, monitored environments (at the University of Colorado, PennState or AWS); all systems are encrypted at rest; and all data transmissions are encrypted at AES-1024 or higher level of encryption. Physical servers at the University of Colorado are in a climate- and access-controlled environment with 24-hour video monitoring as well as access monitoring at the individual level. Nightly, weekly, and monthly back-ups include transaction level files and images that are stored both locally and in the cloud. The University of Colorado runs a Palo Alto firewall with multiple layers of intrusion detection. Only limited systems are available through the firewall. All other systems require VPN, multi-factor authentication to access. The DARTNet servers sit in a specific sub-network that is not visible to other users within the University behind a second firewall and intrusion detection system, with IP filtering for access. User accounts for both organizations require strong passwords and all local machines run centrally monitored and updated anti-virus and malware software.

Pennsylvania State Security: Privacy and data integrity are of critical importance to the DPHS. Network access is controlled through multiple layers of protection which, at a minimum, consists of unique username and password authentication. Multi-factor authentication is employed in most cases. Strict password strength and aging policies are applied to all user accounts from the operating system to custom-developed DPHS applications. Access to systems, data, and other network IT resources are always controlled using the principle of least privilege, role-based authorization. Additionally, the DPHS network and IT systems are protected from security threats by enterprise level firewall and intrusion detection systems managed by our cyber security partners at Penn State Health and College of Medicine as well as Penn State University Park network levels. Different levels of encryption are used to protect data at various stages. Data transmitted across the internet is secured via 2048-bit SHA-2 Secure Sockets Layer (SSL) and/or Virtual Private Network (VPN)/Internet Protocol Security (IPSec) encryption. Applications developed by DPHS staff encrypt identifiers before storing the values to the database. All host servers operate under encryption at rest protection implemented through enterprise-level SAN hardware, compliant with IEEE 1619-2007 and NIST Special Publication 800-38E. All VMware host servers are physically attached to the protected SAN infrastructure and all guest servers are provisioned under encryption at rest protection.

Biospecimen data will be stored initially at Auburn University after testing has been completed. Data files will be transferred to DARTNet's AWS site via sFTP when files are complete. See next section for details on data security at Auburn University.

LOCAL DATA SECURITY

AAFP NRN (Now a part of DARTNet)

AAFP NRN will primarily store data on the iTREAT-PC Egnyte system. Any human subjects data stored locally will be stored on secured research servers at the University of Colorado. University of Colorado provides secure physical server space for DARTNet through a service contract that includes informatics support. Research data housed on research specific servers are not only behind the

University of Colorado firewall, but visible only to select IP groups within the overall University of Colorado network. In addition, these data are stored on directories with limited user access. Data servers are managed by the University of Colorado Department of Family Medicine, which includes a locked, environmentally controlled, 24-hour monitored server farm with redundant backup systems. Analysis will be performed on University of Colorado servers maintained by the campus information services, located on core or local workstations maintained by the Department of Family Medicine. No data will be stored on local workstations. The research team has been certified and trained by the CITI Program.

DARTNet Institute Partners

DARTNet collaborates with over 1200 clinical organizations across the country across our portfolio of activities. DARTNet partners with several practice-based research networks that have electronic data capabilities. We partner with numerous larger health care systems on specific projects related to the use of existing data. We have over 5000 clinical organizations that send us EHR data for our Practice Performance Registry through vendor agreements, through self-pull of their EHR data or through DARTNet operated data extraction systems. DARTNet currently has recent EHR data sets that cover over 40 million people.

Data Handling Capacity

DARTNet operates its own physical servers and data storage space in a HIPAA compliant server room within the University of Colorado Informatics infrastructure. DARTNet also rents HIPAA compliant cloud servers and space from AWS. DARTNet owns multiple physical servers and approximately 1 PB of storage space in multiple environmental tiers and behind several layers of security within these environments. Within the University of Colorado environment DARTNet operates a multi-tiered, multi-dimensional business intelligence system, secure file transfer systems (using Egnyte and the AWS cloud) as well as software to merge, translate and de-identify existing electronic health data – EHR, claims and patient reported data – into standardized data sets for analytical purposes. We operate SAS servers in this secure environment for remote access data analytics as well having SAS, R and other analytical packages available to all analysts for local usage. The space is monitored 24/7 by the University of Colorado police and all access is controlled and monitored. The University operates a Palo Alto firewall with additional intrusion detection software while DARTNet operates a second fire wall within their sub-network with a second level of intrusion detection. All servers are encrypted at rest and particularly sensitive databases use embedded database encryption in addition. No DARTNet servers in the University space traverse the firewall. They are all only addressable after establishing a VPN connection to the network using two factor authentication.

DARTNet handles EHR data that arrives in multiple formats, including CSV files pulled by sites, vendors or using our own software, CCDs, CCDAs and are adding FHIR at this time. We are very familiar with the problems with all of these data extraction methods and can provide extensive use case support for the project. Files are transferred using sFTP with a minimum of 2048 bit key.

DARTNet physical servers undergo incremental back-ups nightly into our NAS local storage. Weekly full images are also stored locally. Monthly images are also stored in the AWS cloud and retained for 1 year. AWS servers are backed up by AWS on a continuous basis

DARTNet Assets

All DARTNet computers, primarily laptops, have DARTNet-installed and centrally monitored anti-virus, anti-malware systems. Updates are pushed regularly. All activity of DARTNet assets is centrally monitored. No data is stored on any laptop or other remote device. Laptops are used to run Office

functions and to connect to either the physical servers or various cloud-based systems used by DARTNet, including partner systems on which DARTNet staff carry out data manipulation tasks.

REDCap
DARTNet maintains an instance of REDCap in our AWS HIPAA compliant workspace. The system is encrypted with a SSL interface. DARTNet staff routinely monitor the REDCap community / messaging for new updates (such as the recent security concerns) and if any updates include high risk concerns will update the system typically within 2 hours. Routine updates are performed regularly.

The Department of Public Health Sciences (DPHS) at Penn State University College of Medicine
DPHS Information Technology Management Team: The DPHS has dedicated system architects, administrators, and technical support/helpdesk staff that design, implement, and support the computing environment and specialized technical requirements of faculty, investigators, students, collaborative researchers, and staff. The primary environment includes an on-site data center housing highly-available VMware vSphere virtualization infrastructure host servers. The virtualization infrastructure is leveraged to host dedicated, high performance servers providing both dynamic computing scalability and system redundancy. Within this enterprise-level configuration is an integrated network of servers running primarily Microsoft Windows Server and Red Hat Enterprise Linux computing platforms.

The department's Windows servers are used primarily for utility and operational services such as secured remote access, department-level application services, and VDI/Virtual Desktop Infrastructure (Citrix XenApp, XenDesktop). Additional DPHS-dedicated Information Technology stacks include financial/operational systems, educational/learning management systems, communication, and collaboration services (e.g. Microsoft Exchange email, SharePoint, document management, process workflows, etc.). Linux servers are primarily utilized to provide higher performance platforms for Bioinformatics, research, and clinical trials hosting as well as a technology innovation sandbox and custom statistical, web application, and database development ecosystem. A four-tier configuration is implemented to provide discrete proof of concept/pilot/application development, quality assurance/acceptance/scalability testing, staging and production hosting environments. This architecture provides a proven, stable base for development and testing of custom web applications and databases, staging of updates, and deployment of finished software into production. Enterprise-level SAN (Storage Area Network) services are based on a highly available RAID configuration with additional protection provided through automated hot spare fail-over disks and self-healing file systems. All critical and production infrastructure are configured with subsystem redundancies and proactive hardware, operating system, database and application monitoring to support high availability.

Additional highlights of the DPHS standard operational computing services include a 10 gigabit Ethernet backbone with at least 1 gigabit service to all department servers and clients. Distributed file systems are centrally administered, provide over 250 terabytes redundant disk array (RAID) storage capacity, and are available to all computing platforms through the use of additional secured technologies including Samba, NFS, and SMB/CIFS protocols.

Modeling best practice ITIL (Information Technology Infrastructure Library) and ITSM (IT Service Management) principles, DPHS IT staff regularly utilizes critical IT management tools to proactively identify and mitigate performance problems. Some of these tools include Oracle Enterprise Manager, OSSEC (system health, log and intrusion detection monitoring), Solarwinds Network Performance Monitor, Microsoft System Center Configuration Manager (SCCM), BMC Track-It! and ServiceNow (helpdesk/technical request/service delivery management).

The DPHS employs a dedicated, private fiber optic back-up network (separate from the primary network) to provide high-speed, high-capacity backup and recovery services. Penn State Health and College of Medicine (including DPHS) are protected by enterprise backup solutions that span two geographically separate locations. This system maintains development, test, production, and research data from various operating systems and physical locations onto redundant spinning disk arrays or archival tape. Data is maintained under retention periods as short as seven days to over 10 years depending on requirement. The solution is capable of standard file level back-ups to complete system snap shots (physical and virtual images) to dedicated software specific copies. This enterprise solution maintains over 3 PB of data with a current daily ingest of ~40 TB from over 1200 systems. Included in the backup technology stack protecting DPHS are vendor software and services provided by IBM Tivoli Storage Manager (TSM), Commvault Data Management, and Veeam Back-up/Replication. This robust, multi-vendor service model provides multiple layers of redundancy in backup and recovery services, helping to ensure complete disaster recovery capabilities and the ability to comply with any regulatory or research project/data archival requirement. Along with daily monitoring and reporting, backup integrity is regularly tested through disaster recovery exercises.

Security, privacy, and data integrity are of critical importance to the DPHS. Network access is controlled through multiple layers of protection which, at a minimum, consists of unique username and password authentication. Multi-factor authentication is employed in most cases. Strict password strength and aging policies are applied to all user accounts from the operating system to custom-developed DPHS applications. Access to systems, data, and other network IT resources are always controlled using the principle of least privilege, role-based authorization. Additionally, the DPHS network and IT systems are protected from security threats by enterprise level firewall and intrusion detection systems managed by our Cyber Security partners at Penn State Health and College of Medicine as well as Penn State University Park network levels. Access and audit logs provide a chronological record of access and changes to system configurations and data at all levels.

Different levels of encryption are used to protect data at various stages. Data transmitted across the internet is secured via 2048 bit SHA-2 Secure Sockets Layer (SSL) and/or Virtual Private Network (VPN)/Internet Protocol Security (IPSec) encryption. Applications developed by DPHS staff encrypt identifiers before storing the values to the database. All portable computing file systems are fully encrypted including laptops, tablets, and MacBooks. Critical workstation and server file systems are also encrypted. Additionally, all host servers operate under encryption at rest protection implemented through enterprise-level SAN hardware, compliant with IEEE 1619-2007 and NIST Special Publication 800-38E. All VMware host servers are physically attached to the protected SAN infrastructure and all guest servers are provisioned under encryption at rest protection. DPHS faculty, investigators, and staff also utilize LOK-IT flash (thumb) drives, which provide both encryption and a physical locking mechanism that requires entry of a PIN code to gain access. Per DPHS policy, standard (non-encrypted) flash drives and other personal storage medium are not permitted within the department. Secure email services are available through Cisco Registered Envelope Services (CRES). DPHS faculty and staff are able to send TLS (Transport Layer Security) encrypted messages via a registered electronic envelope. The registered envelope is a password-protected, encrypted email that can only be opened by authorized recipients who authenticate themselves.

The department employs anti-virus, anti-malware and anti-spam protection on all servers, workstations, portable computing platforms, and the email gateway to further protect from risk of compromise. All department server and work stations are maintained with security patches and software updates released by manufacturers through a regularly scheduled rhythm of monthly automated and immediate manual (when needed) maintenance services. Security awareness

campaigns and threat announcements are also regularly provided to department faculty, investigators, students, and staff.

For each project, a departmental security team ensures that systems are secure, meet regulatory requirements such as HIPAA-compliant storage, HIPAA de-identified datasets and obtaining HIPAA waivers where required, and adhere to information technology polices developed by Penn State University and the Penn State Health IS, Cyber Security, and Risk Management departments which periodically audit DPHS processes and procedures. Penn State Health Cybersecurity scans each server within the department nightly and provides a vulnerability report to DPHS systems administrators, who remediate any findings. In addition, all systems are patched regularly. The DPHS databases are proactively monitored and backed up through multiple levels of redundancy using Oracle Enterprise Manager, RMAN, and IBM Tivoli Storage Manager. IBM Tivoli Storage Manager is used to backup other servers on the network including the web servers. Backups are retained locally, archived at the Penn State Health secure data center and collocated at an identical data center at University Park. Disaster recovery exercises are performed regularly to insure DPHS staff has the ability to recover a database, database server, or web server. All applications are assessed against a Cyber Security Governance Framework based on the National Institute for Standards and Technology Special Publication 800-18, are HIPAA compliant.

The DPHS hosts and manages a dedicated Citrix XenApp/XenDesktop research environment to provide a number of collaborative research capabilities including customizable Virtual Desktop Infrastructure (VDI) services. Almost any operating system or software package can be published and made available to launch through a Citrix VDI session.

RAND

RAND will primarily store data on the iTREAT-PC Egnyte system and store only limited data separately at RAND where necessary for analyses. And Human subjects data stored at RAND will be stored in locked filing cabinets or on encrypted, password-protected computers at RAND to which only investigators and staff directly associated with the study will have access. These data will be reported only as summaries, in aggregate. Where it is necessary to report individual data such as quotations, names will not be disclosed and the source will be de-identified. The research team has been certified as trained by the CITI Program and will have current certifications on file for the duration of the project. The principal investigator will conduct regular checks with the team to review the status of all study data. Any unauthorized use or disclosure of the interview data would immediately be reported to the RAND Human Subject Protection Committee.

University of North Carolina

Microsoft Teams will be used to store and share a screening log accessible to only IRB approved personnel (no accounts outside of UNC). The owner of this of this file is required to manage users and permissions. This file will never be downloaded from the Teams platform. These files will include name, address, subject ID, MRN and other PHI. Microsoft Teams provides a secure platform that can be used to collect and share data. Access to all data (both PHI and non-PHI) on Teams will require a 2-step verification via Office 365. Only authenticated users, study personnel and select technical personnel, will have access.

Brigham and Women's Hospital

Data obtained by Mass General Brigham, including recruitment logs and tracking data, will be collected and stored electronically on secure servers located within the Mass General Brigham network. Access to the data will be restricted to authorized personnel only. All study data will be kept secure for a minimum of 7 years after study completion. After this period, the data will be deleted in accordance with Mass General Brigham policies and federal regulations. Data

management will be overseen by the principal investigator and research staff, who will ensure the accuracy and integrity of the data throughout the study. Data backups will be conducted regularly to prevent data loss due to technical failures. Any breaches or potential breaches of data security will be reported to the Mass General Brigham data security officer and the institutional review board promptly.

Kelsey-Seybold
Data obtained by Kelsey Research Foundation, including recruitment logs and tracking data, will be collected and stored electronically on secure servers located within the Kelsey Research Foundation network. Access to the data will be restricted to authorized personnel only. All study data will be kept secure for a minimum of 7 years after study completion. After this period, the data will be deleted in accordance with Kelsey Research Foundation policies and federal regulations. Data management will be overseen by the principal investigator and research staff, who will ensure the accuracy and integrity of the data throughout the study. Data backups will be conducted regularly to prevent data loss due to technical failures. Any breaches or potential breaches of data security will be reported to the Kelsey Research Foundation data security officer and the institutional review board promptly.

University of Colorado
The University of Colorado will collect data including recruitment logs and tracking data and store it electronically on university secure servers. Only authorized members of the research team will have access, and we will put protocols for accessing data in place. We will maintain secure storage of collected data for 7 years after study completion. University and Federal policies will determine data deletion after that. The Principal Investigator will oversee all data management, with research staff. We will regularly back up data, to avoid data loss. Any breaches or potential data security breaches will be immediately reported to the University of Colorado data security office and the IRB.

University of Washington
Data obtained by the University of Washington team, including recruitment logs and tracking data, will be collected and stored electronically on secure servers located within the university's network. Access to the data will be restricted to authorized personnel only. All study data will be kept secure for a minimum of 7 years after study completion. After this period, the data will be deleted in accordance with university policies and federal regulations. Data management will be overseen by the principal investigator and research staff, who will ensure the accuracy and integrity of the data throughout the study. Data backups will be conducted regularly to prevent data loss due to technical failures. Any breaches or potential breaches of data security will be reported to the university's data security officer and the institutional review board promptly.

Reliant Health System
To maintain the confidentiality of data collected as part of the iTREAT-PC protocol, Reliant will:

- Utilize Velos (A Clinical Trial Management System) for all iTREAT-PC study activities: for more information please see https://www.wcgclinical.com/services/eresearch-ctms/
- Ensure research personnel are appropriately trained
- Restrict access to those who have a need to know for performance of their job duties
- Store paper records (if any) in a secure location accessible to research personnel only

Rutgers
Study data will be collected at the study visits and entered into a secure Electronic Data Capture system, as may be provided by the sponsor. Data entry will be done by research nurse/research assistant or Investigator and access will be limited to research personnel through password protection.

All research related source documents and all raw data will be placed in separate binders for each subject and stored and locked in the site PI's office, currently *Room 1330 at 89 French Street*. Only study staff will have access to subject binders. Data will not routinely be stored on mobile computers or flash drives; in the unlikely event that mobile storage is necessary study personnel will ensure that all devices on which patient information is stored are encrypted to meet or exceed Rutgers security requirements for PHI, including HIPAA compliance and that these are securely scrubbed clean of these data to ensure privacy in a timely manner.

Investigators and staff are well trained on protecting privacy and confidentiality of health information of study subjects, having received Rutgers required HIPAA Compliance and Collaborative Institutional Training Initiative (CITI) training for Biomedical Responsible Conduct of Research and Biomedical/Clinical Research Investigators or for Social & Behavioral Research. Subject information with PHI will never be transmitted via email. Private information collected will be limited to that necessary to conduct the research.

Mt. Sinai
Recruitment tracking and research data collection will be performed by a team of clinical research coordinators trained on the study's protocol using REDCap software. Each subject will be assigned a unique alphanumeric study identification number. A cross walk linking study participants to their study ID will be maintained via a REDCap report in the recruitment tracking database. Data downloaded from REDCap will be stored on secure drives supported by the encrypted Mount Sinai server network. Research data will be collected and stored using REDCap software in a separate REDCap database. Only members of the research team will have access to the REDCap databases. Any paper-based study documentation such as consent forms and HIPAA documents will be stored in locked cabinets within locked offices of Division of General Internal Medicine. Only members of the research team will have access to these files. During the study period, the study team will follow all Icahn School of Medicine at Mount Sinai policies regarding data transfer and security.

Atrium Health
Atrium Health uses the computing infrastructure of Wake Forest University School of Medicine (WFUSM). At WFUSM, REDCap is hosted through the Clinical and Translational Science Institute (CTSI). This system offers easy data manipulation with audit trails and reports for reporting, monitoring, and querying patient records. While REDCap can be used to collect virtually any type of data in any environment (including compliance with 21 CFR Part 11, FISMA, HIPAA, and GDPR), it is specifically geared to support online and offline data capture for research studies and operations. User logins are tied to an individual's medical center ID and authenticated across platforms. OnCore is the enterprise-wide Clinical Research Management System. This system is used to address all areas of clinical research management, including regulatory, subject, and protocol management; data management and study design; billing and financial management; and reporting. OnCore is used by the Clinical and Translational Science Institute (CTSI) as the repository and reporting of enrollment on all clinical research.

Auburn
The data related to this project will be recorded in Excel file and shared among investigators. During the whole process of the research, the original data will be recorded on the hand-written notebook which will be kept in a secure location. Simultaneously, the data will be recorded on the university computer. The computer and PCR machines belong to Auburn University; a password is needed to log in and access the data. The data will be periodically archived in the external hard drive with encryption protection. In addition, the data is also backed up to Auburn's networked storage

through the Office of Information Technology at Auburn University. The Auburn OIT provides Box, which is protected by two-factor authentication.

14.5) Future Use of Data

Per research best practices a fully de-identified data set of participant demographics, baseline characteristics, outcomes, and biospecimen data will be available for other researchers once the main effects paper has been accepted. PCORI data retention guidelines require data to be retained for 7 years. PCORI provides a central storage location for these data. Data release guidelines will follow PCORI guidelines. These policies are available on the PCORI website. The third-party data request policies are copied below.

Third Party Data Requests to a PCORI-Designated Repository

1. Submission of Data Requests

a. *Data request process* – Individual investigators or teams of investigators seeking access to data from PCORI-funded studies must complete and submit a data request form to a PCORI-designated repository. The repository will independently review requests for data based on qualifications of the data requestors and the scientific merit of the request (see below). If the data request is approved, the data requestor's institution must enter into a Data Use Agreement (DUA) with the repository. The DUA specifies the terms and conditions of data use, as well as the responsibilities and obligations of data requestors. Individual investigators must enter into an assurance of compliance with the terms of the DUA that shall be incorporated as an exhibit to the DUA.

b. *Data requestor qualifications* – A data requestor that submits a data request will be evaluated for its overall qualifications and experience (e.g., across a proposed team of specified individuals) to achieve the stated research purpose underlying the data request. Neither PCORI nor the Awardee investigators will provide technical assistance directly to data requestors. However, either party may provide input to the repository upon request.

c. *Required documentation for data requests* – At a minimum, requests for Awardee data must include the following elements: a statement of the proposed research purpose, an assurance that the data requested will be used to develop or contribute to generalizable knowledge, a justification that the proposed research can be achieved using the requested data, and a data security plan.

i. Data requests for nonscientific uses, such as in support of litigation, general educational purposes, quality improvement projects, and for promotional/marketing purposes will not be accepted.

ii. Requestors submitting incomplete or unclear requests for data access will be asked to revise their request and/or provide all required information.

2. Review of Data Requests

a. *Review process* – Upon receipt, all requests for data will undergo review by an independent committee directed by a PCORI-designated repository. The purpose of the review is to ensure that the proposal has scientific merit, in that: the research purpose is clearly described; the data requested will be used to develop or contribute to generalizable knowledge to inform science, medicine, and/or public health; the proposed research can be reasonably addressed using the requested data; the data requestor team has the appropriate expertise to conduct the proposed research; and the proposed research includes questions and outcomes that are relevant to patients.

b. *Review committee* – The independent review committee will be convened as needed and will be comprised of five voting members: a representative from the PCORI-designated repository, a data scientist, a clinical researcher with expertise germane to the data request, a PCORI staff member, and a patient representative. Other relevant stakeholders (e.g., payers, policy makers) may be invited to participate, as warranted. PCORI Awardees who

generated the data being requested will be invited to attend the review as nonvoting participants. The review panel will be administered by the PCORI-designated repository.

c. *Prohibitions against re-identification and redistribution of data* – This Policy and the required DUA strictly prohibit re-identification of any individual who is a subject of the data, as well as the redistribution of the data to any entities that are not party to the DUA or individuals who have not entered into an assurance of compliance as an exhibit to the DUA.
d. *Transparency of data requests* – The PCORI-designated repository will post a summary of each approved data request that includes the research purpose and identity of requestors to its website. Awardees will be notified in the event that a request for their data is approved. The posting and notification will occur within five (5) business days of the approval.
e. *Transparency of research findings related to data requests* – Requestors are required to provide a summary of all findings (including negative findings) related to the secondary use of Awardee data to the repository for posting to the repository's website within 12 months of the date of approval of the data request.
f. *Acknowledgment of Awardees and PCORI* – Requestors are required to acknowledge the Awardee as the primary source of the data and PCORI as the funder in all publications or presentations resulting from secondary use of Awardee data.

Awardee Data Sharing Costs

For Awardees depositing the Full Data Package (or required data elements, as applicable) into a PCORI-designated repository, PCORI will cover reasonable costs associated with the time and effort needed for preparing, depositing, and maintaining the Full Data Package in the repository for a period of at least seven (7) years following acceptance by PCORI of the Final Research Report.

13) PROTECTING THE PRIVACY OF SUBJECTS

The majority of participants are expected to be consented using telehealth approaches. Thus, consenting adults and assenting adolescents will be in a location of their choosing, presumably their own homes. For those individuals consented within a clinical environment, research coordinators will be encouraged to contact possible participants prior to a routine clinic visit and meet them at the clinical site upon agreement to consider study participation. The research staff would then use a private space within the clinical area to complete the consent process. The only other possible face to face interaction with research staff or clinical staff for sample collection would be for a phlebotomy. This visit would not be distinguishable to any other clinically oriented visit for a phlebotomy and thus does not expose the participant to loss of confidentiality related to study participation.

After consent, risks to data confidentiality will be mitigated by removal of all but study IDs before secure transfer from the DARTNet data collection site to Penn State and by security protocols for the participant-reported outcomes data capture and exacerbation and severe adverse event tracking systems. All users of REDCap will be tracked and only provided access in a secure fashion following established DARTNet Standard Operating Procedures. These include strong passwords, changed every 90 days, two factor authentication and strong recommendations of the use of a local VPN for connectivity. Connectivity over public wi-fi is prohibited. DARTNet utilizes REDCap to handle multiple research and clinical data collection processes across thousands of individuals simultaneously. This project will be totally isolated from all other ongoing research activities. Participants will only have access to their personal information, questionnaires appropriate for their study arm, and the educational video(s) associated with their arm of the study. Site research staff will only have access to the participants enrolled by their site. AAFP NRN/DARTNet staff will have access to participant contact data for all participants, as well as reports indicating questionnaire completion status for each individual. The REDCap system will automatically lock the monthly questionnaire for six weeks following completion by an individual assuring that we do not have duplicate data completion. The system will automatically remind individuals to complete

questionnaires and unlock them at appropriate times. Missed questionnaires will not be locked until another questionnaire is completed. The risks of loss of confidentiality are minimal given the secure, central handling of data.

14) ENSURING THE SAFETY OF SUBJECTS

1. Recruitment and Informed Consent

The research team will work with the Operations Committee and patient partners to draft an Informed Consent Template that is as brief as possible and meets IRB requirements. Consent forms will be uniform throughout the sites except for minor modifications as required by a site's IRB. We expect all sites to use the BRANY IRB. We will work on multiple approaches to completion of informed consent, including online, a web (video) conference, over the phone or in person. Each site will have a specific consent form present on the online system, and consent will be recorded in the online system by the participant or research staff no matter which form of communication is used. If a local site requires that a paper copy of the consent be retained, sites will be responsible for this retention. Participants will be able to download a copy of the consent or will have one mailed to them if they wish a hard copy. No participants will be enrolled without documentation of informed consent. A waiver of consent for a limited EHR data set will be requested for the analysis. EHR data will be collected at the end of the study one time.

2. Risk of asthma exacerbation

This study is directed toward the reduction of asthma exacerbations. Acute management of participants' asthma is not changed by the study and will be handled by the participant's clinician or health system. The use of R-ICS for acute symptom relief or AZ is intended to further reduce the risk of exacerbations; no data have been published to show that the use of R-ICS or macrolides increases exacerbation potential. Data collection will include assessment of exacerbations. Due to the pragmatic nature of the study, no additional interventions will be provided unless the participant has an allergic reaction to the ICS/LABA or AZ used for this study. If such is the case both the participant and their care site will be notified to assure they have information on the exact medication to which the reaction occurred, and the participant's use of the medication will be discontinued. The participant will be asked to remain in the study.

3. Adverse Event Monitoring

(a) Asthma-Related Adverse Events: Data collection will include assessment of exacerbations. Exacerbation care will be at the discretion of treating clinicians and the participant.
(b) Non-Asthma Adverse Events: We won't monitor for minor events as these are well characterized. We will monitor how many participants require step-down AZ therapy due to side effects.
(c) Serious Adverse Events: These events meet the following criteria: results in death, is life-threatening, requires or prolongs hospitalization, results in persistent/significant disability, or results in a congenital anomaly/birth defect. These also include any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the outcomes listed above. These will be monitored and reported to the DSMB by study arm through the DCC on a bi-annual basis. The DSMB will have the discretion to stop the study or one arm of the study if excess severe adverse events occur in one arm of the study. The full description for handling adverse events, both serious and non-serious are discussed more fully in the DSMP.

4. Management of Asthma Exacerbations

Acute management of participants' asthma is not changed or mandated by the study and will be handled by the participant's clinician in their usual manner. Clinicians and participants using R-ICS therapy will be advised, per recent US asthma guidelines, to not increase their ICS controller

medication in an attempt to treat an exacerbation.

5. Data and Safety Monitoring Plan/Board

A Data and Safety Monitoring Plan and Board will be appointed by the DCC in the first year and will include the type of data to be monitored, the frequency of monitoring and monitoring procedures. The monitoring plan will be developed with review and modification/agreement of the patient partners and stakeholders with final approval by the DSMB. All participants will receive written instructions on the use of their medications. If participants experience an adverse event, they will contact their local physician, who will evaluate the participant and determine the nature and severity of the event, working with the local site PI a determination of whether the event it is related to the study procedures or medications will be made and reviewed and verified by the central research staff. The site PI will ensure appropriate documentation, participant management, and follow up to resolution. The DCC will prepare bi-annual reports to be reviewed by the DSMB. Annual reports will also be prepared by the clinical coordinating center for IRB review as needed.

The DSMB members will be recruited by Drs. Mauger and Kong with assistance from Dr. Pace, if requested. The DSMB members will not be affiliated with any of the organizations participating in iTREAT-PC, and will include: at least one individual with asthma expertise, one biostatistician, one clinical trialist, one member of the public and one ethicist. The DCC will provide administrative support to the DSMB. All communications between the DSMB and research staff will be conducted through the DCC through Dr. Kong. The DSMB Charter is attached as Appendix 2.

15) WITHDRAWAL OF SUBJECTS

The only circumstance we can envision where we would withdraw a study participant is if we discovered that they knowingly falsified information to be enrolled in the study, in particular, that they did not have asthma. We see this circumstance as extremely unlikely as the enrollment criteria require a verified clinician's diagnosis of asthma at least one year prior to enrollment. Should an enrollee elect to stop all study medications or not wish to use the Asthma Symptom Monitoring system s/he would still be asked to complete all data collection until the end of their expected enrollment period and would be paid for submitting data and be eligible for raffle payments. The primary outcome is based on an intent to treat analysis and thus we have no intent to remove subjects whether they follow study protocols or not. As we are not providing study interventions, in the unlikely event we remove someone from the study we would contact them and indicate that we no longer need them to continue to provide data. We would shut down their REDCap account. If the individual wished to continue on any study medications they have been prescribed they may do so as their prescription is not being paid for by the study. Renewals of the prescription(s) would be between the individual and his/her asthma clinician. There are no required procedures as part of the study. If requested to have either a CBC drawn of if requested to provide a blood draw for infectious biomarkers, an individual may decline and it will not impact their ongoing enrollment in the study.

16) RISKS TO SUBJECTS

This study will add interventions to the participant's current therapy: PRN ICS/ LABA, (potentially PRN ICS/ SABA,) AZ (initially at 500 mg/three times per week or 10 mg/kg three times per week to a maximum of 500 mg/dose), or a combination of these. Participants in the R-ICS arms may require a change in their controller medication if they are on an ICS/LABA containing salmeterol. In these individuals a change to budesonide/formoterol, guided by the individual's current ICS dosage, will be made. All other changes in participant medications will be made by the participant's personal clinician or a research clinician who is clinically active within the participant's Research Implementation site. At baseline, participants will either be on ICS/LABA combination, or on ICS

monotherapy, and will continue on similar therapy.

Medication Fulfillment

Participants randomized to the pharmacology intervention arms will receive a prescription to fill at their usual pharmacy. Those currently having an asthma exacerbation will be considered to be uncontrolled and will be asked to see their physician to re-evaluate treatment before enrolling. They will be eligible 30 days after the current exacerbation. All participants will be informed that the alternative to participation is to continue their baseline asthma therapies. We will continue to work with budesonide/formoterol manufactures to determine if any of them (currently 3 in the US) would consider donating product for the study (TEVA donated ICS for the PREPARE study) but given the current package insert none of them will currently consider this nor are they offering a MAP programs specifically for SMART. We will utilize MAP programs with a focus on "controller" therapy if required for the conversion to budesonide/formoterol. AZ is relatively inexpensive and as a generic offered by many companies does not have an available MAP program.

Inhaled Corticosteroids Risks

All participants will be prescribed daily ICS maintenance therapy prior to enrollment. Low adherence to controller medication will not impact enrollment. Overall corticosteroid dosing may be increased in the R-ICS intervention groups, especially in the short term. However, efficacy studies of the R-ICS approach suggest that total ICS dose will actually decrease due to improved participant control. Additionally, since we are targeting a group that has a high risk of exacerbation, for many participants the total yearly dose of corticosteroids will be decreased even further due to avoidance of oral corticosteroid bursts resulting from the decrease in asthma exacerbations. Participants will be informed that when taken at high doses for extended periods, ICS can produce hoarseness, sore throat, and thrush, as well as rarely cause osteoporosis, adrenal gland suppression, weight gain, bruising of the skin, and diabetes, and to see their physician if they experience bruising, acne, hoarseness, or fatigue. ICS use has also been associated with reduced growth velocity in children, but mostly at ages under 12.

Azithromycin Therapy

Azithromycin is approved for all ages included in this study. When taken with asthma medications, AZ has no greater risk for side effects than amoxicillin. AZ should not be used in people with an allergy to a macrolide, or on other medications known to prolong the QT interval (we will provide a list to prescribers which will be checked by the research assistants at consent). Azithromycin, like most antibiotics, can result in *Clostridium difficile* associated diarrhea. Individuals developing diarrhea will be instructed to stop AZ and, if they develop a fever or severe diarrhea, to be tested for *C. difficile.* If the diarrhea resolves in ≤5 days they will be restarted using a step-down dose. AZ is associated with hearing loss in a small percentage of people. This is typically reversible when stopping AZ. Participants will be asked to report any hearing loss and will be asked about hearing with each bi-monthly survey. AZ is associated with nausea, vomiting, and abdominal pain in 2–5% of people taking multiple doses. Other side effects in <1% of people include dizziness, vertigo, headache, fatigue, somnolence, and chest pain. Participants who experience mild side effects will have the medication stopped for 5 days and then restarted at the next step-down dose. The step-down doses will be from 500 mg 3x weekly (10 mg/kg) to 500 mg 2x weekly (10 mg/kg) to 250 mg 3x weekly (5 mg/kg/dose 3x weekly). AZ is considered safe for use in pregnancy, but we will not enroll women who are pregnant or breastfeeding. If a woman becomes pregnant during the study while on AZ, we will recommend that she stop therapy but continue in the study. If her maternity care clinician believes that continued use of AZ is beneficial then she will be allowed to continue the therapy until delivery or 38 weeks gestation, then therapy will be stopped to avoid exposure to her infant through breastfeeding. We will recommend that participants in the AZ interventions who start taking other antibiotics during the course of the study, stop taking AZ. Participants can restart AZ

after 72 hours (3 days) of taking other antibiotics.
The informed consent language is provided below related to AZ.

Azithromycin. The Informed Consent will state: *Azithromycin is an antibiotic approved for use in the US and is frequently prescribed to treat respiratory infections. Long-term use of azithromycin has recently been included in all major asthma guidelines as a treatment option for people with severe asthma. We are using the same weekly dose of azithromycin that is FDA-approved to treat respiratory infections, and repeating this dose weekly to see if we can identify which people with uncontrolled asthma will benefit and who will not. This knowledge will help doctors to prescribe azithromycin for asthma more accurately and will help to avoid antibiotic overuse in the future. Azithromycin is generally well tolerated but there are a number of possible side effects. These include:*

- *Diarrhea (5%)*
- *Abdominal pain (3%)*
- *Nausea (3%)*

Side effects reported with a frequency of less than 1%:

- *Rash, itching, swelling, sun sensitivity)*
- *Palpitations, chest pain*
- *Flatulence, black stool, yellow skin*
- *Yeast infection, vaginal irritation, kidney inflammation*
- *Abnormalities of liver enzymes*
- *Fatigue*

All these side effects improve by either reducing the dose of the drug or stopping it. The dose of azithromycin may be cut by 50% for side effects.

Another potential problem with azithromycin is due to its bacteria-killing properties, which could lead to the development of resistance in bacteria that might be in your airways (that means that bacteria lose their sensitivity to being killed by azithromycin). There is evidence that this can happen, but so far, no adverse consequences have been seen. Importantly, if you should develop a chest infection and the bacteria are resistant to azithromycin there are many other types of antibiotics that can be used. You should also know that people randomized to long-term azithromycin in several large studies actually had significantly fewer episodes of bronchitis and pneumonia compared to the people in the same studies who did not receive azithromycin. Although there is no evidence that antibiotic resistance will harm you directly our study will look for spread of resistant bacteria into your community by monitoring locally available clinic and hospital antibiotic resistance patterns.

Some studies of long-term azithromycin have reported a low frequency (<1%-2.8%) of hearing loss that was mostly reversible after stopping azithromycin so please contact our study personnel if you start having trouble hearing while taking azithromycin.

Asthma Symptom Monitoring

The risks of use of Asthma Symptom Monitoring, such as with the smartphone application, are considered minimal. There is a small risk of loss of data confidentiality during data collection and transmission. The various data collection approaches will include encrypted data transmission and encryption at rest for the stored data. Once in the clinical EHR, the data is at no greater risk than other EHR data for loss of confidentiality. For adolescents there is the requirement for shared information with parents/guardians. There is a small risk that individuals having a severe exacerbation would delay seeking treatment at an emergency room or urgent care center while waiting for a reply from their office. It will be clearly indicated that Asthma Symptom Monitoring is not for emergency communication. All ASM applications will specifically instruct people to expect a

call no sooner than 24 hours and to seek care directly if they need help sooner. As noted above ASM will be offered to all study participants as well as to any individual with asthma in all participating practices that wish to do use the system as part of routine care.

Pregnancy and Breast Feeding

Pregnancy is not a contraindication to asthma controller therapy, including ICS, azithromycin, or use of ASM. Improved asthma control has been shown to be associated with improved pregnancy outcomes. It is unknown if AZ is excreted in breastmilk but is assumed that it is. Out of an abundance of caution we will only enroll women that are pregnant or breastfeeding after she has consulted with her maternity or infant care provider with approval of that provider. We will not require a pregnancy test or effective birth control be used to be enrolled for women of child-bearing age but will ask that they inform us if they become pregnant. We will recommend that pregnant women on AZ (either arm) to stop this treatment until discussing with her maternity care provider. We will advise all women to seek maternity care as soon as they are aware of the possibility of pregnancy and to inform their maternity care clinician of their study participation. Should the participant and her maternity care clinician feel that continued use of AZ is warranted then she may continue on therapy until delivery or 38 weeks gestation, whichever comes sooner. Pregnant or breastfeeding women in the R-ICS or control arms of the study will be allowed to continue without interruption.

Asthma Questionnaires Risks

There are minimal risks associated with questionnaires. The surveys do not ask sensitive questions or about mental health. The main risk from the surveys is loss of confidentiality if someone were to hack an email or text message or if the survey database is breached. Someone with illicit access to a participant's email or text messages would not be able to see any of the participant's answers, but by seeing the survey would know the person has asthma. The database servers for REDCap related systems are located in secure, HIPAA compliant data centers with multiple layers of intrusion detection. The servers are encrypted at rest and all transmissions are encrypted in transit. The greatest threat to a data breach were if someone were to intercept an email or text message to a participant or uncover a username and password for site personnel. If this was for a participant, then the hacker may be able to see the participant's latest survey data, but generally the messages link to a new survey, and old information will not be viewable. If this was a research staff member's login then the hacker could see potentially all participants' information for that site or if it was one of the central staff they could see all participant's information. Research staff will be required to use strong passwords and change them every 90 days. We will institute 2 factor authentication for REDCap for all research members but not for participants. All our data systems have strong firewalls and multiple layers of intrusion detection.

Procedural Risks

No study specific procedures other than phlebotomy, data collection, and medical record review are planned. Participants who do not have an historical CBC with differential will be offered to have one performed by the local site or a centrally contracted laboratory. Individuals in the AZ arms will be offered the opportunity to undergo mycoplasma and chlamydia serology testing and chlamydia PCR testing. These blood tests involve a venipuncture that poses no greater risk than usual clinical care.

17) POTENTIAL BENEFITS TO SUBJECTS

The potential benefit to participants in the intervention arms is unknown, but may include decreased exacerbations, decreased symptoms, and reduced need for asthma medications. Implementation of ASM at all primary care practices may improve rates of asthma control. The potential for benefit to society and individuals with asthma is very significant as the study interventions represent newer approaches to asthma therapy, and the study will inform who may respond best to a given approach and if approaches work using alternative delivery approaches for R-ICS. Any chance to determine ways to reduce asthma exacerbations and learn how to better treat

individuals presents a clear benefit to people with asthma. If the study shows that these approaches reduce exacerbations or improve other important outcomes differentially, then each approach can easily be adopted in the context of current care.

18) COMMUNITY-BASED PARTICIPATORY RESEARCH

This research is not a classic community-based participatory research project. That said, it has and will be heavily guided by Community Advisors, including patients and caregivers, that are invested in the project and its results. Thus, we have included our engagement approach here, but again, it is **not CBPR.**

Substantial commitment to and demonstrated experience with effective stakeholder engagement is a major strength of iTREAT-PC. A variety of stakeholders have been involved throughout the study design and will continue to inform the project in both phases as well as implementation, interpretation, and dissemination efforts. Eight stakeholder groups including 1) patients/caregivers, 2) patient advocacy groups, 3) clinicians (physicians, nurses, and pharmacists), 4) professional societies, 5) healthcare policy experts, 6) payers, 7) asthma experts and researchers, and 8) site research teams have all been engaged in formulating our questions, identifying the study groups, selecting the interventions, choosing outcomes, and suggesting the exploratory aims and analyses for this study. Experienced individuals have accepted stakeholder roles for all these groups; each iTREAT-PC implementation site will provide clinical and local researcher stakeholders along with two patient stakeholders. Due to their in-depth understanding of local contexts concerning community and research partnerships, site PIs are best suited to identify appropriate participant stakeholders from sites. Site PIs have been consulted during the development process. In addition to ongoing engagement of select stakeholders from PREPARE, we have worked with several new stakeholders in all categories to provide continuous feedback in the development of this proposal.

For iTREAT-PC, we have support from the American Lung Association, Asthma and Allergy Foundation of America; stakeholders who represent payers, policy makers; and individuals that will represent the American Academy of Family Physicians, the American Academy of Allergy, Asthma and Immunology and the American College of Asthma, Allergy, and Immunology. The American Academy of Pediatrics, the National Medical Association and the National Hispanic Medical Association will only appoint representatives after a project is funded due to high request volume. Our scientific advisors are experienced asthma researchers. Once these groups have met with the central research staff, stakeholders will advise if additional groups or individuals from a specific group should be added to support project activities.

Our stakeholders will be integral members of the study team with decision making authority. Specific changes will continue to be made to the iTREAT-PC study based on input, meeting outcomes, and comments from our stakeholders. The eight stakeholder groups will be divided into six work groups (WGs): 1) those directly impacted by asthma or aligned with individuals impacted by asthma (**WG 1:** patients and caregivers); 2) decision-makers related to informing and advocating for therapeutic options (**WG 2:** advocacy, policy, and payers); 3) organizations that notify medical professionals about cutting-edge research advancements (**WG 3**: professional societies); 4) individuals who would deliver demonstrated options (**WG 4:** clinicians; clinical administrators); 5) individuals who oversee and guide the research process (**WG 5:** asthma experts and researchers); and 6) individuals implementing research activities within their practices (**WG 6:** site research teams). These groupings were vetted and recommended by the stakeholders themselves. We will have separate meetings with the six WGs. A few of our stakeholders hold multiple roles (e.g., individual with asthma who is caregiver of a child with asthma, with scientific knowledge). These individuals possess unique perspectives and can share experiential knowledge from multiple viewpoints. All individuals will have a primary stakeholder role and may be asked to participate in a secondary role based on their experience. All WGs will have one or two members on the Ececutive Committee (a WG can chose to have one or two). These individuals will present to the Executive Committee at each meeting to facilitate communication. During WG meetings information that is

relevant from one WG will be presented to another group. WGs will also combine for meetings as appropriate or requested by the WGs. Differing recommendations across WGs wil be presented to the Executive Com. (and the Scientific Com if the recommendation impacts the science of the study) for consideration. Final decisions will take into consideration the Scientific Com if required and adjudicated by the Executive Com which has representation from all WGs.

Engagement Approach:

The primary research question has been affirmed as patient-centered and crucially important by key stakeholder partners from all categories: asthma patient stakeholders, asthma researchers, policy stakeholders (a former state Medicaid director and a former PBM manager), and clinicians (primary care, allergy and pulmonology). Each stakeholder group will have two representatives on the Executive Committee (EC). The full stakeholder group will meet at least annually; subgroups will meet regularly based on project and stakeholder input/needs. Stakeholders will meet frequently during the feasibility phase and first year of the full project (see Table 7). All final study directions and major decisions will be reviewed and approved by the EC; thus, all stakeholder groups will have decision making authority. At a minimum, all patient facing information will be approved by the full patient stakeholder group. All implementation activities will be reviewed by the clinician group, and all research decisions will be reviewed by the Scientific group. All outcome assessments will be reviewed by all groups with attention from the patient/caregiver, advocacy/policy/payer, professional society, and scientific groups. Using this engagement approach, our PREPARE stakeholders have consistently indicated they feel valued, involved, and listened to. (See "Other Stakeholders" section below for information about expanding or changing stakeholder group composition.)

Convening Stakeholders: See Table 7 for stakeholder meeting timing and frequency in both phases of the study. Dr. Calhoun and Ms. Brooks-Greisen will coordinate all stakeholder activities, with support from Drs. Filippi and Hester. In addition to regular meetings of the EC, Operations Committee, and stakeholder sub-groups, the full stakeholder panel and study team will meet once a year in person, virtually or in a hybrid format for 1 ½ days. Goals for the annual full group gathering will be to work collaboratively on major ideas, share ideas, and encourage co-learning. All meetings will be conducted utilizing partnership principles guided by an honest, transparent and trustworthy process.

Table 7 - Schedule of in-person meetings and conference calls for various stakeholder groups

Work Groups & Committees	**Phase 1**		**Phase 2**	
	Startup (8 mos) Vanguard (6mos) Finalize (4 mos)	Startup (6 mos)	Enrollment/ Follow-up (45 mos)	Data Analysis/ Dissemination (9 mos)
	In-Person Convenings			
Full Stakeholder and Study Team	Once in first year	Once at initiation	Annually	Once for wrap up
	Virtual Convenings			
1: Patients & Caregivers	Up to bi-monthly	Up to bi-monthly	Monthly	Monthly
2: Advocacy, Policy, & Payers	Quarterly	Quarterly	Quarterly	Monthly
3. Professional Societies	Quarterly	Quarterly	Quarterly	Monthly
4: Clinicians 5: Scientific Advisors	Up to monthly	Up to monthly	Quarterly	Quarterly
6: Site Research Teams	Up to monthly	Up to monthly	Up to monthly	Up to monthly
7: Operations Committee	Bi-weekly	Bi-weekly	Bi-weekly	Bi-weekly

8: Executive Committee	Monthly	Monthly	Monthly	Monthly

Table 8 - Key Committed Stakeholders

Patients & Caregivers (primary, secondary role*)	***Advocacy, Policy& Payers (relevant experience)***	***Professional Societies****	***Scientific Advisors***
Alex D. Colon Moya (patient) Aracelis Diaz (patient) Allyson Jasper (caregiver) Margie Lorenzi (patient) Suzanne Madison (patient) Kathy Monteiro Williams (patient) Wilfredo Morales-Cosme (patient) Addie Perez (patient) Janet Robles (patient) Marsha Santiago (patient) Nikki Schultek (patient, caregiver) Opal Thompson (patient) Mary White (patient)	Gretchen Hammer (past Medicaid Director) Amy Howell-Nguyen, MD (OptumCare) Hemal Shah (Value Matters, LLC) Jack Westfall, MD (Robert Graham Policy Center) Barbara Kaplan (American Lung Association) Sanaz Eftekhari (Asthma and Allergy Foundation of America)	Michael Blaiss, MD (President, ACAAI) Kurt Elward, MD (AAFP; NAEPPCC , EWG4) (Dr. Elward has joined the DSMB) Giselle Mosnaim, MD (President, AAAAI) AAP, NMA, NHMA will only offer stakeholders after funding due to request overload. PREPARE had stakeholder from NMA and NHMA.	Tyra Bryant-Stephens, MD (pediatrician, EWG-4) Tom Casale, MD (Allergist) Juan Carlos Cardet, MD (Allergist) Anne Fuhlbrigge, MD (Pulmonology) Neil Skolnik, MD (Family Medicine) Jacques Turgeon, MD (PharmD) Juan Wisnivesky, MD (Internal Med., NAEPPCC) Barbara Yawn, MD (Family Medicine, EWG3)

*Secondary role if applicable. Stakeholders may be consulted to provide perspective for secondary role but will primarily represent primary roles.

** AAAAI = American Academy of Allergy, Asthma & Immunology; ACAAI = American College of Allergy Asthma and Immunology; AAFP = American Academy of Family Physicians; EWG4 = Expert Work Group 4; EWG3 = Expert Work Group 3; NAEPPCC = National Asthma Education and Prevention Program Coordinating Committee

Other Stakeholders

In the feasibility phase and throughout the implementation of the entire project, other stakeholder groups may be deemed important. Should the need for inclusion of new or different stakeholder representation emerge, we will identify, engage, and integrate new stakeholders as appropriate. Through the feasibility phase, the patient and other stakeholder partners will have direct roles and influence in re-drafting the study materials, videos, and implementation of the project. The initial draft protocol will be presented to the EC for approval to begin the Vanguard. During the Vanguard implementation and interpretation, protocol adjustments may be made keeping the EC informed, and a final protocol will be developed for EC approval. After the Vanguard process, conference and webinar-supported calls with our stakeholders will continue to assure continued engagement with all stakeholders on schedules that change with the phase of the trial (Table 7). At least one member of the operations committee will be assigned to one stakeholder partner WG ensuring continuity in communication.

19) SHARING OF RESULTS WITH SUBJECTS

The iTREAT-PC study team is committed to returning results to the individuals who take part in this project. We have experience sharing information with participants, even prior to the end of the study, even within the confines of a randomized trial. We have done this in our PREPARE study when we needed to communicate with patients about COVID-19. We also shared information about how to establish ongoing treatment as people exited the study.

For iTREAT-PC, Drs. Pace and Mauger, working in particular with Drs. Callen and Filippi, will ensure that processes are in place to achieve and maintain timely and accessible information in a manner that is understandable and usable. We will develop a lay summary of the findings through a collaborative process with all stakeholder groups, particularly the patient and parent/caregiver

stakeholders. The goal will be to create a comprehensive summary that is relevant and understandable to a wide array of readers. We expect that the summary will include graphical displays of information as well as textual information. We will use our technical communication experts to draft initial versions of the summary, which will then be iteratively revised based on stakeholder feedback.

To distribute the final summary, we will post them to the DARTNet, AAFP and partner organizations' websites, and let participants, stakeholders and AAFP members know when and where the results are available. To reach individual participants, we will rely on a key aspect of the study design: the regular contact the research team has with enrolled participants due to the need to obtain patient-reported outcomes. The patient-reported outcomes will be solicited via phone, email, or text through REDCap. Because we require this ongoing interaction with participants during the trial, we can harness the same communication technologies to distribute information about the findings of the study, both at the conclusion and throughout the study period. We will ensure that this aspect is included in consent forms so that we have full ability to communicate with patients regarding aggregate study results after the end of the trial. We will also ensure that this communication is in accordance with all applicable laws.

Our first approach to returning the summary of the study results will be an automated communication to participants that includes an explanation of the purpose of the communication, along with a URL to an online presentation of the study findings summary. Second, for patients who do not access the URL or who request a hard copy, we will mail a summary to ensure thorough outreach to our participants. Combined, these approaches will provide wide access to research findings, both to study participants as well as the broader public.

We also have the capability of creating personalized feedback reports at the end of the study that summarize individual information over the 16+ months in the trial. We will work with our patient partners and determine if they believe this is an important value add that we should implement.

20) PRIOR APPROVALS

Local IRBs will be asked to sign a reliance agreement with BRANY. The consent and assent forms will be created with editable sections. Each local IRB will be asked to review the consent and make locally REQUIRED edits within these sections. Once these edits have been made the consent/assent forms will be returned to BRANY for final approval.

21) COMPENSATION FOR RESEARCH-RELATED INJURY

We believe the research will be considered minimal risk as all interventions are currently available for the treatment of asthma. Each site will review, edit if necessary and approve the research related injury clause in the consent form. This clause will indicate that the site will provide care for a research related injury, or refer the individual to a location that can provide care. Such care will be billed to the individual's insurance carrier.

There is no relevant contract language related to compensation for research-related injuries.

22) ECONOMIC BURDEN TO SUBJECTS

Participants will be responsible for paying for any co-pays required for study prescribed medications, should they elect to take the medication. PCORI specifically prohibits the inclusion of these costs as part of study costs. Medication selection for the different approaches to ICS rescue therapy may be made on the basis of cost to the participant. Virtually all insurance plans include a stand-alone ICS as a Tier 1 medication with either no co-pay or very low co-pays. Azithromycin is covered as a Tier 1

medication by virtually all insurance carriers. For individuals without any insurance coverage azithromycin as the full dose of 500mg three times a week is available for a little as $12/month. The 250mg dose can be found for under $6/month. Inhaled corticosteroids are more expensive with Pulmicort one of the lowest cost ICS MDIs. Pulmicort costs approximately $85 per MDI. Given that this medication is used PRN it is not possible to provide exact monthly costs. The majority of participants (based on our previous study results) can be expected to use 2 to 4 MDI canisters over the life of the study.

23) CONSENT PROCESS AND DOCUMENTATION

Routine Consent

Study coordinators at each research site will perform the consents. These are research trained individuals with human subjects training that the central team will work with to be sure they understand the consent, the study and their role. We expect many will have master's degrees and virtually all the rest will have bachelor's degrees. We will train them. Have them watch a mock consent by one of our central team and then ask them to perform a teach back where they walk through the process and then consent one of the central team that will have sets of questions concerning the study to be asked of the site personnel. We have used this approach on numerous multi-site studies with a high level of success.

The consent process will be either in person or done remotely by video conferencing or via phone. We expect the eligibility and consent process to take 30 – 40 minutes. Individuals will have ample time to ask questions be sure they are fully informed. We will generally provide a copy of the consent document prior to the interaction electronically. If someone wishes a hard copy it will be mailed to them. After consent is complete the individual will receive a signed electronic or hard copy depending on their wishes.

While many studies expect a clinician to perform the consent, for low-risk studies of this nature we find that approach is more coercive than have an individual the patient does not know well or at all conduct the consent. We will emphasize to study coordinators that it is essential the people are free to decide to participate or not and free to drop out at any time. In a study where each site generally has hundreds if not thousands to eligible individuals the need to obtain consent from any one individual should be lessened. Given that we are not providing free medication access or a large sum of money for participation we believe the study protocol has focused on avoiding coercion and we will strive to impart that approach to all consenting individuals.

The consent form has "check questions" built into it to try and capture misunderstandings of key points. Consent check questions are provided in Appendix 8. While these questions are not designed to stop the consent process but to provide points where further clarification can be provided by the study coordinators. The consent itself is written in simple terms and will be extensively reviewed by our patient advisors to be sure it is understandable. Study coordinators will be instructed to read the consent aloud if any appears to be having issue interpreting the document. We do ask health literacy questions as the first part of our enrollment process to help guide the study coordinator's work with patients, but that is by necessity after the consent process. If an individual is at risk for health literacy issues once those questions are asked we will have the study coordinator's check along the way with people about their understanding of their activities related to the study.

The study will involve standard, formal consent processes for both components of the feasibility phase. For the full study feasibility component consent/assent will be primarily by telehealth approaches including telehealth systems available at the sites, commercial video conferencing systems or plain phone conversations. These same approaches will be used for the Asthma Symptom Monitoring component of the feasibility phase of the project. Either consent/assent process could

be conducted at a central research site for the clinical site if the potential participant is willing to travel to that site or within the primary care office where the participant receives usual care. If at home or office, the participant will have control of and decision-making authority for continuing, waiting, or changing to a more private location if desired. If in a central research site then consent will occur in a private space that is typically reserved specifically for consent and/or interview like activities. If in a clinical site then the consent will take place in a private area, such as an exam room, within the clinical space. It is not expected that many consents will be done in clinical settings.

Consents will be available in REDCap in both English and Spanish. The participant will "sign" the consent using their finger or a mouse within the REDCap system. This will be the same approach for the assent process. Should consent be obtained over the phone then the consent will be obtained after two paper copies of the consent/assent has been sent to the potential participant. Consent and assent will then be recorded over the phone and the participant and adolescent if assent is required will be asked to physically sign one copy of the consent and assent and mail them back in a provided, postage paid envelope. These "hard copies" will be scanned and uploaded to REDCap. The recording will also be uploaded to REDCap.

Non-English Consents

Study staff obtaining consent in Spanish will be bilingual. If a site needs support for the consent process in Spanish the site will, through a locally used interpreter process, ask the potential participant if a member of the central research staff can join the consent meeting. If the person agrees then a bilingual member of the central research staff will join the meeting to serve as an interpreter who understands the study and has CITI training. This will be done in conjunction with the local research staff that will be the "responsible party" for obtaining consent.
Should the individual indicate they are not comfortable with a central research staff joining the meeting then the meeting can be rescheduled for a time when a local bilingual study staff member is available, the participant can agree to a local translator to translation service or the person will not be consented. At this time the study does not intend to support other languages than English and Spanish.

Assent Processes

The study plans to enroll individuals ages 12 to 17. These individuals will require the consent of one parent or guardian as well providing their own assent. The process is expected to occur in sequence using the same approaches as described above.

Cognitively Impaired or Otherwise Unable to Consent

Individuals that are not able to provide consent or assent in English or Spanish will not be eligible for the study. Primarily this is due to the fact the study outcomes are entirely dependent on participants' ability to answer regularly administered surveys.

Other items

No waiver of consent or waiver of storage of consent is requested. The trial is therapeutic in nature and no devices are being used.

24) DRUGS OR DEVICES

While the project does involve drugs, these drugs will be dispensed by a pharmacy of the participant's choice and only be handled in accordance with typical clinical usage. Neither the central research team nor any of the sites will handle, store or dispense any medications.

References

1. Centers for Disease Control and Prevention. Asthma in the US. Updated May 3, 2011. Accessed October 2, 2021. https://www.cdc.gov/vitalsigns/asthma/index.html
2. Zahran HS, Bailey CM, Damon SA, Garbe PL, Breysse PN. Vital Signs: Asthma in Children - United States, 2001-2016. *MMWR Morb Mortal Wkly Rep*. Feb 9 2018;67(5):149-155. doi:10.15585/mmwr.mm6705e1
3. Healthy Schools Campaign. Five Health-Related Causes of Chronic Absenteeism. Updated August 29, 2016. Accessed October 2, 2021. https://healthyschoolscampaign.org/blog/five-health-related-causes-of-chronic-absenteeism/
4. McGregor MC, Krings JG, Nair P, Castro M. Role of Biologics in Asthma. *Am J Respir Crit Care Med*. Feb 15 2019;199(4):433-445. doi:10.1164/rccm.201810-1944CI
5. Institute for Clinical and Economic Review. Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks. Final Evidence Report. Updated December 20, 2018. Accessed October 2, 2021. https://icer.org/assessment/asthma-2018/
6. Peters M. Single-inhaler combination therapy for maintenance and relief of asthma: a new strategy in disease management. *Drugs*. 2009;69(2):137-50. doi:10.2165/00003495-200969020-00001
7. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med*. Jan 15 2005;171(2):129-36. doi:10.1164/rccm.200407-884OC
8. Rabe KF, Pizzichini E, Stallberg B, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. *Chest*. Feb 2006;129(2):246-56. doi:10.1378/chest.129.2.246
9. Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin*. Sep 2004;20(9):1403-18. doi:10.1185/030079904X2051
10. Jenkins CR, Eriksson G, Bateman ED, et al. Efficacy of budesonide/formoterol maintenance and reliever therapy compared with higher-dose budesonide as step-up from low-dose inhaled corticosteroid treatment. *BMC Pulm Med*. Apr 20 2017;17(1):65. doi:10.1186/s12890-017-0401-y
11. Bisgaard H, Le Roux P, Bjamer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest*. Dec 2006;130(6):1733-43. doi:10.1378/chest.130.6.1733
12. Global Initiative for Asthma. Global strategy for asthma management and prevention 2021 report. Accessed October 2, 2021. https://ginasthma.org/gina-reports/
13. Global Initiative for Asthma. Difficult-to-treat and severe asthma in adolescent and adult patients. Diagnosis and management. Accessed October 2, 2021. https://ginasthma.org/gina-reports/gina-2020-full-report_-final-_wms
14. National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. 2020 Focused Update to the Asthma Management Guidelines Summary from: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Accessed October 1, 2021. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines
15. Centers for Disease Control and Prevention. Asthma Attacks in the Past 12 Months by Year. Accessed October 2, 2021. https://www.cdc.gov/asthma/data-visualizations/health-outcomes.htm#anchor_1569609411376
16. Centers for Disease Control and Prevention. Asthma Attacks among People with Current Asthma, 2014–2017. Accessed October 2, 2021. https://www.cdc.gov/asthma/asthma_stats/attacks-current-asthma.htm

17. Centers for Disease Control and Prevention. Asthma as the Underlying Cause of Death. Updated April 24, 2018. Accessed January 6, 2021. https://www.cdc.gov/asthma/asthma_stats/asthma_underlying_death.html
18. Moorman JE, Akinbami LJ, Bailey CM, et al. National surveillance of asthma: United States, 2001-2010. *Vital Health Stat 3*. Nov 2012;(35):1-58.
19. Szentpetery SE, Forno E, Canino G, Celedón JC. Asthma in Puerto Ricans: Lessons from a high-risk population. *J Allergy Clin Immunol*. Dec 2016;138(6):1556-1558. doi:10.1016/j.jaci.2016.08.047
20. Bartolomei-Díaz JA, Amill-Rosario A, Claudio L, Hernández W. Asthma mortality in Puerto Rico: 1980-2007. *J Asthma*. Mar 2011;48(2):202-9. doi:10.3109/02770903.2010.528498
21. Calmes D, Huynen P, Paulus V, et al. Chronic infection with Chlamydia pneumoniae in asthma: a type-2 low infection related phenotype. *Respiratory Research*. 2021/02/26 2021;22(1):72. doi:10.1186/s12931-021-01635-w
22. Ray A, Camiolo M, Fitzpatrick A, Gauthier M, Wenzel SE. Are We Meeting the Promise of Endotypes and Precision Medicine in Asthma? *Physiological Reviews*. 2020/07/01 2020;100(3):983-1017. doi:10.1152/physrev.00023.2019
23. Wenzel SE. Severe Adult Asthmas: Integrating Clinical Features, Biology, and Therapeutics to Improve Outcomes. *Am J Respir Crit Care Med*. Apr 1 2021;203(7):809-821. doi:10.1164/rccm.202009-3631CI
24. Expert Panel Working Group of the National Heart Lung and Blood Institute, National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier MM, et al. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. Dec 2020;146(6):1217-1270. doi:10.1016/j.jaci.2020.10.003
25. Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, LeBoff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med*. Sep 27 2001;345(13):941-7. doi:10.1056/NEJMoa002304
26. Peters SP. Safety of inhaled corticosteroids in the treatment of persistent asthma. *J Natl Med Assoc*. Jun 2006;98(6):851-61.
27. Zhang L, Prietsch SO, Mendes AP, et al. Inhaled corticosteroids increase the risk of oropharyngeal colonization by Streptococcus pneumoniae in children with asthma. *Respirology*. Feb 2013;18(2):272-7. doi:10.1111/j.1440-1843.2012.02280.x
28. Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: effects on growth. *Cochrane Database Syst Rev*. Jul 17 2014;(7):CD009471. doi:10.1002/14651858.CD009471.pub2
29. Zollner EW, Lombard CJ, Galal U, Hough FS, Irusen EM, Weinberg E. Hypothalamic-pituitary-adrenal axis suppression in asthmatic school children. *Pediatrics*. Dec 2012;130(6):e1512-9. doi:10.1542/peds.2012-1147
30. Htun ZM, Aldawudi I, Katwal PC, Jirjees S, Khan S. Inhaled Corticosteroids as an Associated Risk Factor for Asthmatic Pneumonia: A Literature Review. *Cureus*. Jun 20 2020;12(6):e8717. doi:10.7759/cureus.8717
31. Pandya D, Puttanna A, Balagopal V. Systemic effects of inhaled corticosteroids: an overview. *Open Respir Med J*. 2014;8:59-65. doi:10.2174/1874306401408010059
32. Papi A, Canonica GW, Maestrelli P, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med*. May 17 2007;356(20):2040-52. doi:10.1056/NEJMoa063861
33. Papi A, Caramori G, Adcock IM, Barnes PJ. Rescue treatment in asthma. More than as-needed bronchodilation. *Chest*. Jun 2009;135(6):1628-1633. doi:10.1378/chest.08-2536
34. 1900-2012: History of steroid use for asthma x. Updated January 9, 2012. Accessed January 6, 2021. https://hardluckasthma.blogspot.com/2011/05/history-of-antiinflammatories-for-use.html

35. Israel E, Cardet JC, Carroll JK, et al. Reliever-Triggered Inhaled Glucocorticoid in Black and Latinx Adults with Asthma. *N Engl J Med*. Feb 26 2022;doi:10.1056/NEJMoa2118813
36. Papi A, Corradi M, Pigeon-Francisco C, et al. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med*. Mar 2013;1(1):23-31. doi:10.1016/S2213-2600(13)70012-2
37. Kew KM, Karner C, Mindus SM, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. *Cochrane Database Syst Rev*. Dec 16 2013;(12):CD009019. doi:10.1002/14651858.CD009019.pub2
38. Pauwels RA, Lofdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med*. Nov 13 1997;337(20):1405-11. doi:10.1056/NEJM199711133372001
39. Calhoun WJ, Ameredes BT, King TS, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA*. Sep 12 2012;308(10):987-97. doi:10.1001/2012.jama.10893
40. Israel E, Cardet JC, Carroll JK, et al. A randomized, open-label, pragmatic study to assess reliever-triggered inhaled corticosteroid in African American/Black and Hispanic/Latinx adults with asthma: design and methods of the PREPARE trial. *Contemporary Clinical Trials*. 2021;101, 106246doi:10.1016/j.cct.2020.106246
41. AstraZeneca Pharmaceuticals LP. SYMBICORT Prescribing Information. Accessed January 6, 2021. https://www.azpicentral.com/symbicort/symbicort.pdf
42. Shavit O, Swern A, Dong Q, Newcomb K, Sazonov Kocevar V, Taylor SD. Impact of smoking on asthma symptoms, healthcare resource use, and quality of life outcomes in adults with persistent asthma. *Qual Life Res*. Dec 2007;16(10):1555-65. doi:10.1007/s11136-007-9267-4
43. Wenzel SE, Schwartz LB, Langmack EL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med*. Sep 1999;160(3):1001-8. doi:10.1164/ajrccm.160.3.9812110
44. Stapleton M, Howard-Thompson A, George C, Hoover RM, Self TH. Smoking and asthma. *J Am Board Fam Med*. May-Jun 2011;24(3):313-22. doi:10.3122/jabfm.2011.03.100180
45. Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. *Eur Respir J*. Mar 2013;41(3):716-26. doi:10.1183/09031936.00073312
46. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet*. Aug 12 2017;390(10095):659-668. doi:10.1016/S0140-6736(17)31281-3
47. Hiles SA, McDonald VM, Guilhermino M, Brusselle GG, Gibson PG. Does maintenance azithromycin reduce asthma exacerbations? An individual participant data meta-analysis. *Eur Respir J*. Sep 12 2019:DOI: 10.1183/13993003.01381-2019. doi:10.1183/13993003.01381-2019
48. Hahn DL, Grasmick M, Hetzel S, Yale S. Azithromycin for bronchial asthma in adults: an effectiveness trial. *J Am Board Fam Med*. Jul-Aug 2012;25(4):442-59. doi:10.3122/jabfm.2012.04.110309

25/4/442 [pii]
49. Wagshul FA, Brown DT, Schultek NM, Hahn DL. Outcomes of Antibiotics in Adults with "Difficult to Treat" Asthma or the Overlap Syndrome. *J Asthma Allergy*. 2021;14:703-712. doi:10.2147/JAA.S313480
50. Steel HC, Theron AJ, Cockeran R, Anderson R, Feldman C. Pathogen- and host-directed anti-inflammatory activities of macrolide antibiotics. *Mediators Inflamm*. 2012;2012:584262. doi:10.1155/2012/584262

51. Kraft M, Cassell GH, Henson JE, et al. Detection of Mycoplasma pneumoniae in the airways of adults with chronic asthma. *Am J Respir Crit Care Med*. Sep 1998;158(3):998-1001. doi:10.1164/ajrccm.158.3.9711092
52. Wood PR, Hill VL, Burks ML, et al. Mycoplasma pneumoniae in children with acute and refractory asthma. *Ann Allergy Asthma Immunol*. May 2013;110(5):328-334 e1. doi:10.1016/j.anai.2013.01.022
53. Essilfie AT, Horvat JC, Kim RY, et al. Macrolide therapy suppresses key features of experimental steroid-sensitive and steroid-insensitive asthma. *Thorax*. May 2015;70(5):458-67. doi:10.1136/thoraxjnl-2014-206067
54. Hansbro PM, Starkey MR, Mattes J, Horvat JC. Pulmonary immunity during respiratory infections in early life and the development of severe asthma. *Ann Am Thorac Soc*. Dec 2014;11 Suppl 5:S297-302. doi:10.1513/AnnalsATS.201402-086AW
55. Hahn DL. *A Cure for Asthma? What Your Doctor Isn't Telling You, and Why.* Peoples Pharmacy Press; 2013.
56. Hahn DL. Chlamydia pneumoniae and chronic asthma: Updated systematic review and meta-analysis of population attributable risk. *PLoS One*. 2021;16(4):e0250034. doi:10.1371/journal.pone.0250034
57. Undela K, Goldsmith L, Kew KM, Ferrara G. Macrolides versus placebo for chronic asthma. *Cochrane Database Syst Rev*. Nov 22 2021;11:CD002997. doi:10.1002/14651858.CD002997.pub5
58. Hahn DL, Plane MB, Mahdi OS, Byrne GI. Secondary outcomes of a pilot randomized trial of azithromycin treatment for asthma. *PLoS Clin Trials*. 2006;1(2):e11 DOI: 10.1371/journal.pctr0010011.
59. Brusselle GG, Vanderstichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax*. Apr 2013;68(4):322-9. doi:10.1136/thoraxjnl-2012-202698
60. GINA. Difficult-to-Treat and Severe Asthma in Adolescent and Adult Patients: Diagnosis and Management. 2019;https://ginasthma.org/severeasthma/ accessed August 1, 2021
61. Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. Jan 2020;55(1)doi:10.1183/13993003.00588-2019
62. Smith D, Du Rand IA, Addy C, et al. British Thoracic Society guideline for the use of long-term macrolides in adults with respiratory disease. *BMJ Open Respir Res*. Apr 2020;7(1)doi:10.1136/bmjresp-2019-000489
63. Webley WC, Hahn DL. Infection-mediated asthma: Etiology, mechanisms and treatment options, with focus on Chlamydia pneumoniae and macrolides. *Respiratory Research*. 2017;18(1)98. doi:10.1186/s12931-017-0584-z
64. Crocker DD, Kinyota S, Dumitru GG, et al. Effectiveness of home-based, multi-trigger, multicomponent interventions with an environmental focus for reducing asthma morbidity: a community guide systematic review. *Am J Prev Med*. Aug 2011;41(2 Suppl 1):S5-32. doi:10.1016/j.amepre.2011.05.012
65. Lang DM. New asthma guidelines emphasize control, regular monitoring. *Cleveland Clinic journal of medicine*. 2008;75(9):641-653.
66. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis c and advanced hepatic fibrosis. *JAMA*. 2012;308(24):2584-2593. doi:10.1001/jama.2012.144878
67. Shingo S, Zhang J, Reiss T. Correlation of airway obstruction and patient-reported endpoints in clinical studies. *European Respiratory Journal*. 2001;17(2):220-224.
68. Teeter JG, Bleecker ER. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. *CHEST Journal*. 1998;113(2):272-277.
69. Braido F. Failure in asthma control: reasons and consequences. *Scientifica*. 2013;2013

70. Yawn BP, Bertram S, Wollan P. Introduction of Asthma APGAR tools improve asthma management in primary care practices. *J Asthma Allergy*. Aug 31 2008;1:1-10. doi:10.2147/jaa.s3595
71. Marcano Belisario JS, Huckvale K, Greenfield G, Car J, Gunn LH. Smartphone and tablet self management apps for asthma. *Cochrane Database Syst Rev*. Nov 27 2013;(11):CD010013. doi:10.1002/14651858.CD010013.pub2
72. Rasmussen LM, Phanareth K, Nolte H, Backer V. Internet-based monitoring of asthma: a long-term, randomized clinical study of 300 asthmatic subjects. *Journal of Allergy and Clinical Immunology*. 2005;115(6):1137-1142.
73. Okelo SO, Butz AM, Sharma R, et al. Interventions to modify health care provider adherence to asthma guidelines: a systematic review. *Pediatrics*. 2013:peds. 2013-0779.
74. Wisnivesky JP, Lorenzo J, Lyn-Cook R, et al. Barriers to adherence to asthma management guidelines among inner-city primary care providers. *Annals of Allergy, Asthma & Immunology*. 2008;101(3):264-270.
75. Whitehead L, Seaton P. The Effectiveness of Self-Management Mobile Phone and Tablet Apps in Long-term Condition Management: A Systematic Review. *J Med Internet Res*. May 16 2016;18(5):e97. doi:10.2196/jmir.4883
76. Rudin RS, Fanta CH, Predmore Z, et al. Core Components for a Clinically Integrated mHealth App for Asthma Symptom Monitoring. *Appl Clin Inform*. Oct 2017;8(4):1031-1043. doi:10.4338/aci-2017-06-ra-0096
77. Rudin RS, Fanta CH, Qureshi N, et al. A Clinically Integrated mHealth App and Practice Model for Collecting Patient-Reported Outcomes between Visits for Asthma Patients: Implementation and Feasibility. *Appl Clin Inform*. Oct 2019;10(5):783-793. doi:10.1055/s-0039-1697597
78. Pew Research Center. Mobile Fact Sheet. Accessed December 17, 20214. https://www.pewresearch.org/internet/fact-sheet/mobile/
79. !!! INVALID CITATION !!! 75;
80. Lella A. U.S. Smartphone Penetration Surpassed 80 Percent in 2016. 2017. February 3, 2017. https://www.comscore.com/Insights/Blog/US-Smartphone-Penetration-Surpassed-80-Percent-in-2016
81. Graetz I, Huang J, Brand RJ, Hsu J, Yamin CK, Reed ME. Bridging the digital divide: mobile access to personal health records among patients with diabetes. *Am J Manag Care*. Jan 2018;24(1):43-48.
82. Rudin RS, Perez S, Rodriguez JA, et al. User-centered design of a scalable, electronic health record-integrated remote symptom monitoring intervention for patients with asthma and providers in primary care. *J Am Med Inform Assoc*. Oct 12 2021;28(11):2433-2444. doi:10.1093/jamia/ocab157
83. Fiks AG, DuRivage N, Mayne SL, et al. Adoption of a Portal for the Primary Care Management of Pediatric Asthma: A Mixed-Methods Implementation Study. *J Med Internet Res*. Jun 29 2016;18(6):e172. doi:10.2196/jmir.5610
84. Loskutova NY, Callen E, Pinckney RG, Staton EW, Pace WD. Feasibility, Implementation and Outcomes of Tablet-Based Two-Step Screening for Adult ADHD in Primary Care Practice. *J Atten Disord*. Apr 24 2019:1087054719841133. doi:10.1177/1087054719841133
85. DeAlleaume L, Parnes B, Zittleman L, et al. Success in the Achieving CARdiovascular Excellence in Colorado (A CARE) Home Blood Pressure Monitoring Program: A Report from the Shared Networks of Colorado Ambulatory Practices and Partners (SNOCAP). *The Journal of the American Board of Family Medicine*. September 1, 2015 2015;28(5):548-555. doi:10.3122/jabfm.2015.05.150024
86. Bousquet J, Boulet LP, Peters MJ, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med*. Dec 2007;101(12):2437-46. doi:10.1016/j.rmed.2007.07.014
87. National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working

Group. National Heart, Lung and Blood Institute. Accessed January 8, 2021. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines
88. Global Initiative for Asthma (GINA). Science Committee. Updated August 2020. Accessed January 8, 2021. https://ginasthma.org/science-committee/
89. Wagshul FA, Brown DT, Schultek NM, Hahn DL. Long-term (>1 year) Outcomes of Antibiotics to Treat Asthma. *Chest*. under review;
90. Hahn DL. Treatment of Chlamydia pneumoniae infection in adult asthma: A before-after trial. *Journal of Family Practice*. 1995 1995;41(4):345-51. Not in File.
91. Schatz M, Zeiger RS, Drane A, et al. Reliability and predictive validity of the Asthma Control Test administered by telephone calls using speech recognition technology. *J Allergy Clin Immunol*. Feb 2007;119(2):336-43. doi:10.1016/j.jaci.2006.08.042
92. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. Jan 2004;113(1):59-65. doi:10.1016/j.jaci.2003.09.008
93. Erskine J, Lanigan A, Emsermann CB, Manning BK, Staton EW, Pace WD. Use of the Americans in Motion-Healthy Intervention (AIM-HI) to create a culture of fitness in family practice. *J Am Board Fam Med*. Sep-Oct 2012;25(5):694-700. doi:10.3122/jabfm.2012.05.110071
94. Yawn BP, Wollan PC, Rank MA, Bertram SL, Juhn Y, Pace W. Use of Asthma APGAR Tools in Primary Care Practices: A Cluster-Randomized Controlled Trial. *Ann Fam Med*. Mar 2018;16(2):100-110. doi:10.1370/afm.2179
95. Carroll JK, Pulver G, Dickinson L, et al. Effect of 2 clinical decision support strategies on chronic kidney disease outcomes in primary care: A cluster randomized trial. *JAMA Network Open*. 2018;1(6):e183377. doi:10.1001/jamanetworkopen.2018.3377
96. Wechsler ME, Yawn BP, Fuhlbrigge AL, et al. Anticholinergic vs Long-Acting beta-Agonist in Combination With Inhaled Corticosteroids in Black Adults With Asthma: The BELT Randomized Clinical Trial. *JAMA*. Oct 27 2015;314(16):1720-30. doi:10.1001/jama.2015.13277
97. Yawn BP, Dietrich AJ, Wollan P, et al. TRIPPD: A Practice-Based Network Effectiveness Study of Postpartum Depression Screening and Management. *Ann Fam Med*. Jul 2012;10(4):320-9. doi:10/4/320 [pii]

10.1370/afm.1418
98. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J*. Jul 1999;14(1):32-8. doi:10.1034/j.1399-3003.1999.14a08.x
99. Busse WW, Morgan WJ, Taggart V, Togias A. Asthma outcomes workshop: overview. *J Allergy Clin Immunol*. Mar 2012;129(3 Suppl):S1-8. doi:10.1016/j.jaci.2011.12.985
100. Shen J, Johnston M, Hays RD. Asthma outcome measures. *Expert Rev Pharmacoecon Outcomes Res*. Aug 2011;11(4):447-53. doi:10.1586/erp.11.48
101. Ko FWS, Hui DSC, Leung T-F, et al. Evaluation of the asthma control test: A reliable determinant of disease stability and a predictor of future exacerbations. *Respirology*. 2012;17(2):370-378. doi:https://doi.org/10.1111/j.1440-1843.2011.02105.x
102. Przybyszowski M, Polczyk R, Sliwka A, et al. Asthma Control Test (ACT) result as a predictor of asthma exacerbations. *European Respiratory Journal*. 2017;50(suppl 61):PA1124. doi:10.1183/1393003.congress-2017.PA1124
103. National Asthma Education and Prevention Program Third Expert Panel on the Diagnosis and Management of Asthma, National Heart Lung and Blood Institute. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Clinical Practice Guidelines. Report No.: 07-4051. National Heart, Lung, and Blood Institute (US). Accessed January 6, 2021. https://www.ncbi.nlm.nih.gov/books/NBK7232/

104. Chantadul V, Poachanukoon O. Mini version of the pediatric asthma quality of life questionnaire (MiniPAQLQ): validity among Thai asthmatic children. *J Med Assoc Thai*. Mar 2015;98 Suppl 2:S92-100.
105. National Center for Health Statistics, Centers for Disease Control and Prevention. National Health Interview Survey (NHIS), 2003, 2008, 2013: question, "During the past 12 months, how many days of [daycare or preschool, school, school or work] did child miss because of his/her asthma? Updated March, 2016. Accessed October 2, 2021. https://www.cdc.gov/asthma/nhis/default.htm
106. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. *Chest*. May 1999;115(5):1265-70. doi:10.1378/chest.115.5.1265
107. Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. *Eur Respir J*. Dec 2010;36(6):1410-6. doi:10.1183/09031936.00117509
108. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in the parents of children with asthma. *Qual Life Res*. Feb 1996;5(1):27-34. doi:10.1007/BF00435966
109. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. *Qual Life Res*. Feb 1996;5(1):35-46. doi:10.1007/bf00435967
110. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol*. Jan 1994;47(1):81-7. doi:10.1016/0895-4356(94)90036-1
111. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. May 2005;99(5):553-8. doi:10.1016/j.rmed.2004.10.008
112. Schatz M, Sorkness CA, Li JT, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol*. Mar 2006;117(3):549-56. doi:10.1016/j.jaci.2006.01.011
113. Schatz M, Mosen DM, Kosinski M, et al. Validity of the Asthma Control Test completed at home. *Am J Manag Care*. Dec 2007;13(12):661-7.
114. Cloutier MM, Schatz M, Castro M, et al. Asthma outcomes: composite scores of asthma control. *J Allergy Clin Immunol*. Mar 2012;129(3 Suppl):S24-33. doi:10.1016/j.jaci.2011.12.980
115. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials*. Dec 1989;10(4):407-15. doi:10.1016/0197-2456(89)90005-6
116. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol*. Oct 2009;124(4):719-23 e1. doi:10.1016/j.jaci.2009.06.053
117. Leidy NK, Coughlin C. Psychometric performance of the Asthma Quality of Life Questionnaire in a US sample. *Qual Life Res*. Feb 1998;7(2):127-34. doi:10.1023/a:1008853325724
118. Raat H, Bueving HJ, de Jongste JC, Grol MH, Juniper EF, van der Wouden JC. Responsiveness, longitudinal- and cross-sectional construct validity of the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) in Dutch children with asthma. *Qual Life Res*. Feb 2005;14(1):265-72.
119. Wing A, Upton J, Svensson K, Weller P, Fletcher M, Walker S. The standardized and mini versions of the PAQLQ are valid, reliable, and responsive measurement tools. *J Clin Epidemiol*. Jun 2012;65(6):643-50. doi:10.1016/j.jclinepi.2011.12.009
120. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis*. Apr 1993;147(4):832-8. doi:10.1164/ajrccm/147.4.832
121. Juniper EF, Johnston PR, Borkhoff CM, Guyatt GH, Boulet LP, Haukioja A. Quality of life in asthma clinical trials: comparison of salmeterol and salbutamol. *Am J Respir Crit Care Med*. Jan 1995;151(1):66-70. doi:10.1164/ajrccm.151.1.7812574

122. Rutten-van Molken MP, Van Doorslaer EK, Jansen MC, Kerstjens HA, Rutten FF. Costs and effects of inhaled corticosteroids and bronchodilators in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. Apr 1995;151(4):975-82. doi:10.1164/ajrccm.151.4.7697275
123. Drazen JM, Israel E, Boushey HA, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. Asthma Clinical Research Network. *N Engl J Med*. Sep 19 1996;335(12):841-7. doi:10.1056/nejm199609193351202
124. Israel E, Cohn J, Dube L, Drazen JM. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. A randomized controlled trial. Zileuton Clinical Trial Group. *JAMA*. Mar 27 1996;275(12):931-6.
125. Kemp JP, Cook DA, Incaudo GA, et al. Salmeterol improves quality of life in patients with asthma requiring inhaled corticosteroids. Salmeterol Quality of Life Study Group. *J Allergy Clin Immunol*. Feb 1998;101(2 Pt 1):188-95. doi:10.1016/s0091-6749(98)70383-5
126. Turner MO, Taylor D, Bennett R, Fitzgerald JM. A randomized trial comparing peak expiratory flow and symptom self-management plans for patients with asthma attending a primary care clinic. *Am J Respir Crit Care Med*. Feb 1998;157(2):540-6. doi:10.1164/ajrccm.157.2.9703060
127. Boulet LP, Boutin H, Cote J, Leblanc P, Laviolette M. Evaluation of an asthma self-management education program. *J Asthma*. 1995;32(3):199-206. doi:10.3109/02770909509089508

Appendix 1 – Drugs to be Avoided with Azithromycin

Drugs that may increase risk of prolonged QT and/or torsades de pointe (TdP) that are exclusion criteria for iTREAT-PC

Source: CredibleMeds: https://crediblemeds.org/, accessed 12/5/2022

KNOWN RISK= prolong QT and associated with TdP even when taken as recommended

Table 9 - Drugs in the US market with KNOWN RISK to prolong QT & induce torsades de pointes (TdP)

ANTIARRYTHMICS (n=9)	Ibutilide Dronedarone Sotalol Quinidine Procainamide Flecainide Disopyramide Dofetilide Amiodarone
ANTIBIOTICS (n=6)	Levofloxacin Moxifloxacin Clarithromycin Erythromycin Ciprofloxacin
ANTIPSYCHOTICS (n=5)	Haloperidol Droperidol Chlorpromazine Thioridazine Pimozide
ANTI-CANCER (n=4)	Arsenic trioxide Vandetanib Oxaliplatin Mobocertinib
ANESTHETICS (n=3)	Sevoflurane Cocaine Propofol
ANTIDEPRESSANTS (n=2)	Escitalopram Citalopram
ANTIANGINAL (n=2)	Bepridil Papaverine HCl (Intracoronary)
ANTIFUNGALS (n=2)	Fluconazole Pentamidine
ANTIMALARIAL (n=2)	Chloroquine Hydroxychloroquine
PHOSHODIESTERASE 3 INHIBITOR (n=2)	Anagrelide Cilostazol
CHOLINESTERASE INHIBITOR (n=1)	Donezepril
OPIOID AGONIST (n=1)	Methadone
ANTIEMETIC (n=1)	Ondansteron
TOXIN (n=1)	Cesium Chloride

POSSIBLE RISK= can cause prolonged QT but lack of evidence for risk of TdP when taken as recommended

115 drugs in the US market with POSSIBLE RISK to prolong QT & induce torsades de pointes (TdP)

Table 10 - Selected drugs from this list that are most likely to be encountered in a primary care population

ANTIDEPRESSANTS	Imipramine Notriptylene Venlafaxene Desipramine Lithium
ANTIPSYCHOTIC	Clozapine Promethazine Aripriprazole
ANTIBIOTICS	Ofloxacin Lefamulin
ANALGESIC	Tramadol Hydrocodone ER
OPIOID AGONIST	Buprenorphine
PHOSPHODIESTERASE 5 INHIBITOR	Vardenafil
MUSCLE RELAXANT	Tolterodine
ANTICANCER	Tamoxifen
ANTIVIRAL	Remdesavir

Appendix 2 – DSMB Charter

Charter
Data and Safety Monitoring Board
iTREAT

Version 1.1 6/23/2023

Introduction

This charter is for the Data and Safety Monitoring Board (DSMB) for the Individualizing Treatment for Asthma in Primary Care (iTREAT) trial. The DSMB may review this charter at regular intervals to determine whether any changes are needed.

iTREAT: Twenty-five million people have asthma in the US with over 45% experiencing one or more exacerbations (worsening of symptoms that disrupts their lives) per year. Asthma exacerbations cause many lost days from school or work and account for over 3,500 deaths per year. Guidelines support the use of inhaled corticosteroids as part of rescue therapy, most commonly as Single Maintenance And Reliever Therapy (SMART). Long-term (>6 months) therapy with azithromycin (a macrolide antibiotic) has demonstrated similar reductions in asthma exacerbations to SMART therapy. Asthma is recognized as including clinical and biological variations. Which variations respond best to SMART versus azithromycin is not clear. Furthermore, the two have not been studied when used together.

The *Individualizing Treatment for Asthma in Primary Care* study will be a four-arm study with 3200 people. Treatment will vary randomly at the patient level. Study arms will be SMART therapy versus azithromycin therapy versus SMART plus azithromycin versus control. All participants will be asked to record their asthma symptoms using home monitoring tools. The primary outcome will be yearly asthma exacerbation rates compared across the three intervention arms to the control arm. Secondary outcomes will be asthma control (Asthma Control Test or ACT) and asthma quality of life (mini-Asthma Quality of Life Questionnaire.) To study the impact of asthma variations, the analyses will include total blood eosinophil counts, infectious biomarkers for *Mycoplasma pneumoniae and Chlamydia pneumoniae,* smoking status, health literacy, onset of asthma associated with a lower respiratory tract infection and Black/African American race. We hypothesize that all treatment arms will be better than the control arm. We hypothesize that SMART therapy will work better in non-smokers or those with high total blood eosinophil counts or in people with lower health literacy. We hypothesize that azithromycin will work better in smokers or individuals with an associated lower respiratory tract infection at the time their asthma began or with selected positive biomarkers.

Participants will come from primary care practices from across the United States. Participants must have an asthma diagnosis for at least one year, be at least 12 years old and under 76 years old. They must have had an exacerbation requiring steroid pills or shots or a hospitalization in the past 12 months OR have an ACT score <20. After consent, participants will complete surveys every other month for 16 months. Possible exacerbations will be validated by clinicians who do not know the treatment arm of the participant. People who experience three exacerbations in <12 months will have treatments increased if not already in the dual treatment arm. People in the control arm will move to SMART therapy while people in either single therapy will move to dual therapy. These participants would be followed for an additional 12 months. Individuals who finish either of the azithromycin arms will be offered 6 additional months of follow-up after stopping the azithromycin only. How well participants and people in the practices are able to carry out the study will be tracked using an approach called PRISM/RE-AIM.

The analyses will be based on a model called the Negative Binomial distribution. In addition to treatment arms, the analysis will assess the impact of sex, race, smoking history, asthma treatment at enrollment, total eosinophil count, and ability to use mobile technology, as well as the effect of the organization and practice on the outcomes. The variations of treatment effect will use the same approach as the main analysis with a focus on interactions between the treatments the covariates.

Study results can be used by clinicians and patients to identify appropriate treatment for patients based on their individual characteristics, and by insurers to determine what types of therapy to pay for.

Stakeholders are integral members of the study team with decision making authority Stakeholder groups including 1) patients/caregivers, 2) patient advocacy groups, 3) clinicians (physicians, nurses, and pharmacists), 4) professional societies, 5) healthcare policy experts, 6) payers, 7) asthma experts and researchers, and 8) site research teams have been engaged in formulating the research questions, identifying the study groups, selecting the interventions, choosing outcomes, and suggesting the exploratory aims and analyses.

[https://www.clinicaltrials.gov/ct2/show/NCTxxxx]

Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety, efficacy, and quality of study procedures, and monitoring the overall conduct of the study.

The DSMB is an independent advisory group charged with providing recommendations about starting, continuing, and stopping a study. As appropriate, the DSMB is also asked to review and make recommendations to the Sponsor about the following:

- Study protocol and consent forms, including any amendments
- Whether any new data from other sources affect the equipoise of the studies being monitored
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Performance of individual centers and cores
- Management of abnormal findings (incidental findings and adverse events)
- Selection, recruitment, and retention of participants
- Benefit/risk ratio of procedures
- Participant burden
- Participant safety

Organization and Interactions

DSMB Members and Study Personnel

DSMB members and their expertise are listed in Appendix A. Study Staff and their responsibilities are listed in Appendix B. Consistent with PCORI policy, the DSMB has an assigned Executive Secretary (ES) to provide an unbiased interface between the Sponsor and the DSMB, especially during executive sessions. The Data Coordinating Center Principal Investigator (PI) is responsible for assuring the accuracy and timely transmission of the final recommendations and DSMB summary.

Communication between Investigators and the DSMB

Communication between Study Staff and DSMB will be through the ES in coordination with the PI. It is expected that Investigators will not communicate with DSMB members directly except at meetings.

Scheduling, Timing, and Organization of Meetings

Meetings will occur by video conference. Meetings will be held approximately twice a year, with additional meetings scheduled as needed. Meetings and any interim calls will be scheduled by the ES.

At the first meeting, the PI will convey expectations for DSMB operations and responsibilities. The DSMB will review and discuss this charter, and learn about the iTREAT study. The DSMB will review and make recommendations about human subjects' safety and ethics of the protocol, participant consent document, and other study materials, and discuss the safety monitoring guidelines. Enrollment in the study cannot begin until the DSMB's recommendation for approval has been accepted by the IRBs.

The agenda for DSMB meetings will be drafted by the PI. The ES will finalize the agenda after consultation with the PI and DSMB Chair. ES will make the agenda and meeting materials available to the DSMB members at least 10 working days before each meeting.

At the time the agenda is sent out, and again at the beginning of each meeting, the ES will ask all DSMB members to state whether they have developed any new conflicts of interest since the last annual report. If a new conflict is reported, the Chair and PI will determine if the conflict limits the ability of the DSMB member to participate in the discussion.

The DSMB will review adverse event data, other safety data, quality and completeness of study data, and enrollment data at each meeting to ensure proper trial conduct. The PI should provide any new literature particularly pertinent to the trial, along with their recommendation as to whether it affects the trial conduct or design. The DSMB will review the consent periodically and/or as needed and consider whether the consent form requires revision in light of any new findings or amendments.

In addition to regular meetings, it may be necessary to convene the DSMB urgently on an *ad hoc* basis to discuss new data or other information that raises questions about equipoise, safety, or anything else in the trial.

It is expected that all DSMB members will attend every meeting. However, it is recognized that this may not always be possible. A quorum of this DSMB is considered to be a majority of the members.

DSMB Meeting Format

For each meeting the PI and unblinded statistician will prepare summary reports and tables to facilitate the oversight role of the DSMB. Reports will be separated into Open Session and Closed session sections.

DSMB meetings will be organized into open, closed, and executive sessions.

- During **open sessions**, information will be presented to the DSMB by the investigators with time for discussion. PCORI staff may attend open sessions, unless the DSMB Chair decides that the presence of PCORI staff may inhibit free and open discussion or appear to compromise the DSMB's independence.

- During **closed sessions**, the DSMB and unblinded statistician will discuss confidential data, including any necessary information on efficacy and safety by treatment arm. The DSMB reviews masked data, with option to unmask at any time they choose. If the closed session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session.

- The DSMB may elect to hold an **executive session** in which only the DSMB members are present. The ES may attend the executive session at the invitation of the DSMB Chair. If the ES does not attend the executive session, the DSMB Chair will be responsible for summarizing the DSMB's discussion and recommendations. The DSMB can request to have other staff members attend the executive session to provide additional information as needed.

Voting on recommendations will follow Robert's Rules of Order.

At the conclusion of the closed and executive sessions, the DSMB chair will provide a summary of the preliminary recommendations to the investigators to provide an opportunity for investigators to ask questions to clarify the recommendations. The meeting is then adjourned.

The ES will prepare Meeting Minutes and formal Summary Recommendations to be approved by the DSMB Chair.

Reports of DSMB Deliberations

- Reports for IRBs: If the DSMB does not identify any safety or other protocol-related concerns, within 14 days after a DSMB meeting the PI will prepare a Summary Report of Board Recommendations indicating that:

    - a review of outcome data, adverse events, and information relating to each study performance (e.g., data timeliness, completeness, and quality) across all centers involved in the study took place on a given date;

    - the observed frequency of adverse events did not exceed what was expected and indicated in the informed consent;

    - the DSMB recommends that the study continues without modification of the protocol or informed consent.

The PI will send the Summary Report to the sIRB with copy to study investigators at each clinical centers. It is the responsibility of each investigator to forward this information to the local IRB.

If DSMB identifies concerns necessitating protocol and/or informed consent changes, the Summary Report will outline the concerns, the DSMB's discussion of the concerns and the basis for any recommendations that the DSMB has made in response to the concerns.

- A copy of the Summary Report will also be provided to PCORI. If the DSMB recommends major protocol and/or informed consent changes, they will be reviewed with PCORI prior to implementation.

Statistical Monitoring Guidelines

There is no pre-planned efficacy or futility analysis; study protocol details safety interim analysis.

If requested, this charter and accompanying list of Board members may be sent to an IRB. In the case, this charter will be marked as not for dissemination, and be sent by the Principal Investigator to the IRB Chair, with a cover letter.

APPENDIX A: DSMB Members and Expertise

DSMB member	Expertise
Diane Harper, MD, MPH, MS Professor Department of Family Medicine University of Michigan diane.m.harper@gmail.com	Chair
Benjamin Wilfond, MD Professor Divisions of Bioethics and Palliative Care & Pulmonary and Sleep University of Washington School of Medicine Phone : 206 884-8355 bwilfond@uw.edu	Research Ethics
David DeMets, PhD Max Halperin Emeritus Professor of Biostatistics Department of Biostatistics & Medical Informatics University of Wisconsin School of Medicine & Public Health Phone: 608/263-2947 demets@biostat.wisc.edu	Statistics and Study Design/Implementation
Kurt Elward, MD kselward@me.com	Clinician
Steven Natrass Steven.Nattrass@fda.hhs.gov	Community representative

APPENDIX B: Study Personnel and Roles

Study Personnel	Role
Wilson Pace, MD, FAAFP Chief Medical and Technology Officer DARTNet Institute Professor Emeritus, University of Colorado Department of Family Medicine Phone: 720-334-6305 email: wilson.pace@dartnet.info	Overall Study PI
David Mauger, PhD Professor of Biostatistics Department of Public Health Sciences Penn State University College of Medicine Phone: 717-531-3584 email: dmauger@psu.edu	Data Coordinating Center Principal Investigator
Lan Kong, PhD Professor of Biostatistics Department of Public Health Sciences Penn State University College of Medicine email: lkong@pennstatehealth.psu.edu	Unblinded Statistician
Abid Kazi Department of Public Health Sciences Penn State University College of Medicine email: akazi@pennstatehealth.psu.edu	Executive Secretary

Appendix 3 – Questionnaires

Eligibility

1. Is another person living with you already in this study?

Yes (1) *Go to General Exit Survey*
No (0) *Go to next question*

2. Are you 12 to 75 years of age?

Yes (1) *Go to next question*
No (0) *Go to Age Exit Survey*

3. Have you had asthma for 1 year or longer?

Yes (1) *Go to next question*
No (0) *go to Asthma Exit Survey*

4. In the past 4 weeks, have you taken steroid pills or shots, like prednisone, or been to the Emergency Room or urgent care, or been in the hospital overnight for problems with your asthma?

Yes (1) *Go to Exacerbation Exit Survey*
No (0) *Go to next question*

5. In the past 6 months, have you had a lung procedure called bronchial thermoplasty?

Yes (1) *Go to Lung Procedure Exit Survey*
No (0) *Go to next question*

6. Are you currently taking oral steroids like prednisone every day or every other day for your asthma or any other medical problem?

Yes (1) *Go to Medication Exit Survey*
No (0) *Go to next question*

7. In the past 6 months, have you started taking new shots or infusions for your asthma (other than allergy shots)?

Yes (1) *Go to Medication Review Survey*
No (0) *Go to next question*

8. Have you been told you have COPD, Chronic bronchitis, emphysema or other chronic lung disease?

Yes (1) *Go to COPD Review Survey*
No (0) *Go to next question*

9. Have you been asked to take one or more of the asthma medicines listed below?

Check all that apply (1 – selected; 0 – not selected)

Airduo Respiclick (add generic names after each)
Advair HFA or Advair Diskus
Symbicort
Breo
Dulera
QVAR
Aerospan
Alvesco
ArmonAir
Flovent diskus or Flovent MDI
Asmanex HFA or Twisthaler
Arnuity Ellipta
Pulmicort Flexhaler
Trelogy
None of the above (Go to Medication Exit Survey, all others proceed to 9)

(Ask to see the canister even if not being taken.)

10. In the past year, have you taken steroid pills or shots, like prednisone or been in the hospital overnight for problems with your asthma?

Yes (1) *Go to consent*
No (0) Go to next question

11. In the **past 4 weeks**, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time (1)
Most of the time (2)
Some of the time (3)
A little of the time (4)
None of the time (5)

12. During the **past 4 weeks**, how often have you had shortness of breath?

More than once a day (1)
Once a day (2)
3 to 6 times a week (3)
Once or twice a week (4)
Not at all (5)

13. During the **past 4 weeks**, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week (1)
2 to 3 nights a week (2)
Once a week (3)
Once or twice (4)
Not at all (5)

14. During the **past 4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day (1)
1 or 2 times per day (2)
2 or 3 times per week (3)
Once a week or less (4)
Not at all (5)

15. How would you rate your asthma control during the **past 4 weeks**?

Not Controlled at All (1)
Poorly Controlled (2)
Somewhat Controlled (3)
Well Controlled (4)
Completely Controlled (5)

If total for items 12-16 is 20 or greater then not eligible – Proceed to General Exit Survey

If total for items 12-16 is less than 20 then eligible – Proceed to Consent

General Exit Survey
Thank you for your time and interest in this study. We are not able to include you in the study at this time. Please answer the questions below so we can understand who we talked to about the study. You may choose the "Prefer not to answer" box if you do not want to give us this information.

1. Gender

Female (1)
Male (0)
Other (2)
Prefer not to answer (98)

2. Ethnicity

Hispanic/Latino (1)
Not Hispanic/Latino (0)
Prefer not to answer (98)

3. Race (check all that apply)

Check all that apply (1 – selected; 0 – not selected, unless other or prefer not to answer)

African American/Black
Caucasian/white
Asian
Hawaiian/Pacific Islander
Native American/Alaska Native
Other (96)
Prefer not to answer (98)

Age Exit Survey
This study is open to people between the ages of 12 and 75. Thank-you for your interest. Please complete the three questions below. You may choose the "Prefer not to answer" box if you do not want to give us this information.

1. Gender

Female (1)
Male (0)
Other (2)
Prefer not to answer (98)

2. Ethnicity

Hispanic/Latino (1)
Not Hispanic/Latino (0)
Prefer not to answer (98)

3. Race (check all that apply)

Check all that apply (1 – selected; 0 – not selected, unless other or prefer not to answer)

African American/Black
Caucasian/white
Asian
Hawaiian/Pacific Islander
Native American/Alaska Native
Other (96)
Prefer not to answer (98)

COPD Review Survey

1. Have you been diagnosed with a chronic lung disease other than asthma, COPD, emphysema or chronic bronchitis? (such as bronchiectasis, pulmonary fibrosis, cystic fibrosis, interstitial lung disease and others)
    a. Yes – to COPD exit
    b. No – to B
2. Are you currently smoking or have you smoked for more than 5 years in your life time?
    a. No – proceed to consent
    b. Yes – to C
3. Have you had pulmonary function testing in the past 2 years or since you stopped smoking?
    a. Yes – to D
    b. No – to COPD Exit
4. Study coordinator do have the latest PFTs?
    a. Yes – go to E
    b. No- Exit needs PFTs review
5. Are the PFTs in the last 24 months?
    a. Yes – to G
    b. No – to F

6. Are the PFTs from after this person stopped smoking?
    a. Yes – proceed to G
    b. No – COPD Exit
7. Is the DLCO normal?
    a. Yes – to consent
    b. No – COPD Exit

Other Chronic Lung Diseases Exit Survey
Thank you for your time and interest in this study. This study is not open to people with some other chronic lung diseases. Please answer the questions below so we can understand who we talked to about the study. You may choose the "Prefer not to answer" box if you do not want to give us this information.

1. Gender

Female (1)
Male (0)
Other (2)
Prefer not to answer (98)

2. Ethnicity

Hispanic/Latino (1)
Not Hispanic/Latino (0)
Prefer not to answer (98)

3. Race (check all that apply)

Check all that apply (1 – selected; 0 – not selected, unless other or prefer not to answer)

African American/Black
Caucasian/white
Asian
Hawaiian/Pacific Islander
Native American/Alaska Native
Other (96)
Prefer not to answer (98)

Need PFT Exit Survey
Thank you for your time and interest in this study. To continue in this study the study coordinator will need to find or get a copy of your latest pulmonary function testing.

1. Where was your lung function testing done?
    a. Inside this medical organization – to C
    b. In another medical organization – to B

2. Can you get a copy of your last lung function test?
    a. Yes – proceed to C
    b. No – COPD Exit survey

3. Please provide a phone number and I will call you back when I find your lung test or when I get your lung test from you.
   Will need to keep the phone number locally

Medication Review Survey
This is study is open to people using injections or infusion medicine called biologics for their asthma if they have been on the same dose of the medication for 6 months or more and have had an exacerbation since being on their current does of medication.

1. Have you been on your current shot or infusion for at least 6 months with the same dose:

   Yes – proceed to 2
   No – Med Exit survey

2. Have you used steroids orally or by shot since you started your current dose of your shot or infusion medication?
   1. Yes – proceed to consent
   2. No – proceed to 3

3. Have you been hospitalized for your asthma for 24 hours or more since you started your current does of your shot or infusion medication?

   Yes – proceed to consent
   No – Med Exit Survey

Medication Exit Survey
This study is open to people using an inhaled steroid asthma medication and not open to people taking daily oral steroids or newly started on injections or infusion medicine for their asthma. If you stop taking daily or every other day steroids or once you are on your shot or infusion for at least 6 months you may be eligible at that time. The local study team may recontact you if those things happen. Thank-you for your interest. Please complete the three questions below. You may choose the “Prefer not to answer” box if you do not want to give us this information.

1. Gender

   Female (1)
   Male (0)
   Other (2)
   Prefer not to answer (98)

2. Ethnicity

   Hispanic/Latino (1)
   Not Hispanic/Latino (0)
   Prefer not to answer (98)

3. Race (check all that apply)

Check all that apply (1 – selected; 0 – not selected, unless other or prefer not to answer)

   African American/Black

Caucasian/white
Asian
Hawaiian/Pacific Islander
Native American/Alaska Native
Other (96)
Prefer not to answer (98)

Intake

iTREAT Intake Questionnaire - Coordinator Administered

Health Literacy
Medical information can be complex and many people have expressed problems with medical information. To be sure we best meet your needs we would like to understand how much of a problem dealing with medical information might be for you. (Ask parent if a child under 16.)

1. How often does someone help you read things your doctor gives you?

◯ Always (4) ◯ Often (3) ◯ Sometimes (2) ◯ Never (1)

2. How easy or hard is it to fill out medical forms by yourself?

◯ Extremely hard (5) ◯ Very hard (4) ◯ Somewhat hard (3) ◯ Easy (2) ◯ Very easy (1)

3. How often is it hard to understand written information about your medical problems?

◯ Always (4) ◯ Often (3) ◯ Sometimes (2) ◯ Never (1)

Demographics

4. What is your birthdate? ____/____/_____ (MM/DD/YYYY) – [move to area where account is created]

5. Sex assigned at birth? ◯ Female (1) ◯ Male (0)

5a. At times we are likely to call you. What pronouns do you use to describe yourself?

◯ He/His/Him (0)

◯ She/Her (1)

◯ They/Them (2)

◯ Other (3):

6. Do you consider yourself Hispanic or Latino? ◯ Yes (1) ◯ No (0)

7. Which races do you identify with? (Please check all that apply)

◯ African American/Black (skip next question)

◯ Asian

◯ Native American/Alaska Native

◯ Hawaiian/Pacific Islander

◯ Caucasian

◯ Other

8. What is the highest level of schooling you have completed?

◯ Less than 8th grade (1)

◯ Less than High School (2)

◯ High School (3)

◯ Some college or technical school (4)

◯ College (5)

◯ Graduate School (6)

◯ Prefer not to answer (7)

9. How tall are you? _____ feet ____ inches

10. How many pounds do you weigh? _____ pounds

Smoking

11. Have you ever smoked at least 100 cigarettes in your life? ◯ Yes (1) ◯ No (0) (If no, go to question 16 for second hand smoke)

12. How old were you when you started smoking regularly? _____ years old

13. Think about now or when you did smoke, how many cigarettes do you or did you usually smoke?

◯ Less than 5 per day (1)

◯ 5-9 per day (2)

◯ 10 (half a pack) per day (3)

◯ 20 (a pack) per day (4)

◯ 30 (one and a half packs) per day (5)

◯ 40 or more (2 packs or more) per day (6)

14. Have you stopped smoking? ◯ Yes (1) ◯ No, I still smoke (0) (skip question 16)

15. When was the most recent time you stopped? (like 1999 or 2013) Enter year: _____.

16. Do others regularly smoke in your home? ◯ Yes (1) ◯ No (0)

17. Do others regularly smoke at your work? ◯ Yes (1) ◯ No (0)

18. Do others regularly smoke in your car? ◯ Yes (1) ◯ No (0)

Asthma Problems

19. In the past 12 months, how many times have you gone to the emergency room or urgent care for your asthma? Enter number of times: _____.

20. In the past 12 months, without staying overnight in a hospital, how many times have youtaken steroid/cortisone/prednisone pills or a shot for your asthma?

    Enter number of times:_____.

21. In the past 12 months, how many times have you stayed in the hospital overnight or longer for your asthma?

    Enter number of times:_____.

Comorbidities

22. Have you ever been told you had any of the following? (Please check all that apply)

    ◯ Heart disease

    ◯ Cancer other than skin cancer

    ◯ Stroke

    ◯ Diabetes

        If yes
        Do you have:
        ◯ Type 1

        ◯ Type 2
        ◯ Both

    ◯ Chronic kidney injury/disease

    ◯ COPD/chronic bronchitis

    ◯ HIV/AIDS

    ◯ Hypertension

    ◯ Depression/Anxiety

    ◯ Sleep disorder

    ◯ Allergies-allergic rhinitis, chronic sinusitis, atopic dermititis, Aspirin, other

    ◯ None of the above

Age of Asthma Diagnosis

23. How old were you when a doctor first told you that you had asthma?

◯ Less than 5 years old (1)

◯ 5 to 12 years old (2)

◯ 13 to 18 years old (3)

◯ 19-40 years old (4)

◯ 41-60 years old (5)

◯ More than 60 years old (6)

◯ I don't remember (9) - if chosen go to 24 if not skip to 25

24. How many years have you had asthma?

◯ 1 to 10 years (1)

◯ 11 to 20 years (2)

◯ More than 20 years (3)

25. Did your very first symptoms that led to an asthma diagnosis begin during or shortly after a respiratory illness such as bronchitis, pneumonia or an influenza-like illness?

◯ Yes (1)
◯ No (0)
◯ Don't Remember (9)

Socioeconomic Status

26. Which of the following best describes your work/school situation?

◯ Working for pay at job, business, or at home (1)

◯ Looking for work (2)

◯ Seasonal worker and not working right now (3)

◯ Taking care of house or family (4)

◯ Working but not for pay at family-owned business or job (5)

◯ Not working and not looking for work (6)

◯ On maternity leave (7)

◯ Student (8)

◯ Retired (9)

◯ Temporarily unable to work due to health (10)

◯ Disabled (11)

◯ On lay off (12)

◯ Prefer not to answer (13)

◯ Other (14)

27. What is your total yearly family household income last year?

◯ Less than $10,000 (1)

◯ $10,001 to $20,000 (2)

◯ $20,001 to $30,000 (3)

◯ $30,001 to $40,000 (4)

◯ $40,001 to $50,000 (5)

◯ $50,001 to $75,000 (6)

◯ $75,001 or more (7)

◯ Prefer not to answer (98)

28. How many other people (adults and children) live in your household? Enter number:_____

Asthma Medicines

We want to know about all of the asthma medicine you use. Check all that apply in each grouping. [Coordinator should use medicine chart with pictures]

29. Are you currently taking any of these rescue or quick reliever medicines? (check all that apply)

◯ Proventil (albuterol)

◯ Pro Air HFA/ProAir RespiClick (albuterol)

◯ Ventolin

◯ Xopenex

◯ Atrovent

◯ Combivent

◯ None of these

30. What do you call the medicine we just talked about? []. Enter patient's exact words

31. Do you carry this medicine with you?

◯ Always (1) ◯ Often (2) ◯ Sometimes (3) ◯ Rarely (4) ◯ Never (5)

32. About how many puffs of your rescue medicine do you use <u>in a usual month</u>?

◯ Less than 10 puffs per month (1)

◯ 10 to 30 puffs in a month (2)

◯ More than 30 puffs but not a whole canister (3)

◯ More than 1 canister per month (200 puffs) but less than 2 canisters (4)

◯ 2 or more canisters per month (400 or puffs per month) (5)

33. Do you ever use a nebulizer when you have shortness of breath or for quick relief, rescue medicines? ◯ Yes (1) ◯ No (0) (if no, skip next questions)

34. In an average week, how many times do you use a nebulizer for these asthma symptoms? Enter number:_____

35. Are you taking any of these inhaled corticosteroids medicines? (check all that apply)

- ◯ Aerospan HFA (flunisolide)
- ◯ Alvesco (ciclesonide)
- ◯ Arnuity Ellipta (fluticasone powder)
- ◯ ArmonAir Respiclick (fluticasone metered dose inhaler)
- ◯ Flovent HFA or diskus (fluticasone inhaler or powder)
- ◯ Asmanex Twisthaler (mometasone)
- ◯ Pulmicort Flexhaler (budesonide)
- ◯ QVAR (betamethasone)
- ◯ None of these

36. Are you taking any of these combination medicines? (check all that apply)

- ◯ Airduo Respiclick (fluticasone/salmeterol)
- ◯ Advair HFA or Diskus (fluticasone/salmeterol
- ◯ Symbicort (budesonide/formoterol)
- ◯ Breo (fluticasone/vilanterol)
- ◯ Dulera (mometasone/formoterol)
- ◯ Trelegy (fluticasone/umeclidinium/vilanterol)
- ◯ None of these

37. Are you taking any of these bronchodilator medicines? (check all that apply)

- ◯ Perforomist (formoterol)
- ◯ Striverdi Respimat (olodeterol)
- ◯ Spiriva (Tiotropium) Respimat or Handihaler)
- ◯ Anoro (umeclidinium/vilanterol)
- ◯ Stiolto Respimat (tiotropium/olodeterol)
- ◯ Incruse Ellipta (umeclidinium)
- ◯ Tudorza Pressair (aclidinium)
- ◯ None of these- if last three answered NONE OF THESE = alert not eligible review

38. What do you call the medicine? Enter patient's exact words._____– enter the one chosen from above?

39. Are you taking any of these pills? (check all that apply)

◯ Singular

◯ Zileuton

40. Are you taking any of these other medicines? (check all that apply)

◯ Omalizumab or Xolair, a shot or IV infusion at the doctor's office

◯ Mepolizumab or Nucala, ashot or infusion at the doctor's office

◯ Reslizumab or Cinquil™, an IV infusion at the doctor's office or infusion center

◯ Dupilumab or Dupixent (currently approved only for eczema), by injection check these

◯ Benralizumab

◯ On biologic but not clear about name

Secure or unsecure email link

41. When you click on the email link to your survey, you can 1) enter a login and password, or 2) go directly to the survey. If you choose to go directly to the survey, the email is not secure. If this email is read by someone else that person could find out that you have asthma. None of your previous answers to any questions would be visible. Do you want to login each time you take the survey or go directly to the survey?

◯ Enter login and password each time (1) ◯ Go directly to survey (0)

Baseline

Asthma Control Test – can be coordinator or self-administered

1. In the **past 4 weeks**, how much of the time did your asthma keep you from getting as much done at work, school, or at home?

◯ All of the time (1)
◯ Most of the time (2)
◯ Some of the time (3)
◯ A little of the time (4)
◯ None of the time (5)

2. During the **past 4 weeks**, how often have you had shortness of breath?

◯ More than once a day (1)
◯ Once a day (2)
◯ 3 to 6 times a week (3)
◯ Once or twice a week (4)
◯ Not at all (5)

3. During the **past 4 weeks**, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

◯ 4 or more nights a week (1)
◯ 2 to 3 nights a week (2)
◯ Once a week (3)
◯ Once or twice (4)
◯ Not at all (5)

4. During the **past 4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

◯ 3 or more times per day (1)
◯ 1 or 2 times per day (2)
◯ 2 or 3 times per week (3)
◯ Once a week or less (4)
◯ Not at all (5)

5. How would you rate your asthma control during the **past 4 weeks**?

◯ Not Controlled at All (1)
◯ Poorly Controlled (2)
◯ Somewhat Controlled (3)
◯ Well Controlled (4)
◯ Completely Controlled (5)

PHQ-2

6. Over the **past 2 weeks**, how often have you been bothered by: little interest or pleasure in doing things?

◯ Not at all (1)
◯ Several days (2)
◯ More than half the days (3)
◯ Nearly every day (4)

7. Over the **past 2 weeks**, how often have you been bothered by: feeling down, depressed, or hopeless?

◯ Not at all (1)
◯ Several days (2)
◯ More than half the days (3)
◯ Nearly every day (4)

If any answers score 3 or 4 go to 8 otherwise skip to 14

PHQ-8

8. Over the **past 2 weeks**, how often have you been bothered by: trouble falling or staying asleep or sleeping too much?

◯ Not at all (1)
◯ Several days (2)
◯ More than half the days (3)
◯ Nearly every day (4)

9. Over the **past 2 weeks**, how often have you been bothered by: feeling tired or having little energy?

◯ Not at all (1)
◯ Several days (2)
◯ More than half the days (3)
◯ Nearly every day (4)

10. Over the **past 2 weeks**, how often have you been bothered by: poor appetite or overeating?

◯ Not at all (1)
◯ Several days (2)
◯ More than half the days (3)
◯ Nearly every day (4)

11. Over the **past 2 weeks**, how often have you been bothered by: feeling bad about yourself-or that you are a failure or have let yourself or your family down?

◯ Not at all (1)
◯ Several days (2)
◯ More than half the days (3)
◯ Nearly every day (4)

12. Over the **past 2 weeks**, how often have you been bothered by: trouble concentrating on things, such as reading the newspaper or watching television?

◯ Not at all (1)
◯ Several days (2)
◯ More than half the days (3)
◯ Nearly every day (4)

13. Over the **past 2 weeks**, how often have you been bothered by: moving or speaking so slowly that other people could have noticed. Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual?

◯ Not at all (1)
◯ Several days (2)
◯ More than half the days (3)
◯ Nearly every day (4)

Mini-Asthma Quality of Life Questionnaire (Adult)

Please complete all questions by circling the number that best describes how you have been during the last 2 weeks *as a result of your asthma*.

In general, how much of the time during the last 2 weeks did you:

14. Feel SHORT OF BREATH as a result of your asthma?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

15. Feel bothered by or have to avoid DUST in the environment?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

16. Feel FRUSTRATED as a result of your asthma?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

17. Feel bothered by COUGHING?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

18. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

19. Experience a feeling of CHEST TIGHTNESS or CHEST HEAVINESS?

All of the time (1)

Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

20. Feel bothered by or have to avoid CIGARETTE SMOKE in the environment?
    All of the time (1)
    Most of the Time (2)
    A Good Bit of the Time (3)
    Some of the Time (4)
    A Little of the Time (5)
    Hardly Any of the Time (6)
    None of the Time (7)

21. Have DIFFICULTY GETTING A GOODNIGHT'S SLEEP as a result of your asthma?

    All of the time (1)
    Most of the Time (2)
    A Good Bit of the Time (3)
    Some of the Time (4)
    A Little of the Time (5)
    Hardly Any of the Time (6)
    None of the Time (7)

22. Feel CONCERNED ABOUT HAVING ASTHMA?

    All of the time (1)
    Most of the Time (2)
    A Good Bit of the Time (3)
    Some of the Time (4)
    A Little of the Time (5)
    Hardly Any of the Time (6)
    None of the Time (7)

23. Experience a WHEEZE in your chest?

    All of the time (1)
    Most of the Time (2)
    A Good Bit of the Time (3)
    Some of the Time (4)
    A Little of the Time (5)
    Hardly Any of the Time (6)
    None of the Time (7)

24. Feel bothered by or have to avoid going outside because of WEATHER OR AIR POLLUTION?

    All of the time (1)
    Most of the Time (2)
    A Good Bit of the Time (3)

Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

How limited have you been during the last 2 weeks doing these activities as a result of your asthma?

25. STRENUOUS ACTIVITIES (such as hurrying, exercising, running upstairs, sports)

Totally Limited (1)
Extremely Limited (2)
Very Limited (3)
Moderate Limitation (4)
Some Limitation (5)
A Little Limitation (6)
Not at all Limited (7)

26. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)

Totally Limited (1)
Extremely Limited (2)
Very Limited (3)
Moderate Limitation (4)
Some Limitation (5)
A Little Limitation (6)
Not at all Limited (7)

27. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)

Totally Limited (1)
Extremely Limited (2)
Very Limited (3)
Moderate Limitation (4)
Some Limitation (5)
A Little Limitation (6)
Not at all Limited (7)

28. WORK-RELATED ACTIVITIES (tasks you have to do at work)*

Totally Limited (1)
Extremely Limited (2)
Very Limited (3)
Moderate Limitation (4)
Some Limitation (5)
A Little Limitation (6)
Not at all Limited (7)

*If you are not employed or self-employed, these should be tasks you have to do most days.

29. In the last 3 months, how many days did you miss work or school **due to your asthma**? *Numeric – max value 90*

30. In the last 3 months did you have days you were unable to carry out your usual activities **due to your asthma**?

    Yes (1) *Go to 32*
    No (0) *Skip to 33*

31. How many days you were unable to carry out your usual activities **due to your asthma**? *Numeric – max value 90*

MARS-5

This question is about your daily maintenance medicine, the inhaler that you call "(insert response from Intake, question[insert number]).”

32. I forget to take my (*insert response from Intake, question [insert number]*).

    ◯ Always (1)
    ◯ Often (2)
    ◯ Sometimes (3)
    ◯ Rarely (4)
    ◯ Never (5)

33. I change the dosage of my (*insert response from Intake, question [insert number]*).

    ◯ Always (1)
    ◯ Often (2)
    ◯ Sometimes (3)
    ◯ Rarely (4)
    ◯ Never (5)

34. I stop taking my (*insert response from Intake, question [insert number]*) for a while.

    ◯ Always (1)
    ◯ Often (2)
    ◯ Sometimes (3)
    ◯ Rarely (4)
    ◯ Never (5)

35. I decide to skip my (*insert response from Intake, question [insert number]*).

    ◯ Always (1)
    ◯ Often (2)
    ◯ Sometimes (3)
    ◯ Rarely (4)
    ◯ Never (5)

36. I use my (*insert response from Intake, question [inset number]*) less than is prescribed

    ◯ Always (1)
    ◯ Often (2)
    ◯ Sometimes (3)

◯ Rarely (4)
◯ Never (5)

Monthly

Asthma Exacerbation Questionnaire

Note: a "yes"/1 to any of questions 1-4 should trigger a notification for a follow-up call to confirm exacerbation.

1. Since the last time you answered a survey on [pre-populated date __/__/_____], have you taken steroids pills or shots, like prednisone to treat an asthma attack?

   ◯ Yes (1)
   ◯ No (0)

2. Since the last time you answered a survey on [pre-populated date __/__/_____], have you visited the urgent care or the emergency room **for your asthma**?

   ◯ Yes (1)
   ◯ No (0)

3. Since the last time you answered a survey on [pre-populated date __/__/_____], have you stayed a day or longer in the hospital **for your asthma**?

   ◯ Yes (1)
   ◯ No (0)

Infection and Antibiotic Questions

4. Since the last survey, did you have an infection that required you to go to the doctor?
   ◯ Yes (1)
   ◯ No (0)

(IF YES)

Check all that apply to you:

◯ You were prescribed antibiotics

◯ The infection cleared up after the first course of antibiotics

◯ A doctor told you the infection was antibiotic resistant

◯ You had to use more than one antibiotic because the first one didn't work

◯ Others? _____

Where was the infection? – check all that apply

◯ Viral infection respiratory (upper or lower)

◯ Skin

◯ Sinus

◯ Lung

◯ Urinary tract

◯ Joint

◯ Other: _____

Please indicate what your "other" infection was: text here

Days Lost from Work or School

5. Since the last time you answered a survey on [pre-populated date __/__/_____], did you miss work or school **due to your asthma**?

   ◯ Yes (1) – *Go to 8*
   ◯ No (0) – *Skip to 9*
   ◯ Don't go to work or school (2) – *Skip to 9*

6. How many days did you miss work or school **due to your asthma**? *Numeric – max value 90* Enter number of times:_____.

7. Since the last time you answered a survey on [pre-populated date __/__/_____], did you have days you were unable to carry out your usual activities **due to your asthma**?

   ◯ Yes (1) *Go to 10*
   ◯ No (0) *Skip to 11*

8. How many days you were unable to carry out your usual activities **due to your asthma**? *Numeric – max value 90 does this need to change given the qom approach?* Enter number of times:_____.

Asthma Control Test

9. In the **past 4 weeks**, how much of the time did your asthma keep you from getting as much done at work, school, or at home?

   ◯ All of the time (1)
   ◯ Most of the time (2)
   ◯ Some of the time (3)
   ◯ A little of the time (4)
   ◯ None of the time (5)

10. During the **past 4 weeks**, how often have you had shortness of breath?

    ◯ More than once a day (1)
    ◯ Once a day (2)
    ◯ 3 to 6 times a week (3)
    ◯ Once or twice a week (4)
    ◯ Not at all (5)

11. During the **past 4 weeks**, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

    ◯ 4 or more nights a week (1)

◯ 2 to 3 nights a week (2)
◯ Once a week (3)
◯ Once or twice (4)
◯ Not at all (5)

12. During the **past 4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

◯ 3 or more times per day (1)
◯ 1 or 2 times per day (2)
◯ 2 or 3 times per week (3)
◯ Once a week or less (4)
◯ Not at all (5)

13. How would you rate your asthma control during the **past 4 weeks**?

◯ Not Controlled at All (1)
◯ Poorly Controlled (2)
◯ Somewhat Controlled (3)
◯ Well Controlled (4)
◯ Completely Controlled (5)

Mini-Asthma Quality of Life Questionnaire - Adult

Please complete all questions by circling the number that best describes how you have been during the last 2 weeks *as a result of your asthma*. (Note this will be adjusted when the REDCap option choices are clear)

In general, how much of the time during the last 2 weeks did you:

14. Feel SHORT OF BREATH as a result of your asthma?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

15. Feel bothered by or have to avoid DUST in the environment?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

16. Feel FRUSTRATED as a result of your asthma?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

17. Feel bothered by COUGHING?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

18. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

19. Experience a feeling of CHEST TIGHTNESS or CHEST HEAVINESS?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

20. Feel bothered by or have to avoid CIGARETTE SMOKE in the environment?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

21. Have DIFFICULTY GETTING A GOODNIGHT'S SLEEP as a result of your asthma?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

22. Feel CONCERNED ABOUT HAVING ASTHMA?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

23. Experience a WHEEZE in your chest?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

24. Feel bothered by or have to avoid going outside because of WEATHER OR AIR POLLUTION?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

How limited have you been during the last 2 weeks doing these activities as a result of your asthma?

25. STRENUOUS ACTIVITIES (such as hurrying, exercising, running upstairs, sports)

Totally Limited (1)
Extremely Limited (2)
Very Limited (3)
Moderate Limitation (4)
Some Limitation (5)
A Little Limitation (6)
Not at all Limited (7)

26. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)

Totally Limited (1)
Extremely Limited (2)
Very Limited (3)
Moderate Limitation (4)
Some Limitation (5)
A Little Limitation (6)
Not at all Limited (7)

27. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)

Totally Limited (1)
Extremely Limited (2)
Very Limited (3)
Moderate Limitation (4)
Some Limitation (5)
A Little Limitation (6)
Not at all Limited (7)

28. WORK-RELATED ACTIVITIES (tasks you have to do at work)

Totally Limited (1)
Extremely Limited (2)
Very Limited (3)
Moderate Limitation (4)
Some Limitation (5)
A Little Limitation (6)
Not at all Limited (7)

*If you are not employed or self-employed, these should be tasks you have to do most days.

Medication Adherence
[ICS Adherence - These questions are for the two groups using ICS as rescue]

29. When you used your rescue inhaler / puffer/ nebulizer did you use the inhaler that also contained ICS or the extra inhaler that was an ICS:
    ◯ Most or all of the time (1)
    ◯ More than half the time (2)
    ◯ About half (3)
    ◯ Less than half (4)
    ◯ Not very often or not at all (5)

Change in Rescue Medication

30. Did you change your rescue medication since you last answered this questionnaire on **<<insert date>>**?
    Yes – call participant (1)
    No – done (0)
    Not sure – call participant (2)

[This question is for the two groups on AZ – note one group will get both of these groups of questions]

30. Since the last time you answered a survey on [pre-populated date __/__/_____] have you taken your azithromycin:

◯ Took it three times a week all or most of the time (1)
◯ Missed up to one dose, or sometimes even two doses in a week but usually took that dose before my next dose (2)
◯ Totally missed one and sometimes even two doses a week (3)
◯ Took less than half of the doses I was asked to take (4)
◯ Didn't take my azithromycin at all (5)

Change in Contact Information

31. Do you or will you have in the next two months a new home address?

◯ Yes (1)
◯ No (0)

32. Do you or will you have (in the next two months) a new phone number?

◯ Yes (1)
◯ No (0)

Exit

Study ID:
Last survey date:
Today's date:_____

Asthma Exacerbation Questionnaire
Note: a "yes"/1 to any of questions 1-4 should trigger a notification for a follow-up call to confirm exacerbation.

1. Since the last time you answered a survey on [pre-populated date __/__/_____], have you taken steroids pills or shots, like prednisone to treat an asthma attack?

◯ Yes (1)
◯ No (0)

2. Since the last time you answered a survey on [pre-populated date __/__/_____], have you visited the urgent care or the emergency room **for your asthma**?

◯ Yes (1)
◯ No (0)

3. Since the last time you answered a survey on [pre-populated date __/__/_____], have you stayed a day or longer in the hospital **for your asthma**?

◯ Yes (1)
◯ No (0)

Infection and Antibiotic Questions

4. Since the last survey, did you have an infection that required you to go to the doctor?
   - ◯ Yes (1)
   - ◯ No (0)

(IF YES)

Check all that apply to you:

- ◯ You were prescribed antibiotics
- ◯ The infection cleared up after the first course of antibiotics
- ◯ A doctor told you the infection was antibiotic resistant
- ◯ You had to use more than one antibiotic because the first one didn't work
- ◯ Others? _____

Where was the infection? – check all that apply

- ◯ Viral infection respiratory (upper or lower)
- ◯ Skin
- ◯ Sinus
- ◯ Lung
- ◯ Urinary tract
- ◯ Joint
- ◯ Other: _____

Please indicate what your "other" infection was: text here

Days Lost from Work or School

5. Since the last time you answered a survey on [pre-populated date __/__/_____], did you miss work or school **due to your asthma**?

   - ◯ Yes (1) – *Go to 8*
   - ◯ No (0) – *Skip to 9*
   - ◯ Don't go to work or school (2) – *Skip to 9*

6. How many days did you miss work or school **due to your asthma**? *Numeric – max value 90* Enter number of times:_____.

7. Since the last time you answered a survey on [pre-populated date __/__/_____], did you have days you were unable to carry out your usual activities **due to your asthma**?

   - ◯ Yes (1) *Go to 10*
   - ◯ No (0) *Skip to 11*

8. How many days you were unable to carry out your usual activities **due to your asthma**? *Numeric – max value 90 does this need to change given the qom approach?* Enter number of times:_____.

Asthma Control Test

9. In the **past 4 weeks**, how much of the time did your asthma keep you from getting as much done at work, school, or at home?

    ◯ All of the time (1)
    ◯ Most of the time (2)
    ◯ Some of the time (3)
    ◯ A little of the time (4)
    ◯ None of the time (5)

10. During the **past 4 weeks**, how often have you had shortness of breath?

    ◯ More than once a day (1)
    ◯ Once a day (2)
    ◯ 3 to 6 times a week (3)
    ◯ Once or twice a week (4)
    ◯ Not at all (5)

11. During the **past 4 weeks**, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

    ◯ 4 or more nights a week (1)
    ◯ 2 to 3 nights a week (2)
    ◯ Once a week (3)
    ◯ Once or twice (4)
    ◯ Not at all (5)

12. During the **past 4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

    ◯ 3 or more times per day (1)
    ◯ 1 or 2 times per day (2)
    ◯ 2 or 3 times per week (3)
    ◯ Once a week or less (4)
    ◯ Not at all (5)

13. How would you rate your asthma control during the **past 4 weeks**?

    ◯ Not Controlled at All (1)
    ◯ Poorly Controlled (2)
    ◯ Somewhat Controlled (3)
    ◯ Well Controlled (4)
    ◯ Completely Controlled (5)

Mini-Asthma Quality of Life Questionnaire - Adult

Please complete all questions by circling the number that best describes how you have been during the last 2 weeks *as a result of your asthma*. (Note this will be adjusted when the REDCap option choices are clear)

In general, how much of the time during the last 2 weeks did you:

14. Feel SHORT OF BREATH as a result of your asthma?

    All of the time (1)
    Most of the Time (2)
    A Good Bit of the Time (3)
    Some of the Time (4)
    A Little of the Time (5)
    Hardly Any of the Time (6)
    None of the Time (7)

15. Feel bothered by or have to avoid DUST in the environment?

    All of the time (1)
    Most of the Time (2)
    A Good Bit of the Time (3)
    Some of the Time (4)
    A Little of the Time (5)
    Hardly Any of the Time (6)
    None of the Time (7)

16. Feel FRUSTRATED as a result of your asthma?

    All of the time (1)
    Most of the Time (2)
    A Good Bit of the Time (3)
    Some of the Time (4)
    A Little of the Time (5)
    Hardly Any of the Time (6)
    None of the Time (7)

17. Feel bothered by COUGHING?

    All of the time (1)
    Most of the Time (2)
    A Good Bit of the Time (3)
    Some of the Time (4)
    A Little of the Time (5)
    Hardly Any of the Time (6)
    None of the Time (7)

18. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?

    All of the time (1)
    Most of the Time (2)
    A Good Bit of the Time (3)

Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

19. Experience a feeling of CHEST TIGHTNESS or CHEST HEAVINESS?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

20. Feel bothered by or have to avoid CIGARETTE SMOKE in the environment?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

21. Have DIFFICULTY GETTING A GOODNIGHT'S SLEEP as a result of your asthma?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

22. Feel CONCERNED ABOUT HAVING ASTHMA?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

23. Experience a WHEEZE in your chest?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)

A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

24. Feel bothered by or have to avoid going outside because of WEATHER OR AIR POLLUTION?

All of the time (1)
Most of the Time (2)
A Good Bit of the Time (3)
Some of the Time (4)
A Little of the Time (5)
Hardly Any of the Time (6)
None of the Time (7)

How limited have you been during the last 2 weeks doing these activities as a result of your asthma?

25. STRENUOUS ACTIVITIES (such as hurrying, exercising, running upstairs, sports)

Totally Limited (1)
Extremely Limited (2)
Very Limited (3)
Moderate Limitation (4)
Some Limitation (5)
A Little Limitation (6)
Not at all Limited (7)

26. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)

Totally Limited (1)
Extremely Limited (2)
Very Limited (3)
Moderate Limitation (4)
Some Limitation (5)
A Little Limitation (6)
Not at all Limited (7)

27. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)

Totally Limited (1)
Extremely Limited (2)
Very Limited (3)
Moderate Limitation (4)
Some Limitation (5)
A Little Limitation (6)
Not at all Limited (7)

28. WORK-RELATED ACTIVITIES (tasks you have to do at work)

Totally Limited (1)
Extremely Limited (2)
Very Limited (3)

Moderate Limitation (4)
Some Limitation (5)
A Little Limitation (6)
Not at all Limited (7)

*If you are not employed or self-employed, these should be tasks you have to do most days.

Medication Adherence
[[ICS Adherence - These questions are for the two groups using ICS as rescue

29. Have you changed your rescue inhaler that included a steroid since << enter date of last survey>>?
    Yes
    No
    Don't remember

30. When you used your rescue inhaler / puffer/ nebulizer did you use the inhaler that also contained ICS or the extra inhaler that was an ICS:
    ◯ Most or all of the time (1)
    ◯ More than half the time (2)
    ◯ About half (3)
    ◯ Less than half (4)
    ◯ Not very often or not at all (5)

[[This question is for the two groups on AZ – note one group will get both of these groups of questions

29. Since the last time you answered a survey on [pre-populated date __/__/_____] have you taken your azithromycin:

    ◯ Took it three times a week all or most of the time (1)
    ◯ Missed up to one dose, or sometimes even two doses in a week but usually took that dose before my next dose (2)
    ◯ Totally missed one and sometimes even two doses a week (3)
    ◯ Took less than half of the doses I was asked to take (4)
    ◯ Didn't take my azithromycin at all (5)

For the ICS/AZ arms -

29. Have you had problems using your new medication?

    Yes
    No

If Yes

Tell us about your problems:
Text box

30. Do you want to continue on your new medication?

Yes
No
Will talk with my doctor

If yes
Thank you for being a part of this study. We will try and contract you doctor so you can keep using you new medication.

For the others
Thank you for being a part of this study. We hope you find good treatments for your asthma.

For the ASM only arm:
29. Were you able to use the asthma reporting system?
Yes
No
Didn't try

If yes-

30. Did you have problems with the system?
Yes
No

If yes
Please tell us about your problems:

Text box

If No or after the question above

31. If you could keep using the reporting system would you want to use it?
Yes
No
If it was improved

Thank you for being a part of this study. We hope you find good treatments for your asthma.

Domains	Interview Questions	Notes
REACH – Absolute number, proportion & representativeness of individuals who participate – Who? How many possible participants? Possible reasons for not participating (practice & patient)? External factors?		
Practice level/Care Team Intervention Patient/caregiver level	Now that you have implemented the study for a few months we want to understand the type of patient that has been most likely to participate in the study. How did you decide who to select from your patient panel? Probes: • Given the past couple of weeks implementing the study, who do you think will most experience a health benefit from the study and why? • How were patients approached for study participation (in-person during planned visit, on the phone, via email, etc.)? • What encouraged or motivated patients to participate? What types of strategies influenced or affected patient recruitment? • What do you think will be the main motivation/value for participating in this study? • What other supports would be necessary to best integrate the study into the workflow systems? We would like to better understand the facilitators and barriers to participating in the study. Probes: • Can you tell me a bit about your experience with asthma? • Now that you have heard about the study do you think it would be helpful to you? Why? • What are some reasons or barriers you would not continue to participate in the study? Is there anything that would make it easier for you to continue to participate in the study?	
EFFECTIVENESS – Impact on important outcomes including potential negative effects, quality of life, and economic outcomes. Heterogeneity of effects and reasons for success		
N/A		
ADOPTION – The absolute number, proportion, and representativeness of a) settings; and b) intervention agents (people who deliver the program) who are willing to initiate a program. Reasons for adoption or non-adoption. Setting level factors that may affect adoption		
Practice Level/Care Team Intervention	How was it to integrate the study into your workflow processes? Probes: Barriers? Cost, time, resources, cultural, biases? Facilitators? People, resources, structures • What immediate concerns (from a patient and practice perspective) do you have participating in this study? •	
	•	

Patient – Full Feasibility

As part of the iTREAT study I would like to talk with you for about 20 minutes. This conversation will be recorded so we can review your comments at a later time. There are no right or wrong answers to the questions. We are interested in your thoughts about your experience in the study and your experiences with asthma. Do you agree to the interview and my recording of the interview? Yes – thank you – you will be paid $25 for your time. No – We understand you do not wish to participate in the interview; however, we thank you for your continued participation in the full study.

1. **Can you tell me a bit about your experience with asthma?**

a. How did your asthma begin?

b. How much does it interfere with your life?

For teenagers:

- *Are there activities you engage in that you wish you could but now you cannot?*
  Are there activities that you engage in that you know you shouldn't but sometimes you do?

c. Do feel like the medications you were on before starting the study were generally working for you?

2. **What helped you decide to join the study?**

a. Did your doctor talk with you about the study?

b. Have you been involved in other studies

c. What are you hoping to get out of being in the study

3. **Have you had issues or problems with new medications you were asked to take for the study?**

(For Inhaled Corticosteroids (ICS) SMART or PARTICS (Patient Activated Reliever Trigger Inhaled Corticosteroids) group)

a. Was it hard to decide on which of the new inhaler treatments to use?

b. Are you concerned with increasing the usage of ICS substantially? If yes, why and have you been able to do so as asked?

c. Did you have any problems at the pharmacy or with your insurance in getting the new inhaler treatment?

d. Have you had problems trying to follow the new inhaler treatments?

For teenagers:

So you sometimes not follow what you doctor has asked? When are these times(For azithromycin groups)

e. Do you or did you have concerns with using the azithromycin for a long time? Have you been able to take it as asked?
f. Have you had any problems at your pharmacy or with your insurance in getting the medication?

4. **Is there anything else you'd like to share about participating in the study that we may have missed?**

Patient – Asthma Symptom Monitoring (ASM) only

1. **Can you tell me a bit about your experience with asthma?**

a. How did your Asthma begin?
b. How much does it interfere with your life?
c. How well do you think your current medications are working for you?

2. **What helped you decide to try out the ASM monitoring system?**

a. Did you doctor talk with you about the system?
b. What are you hoping to get out of using the system?

3. **How has the ASM reporting system worked for you so far?**

a. Do you think using this system would help you work with your doctor to keep you asthma better controlled?
b. Have you had problems with the system or notice any areas for improvement? Did you ask for someone from your practice to call you through the system? If so- did they?If you were allowed to continue to use the system would you want to?

4. **Is there anything else you'd like to share about using the monitoring system that we may have missed?**

Prescribing Clinicians

1. **What has your experience been like in trying to get people their prescriptions? Has it been difficult to get ahold of people after they are consented?**

   Do you feel like you are able to answer any questions patients may have?

Have you converted people to Single Maintenance And Reliever Therapy (SMART)? If so, how has that gone?

Have people had concerns about azithromycin? Do you feel comfortable answering these concerns?

2. **How has deciding upon the Inhaled Corticosteroids (ICS) options SMART or PARTICS (Patient Activated Reliever Trigger Inhaled Corticosteroids) gone?**

   Do you feel like you have the information you need to help people with this decision? Has it been difficult to figure out which drug to use based on insurance coverage? Do you generally try and use one of the two options if possible?

3. **Have you had issues from pharmacies or insurance companies for any of the treatments?**

   Were you able to resolve the issues or did you have to change therapy?

   Is there anything you think we can do differently at the full study level to help with these issues?

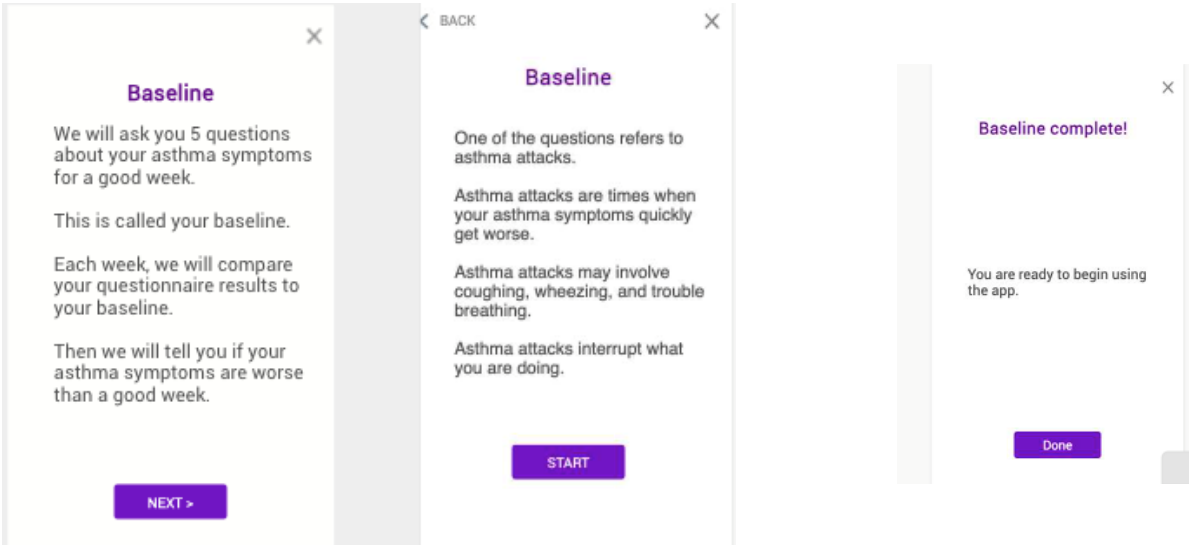
   Would a central study pharmacist help you with any pharmacy or insurance issues?

4. **Anything else you'd like to share about participating in the study that we may have missed?**

Appendix 4 – Asthma Symptom Monitoring App

Text before baseline

Notification text: Complete asthma baseline questionnaire from your doctor.



Questionnaire and Other App Text

During the past week, how often did you have an asthma attack? a. Not at all (0 point) b. Once or twice (5) c. 3 to 6 times (10) d. Once a day (15) e. More than once a day (20)
During the past week, how often have you been awakened at night because of your asthma symptoms? Indent82671-9 a. Never (0 point) b. Hardly ever (5) c. Several times (10) d. Many times but not every night (15) e. Every night (20)
During the past week, how much did your asthma interfere with your normal activities? Indent82669-3 a. Not at all (0) b. A little (5) c. A moderate amount (10)

d. A lot(15)
During the past week, how often have you used a rescue inhaler that gives quick relief from asthma symptoms? Indent82672-7 a. Never (0) b. Once (5) c. 2 or more times but not daily (10) d. Daily (15) e. Several times a day, most days (20)
During the past week, how often did you have shortness of breath? Indent82670-1 a. Not at all (0) b. Once or twice (5) c. 3 to 6 times (10) d. Once a day (15) e. More than once a day(20)

Note, that the questionnaire for the baseline is the same except it asks “In a good week…” instead of “During the past week…”

Text used directly by app:

```
enums: {
    NoSymptoms: 'No Symptoms',
    BetterThanBaseline: 'Better Than Baseline',
    SameAsBaseline: 'Same As Baseline',
    SlightlyWorseThanBaseline: 'Slightly Worse Than Baseline',
    SomewhatWorseThanBaseline: 'Somewhat Worse Than Baseline',
    WorseThanBaseline: 'Worse Than Baseline',
    BetterThanLastWeek: 'Better Than Last Week',
    SameAsLastWeek: 'Same As Last Week',
    SlightlyWorseThanLastWeek: 'Slightly Worse Than Last Week',
    SomewhatWorseThanLastWeek: 'Somewhat Worse Than Last Week',
    WorseThanLastWeek: 'Worse Than Last Week',
    Severe: 'Severe',
}


resultsScreen: {
```

```
    title: 'Questionnaire Results',
    yourSymptoms: 'Your asthma symptoms are:',
    details: 'Details',
    wouldYouLike: 'Would you like to request a call from a nurse to discuss your
asthma?',
    callMe: 'Call me',
    noThanks: 'No, thanks',
    smallChange: 'This small change in your asthma control may not be a major
concern.',
    reminder:
      "As a reminder, this app doesn't know everything about your asthma. If you
have any further concerns, you can contact your healthcare provider or visit the
emergency room.",
    thingsYouCanDo: 'Things you can do next:',
    viewData: 'View my asthma data',
    addData: 'Add/edit weekly note, triggers, or peak flows'
  },



callRequestScreen: {
    beforeWeRequest: 'Before we request the call, please check all that apply
below.',
    choseNotRequest: 'You chose not to request a call',
    thisWillHelpUs: '(This will help us better assist you.)',
    itsYourResponsibility:
      'Important: Your provider will not be asked to review your questionnaire. ' +
      'It is your responsibility to get help if you need it.',
    toHelpUs: 'To help us keep track of your asthma, check all that apply below.',
    checkAllThatApply: 'Check ALL that apply',
    beenToEd: 'I went to an emergency room or urgent care this week',
    missedDoses: 'I missed some doses of my asthma medications this week',
    confusedAboutMeds: 'I am confused about the difference between my rescue
inhaler and my controller inhaler',
    alreadyRequestedCall: 'I already contacted my provider and am waiting for a
call back',
    none: 'None',
    next: 'Next'
  },
  confirmNumberScreen: {
    pleaseEnter: 'Please enter the phone number',
    isThisTheBest: 'Is this the best number to reach you in the next 24 hours?',
    callMe: 'Yes, call me',
    changeNumber: 'Change number'
  },



expectCallScreen: {
    expectCall: 'Expect a call within 24 hours.',
```

```
    ifYouNeedHelp:
      'If you need help sooner, contact your healthcare provider directly, call
911, or visit your local emergency room.',
    thingsYouCanDo: 'Things you can do while you wait for the nurse to call you:',
    thingsYouCanDoDecline: 'Things you can do next:',
    viewData: 'View my asthma data',
    addWeeklyData: 'Add/edit weekly note, triggers, or peak flows'
  },
```

```
symptomCheck: {
    question: 'In the past week, did you have any of the following?',
    symptom1: '- Asthma attacks',
    symptom2: '- Awakened at night',
    symptom3: '- Asthma interfered with normal activities',
    symptom4: '- Used your rescue inhaler',
    symptom5: '- Shortness of breath',
    yes: 'YES\n\nI had one or more of these',
    no: "NO\n\nI didn't have any of these",
    areYouReady: 'Are you sure?',
    notReady: 'No, go back',
    submit: 'Yes, proceed'
```

Notification logic

Definitions

- Callback
  - OFFER_CALLBACK
  - NO_OFFER_CALLBACK
- Symptom_summary: color
  - NO_SYMPTOMS: blue
  - BETTER_THAN_BASELINE: blue
  - SAME_AS_BASELINE: blue
  - SLIGHTLY_WORSE_THAN_BASELINE: orange
  - SOMEWHAT_WORSE_THAN_BASELINE: yellow
  - WORSE_THAN_BASELINE: red
  -
  - BETTER_THAN_LAST_WEEK: blue
  - SAME_AS_LAST_WEEK: blue
  - SLIGHTLY_WORSE_THAN_LAST_WEEK: orange
  - SOMEWHAT_WORSE_THAN_LAST_WEEK: yellow
  - WORSE_THAN_LAST_WEEK: red

    - SEVERE: red
- Scores
    - TWS = this week score
    - PWS = previous week score
    - BL = baseline score
- Directionality
    - Higher means more symptoms (0 = no symptoms, 95= extreme symptoms). Multiply the score for each item by 5.
- # comments start with "#"

Branching Logic

If TWS is most severe on 1 or more items

{

Callback(OFFER_CALLBACK)

Symptom_summary (SEVERE)

}

else if TWS is perfect (no symptoms)

{

Callback(NO_OFFER_CALLBACK)

Symptom_summary (NO_SYMPTOMS)

}

else if PWS == NULL

{

case TWS

{

Higher than BL by 30 or more:

Callback(OFFER_CALLBACK);

Symptom_summary(WORSE_THAN_BASELINE)

Higher than BL by 15, 20, or 25:

Callback(OFFER_CALLBACK);

Symptom_summary(SOMEWHAT_WORSE_THAN_BASELINE)

Higher than BL by 5 or 10:

Callback(NO_OFFER_CALLBACK);

Symptom_summary(SLIGHTLY_WORSE_THAN_BASELINE)

Same as BL:

Callback(NO_OFFER_CALLBACK);

```
                    Symptom_summary(SAME_AS_BASELINE)
            Lower than BL:
                    Callback(NO_OFFER_CALLBACK);
                    Symptom_summary(BETTER_THAN_BASELINE)
        }
}
else if PWS == BL
{
        case TWS
        {
            Higher than PWS by 30 or more:
                    Callback(OFFER_CALLBACK)
                    Symptom_summary(WORSE_THAN_LAST_WEEK)
            Higher than PWS by 15, 20 or 25:
                    Callback(OFFER_CALLBACK);
                    Symptom_summary(SOMEWHAT_WORSE_THAN_LAST_WEEK)
            Higher than PWS by 5 or 10:
                    Callback(NO_OFFER_CALLBACK);
                    Symptom_summary(SLIGHTLY_WORSE_THAN_LAST_WEEK)
            Same as PWS:
                    Callback(NO_OFFER_CALLBACK);
                    Symptom_summary(SAME_AS_LAST_WEEK)
            Lower than PWS:
                    Callback(NO_OFFER_CALLBACK);
                    Symptom_summary(BETTER_THAN_LAST_WEEK)
        }
}

else    # PWS != BL && PWS !=NULL
{
        if  (TWS-BL >=30) || (TWS-PWS >=30)
        {
            Callback(OFFER_CALLBACK);
```

If BL < PWS #display page for whichever difference is biggest

Symptom_summary(WORSE_THAN_BASELINE)

Else

Symptom_summary(WORSE_THAN_LAST_WEEK)

}

else if (TWS-BL == [15, 20, or 25]) || (TWS-PWS == [15, 20, or 25])

Callback(OFFER_CALLBACK);

If BL < PWS #display page for whichever difference is biggest

Symptom_summary(SOMEWHAT_WORSE_THAN_BASELINE)

Else

Symptom_summary(SOMEWHAT_WORSE_THAN_LAST_WEEK)

else if (TWS-BL == [5 or 10]) || (TWS-PWS ==[5 or 10])

Callback(NO_OFFER_CALLBACK);

If BL < PWS #display page for whichever difference is biggest

Symptom_summary(SLIGHTLY_WORSE_THAN_BASELINE)

Else

Symptom_summary(SLIGHTLY_WORSE_THAN_LAST_WEEK)

else if (TWS == BL) || (TWS == PWS)

Callback(NO_OFFER_CALLBACK);

If BL = **TWS** #display page for whichever is correct

Symptom_summary(SAME_AS_BASELINE)

Else

Symptom_summary(SAME_AS_LAST_WEEK)

else if (TWS<BL) || (TWS<PWS) #will always be better than both if it gets here

Callback(NO_OFFER_CALLBACK);

If BL < PWS #display page for whichever difference is smallest

Symptom_summary(BETTER_THAN_BASELINE)

Else

Symptom_summary(BETTER_THAN_LAST_WEEK)

}

}

Appendix 5 – iTREAT Phone Recruitment Script

This is **[insert name]**_____ from **[name of practice]**_____. Can I speak to _____?

[When the person answers, tell the patient]: This is _____ calling from Dr. _____'s office. Dr. _____ invites you to be part of a national study that tests different ways to deal with asthma symptoms in order to reduce asthma attacks, emergency room or hospital visits, and missed work or school.

We're calling patients like you who may be eligible to participate in this **voluntary** study. Would you like to hear more?" **[If person responds "yes", then continue. If person responds "no", please thank them for their time and end call].**

Our records indicate that you have had an asthma attack in the past year or that your asthma may not be fully controlled. Over the 3 months of this study you will have one study contact to enroll. This can be done virtually or you can come into the research office and will take about one hour. We will review the consent form, and if you agree to participate be randomly assigned (like the flip of a coin) to one of four study groups. Every participant will be given access to online asthma symptom tracking tools called **Asthma Symptom Monitoring (ASM)** that has been shown to help manage asthma symptoms. The four groups are:

- Group One: only use ASM and continue with your normal asthma care.
- Group Two: use ASM and an antibiotic pill added to your current asthma medicines. This pill has been demonstrated to help many people with asthma.
- Group Three: use ASM with the addition of inhaled corticosteroids with your rescue medicine – also known as Rescue Inhaled

CorticoSteroids (R-ICS). Another approach which has been shown to help many people with asthma.

- Group Four: use ASM and both an antibiotic pill and R-ICS.

If you are in a group that adds new medicines or inhalers, you and/or your insurance will be responsible for paying for them. No medications are provided by the study.

Each month during the study you will answer questions about your asthma, asthma medication use and how your asthma is affecting you. These can be answered online with a smart phone, with a research staff person over the phone, or a computer. The surveys take about 10 minutes each month. You will be compensated for your participation.

Whatever you decide about being in the study will have no effect on your medical care here. The doctor and practice will provide all care as usual if you decide not to participate in this study.

What questions do you have?

[Answer all questions- if you don't know the answer, please contact study staff so that we can answer!]

If patient is willing to participate, schedule next appointment.

Appendix 6 – Text Survey Reminder Messages

Day 26

- Take your iTREAT survey at xxxx://xxxxxxx.xx/xxxx. Payment will be added about 2 business days after completion. Do it within 6 days to enter raffle.

Day 28

- Take your iTREAT survey at xxxx://xxxxxxx.xx/xxxx. Payment will be added about 2 business days after completion. Do it within 4 days to enter raffle.

Day 30

- Take your iTREAT survey at xxxx://xxxxxxx.xx/xxxx. Payment will be added about 2 business days after completion. Only 2 days left to enter raffle.

Appendix 7 – Email Survey Reminder Message

Subject: iTREAT Monthly Survey Reminder

Hello [name],

Please complete your iTREAT monthly survey. Just a reminder, your payment will be added about 2 business days after you finish your survey.

Please click the link below to access the survey.

[INSERT SHORT URL]

If the link above does not work, try copying the link below into your web browser:
[INSERT LONG URL]

This link is unique to you and should not be forwarded to others.

Thank you,

The iTREAT Team

Appendix 8 – Consent Check Questions

1. You will be asked to complete surveys…[INSERT AT THE END OF SECTION, "NUMBER OF SUBJECTS AND LENGTH OF STUDY PARTICIPATION"]

   ◯ Once more

   ◯ Every 6 months

   ◯ Each month

2. How many more study visits will you have after today? [INSERT AT THE END OF SECTION, "SUBJECT RESPONSIBILITIES"

   ◯ 0

   ◯ 1

   ◯ 2

   ◯ 3

3. Will you still be able to get medical care for asthma from your usual clinicians whether or not you decide to be part of this study? [INSERT IMMEDIATELY BEFORE SECTION, "RISKS FOR STUDY ACTIVITIES"

   ◯ Yes

   ◯ No

Appendix 9 – Follow-up Message to Participants that Didn't Receive the End of Study Question(s) at 3 Months.

Dear iTREAT participant,

Thank you for recently completing your Month 3 survey. Please take a moment to complete 1 to 3 questions that were not included in the last survey. You may access the questions by clicking this link. For questions or comments, you may respond directly to this email or call 1-800-460-9052.

Thank you,

iTREAT Study Team

Appendix 10 – End of Study Email Notification to Participants

Thank you for participating in the iTREAT feasibility study. Your participation will help us develop a better study and hopefully find better ways to treat asthma. We hope your asthma has improved.

If you are taking study medications, discuss with your doctor whether to continue your study medication. Thanks again, please contact us at itreat@dartnet.info or 1-800-460-9052 if you have any further questions.

The iTREAT Study Team