Detailed Protocol

Protocol Title: 'Patient Empowered Strategy to Reduce Asthma Morbidity in Highly Impacted Populations (PREPARE)

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Protocol Summary

Asthma imposes a significant burden on the US population in terms of morbidity, costs to society, individual suffering, loss of productivity and mortality. African Americans (AA) and Hispanic/Latinos (H/L) bear a disproportionate share of that morbidity. Despite introduction of national guidelines for asthma treatment, the gap between these groups and whites has been stable or widening. The need for pragmatic research to address the continuing burden is widely recognized. Patients use asthma reliever inhalers to provide immediate relief of symptoms. Controller inhalers (inhaled corticosteroids (ICS)) are intended to be used regularly to prevent symptoms and attacks. Guidelines suggest that they be used daily, on a fixed basis, in all but the mildest asthma. However, adherence by patients and implementation of evidence-based guideline recommendations by clinicians has been poor. Gap analysis suggests that it is difficult to improve adherence to the current recommendations without complex and resource- intensive interventions.

Studies have examined symptom-activated use of ICS triggered by use of a reliever medication. We call this approach PARTICS – Patient Activated Reliever-Triggered Inhaled CorticoSteroid. Explanatory, non-real world studies suggest that PARTICS can produce up to 50% reductions in asthma attacks compared with usual care, while reducing ICS use by half or more. However, these studies have been performed in pre- selected populations, which represent less than 5% of patients with asthma. They have been done with repeated education and adherence checks in both the intervention and control arms.

We have consulted with AA and H/L patients, health care providers, leaders of professional societies, advocacy groups, health policy leaders, pharmacists, and pharmaceutical manufacturers. All groups have indicated that asthma decision making would be changed if we demonstrated that implementing PARTICS improves important asthma outcomes such as reducing rates of exacerbations. Together with our partners and stakeholders, we have designed a study to determine whether PARTICS can improve outcomes that are important to patients when superimposed on a background provider-educated standard care through the Asthma IQ system. We therefore propose a study entitled PREPARE: Patient Empowered Strategy to Reduce Asthma Morbidity in Highly Impacted Populations. We aim to determine whether a PARTICS strategy can reduce asthma morbidity in AA and H/L. Our primary outcome will be asthma exacerbations which have been shown to be important to patient and healthcare stakeholders. Our secondary outcomes will include additional outcomes important to patients (i.e. days lost from work or school, asthma control, & asthma quality of life). We have broad input and involvement from multiple stakeholder groups in study design, implementation, and commitments for dissemination. AA and H/L patients and their advocates have been involved and will continue to play a central role in all phases of the study.

I. Introduction

A. Research Questions, Hypotheses, and Study Aims

1. Vanguard

Research Questions:

a) Are our study operations and processes functional?

These operations and processes include:
- enrollment process for sites
- enrollment process for study participants
- communication with patients
- communication with physicians
    - is each of our methods of communication effective?
        - Written
        - Teleprompt response system
        - Web system
            - Mobile
            - Desktop
- drug delivery system
    - does the Propeller system help us understand whether patient adherence based on patient-reported outcomes is accurate?

b) What are the barriers to study implementation?

c) Do patients understand what we mean to communicate to them?

Specific Aims:

a) To determine whether our study operations and processes are functional.

- These operations and processes include the enrollment process for sites and for study participants, our communication with patients and with physicians (which include written communication, teleprompt response system, web system via mobile and desktop), our drug delivery system, and the Propeller system.

b) To determine what are our barriers to study implementation.

c) To determine whether patients understand what we mean to communicate to them.

2. Full study

Full study differences from the Vanguard: The Vanguard is testing the study design and process with no Hypothesis testing. The full study outcomes are listed below as well as the hypothesis.

Research Question:

Primary:
In patient populations that bear a disproportionate burden of asthma morbidity (African American and Hispanic/Latino adults) can a patient-empowered PARTICS (Patient- Activated Reliever-Triggered Inhaled CorticoSteroid) strategy improve outcomes of importance to patients, providers, and the health care system?

Secondary:

1) Does the effectiveness of PARTICS differ by race/ethnic group (AA vs. H/L).

2) Does the effectiveness differ by smoking status?

Exploratory**:** How do patient characteristics and patient reported barriers influence PARTICS' effectiveness?

Hypothesis:

In these populations, a patient-empowered strategy of use of ICS triggered by patient use of short-acting beta-agonist (SABA) reliever for quick symptom relief ("rescue use") will reduce asthma exacerbations and improve other outcomes important to patients and the health care system.

Study Aims:

Working with patient & health system stakeholders, we will conduct a pragmatic real-life study in a population of African American and Hispanic/Latino adults disproportionately impacted by asthma.

Specific Aim 1: To assess whether a Patient Activated, Reliever-Triggered Inhaled CorticoSteroid (PARTICS) strategy can reduce asthma morbidity in this population.
-Our primary outcome will be asthma exacerbations which have been shown to be important to patients and healthcare stakeholders.
-Our secondary outcomes will include additional outcomes important to patients such as days lost from work or school, asthma control, and asthma related quality of life.

Specific Aim 2: To examine whether the effectiveness of a Patient Activated, Reliever-Triggered ICS (PARTICS) strategy differs between African American or Hispanic/Latino adults or by smoking status.

Exploratory Aim: To examine, whether particular patient clinical characteristics (e.g. prior exacerbations) or specific barriers to adherence (e.g. beliefs, depression) impact the effectiveness of a PARTICS approach in these populations.

B. Background

a. Impact of asthma in the general population

Almost 1 in 12 Americans currently have asthma--18.7 million adults (CDC 2014). It

accounts for 1.75 million emergency room visits in the US each year, more than 14.2 million outpatient visits, and 439,000 hospitalizations, with average stay length at 3.6 days (CDC 2014). From 2002-2007, annual direct costs of asthma in the US was $50.1 billion; indirect costs such as lost productivity contributed an additional $5.9 billion (Barnett 2011). Given rising asthma rates, this is likely an underestimate of current costs. Asthma attacks, or exacerbations, result in extensive morbidity. In 2011, an estimated 9.1 million Americans had an asthma attack (CDC 2012). These attacks result in significant individual suffering and loss of productivity. Thirty-three percent of adults who had asthma attacks missed work as a result. On average, adults miss five days of work per year because of asthma attacks (CDC 2011). Among adults, asthma is the fourth leading cause of work absenteeism and "presenteeism," accounting for more than 10 million missed days of work and an additional 5 million days of "less productive" workdays each year (MMWR 2002). Asthma exacerbations drive more than 50% of asthma-related acute health care costs (Reddel 2009, Lane 2006) and are associated with progressive loss of lung function (O'Byrne 2009), leading to long-term morbidity and disability. Avoiding exacerbations is a high priority for patients. Asthma can also be deadly. In 2011, 3,345 Americans died of asthma; 94% were adults (Hoyert 2012).
These death rates are twice that of thyroid cancer and 35% that of melanoma.

2. Asthma in African Americans and Hispanics and Latinos

Asthma has a broad impact on African American (AA) and Hispanic and Latino (H/L) populations stemming from disparities in disease-specific and healthcare-specific factors. These groups bear a disproportionate share of asthma morbidity and mortality (Gold 2005). Asthma is more prevalent in these populations (35% and 100% higher in AA and H/L, respectively than in Caucasians) (Akinbami 2011, Moorman 2011, Rose 2006, Smith 2005). There are also disparities in morbidity independent of prevalence. Both AAs and H/Ls have double the rates of asthma related ED (emergency department) visits and hospitalizations as Caucasians (Crocker 2009, Ginde 2008, Law 2011, Ash 2006, Boudreaux 2003, Gupta 2006), and 50% higher rates of re-hospitalization (Ash 2006). African Americans experience two to three times the death rate due to asthma as Caucasians. Among Puerto Rican H/Ls, rates of asthma exacerbations are 30% higher (Moorman 2013) and asthma-related death rates are 75% to 200% higher (Homa 2000). *Our team recently completed a study comparing two long-acting bronchodilator asthma medications in >1,000 African Americans across the country (BELT study submitted for publication). One-third of the subjects had an exacerbation requiring corticosteroids in a year.*

Health care and use of asthma medications differs in AA and H/L populations compared with whites as well. AAs are less likely than non-Hispanic whites to receive asthma care that follows guidelines (e.g., use of inhaled corticosteroids), and to be educated on self- management strategies (Krishnan 2001). H/Ls with current asthma have a 60% higher likelihood of having a health service deficit (a composite variable defined as health insurance status, having a healthcare provider and a routine physical exam, and deferring medical care due to cost) (Lutfiyya 2011). They also are found to have decreased access to asthma specialists (Clement 2008) and to insufficiently use anti- inflammatory medications (Hunninghake 2006). Both AAs and H/Ls are less likely than whites to receive adequate and timely follow up after ED treatment for asthma (64% and 41% less likely, respectively) (Shields 2004). Of greatest concern, although the morbidity seems to be decreasing among whites, it is not changing among minorities. Asthma ED visits decreased by 25% in whites (p=0.02) from 1993 to 2005 but did

not change in AA (p=0.8) (Ginde 2008) and the gap in hospitalizations appears to be widening (Getahun 2005).

3. Personal burden of asthma—our patient collaborators' perspective

The personal burden of asthma cannot be overlooked. Here are just three comments from stakeholder patients with asthma that we obtained from focus groups with AA and H/L patients with asthma in the spring of 2014: *"I felt like we had to live in a cocoon to manage asthma." "My mom had a scared look in her eye when I was in the ED. I couldn't breathe, but it made me feel even worse to see my mom with that scared look." "My employer said to me 'You have a choice to make: either be at work or be at home.' The realistic fact is I am at home and I am broke, but my children's well-being means the world to me."*

4. Gaps in evidence: problems with current asthma treatment guidelines

As reviewed above, asthma morbidity continues to remain high and mortality persists. Current National Asthma Education and Prevention Program (NAEPP) **guidelines recommend regular use of an inhaled corticosteroid** in all but the mildest cases (NAEPP 2007). Increased use of inhaled corticosteroids has been associated with decreased asthma mortality independent of asthma severity (Suissa 2000).
Unfortunately, clinicians have failed to implement these guidelines. Further, patient do not use daily inhaled corticosteroids when prescribed. They fill an average of only three months of prescriptions (rather than 12 months) over the course of a year (Apter 2011, Williams 2010, Stempel 2005, Delea 2008). Many efforts have been aimed at improving patient and provider guideline directed care with little success.

A Cochrane review examined efforts to increase use of guidelines in chronic diseases, including asthma. It evaluated studies that measured both implementation of guidelines and outcomes (Haynes 2008). It concluded that "almost **all of the interventions that were effective for long-term care were complex,** including combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counseling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, and supportive care. **Even the most effective interventions did not lead to large improvements in adherence and treatment outcomes."** Given the difficulty of managing asthma, the Institute of Medicine (2009) believes that new approaches are necessary. It lists evaluations of **alternative strategies for managing asthma** in its top 100 comparative effectiveness research priorities.

Thus, systematic reviews suggest that we have not been able to improve implementation of guidelines and patient self-management without using complex interventions. This problem is acute in asthma, especially in AA patients and subsets of H/L patients (see above **section I.B.2),** who bear a disproportionate share of asthma morbidity. A cross-sectional retrospective analysis from the National Ambulatory Medical Care Survey from 1998 to 2004 showed that implementation of NAEPP guidelines was inadequate, especially for minority patients (Navaratnam 2008). Further, as mentioned above, despite improvements in overall asthma care, the disparities persist and may be widening (Ginde 2008, Gatahun 2005).

5. Barriers to adherence to controller asthma therapy

This approach leverages the way patients use their medicines for symptoms and **bypasses** many barriers to adherence such as forgetfulness, motivation, and fear of steroids discussed by our patients.

and the extent to which this intervention overcomes known potential barriers to asthma self-management, such as beliefs about medication, cost, forgetting medication, health literacy and depression.

6. Alternative approaches to managing asthma:

(a) the 'Patient-Activated Reliever-Triggered Inhaled CorticoSteroid (PARTICS)' strategy As reviewed in **section I.C.3,** 'Potential to Improve Outcomes', we haveidentified

a low-complexity alternative strategy for reducing exacerbations that appears to have a high likelihood of being effective. It is a strategy that empowers patients. It bypasses much of the issue of adherence to regular ICS since it does not depend on the regular use of ICS. Rather than relying on complex interventions to increase adherence, it leverages current patient patterns of medication use--whenever a patient uses an asthma reliever medication, he or she will also use an inhaled corticosteroid (ICS). We call this a Patient-Activated Reliever-Triggered Inhaled CorticoSteroid (PARTICS) strategy.

(b) Effectiveness and Efficaciousness of comparator group in situations outside PFA

To reduce heterogeneity of the underlying treatment that is provided in boththe intervention and the control, all sites will be applying what we refer to as "provider- educated care" which will be standardized by implementation of the instructional component of the Asthma IQ system Primary Care Version (www.asthmaiq.org). The comparison will be between adding the PARTICS intervention to provider educated care vs. continuing provider educated care alone. We will use the on-line provider instructional component of the Asthma IQ to provide the standard of "provider- educated care". The Asthma IQ program was jointly developed by the American Academy of Allergy Asthma and Immunology (AAAAI) and the American Academy of Family Physicians. The *complete* program has two components; 1) an on-line instructional component for providers and 2) a web-based clinical decision support tool utilizing metrics from visits with feedback to providers regarding next treatment steps.

The on-line instructional component of the Asthma IQ requires ~20 minutes to complete. The instructional component of the Asthma IQ has been shown to produce outcomes no different than the entire program. Further, it was shown to improve asthma outcomes as compared with baseline. Thus, based on the recommendations of our provider stakeholders, patient stakeholders, the Principal Investigator of the Asthma IQ study (Dr. Thomas Casale, who will serve as an expert advisor for Asthma IQ implementation) and expert stakeholders, we have adopted the instructional component of the Asthma IQ as our underlying standard of care. Only providers who have completed the instructional Asthma IQ will be able to enter and randomize their patients. The AAAAI has graciously agreed to make the modifications to the existing Asthma IQ site to accommodate "certification" of providers in our study (www.asthmaiq.org). While the Asthma IQ will not absolutely standardize all care, it will reduce variation across the enrollment sites. As noted in **section III.E.9**, 'exploratory analyses', we will examine in an exploratory manner, the effect of provider adherence on our comparison. While the Asthma IQ provider-educated care will likely improve outcomes as compared to non- standardized treatment at our sites, we do not believe that it will substantially interfere with our ability to demonstrate the superiority of PARTICS. PARTICS has been shown to be superior even to *enforced* NAEPP care.

7. Evidence supporting the PARTICS strategy

Systematic reviews of efficacy studies suggest that a PARTICS approach can reduce exacerbations by 25 to 50% (Cates 2013, Kew 2013) and more likely 40-50% in adults (O'Byrne 2006, Rabe 2006, Buhl 2012, Papi 2013, Calhoun 2012). One major gap in

knowledge is whether such results are achievable in a real-world setting with high-risk populations. Previous studies were explanatory studies with restricted patient entry. It is estimated that only 5% of asthmatics can enter such trials (Herland 2005, Travers 2007). The trials contained few if any AA or H/L. Further, some of these studies involved long- acting beta-agonist withdrawal during the run in, and thus may have made the study populations more likely to respond to PARTICS (Cates 2013). Another knowledge gap is whether this reliever-triggered approach can be implemented in health care systems that treat substantial numbers of minority patients. Review articles and a recent editorial have called for this strategy to be tested in different asthma populations and varied real-world settings (Beasley 2014, Papi 2009). We have strong data from efficacy studies to suggest that a PARTICS approach will be successful. As mentioned in **section I.B.5** above, 'barriers to adherence to controller asthma therapy', a major implementation barrier to asthma pharmacotherapy involves issues of patient acceptance and patient activation. Current national guidelines recommend daily ICS therapy for asthma control. However, patients fill less than a quarter of their ICS prescriptions and asthma morbidity remains high (Apter 2011, Williams 2010). Dr.
Israel (senior author) and his colleagues first demonstrated that symptom-based (but not reliever-triggered) use of inhaled corticosteroids yields levels of asthma control no worse than those produced by regular use of inhaled corticosteroids (Boushey 2005). This led us and others to develop and study the PARTICS approach, which involves using an ICS triggered by the use of a reliever medication. **ICS + SABA and ICS/Long-acting beta-2 agonists (LABA)**
PARTICS-type approaches have been shown to substantially improve asthma outcomes. A PARTICS strategy reduced exacerbations by >70% compared with beta- agonists alone and produced outcomes equal to that of enforced continuous ICS therapy in a clinical efficacy trial (Papi 2007). Further, tightly controlled trials have compared: 1) PARTICS (in this case using symptomatic use of a LABA as the trigger) plus regular LABA/ICS therapy; 2) regular LABA/ICS; and 3) higher dose ICS therapy. PARTICS plus ICS/LABA was shown to reduce exacerbations by more than 50% when compared to ICS/LABA or higher dose ICS (O'Byrne 2005). These results have been reproduced multiple times (Rabe 2006, Buhl 2012, Papi 2013). A systematic review of efficacy studies comparing PARTICS-type strategies with LABA plus ICS to regular LABA-ICS estimated a 17%-47% reduction in exacerbations (Kew 2013, Cates 2013). This reduction occurred in the setting of reducing overall ICS use by almost half in the PARTICS groups. In addition to reducing exacerbations, these PARTICS strategies decreased asthma symptoms and nocturnal awakenings, and improved lung function, relative to fixed-dose ICS treatment regimens. Most importantly, Dr. Israel initiated and participated in a study in patients with moderate asthma in which we compared the PARTICS approach to enforced NAEPP care (q 6 week visits with NAEPP-adjusted care by study staff). In that study, the PARTICS approach produced asthma control as good as or better than NAEPP care (Calhoun 2012). The PARTICS patients used only half the amount of ICS as those receiving every-six-week enforced physician-adjusted care. The magnitude of reduction of treatment failures was equivalent to that seen in other studies (41%) although it did not reach statistical significance in this 100 patient/arm 9-month study that was underpowered for this difference (20 exacerbations compared with an anticipated >350 in PREPARE). It is critical to understand that the improved outcomes with PARTICS occurred **despite the fact that the NAEPP guidelines were enforced with a reported 90% adherence rate with ICS.** As mentioned above, real world adherence rates are about 25%. Of note, the PARTICS approach **significantly reduced days lost from school or work by more than half, again while using half the amount of ICS.** In addition to the likelihood that PARTICS will improve outcomes including the use of oral corticosteroids, which is so dreaded by asthma patients, it has an additional benefit of generally resulting in less use of inhaled corticosteroid. Our patient partners, especially our H/L partners, have indicated that excess ICS use is a concern to them in addition to their fear of oral

corticosteroids. Decreasing ICS use does have the potential for reducing the small, but very real morbidity associated with ICS use, including osteoporosis (Israel 2001), and cataracts (Cumming 1997). Studies suggest that PARTICS can reduce ICS use by 50%-80% (Boushey 2005, Papi 2007, Calhoun 2012, Cates 2013, Kew 2013).

Although PARTICS-type strategies have been shown to significantly reduce exacerbations in carefully controlled efficacy studies by nearly 50%, “a key point to more generalized acceptance will be the need to conduct these trials in a real life environment,” writes Dr. Busse in a letter supporting this proposal (see Letter of Support, Organizational Support). Further, a pragmatic trial of the PARTICS approach among AAs and H/Ls has been strongly endorsed by our patient and professional stakeholders (see Section E. Engagement & Appendix).

C. Significance

1. Support by Patient Partners and Stakeholders

Our patient partners have explicitly, and unanimously, agreed that if a PARTICS approach reduces exacerbations they would be interested in using this therapy and advocating for it**.** They have done so because the outcomes we propose to alter are important to them and the intervention is simple and might actually result in a decreased use of ICS as well as oral corticosteroids. Our other stakeholders have also been enthusiastic, including leaders of professional societies and advocacy groups. The president of one of the major allergy organizations said he “would invest in the company that makes” a PARTICS- type inhaler. Teva, a major drug company, has agreed to provide free inhaled corticosteroids because they believe that this approach will benefit patients**.** Teva has also agreed to act as our central pharmacy and set up electronic prescriptions for electronic health records. The Centers for Medicare & Medicaid Services has agreed to work as a stakeholder as well.
Thus, we have extensive, enthusiastic support from patients and stakeholders.

2. Dissemination and Sustainability

As discussed in **II.C.15.a**, ‘Complexity of Intervention’, our patient partners and other stakeholders are attracted to this study due to the simplicity of the PARTICS intervention and the likelihood that it will succeed. The approach is intuitive and relies on the patient-preferred pattern of use of reliever medication. This will help make the intervention sustainable. We have concrete buy-in from partners and stakeholders who are key to supporting the sustainability and implementation of our intervention based on our findings. Several companies have begun to discuss development of a single device SABA/ICS should our study be positive. By involving Teva, who has agreed to manage the drug delivery, we will de facto be able to demonstrate that the delivery is feasible, sustainable, and scalable across the United States. We are also designing our intervention to be easily scalable and sustainable on the patient side by solely using short (5 minute or less) YouTube-type videos that will be available on the internet for instructions and explanation of the intervention, which will be shown in the office when the patient is enrolled. It would subsequently be easy to use these in any practice adopting this approach. Post-study, physicians wishing to learn the NAEPP guidelines could access it for 20 minutes on the publicly available Asthma IQ site and receive CME credits and possibly maintenance of certification credits, further supporting sustainability on the provider-side. Our patient partners have agreed to help us present data in in their e-communities, and to their peers. Advocacy groups and professional society stakeholders have agreed to disseminate the results to their members and thus potentially create grass-roots demand. Our policy

stakeholders have received commitments to review these findings in their decision making bodies when the results have become available to classify the medications in the approach as the most reimbursable. The NAEPP has just determined that evaluation of the PARTICS approach will be among its top priorities for the next revision (Kiley 2015). We have indications from the prior chair of the last NAEPP that the study results would weigh heavily in consideration of the evidence based recommendations regarding PARTICS approaches.

We have included specific proposals from each of our stakeholders in the Dissemination Section. We will have each stakeholder group have a representative on a Dissemination Committee led by Dr. Yawn who has extensive experience in implementation in primary care and family medicine practices. Some examples of how our stakeholders have already indicated their role in dissemination include:

1. Participating in our presentation at public forums and peer led blogs and social media;
2. Advocacy Groups – supporting grass roots campaigns for adoption of PARTICS;
3. Specialty Societies providing forums for provider and patient presentations using new formats including webinars, and online programs;
4. Insurers identifying pathways to get coverage for PARTICS medications, should the study be positive. See the Letters of Support, Organizational Support, for details. To consolidate and coordinate the plans for dissemination, we will devote part of our two-day meeting at the end of the study to review and plan dissemination.

Our structure reinforces the PCORI engagement principles:

(a) Reciprocal Relationships:

Reciprocal relationships are reflected in the use of stakeholders' insights and suggestions in the crafting of the study and this application as well as in ongoing study governance. The Executive Committee (EC) combines representatives from all stakeholder groups, not just the academic researchers to review and approve all major study decisions. The Operations Committee (OC) has assigned individuals to all stakeholder groups assuring participation and seeking feedback. Our initial attention to the recommendations of the stakeholders, as well as the initial face to face meeting, will further facilitate bidirectional communication and foster trust.

(b) Co-learning:

Co-learning has already occurred in the planning phases of this study. Each of the stakeholder groups has provided new insight and understanding incorporated into the development of PREPARE. The Vanguard cohort will provide another intense period of co- learning from the patients enrolled in this testing period as well as the stakeholders who will help assemble and interpret the feedback. The academic research team includes experts in interaction with each of our stakeholder groups with special emphasis on interaction and co- learning with the AA and H/L groups: Maureen Fagan, DNP; Jacqueline Rodriquez-Louis, MPH, MEd (AA asthma educator from the Caribbean); and co-investigator Juan Carlos Cardet, MD (allergist and native of Puerto Rico).

(c) Partnership:

All PREPARE stakeholders are equally valued partners. This is reflected in the structure of the EC, which includes representatives from patient and other stakeholder groups who will be a majority of the members of the EC. To ensure there are no barriers to communication, and thus

to partnership, interpreters and facilitators will be week available at all meetings. We have calibrated all stakeholder involvement to be respectful of the stakeholders' time. Finally, all members of all stakeholder groups will receive equal compensation ($75/hr).

(d) Trust, Transparency, Honesty:

All stakeholders will participate in making major decisions and will have access to all study information beginning with representation of all groups on the EC. To date we have summarized and shared the comments from all stakeholders and highlighted back to the groups how this information has improved the study design including, for example, selection of outcomes, inclusion of the Vanguard cohort, and expansion of our Aims to include an important exploratory aim to better understand patient characteristics that may affect the success of the PARTICS strategy. Our stakeholders have continued to be willing to interact with the academic researchers and have been open in criticism as well as support for study design specifics. We believe this clearly demonstrates the great potential for ongoing trust and honesty in view of the transparency.
We have used the elements of the PRISM (Practical, Robust Implementation and Sustainability Model) as described by Feldstein et al (Feldstein, 2008) to evaluate and structure our dissemination and implementation model and to evaluate and promote sustainability. The model emphasizes 6 elements within an effective PRISM model (Intervention (Organizational and Patient Perspective), External Environment, Implementation and Sustainability Structure, and Recipients (Organizational and Patient)).

3. Potential to improve healthcare and outcomes

Our proposal is important to patients and to healthcare systems because it: 1) is based on strong preliminary data suggesting that the proposed approach will lead to sizeable improvements in outcomes important to patients **even when compared to enforced implementation of the NAEPP guidelines;** 2) addresses an important gap— the disproportionate asthma morbidity among affected minority populations (see **I.B.2);**
3) is strongly supported by patient and other relevant stakeholders; 4) is likely to be easy to disseminate; 5) will likely be sustainable because; a) it is intuitive for patients (treatment-preference concordance); b) it will be conducted with a real-life distribution system (Teva and electronic scripts in the EHR); and c) it is implemented with an easy, internet-accessible patient instruction system of **short** YouTube-like videos. We first review our preliminary data regarding PARTICS-type approaches, then review these other criteria of significance.

The proposal has *strong endorsement from all of our patient and other stakeholders.* Our patient partners have all indicated support of this approach to reduce asthma morbidity in a way that they feel would be helpful to them. This has been seconded by our advocacy stakeholders and our professional society stakeholders**.** Our health policy and insurance stakeholders have similarly indicated enthusiasm. As further evidence of buy-in, Teva has agreed to collaborate with us to implement the study, and agreed to donate drug, retail cost almost $1 million**.**

4. Patient-Centeredness

(a) Appropriate Engagement of Patients and Stakeholders

We have already identified and engaged patients and stakeholders in study design and choice of outcomes (patients in our BELT study indicated they would like to experience fewer exacerbations). As discussed in those sections, patients and stakeholders will be active, important participants in choosing final study outcomes, study implementation, analysis, and dissemination. Patients and other stakeholders will serve on the trial's governing Executive Committee. Each member of the Operations Committee will serve as a liaison to each stakeholder group, ensuring bidirectional communication throughout the study timeline. We have engaged patient participation facilitators to assure continued engagement throughout the study. All stakeholders are valued for their contribution and are equally compensated.

(b) Assuring Representativeness of the Population and the Data

Our plans for assuring representativeness are described extensively in **II.C.15.c,** in addition to representative recruitment, we are reducing barriers to enrollment and participation by providing the option of enrolling patients at home visits and with opportunities for patients with low literacy via verbal consent and the option to do the monthly surveys via phone interview by trained staff.

(c) Using Patient Reported Outcomes

We use patient reported outcomes almost exclusively. Asthma task forces have identified them as critical outcomes. Our outcome, asthma exacerbations, is now used as THE major outcome for studies of new therapies in asthma. These outcomes are of interest to patients and focus on events or states of health that adversely affect patients' quality of life and ability to participate in usual activities, and result in loss of income or require financial expenditures. Our primary outcome, the rate of asthma exacerbations per year, is defined as the number of exacerbations, emergency room visits, or hospitalizations requiring oral or parenteral corticosteroids, per patient per year. It will be captured by subject self-report via a monthly asthma exacerbations questionnaire with follow up to the medical record or patient interview. All the study outcomes, their patient centeredness, and validation and properties are detailed in **section III**.

(d) Supporting Dissemination

PREPARE provides a strategy to help reduce excess asthma morbidity in AA and H/L populations. Our stakeholders are excited by this possibility. They have already indicated ways they will help to disseminate and implement this strategy by engaging with constituencies, insurance companies, distribution networks, and regulatory bodies to increase uptake and sustainability**.** Further, they will participate in a Dissemination Committee led by Dr. Yawn to help assure dissemination success.

5. Summary

(a) Vanguard:

The Vanguard cohort of a subset of study participants will allow us to observe how well the protocol and materials work. This is a large, multi-centered, pragmatic trial, which implies

that the degree of investigator oversight is limited compared to traditional efficacy trials. The vanguard process attempts to compensate for limited oversight by testing appropriateness of our methods. The methods and issues we will test with the vanguard process include participant recruitment; the quality of our instructional videos and whether participants learn from them what we want them to learn; the accuracy of our eligibility questions to capture our population of interest; suitability of our consent form and registration process; capacity of our baseline intake and monthly surveys to capture variations in asthma control and exacerbations; randomization process; to assess the patients' understanding and acceptance of the PARTICS strategy; and finally allow us to better understand how our group of researchers will interact with our patient stakeholders and others through our Operations Committee and our Executive Committee. We will use data from the vanguard process to modify our methods and approach to conducting the full PREPARE study.

Full study difference: The Vanguard is testing process whereas the Full Study is testing the research question regarding PARTICS, explained below:

(b) Full Study

The optimal strategy for ICS use for the management of persistent asthma remains unknown. Daily ICS use seems excessive to some patients when their asthma symptoms are controlled, and insufficient when they experience asthma exacerbations. In this PREPARE trial we will determine whether the PARTICS strategy--of using additional ICS concomitantly with rescue inhaler use--can reduce asthma exacerbations while allowing patients to adjust their ICS dose based on their perception of the intensity of their symptoms. We will do this in the setting of a pragmatic, patient-centered clinical trial which allows for greater generalizability and easier implementation of our results. While asthma is burdensome in terms of morbidity, mortality and costs, it is disproportionately so for the African American (AA) and Hispanic/Latino (H/L) communities. Conversely, these racial/ethnic groups constitute the minority of participants recruited in clinical trials.

PREPARE will address the need for pragmatic research to address the continuing burden of asthma in AA and H/L patients. In consultation with AA and H/L patients, health care providers, leaders of professional societies, advocacy groups, health policy leaders, pharmacists, and pharmaceutical manufacturers, results from PREPARE may demonstrated that implementing PARTICS may improve important asthma outcomes in these highly-impacted populations.

II. Study Design, Population, and Participant Recruitment

A. Study Overview and Organization

1. Vanguard

This is a randomized, open-label trial in AAs and H/Ls 18 years and older* with asthma in which a standard of usual care, as requested by PCORI, is introduced (guided by the Asthma IQ educational program+ which we will call "provider educated care"), and then patients are randomized to addition of a PARTICS strategy vs. continuing this standard of provider-educated enhanced usual care. Underlying care will be standardized via provider certification in the educational component of the online Asthma IQ program. Self-identified+ AA and H/L patients at risk for exacerbations (e.g. on controller ICS with poor control, previous history of an exacerbation in previous 12 months or using ICS/LABA) will be identified from the clinical sites'

electronic health records and invited through their local provider's office* to come for an enrollment visit.

The "Vanguard" cohort of 36 patients (16 AA and 20 H/L) from four sites represent our study sites' geographic, health system and practice size diversity; and patients that represent our anticipated enrollment of race, sex and age groups. Thirty two of the 36 (16 AA and 16 H/L) Vanguard patients will be English speaking patients enrolled 3:1 intervention (PARTICS) to non-intervention (enhanced usual care/Asthma IQ) so that we may observe how well the protocol and materials work**.** To test how the materials translated into Spanish work for the Spanish speaking patients, we will enroll 4 additional patients (total Vanguard patients 36) at one of the Vanguard sites that has a large Spanish speaking population (Mount Sinai). All 4 Spanish speaking patients will be in placed in the intervention group to be able to sufficiently test the intervention materials. The intervention materials include everything included in the Usual Care group with additional materials. Each participant will be in the vanguard process for three months. After registration, vanguard participants will complete questionnaires at baseline (during registration) then two monthly questionnaires as the full study. In addition, the Vanguard cohort will be called at 1 week, 6 weeks and at 12 weeks to answer questions about the enrollment process, filling out the monthly questionnaires and the videos. The intervention group will be asked about the receiving the medication supplied by the study. The interviews will be audio recorded. This will enable transcription of the open-ended questions for the qualitative analysis. Those agreeing to attend the enrollment visit will have the study explained and complete informed consent facilitated by onsite study personnel or through video conferencing with central study staff. At the enrollment visit, entry criteria will be confirmed, consent obtained (potentially through a centralized 2-way video consent, baseline questionnaires completed, and the patient randomized (using a central randomization algorithm) to PARTICS with continuation of their provider-educated care or continued with their provider-educated care alone. Patients randomized to either study arm will watch a culturally appropriate video on proper inhaler technique followed by observation of the patient's inhaler technique. All enrollees will also receive instructions on completion of monthly questionnaires and general questions will be answered via the video communications or by local staff as necessary. Each enrollee will select one of the patient-partner designed inhaler pouches and clip* to hold their quick relief inhaler(s). Those randomized to PARTICS will also view a patient partner-approved culturally appropriate video* that explains how and why to use the PARTICS dual quick relief medications (ICS+SABA). Patient questions regarding PARTICS will be answered in real time via video communication. At the close of the visit, PARTICS patients will receive or be mailed an ICS inhaler with a counter and a Velcro band* (used to attach the rescue ICS inhaler to the patient's current SABA (ICS study drug donated by Teva**.** For PARTICS ICS refills, patients will call the 800 number printed on the Velcro band when their counter reaches 40. Teva will send a new ICS inhaler directly to the address designated by the patient.

All patients (both PARTICS and control groups) will be asked to complete monthly questionnaires using validated instruments to assess exacerbations, symptoms, medical visits primarily driven by asthma (visits, ED visits, and hospitalization) and medication use. At enrollment patients will choose how they wish to receive reminders as well as primarily complete the questionnaire (online, smart phone, mailed—exactly same questions and multiple choice answers for each method). Patients will be allowed to changes methods whenever requested. Several of the instruments have been validated to be comparable across these response methods (Schatz 2007a, Schatz 2007b, and Schatz 2007c).

Before sites begin enrolling patients the study team will host centralized training for the site PI and key practice personnel, and all clinic team members will be instructed about the overall study protocol and the PARTICS approach.

2. Full study

B. Full study differences:

The Full study will enroll up to 1210 patients and will be conducted in up to 20 diverse health care settings across the country, the patients will be enrolled 1:1 intervention (PARTICS) to non-intervention. There will be one follow up call within the first month of enrollment to ask questions about the patients experience filling out the survey. There will be NO follow up calls to the patients at week 1, 6 and 12 to answer questions about the enrollment process, filling out questionnaires and the informational and instructional videos or questions to the intervention group about the medication supplied by the study. The patients will have one in person visit to enroll in the study then will receive monthly questionnaires for 12 to 15 months depending on when they are enrolled. Patients may also be given the option to enroll during a home visit. Home enrollment visits will include the same methods as on-site enrollment visits.

Those agreeing to enroll will have the study explained and complete informed consent facilitated by study personnel. At the enrollment visit, entry criteria will be confirmed, consent obtained, baseline questionnaires completed, and the patient randomized (using a central randomization algorithm) to PARTICS with continuation of their provider-educated care or continued with their provider-educated care alone. Patients randomized to either study arm will watch a culturally appropriate video on proper inhaler technique followed by observation of the patient's inhaler technique. All enrollees will also receive instructions on completion of monthly questionnaires and general questions will be answered staff as necessary. Each enrollee will select one of the patient-partner designed inhaler pouches and clip* to hold their quick relief inhaler(s).

During the study visit, we will ask participants to exhale into a machine that determines nitric oxide gas levels in their breath. This procedure was not conducted in the Vanguard phase, and will only be conducted during the full study. In addition, patients will be asked if they agree to have 3 mL's of blood drawn for a complete blood count (CBC) with differential. The CBC results will include eosinophil counts that are associated with patients' response to inhaled corticosteroids. Depending on the site, the patients will either have their blood drawn during their enrollment or be sent to a contracted laboratory in the area. Samples will be processed either at the facility where the enrollment takes place, or by a contracted diagnostics company such as LabCorp.

Those randomized to PARTICS will also view a patient partner-approved culturally appropriate video* that explains how and why to use the PARTICS dual quick relief medications (ICS+SABA). At the close of the visit, PARTICS patients will receive or be mailed an ICS inhaler with a counter and a Velcro band* (used to attach the rescue ICS inhaler to the patient's current SABA (ICS study drug donated by Teva**.** In addition, patients randomized to PARTICS who answer "yes" to using a nebulizer on the intake questionnaire will receive a second ICS and an extra pouch to hold the ICS along with a Velcro strap to attach the additional pouch with the ICS to the nebulizer. For PARTICS ICS refills, patients will call the 1-800 number printed on the

Velcro band when their counter reaches 20. Teva will send a new ICS inhaler directly to the address designated by the patient. All patients (both PARTICS and control groups) will receive a refrigerator magnet with adherence instructions.

All patients (both PARTICS and control groups) will be asked to complete monthly questionnaires using validated instruments to assess exacerbations, symptoms, medical visits primarily driven by asthma (visits, ED visits, and hospitalization) and medication use. At enrollment, patients will choose how they wish to primarily complete the questionnaire (online, smart phone, mailed—exactly same questions and multiple-choice answers for each method). Monthly reminders to complete each monthly survey will be sent to patients through all methods of communication that the patient provides (text**,** email, phone call). Patients will be allowed to change methods whenever requested. Several of the instruments have been validated to be comparable across these response methods (Schatz 2007a, Schatz 2007b, and Schatz 2007c). In addition to monthly survey reminders, patients will also receive quarterly reminder text messages about the study and monthly surveys. Patients may opt out of the text messages at any time.

Before sites begin enrolling patients, the study team will host centralized training for the site PI and key practice personnel, and all clinic team members will be instructed about the overall study protocol and the PARTICS approach.

A. Patient Population

Sample size, age, gender, race, ethnicity, clinical status

1. Vanguard

We will enroll 36 patients (16 AA and 20 H/L) that represent our study sites' geographic, health system and practice size diversity. Each site will be asked to recruit a specific Race or Ethnicity for this small pilot based on the predominant Ethnic/Racial group at that site. 18-75 years old without regard to gender. Race/ethnicity assignment will be based on self-identification. For patients who self-identify in both categories, they will be randomized as H/L since studies on asthma in H/L include those patients as such. Based on our past experience, more than 70% will be female. We also expect that almost half will be active smokers or have a significant smoking history. Broadly, these patients will have asthma and be at risk for exacerbations. They either will have been prescribed ICS/LABA or if taking ICS without LABA will still have symptoms or have had an exacerbation in the past year. In our BELT study looking at use of long-acting bronchodilators, among >1,000 AA patients that we recruited who were either symptomatic on ICS or taking ICS+LABA, more than one- third had an exacerbation, of which 80% went to the emergency room.

2. Full Study

Full study difference**:** We will enroll up to 1210 patients: 605 AAs and 605 H/Ls.

3. Participant subgroups (Full study only)

The subgroups of the total study population to be analyzed are AAs, H/Ls, smokers and non-smokers. Regarding AAs and H/Ls**,** the barriers to success of PARTICS may vary in the different racial/ethnic groups. In fact, in one PARTICS-type study, H/L appeared to benefit less from a PARTICS approach (Calhoun 2012).Therefore, we will perform a subgroup analysis in which we analyze AA and H/L separately using the definitions above regarding race/ethnicity assignment.Regarding smoking, according to the CDC's 2010 Behavioral Risk Factor Surveillance System, about 21% of people with asthma are active cigarette smokers (CDC 2010). Active smokers are well known to have increased asthma morbidity compared with non-smokers (Lange 1998, Marquette 1992, Polosa 2013, Shavit 2007, Sippel 1999, Siroux 2000). More importantly, active smokers have a decreased therapeutic response to ICS as measured by asthma control scores, FEV1, and airway reactivity (Pederson 1996, Chalmers 2002, Lazarus 2007). Further, a study showed that this reduced therapeutic response to corticosteroids also occurs in former smokers with a greater than 10 pack-year smoking history (Chaudhuri 2003). In that study, both active smokers and former smokers had reduced FEV1, daytime symptom, and rescue medication use responses to corticosteroids as compared with those who smoke less than 10 pack-years. We will analyze current (within one year) or former smokers (> 10 pack-years) vs. non-smokers (no smoking within 1 year and <10 pack-years). We know that initial patient screening in BELT eliminated 40-50% of the patients who appeared qualified based on current or prior (>10 pack-year smoking history). Thus, we expect that 40-50% of the patients in our current, pragmatic study will be current or former smokers.

Additional subgroups will include patients with high FeNO vs. low and Eosinophil count high vs. low. Regarding the FeNO subgroups measurement of FeNO at baseline, FeNO is a good marker of type 2 inflammation (Silkoff 2017). Type 2 inflammation is (i) driven by type 2 helper T and innate lymphoid cells, (ii) through the actions of the cellular mediators interleukins 4, 5, and 13, (iii) which results among other effects in eosinophil infiltration (Fahy 2015). FeNO is associated with all three of these features of type 2 inflammation. It correlates with the presence of the cellular drivers of type 2 inflammation (Liu 2015), and with high expression levels of interleukins 4, 5, and 13 (Peters 2014). FeNO also correlates with eosinophil infiltration as detected through the several ways of sampling for airway inflammation, including sputum (Gibson 2000), bronchoalveolar lavage fluid (Warke 2002), and bronchial biopsies (Ricciardolo 2012). Knowing that ICS therapy is particularly effective at targeting type 2 inflammation, and that FeNO is a marker of type 2 inflammation, it is not surprising that FeNO is also a marker of responsiveness to ICS therapy, as noted by the American Thoracic Society (Dweik 2011).

We will conduct a binary analysis with pre-specified thresholds (20 ppm and 30 ppm). In addition, we will conduct ROC analysis to identify optimal threshold for sensitivity and specificity. These analyses will be conducted in relation to our primary outcome (exacerbations) and our secondary outcomes. We will examine these outcomes in our intent-to-treat and our per-protocol populations. We will also test for heterogeneity based on race/ethnic status, smoking status, and additional factors enumerated in our primary protocol

Peripheral blood eosinophils identify asthmatics that are most responsive to Patient Activated Reliever-Triggered Inhaled CorticoSteroid (PARTICS). The PARTICS approach utilizes a patient-centric, provider-friendly approach to using inhaled corticosteroids. Inhaled corticosteroids (ICS) are the most effective medications for the treatment of asthma (Adams 2005, GINA guidelines 2014). The PARTICS approach relies on the fact that asthma is responsive to ICS (Haahtela 1991). Evolving data suggest that while the majority of asthma patients respond to ICS (Martin 2007), a significant minority might not (Woodruff 2009). It

appears that the majority that responds has a type of inflammation that is closely associated with eosinophils and is labeled Type 2 inflammation (Fahy 2015, Peters 2014). While this area is evolving, a recent review has suggested that blood eosinophils may be one of the best biomarkers to identify patients likely to respond to ICS or therapies directed at Type 2 patients (Pavord 2017). There has been enthusiasm about blood eosinophils since the sample is easily obtainable and the assay is available in ANY clinical laboratory. We will determine whether peripheral blood eosinophil count serves as an effect modifier of the relationship between treatment (PARTICS vs. usual care) and the study's primary outcome (number of asthma exacerbations per year). We will stratify participants based on a pre-specified peripheral blood eosinophil count threshold of 300/uL. This threshold is based on a frequently-used cutoff for 'eosinophil-high' status in the anti-eosinophil therapy literature (Giannetti 2016).

As discussed in section **III.E**, **Biostatistical analysis**, we will be adequately powered for both these subgroup analyses.

Additional exploratory subgroup will be considered including the following factors: 1) modality in which questionnaires have been returned; 2) patients' attitude towards ICS from the validated BMQ (skeptical (low necessity, high concerns), indifferent (low necessity, low concerns), ambivalent (high necessity, high concerns), accepting (high necessity, low concerns)); 3) presence of depressive symptoms (yes/no); 4) health literacy status (low or marginal versus high); and 5) Discrimination stressors from the everyday discrimination scale (SHORT).

C. Participant Recruitment, Screening, Enrollment, and Follow-up

1. Eligibility Criteria

INCLUSION CRITERIA

- Black or Hispanic based on self-identification (Hispanic if identify as both)
- Male and female, ages 18-75 years
- Ability to provide informed consent
- Clinical history consistent with asthma for > 1 year.
- Prescribed ICS as daily maintenance therapy
- Participant must also have an ACT score of 19 or less, **or** a history of one or more exacerbations in the past year that required patient report of systemic corticosteroid use.

EXCLUSION CRITERIA

- Life expectancy less than one year
- Known allergy to the ICS inhaler used in the study
- Having COPD or other chronic lung disease other than asthma; with the exception of the following:
  - Dx of COPD in a *never smoker* without any other lung disease or any other disease that might cause airway obstruction such as: Cystic Fibrosis, Connective Tissue Disease, premature birth, organ transplantation, bronchiectasis, sarcoid, and obliterative bronchiolitis
  - Dx of COPD in former smoker with normal PFTs done after the person quit smoking
  - Dx of COPD in current smoker with normal PFTs done in past 24 months

- Dx of COPD IN CURRENT OR FORMER SMOKER with obstruction on PFTs: normal diffusing capacity in past 24 months and demonstrated reversibility of 12% or more *at any time*

- Regular systemic corticosteroid use daily or every other day for any reason—including asthma or other medical reasons
- Use of systemic corticosteroid, or visit to the doctor's office, emergency department (ED) or urgent care, or overnight hospitalization for an asthma exacerbation in the past month (can wait and re-check eligibility after one month)
- Use of biologics (injections or infusion medicines): with the exception of the following:
  - the patient has been on a stable dose of a biologic for at least 6 months and,
    - must have had an exacerbation at least 2 months after starting on a biologic to be considered eligible **OR**
    - must have a current ACT score <=19 to be considered eligible.

- Bronchial thermoplasty less than 6 months ago (can re-check eligibility 6 months after procedure)
- Another family member living in the same household already enrolled in study

All sites will initially identify potentially eligible patients through specific searches of their EHR or data repository of EHR data designed to support research. Before contacting any patients, the provider or the practice Medical Director (who has been given permission to recruit on behalf of the practice) gives permission to contact the patient (this is the same for all contact scenarios). When an identified patient does not have a scheduled visit, the research coordinator will send an informational letter about the study that would ask if he/she is interested in hearing more about the study. The research coordinator's information will be listed for the patient to call if interested. Patients who do have a scheduled visit will receive a phone call from the research coordinator giving a brief overview of the study and asking if they would like to hear more about the study during the clinic visit. If the research coordinator was unable to get in touch with the patient by phone the coordinator would approach the patient during the clinic visit (if approved by the medical provider. Patients who are sent a letter and don't respond will be considered opt out. Patients who are called and do not want to learn more about the study will be considered opt out unless they indicate they would like to be contacted a later date. Patients who are seen in the clinic and do not want to participate, will be considered opt out unless indicating that they would like to be contacted at a later date.

Efficacy trials generally include only 5% of eligible asthmatics (Herland 2005, Travers 2007). In contrast, we have set broad eligibility criteria including allowing patients with a COPD diagnosis who meet the following criteria with regard to the COPD diagnosis: patient is a never smoker without any other lung disease or any other disease that might cause airway obstruction such as: Cystic Fibrosis, Connective Tissue Disease, premature birth, organ transplantation, bronchiectasis, sarcoid, and obliterative bronchiolitis; a former smoker with normal PFTs done after the person quit smoking; a current smoker with normal PFTs done in the past 24 months; a current or former smoker with obstruction on PFTs with normal diffusing capacity in the past 24 months and demonstrated reversibility of 12% or more at any time. This study includes smokers and COPD is a common co-diagnosis in patients from communities where smoking is prevalent. This approach is much more pragmatic and inclusive of patients who are likely to benefit from the intervention.

Furthermore, from our BELT study, we know that if we enroll patients on ICS who are not well

controlled using a standard asthma control instrument, or who are on an ICS/LABA, that one third will experience exacerbations over the next year. Additionally, patients with a history of exacerbation are at high risk for others (Miller 2007). In contrast to prior efficacy studies, we are not excluding current smokers (up to 25% of asthmatics), past smokers (10%- 25% of asthmatics and an even higher proportion of those turned away in our prior studies), or those with other comorbidities, or those who use other medications. We exclude only patients who cannot provide consent or who are not able to physically participate. We have included provisions for low literacy by providing oral materials for consent and a voice response system option in English and Spanish for those with limited literacy.

2. Recruitment and Screening

The Vanguard process is designed to track with the full study protocol as closely as possible to provide a piloting of the processes. As such participant recruitment will follow all of the methods outlined for the full study, as follows**.** Participant initial screening will primarily take place through searches of EHR data with an invitation to consider the study coming from the patient's practice. This could be in person at the time of a visit, through a letter, through a phone call or through a secure message in the site's EHR. Sites may use some or all of these techniques as best fits their patient population. For patients that respond with interest the study coordinator will do a brief screening during a real-time interaction, either face to face or via a secure telehealth connection. If the individual remains interested, the patient will then interact with the online enrollment system.

Full study difference: Sites with the ability to enroll patients at home will offer that option to patients who are interested in enrolling.

(a) Patient Enrollment System (PEERS)-

This system will be identical for the Vanguard process as it is for the full study. See **section II.F** for a description of the uses for this system, called Patient Engaged Electronic Reporting System (PEERS).

3. Randomization Scheme

- In the Vanguard study, 36 patients from 4 clinical sites (2 sites enroll AA patients, and the other 2 sites enroll H/L patients). Thirty two English speaking patients will be randomized at the 3:1 ratio (with 6 patients randomized to the intervention arm and 2 patients randomized to the enhanced usual care arm at each site. In other words, the Vanguard randomization scheme will only be stratified by site, and will not be stratified by race/ethnicity. In addition, 4 H/L Spanish speaking patients will be in placed in the intervention group to be able to sufficiently test the intervention materials.

- Full study difference: patients will be randomized stratifying by site, race/ethnicity (AA vs. H/L) using permuted blocks of size 4 and 8 through central randomization available online using the same system which will collect consents. Participants will be randomized in a 1:1 ratio of intervention to enhanced usual care.

4. Allocation Concealment

We will minimize selection bias by concealing the allocation sequence from those assigning participants to intervention groups until after consent has been executed and the patient has been entered into the central database. The allocation will be determined through web-based communication.

5. Blinding/medications

In keeping with a pragmatic trial, this will be an unblinded trial. Since the strategy is patient-activated, we will not enroll more than one patient per household. After knowing the treatment arm randomized to, each patient will watch a video that instructs him/her on how to get the medication he/she is assigned to receive. Although each individual patient or site investigator could know the randomized treatment arm a patient is assigned to, the randomization scheme for the full study will be kept confidential from all the investigators. Randomization scheme will be generated by the unblinded statistician at Duke Clinical Research Institute, and will be implemented by an authorized party who has no involvement in the conduct of the study. This blinding measure aims to eliminate any possibility that the study data is viewed aggregately by randomized treatment before the completion of the trial by anyone outside of the DCRI unblinded statistical team. In order to ensure all the study investigators are unbiased when making decisions during the conduct of the study, it is important to keep them blinded about the possible study results by treatment.

6. Sample size:

- Vanguard: 36 patients (16 AA and 20 H/L) from four sites that represent our study sites' geographic, health system and practice size diversity.
- Full study: Up to 1210 patients (1:1 randomization) will be enrolled in the study.

7. Follow-up Intensity

Aligned with the goals of a pragmatic trial, we have tried to minimize trial follow- up intensity so as to make the findings as applicable as possible. There are no required study visits after the enrollment visit. The patient monthly questionnaires are brief (5-10 minutes required) and will include reminders for both groups. Please reference the separate attachment for exact text to be used for the reminder included at the end of the survey**.** They will be completed by both the intervention and the usual-care group. Additionally, we have adding a modality of assessment of patient use of medications *non-invasively* by examining patient prescription refills in systems where patients receive medications or are centrally reimbursed. We are assessing provider intensity of compliance with NAEPP guidelines *non-invasively* through materials combining information from the

monthly patient questionnaires and information regarding drug prescribing in the EHR. o

Vanguard: Patients will be asked to complete a baseline survey at enrollment

- At 28 days they will receive a reminder to complete the next monthly survey through

their preferred method using their preferred reminder approach.
    - If they have not completed their monthly survey by day 30 they will receive a second reminder using the same method.
    - If they have not completed their survey by day 34 they will be added to a list for the central research team to call and help them complete the process either immediately over the phone or by having them engage their preferred completion method.
    - If patients have not completed their survey for 60 days or longer, they will be considered as having missed visit(s). One question will be added to their next Asthma Exacerbation Questionnaire (AEQ) about the number of asthma exacerbations since their last survey. Since the primary outcome of the full study is the intensity of asthma exacerbations during 15 months of follow-up, this added question will help capturing all the asthma exacerbations happened during follow-up period, even one or more monthly surveys are missed by patients.
    - This will be repeated each month. The next survey will be scheduled to be sent out on the same day of the month (for instance 3rd Tuesday) thereafter.
    - If the initial survey falls on a fifth day of the month the process will be moved to the 4th day of the month.
    - Participants will be asked to participate in short phone calls to assess ability to follow study instructions and study processes at 1, 6, and 12 weeks (see **Appendix C**).

- Full study difference**:** There will be no phone calls to assess ability to follow study instructions and study processes at 1, 6, and 12 weeks. In addition, the Full study will have up to 15 months of follow up questionnaires versus 3 months in the Vanguard.
    - At 26, 28 and 30 days they will receive reminders to complete the next monthly survey through all available methods provided by the patient, until they have completed their survey.
    - At day 27, the local site study coordinator will call the patient to make sure s/he received the monthly survey reminder.
    - If they have not completed their survey by day 32, they will be added to a list for the central research team to call and help them complete the process either immediately over the phone or by having them engage their preferred completion method.
    - If the telephone follow-up process does not produce an adequate response, we will consider mailing a paper survey to patients who do not respond
    - Each monthly survey sent to patients will be based on 30-day periods starting from the Baseline survey. The first month survey will be sent at 30 days, the second month survey will be sent at 60 days, and so on.
    - We completed African American enrollment. We are extending Hispanic/Latino enrollment for 3 months until April 30, 2020, but not extending the project period. If a patient is enrolled in February 2020, they would be followed for 14 months, March for 13 months, April for 12 months.

8. Adherence to the intervention

- Vanguard: will test these systems through our Vanguard cohort. To further assess the patients' understanding and acceptance of PARTICS, we will use inhaler monitors provided by Propeller Health (Madison, WI) attached to the patient's own SABA and the study-provided ICS. These devices record the number and time of each actuation and synch through phone or wireless plug-in wall modules. This information will allow us to

assess how often the SABA is used by each patient and the percentage of times that the study ICS is used in conjunction with the SABA and to cross-reference that information to the patient self-report on the questionnaires. We will cross-reference these data with ICS fulfillment data from TEVA's Specialty Pharmacy, Shared Solutions Pharmacy.

- Full study difference: There will be no sensor attached to the inhaler/s therefore data collected from a sensor with regards to inhaler usage.

We will assess clinician adherence with NAEPP guidelines in the care of the enrolled patients. Specifically, we will assess prescribing of daily controller medication rates for all enrolled subjects (all with have persistent asthma), rates of deteriorations with more than 2 days of symptoms which resulted in office visit but no use of oral steroid bursts, rates of step-up therapy following more than one exacerbations or deterioration within 6 weeks, rates of step-up therapy when patient monthly questionnaires report uncontrolled asthma by ACT or Asthma APGAR for 3 or more consecutive months and patient has an office visit during that time and step down following 6 or more months of no EMR-documented asthma problems or 6 consecutive months of patient reported controlled asthma on the monthly ACT or Asthma APGAR reports and an office visit at the end of that period (e.g. within the next 3 months). Documenting the prescribing of daily controller medications, use of oral steroid bursts and step-up and step-down therapy will also require links to the enrolled patients individual medication lists from the EMR and where possible to pharmacy fulfillment data.
This is a pragmatic trial, so we will be using practices that would be used in routine care to help patients adhere to their treatment arm. We will send two messages to all treating clinicians of patients enrolled in the PARTICS intervention arm. The first message is embedded within the EMR, and notifies the clinician that their patient is participating in the study, and asks them not to change the patient's study medication instructions without contacting the PREPARE study team. The second message is a letter to all treating clinicians with basic information about the study, so clinicians do not interfere with the instructions that are given to the intervention patients in the study. The exact text for these messages are uploaded in a separate attachment.

9. Enrollment and Restriction of participants

Vanguard: We will enroll 36 patients at 4 sites to test the study design process.

Full study difference: We will enroll up to 1210 patients. Using a very conservative estimate that 50% of those approached who are eligible will enroll (2400 leading to 1210) we will need 2400 eligible patients to be approached. Considering our reduced entry criteria and the EHR's ability to identify patients taking the required medications, we assume 80% of those identified will qualify when screened (3000 leading to 2400).

10. Source and volume of patients

All participating sites have searched their respective Electronic Health Records for patients who meet inclusion criteria. Each site is expected to recruit based on results of the EHR search. Recruitment ranges from 20-200 depending on the site. Section IV.F lists all sites and expected enrollment rate. Recruitment should be improved compared with classic RCTs because this study does not require extensive reporting expectations of participants (monthly surveys are streamlined, can be completed through multiple methods, and are linked with reasonable reimbursement for time spent answering them).

The Vanguard activities will assist in identifying major barriers to recruitment not already accounted for to allow for adjustments of the study protocol. During our initial engagement activities with the African American and Hispanic/Latino patients and other stakeholders, we have begun identifying potential barriers to dissemination and implementation of our results. Below are examples of barriers identified by each stakeholder group and suggested solutions developed by the stakeholders and our dissemination work group. Our Vanguard process will further facilitate our understanding and approach to addressing barriers.

11. Justification of expected participation rate

Vanguard: The four sites selected and agreeable to recruit during the Vanguard phase have reported high counts of patients who meet criteria. This was necessary because the Vanguard patients will not be eligible for the Full study. Also, having high counts of eligible patients will enable the sites to recruit 8 patients each in a short period of time.

Most of the sites have successfully recruited asthma patients for previous studies (e.g. the BELT trial). Site-provided numbers of AA or H/L individuals with asthma on an ICS are available from their EHR. A tabular summary of these sites is included in Consortium Contractual Arrangements. We have identified a total of >20,000 eligible patients. Based on previous studies, we believe that we are well within capacity for that recruitment, which we believe will only require 3000 EHR identified patients. Further, study design will improve our ability to enroll identified potential participants. One, our relaxed exclusion criteria will allow for fewer exclusions of identified patients. For example, BELT, sites recruited ~14% of EHR identified patients (1100/~8000). The main reason interested patients were excluded from BELT related to current or past smoking (~40% of EHR identified patients). Using these patient numbers we have budgeted for each site to recruit no more than 10 and 15% of all initially eligible patients into the study. Two, another common reason for not participating in BELT was the 50% chance of receiving an “experimental drug” and having to change current medications. This will not be the case for PREPARE since both treatment arms will continue using their same controller medications, and the experimental arm will test the use of a non-experimental drug (ICS) using a new medication administration strategy (PARTICS). Three, BELT included a genetic analysis which turned many potential participants away from enrolling. Assuming only a 10% increase through avoiding these last two BELT related recruitment issues would bring the recruitment rate to ~25% ((0.14/0.6*1.10). Overall sites can recruit at approximately one half to one quarter of this rate (AA 600/12,871 = 4.7%, H/L 600/7170 = 8.4%) and still fulfill their recruitment expectations. Furthermore, if needed we can add two more sites to the 14 who have already committed to the study. Site specific estimates are supplied in the Participating Sites and Resources section.

Full study difference: Up to 20 clinical sites with experienced investigators and co- investigators will recruit up to 1210 patients meeting eligibility criteria.

12. Maximizing adherence to the enrollment plan

Vanguard: the duration of the Vanguard process is only three months and participants will be contacted at 1, 6 and 12 weeks to be asked about the study process and logistics. We expect this frequency of contact will result in high adherence. Further, the Vanguard process is explicitly designed to test all of our protocol processes and is specifically relies on participant feedback. We expect that this relationship between participants and study coordinators will result in high adherence.

Full study difference: Participants will not be called at 1, 6 and 12 weeks. However, weekly calls between site recruiters and the trial management team will help keep recruiting practices the same from site to site. Most importantly, the use of videos and computer "face-to-face" consenting using centralized coordinator staff from health care system will reduce variability.

13. Literacy and Minority Issues

The PREPARE study focuses on minority populations, limiting its enrollment to AAs and H/Ls. To ensure that literacy does not interfere with trial recruitment or data collection, all written trial material (English and Spanish) will be designed for a low- literacy audience. We will prepare video-based materials in English and Spanish for those who have trouble reading. English or Spanish videos will contain members of the group with which the patient self-identifies. All materials will be trialed and refined in the Vanguard process, in conjunction with feedback from our patient advocates and patient stakeholders.

14. Strategy for Balancing Internal Validity and Generalizability

We propose a randomized, unblinded, pragmatic trial with minimal barriers to patient entry. It is being conducted in vulnerable populations, in multiple real world settings, with minimal invasive" or behavior-altering monitoring, no required follow-up visits, and easy application—all aimed at broadening applicability, easing dissemination, and supporting sustainability. Our considerations are as follows:

(a) Degree of flexibility and complexity of intervention

Vanguard: in keeping with our desire to maximize generalizability and ease dissemination, we have maximized the flexibility by which the experimental intervention is applied. We have also minimized the degree of provider expertise needed to apply and monitor the experimental and comparison interventions. The intervention provides maximum flexibility to patients since they control the frequency and timing of doses in the experimental intervention. Additionally, other medications, including other asthma medications are not restricted. This represents a minimally complex session for providers with low time commitment and provides CME credits, thus enhancing opportunities for successful dissemination and sustainability.

This phase will call for additional phone calls to monitor the study process. These phone calls are also low complexity.

Full study difference: There will be one phone call within one month of enrollment to ask the patient about receiving the survey reminder and filling out the survey.

Vanguard: will test and assess our questionnaires and collection systems through our Vanguard cohort not patient outcomes.

Full study difference: There will be no assessment of questionnaires and collection systems. The outcomes are obtained from a mix of patient self-report on the monthly questionnaires, electronic records, and prescription refill information. Other than the first, they represent no burden for the patient or provider. Based on feedback from our patient advisors, we have

minimized the burden of the patient questionnaires by providing multiple modalities for completion. Many of the instruments have been validated across modalities.

(b) Recruiting and Enrolling a Representative Population and Avoiding Selection Bias

We are focusing on AA and H/L populations since they are highly affected by asthma and represent some of the greatest challenges in terms of therapy implementation. We are striving to obtain a representative population by reasonable geographic distribution across multiple different health systems. In concert with a pragmatic trial, we have set our inclusion criteria quite broadly with few exclusions. We plan to enroll patients with low literacy by having all our consenting and explanatory materials in video formats and apply to IRBs for permission for video/verbal consent. Patients will be identified through searches of provider databases.

A few different basic approaches to recruitment will be utilized. For those patients with scheduled visits, attempts will be made to contact them before the office visit to see if they are willing to spend extra time to learn about the study. At the office visit, the patient will be asked if he or she is interested in hearing more about the study and offered parking or other accommodation (patient-partner recommendation) to stay to review the video information and consent materials. If the patient consents, he or she will be entered into the trial. Sites will also be asked to contact patients who appear to be eligible but make only infrequent office visits through letters or phone calls from their offices. These individuals will be asked to call the study coordinator to learn more about the study. Most individuals who are interested in learning more about the study will be asked to schedule a visit with the study coordinator at their usual care setting.

We will further modify and refine our recruitment and enrollment methods via patient partner advice. By including patients during office visits as well as through **community** outreach, the study will minimize biases towards those patients with higher compliance with office visits or higher severity of disease requiring more frequent visits.

Advertising

A flyer with information about the study will be posted on appropriate research boards at study recruitment facilities. This same flyer will be sent via email to research study distribution lists that are designed for patient recruitment, posted in local newspapers, and disseminated at community centers, such as community churches and local community centers.

15. Other Full study changes

No additional differences from the Vanguard though these areas will be explored during the various phone interactions to collect study process information.

D. Study Procedures

1. Informed Consent

a. Vanguard: Our informed consent documents are meant to be brief while providing the patients with the information required determining their desire to participate in the study and meet the requirements of all involved IRBs. Informed consent form will be uniform

throughout the sites except as required by a site's IRB; a central IRB will apply to all sites where this is feasible. Multiple approaches to completion of informed consent will be available to facilitate enrollment. Most patients will be consented online, using a study consent form embedded in the PEERS data collection, prior to patient registration which may include a web (visual) conference between the subject and the study staff who will review all study details similar to an in-person visit. The consent component of the PEERS system has been used for multiple previous studies. Data collected prior to consent is anonymous and remains so if the patient decides not to participate in the study. Once the patient provides consent not only is that information stored but selected responses from prior to the consent process can be used to supplement the intake survey data.

If a site's IRB requires modifications to the consent forms, a separate consent for that site will be provided which will then link the participants to the central PEERS system. All subjects will be provided with the informed consent form/web site when the study site investigators have determined they may be an acceptable candidate for randomization. An invitational video will be followed by an eligibility questionnaire. Participants not found to be eligible will be requested to voluntarily and anonymously provide their gender, race and ethnicity for tracking purposes for the final study CONSORT diagram. For eligible patients the consent process will include the aims of the study, the data collection, follow-up requirements, and all potential risks and benefits of the study. A research coordinator will be available to discuss the study with the subject or answer questions.

Informed consent will be obtained before any study data is collected in an identifiable manner. All participants' interactions with the system are tracked anonymously prior to consent. Documentation of this process will be required, the subject will e-sign the informed consent document or sign a paper consent form if required by the local IRB. Electronic signatures will be maintained by the PEERS system and documentation of each enrolled participant's consent will be provided to the AAFP NRN by each site obtaining it. Paper consent forms will be maintained at the site as part of the subject's research records (which may be separate from their medical records) as well as a copy provided to the AAFP NRN and to the participant. No participant will be enrolled without documentation of informed consent and no waivers of this process will be sought or granted due to the use of the addition of a medication in the intervention. The PEERS system has been used for many studies with online consent approved by over 15 IRBs across the country.

(b) **Full study difference:** The patient will not have to agree to the Propeller User Agreement because there will be no sensor/s used in the full study.

2. Study Questionnaires

(a) PREPARE questionnaires

Asthma Exacerbation Questionnaire (AEQ):

Our primary outcome, the rate of asthma exacerbations per year, is defined as the number of exacerbations, emergency room visits, or hospitalizations requiring oral or parenteral corticosteroids, per patient per year. It will be captured by subject self-report via a monthly asthma exacerbations questionnaire (AEQ). Reports will be substantiated by verification in the

EHR or direct patient interview. Multiple clinical trials demonstrate convergent validity with other measures of asthma-related health status (Busse 2011, Peters 2010, Lemanske 2010) and their responsiveness to intervention (O'Byrne, 2005). We previously developed, tested, and used the AEQ as part of the BELT trial, in which we enrolled >1,000 AA patients. The AEQ is sensitive but not specific, meaning it overestimates the number of true exacerbations and therefore requires confirmation, but is not likely to miss exacerbations. Therefore, we will use the medical records or, if necessary, contact all patients whose form suggested an exacerbation to confirm. We will categorize these exacerbations as to whether they resulted in a hospitalization or emergency department visit.

Asthma Control Test (ACT)

The ACT is easy to use, patient completed, and assesses the frequency of shortness of breath, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. The ACT has been evaluated in independent study population samples and can be self-administered in person or at home (Schatz 2007a), by telephone (Schatz 2007b) and by mail (Schatz 2007c). The ACT has been recommended by the NAEPP and the NIH Asthma outcome workshop (NAEPP 2007, Cloutier 2012) because of the extensive validation data for these tools, using the widest range of criterion and construct measures, including demonstration of responsiveness to therapy and a minimal clinically important difference (MCID). The MCID is defined as the smallest difference in a given score of interest which *patients* perceive as beneficial and which would support a change in the patient's *management* (Jaeschke 1989). The MCID for the ACT has been defined as 3 for individuals over time and between populations (Schatz 2009) and cut-off values for uncontrolled asthma:

ACT ≤ 19 (Nathan 2004), and "very poorly controlled" asthma: ACT ≤ 15 have been established. (Schatz 2006, Nathan 2004).

Asthma APGAR

The Asthma APGAR is a next generation control assessment that is linked to tools for primary care physicians to suggest next steps. (Yawn 2009). The tool has been shown to produce similar control status to the ACT. (Rank 2014) using 3 questions and considering a score of >2 as inadequate control. The same tool is used for children and adults. By allowing one version for all ages and to require only three responses, the Asthma APGAR may be easier to use that older longer control assessments. In addition, implementing the Asthma APGAR in practice has been shown to reduce asthma exacerbation related emergency department and hospitalizations by 50%. (Yawn 2016 JAMA in press).

Asthma Symptom Utility Index (ASUI)

The ASUI is probably the symptom scale most frequently used in asthma studies including large multicenter clinical trials (Boushey 2005). The ASUI's psychometric properties are well documented and support the reliability and construct validity of the instrument, including internal consistency reliability and test-retest reliability. The minimum clinically important difference has been determined as 0.09 points (Bime 2012).

Days Lost from Work or School

Days lost from work and school will be collected using a validated questionnaire developed and utilized as part of the National Health Interview Survey (NHIS 2014). Our patient partners felt that this was a very important outcome they would be interested in.

Demographics

Eligibility

Co-morbidities

Asthma medications

Smoking status

Exacerbations in past 12 months

Health Literacy-Brief Form

The 3 question version of the health literacy assessment will be used. This has been compared to the longer TOHFL which is not validated for self-administration and is lengthy. The short version of the Watson scale had a AUC of .79 compared to the TOHFL for clinic patients. (Wallson JGIM 2013). The questions are designed to be self- administered.

The Beliefs about Medication Questionnaire (BMQ –Asthma Specific)

The BMQ Asthma Specific is a measure of patient beliefs about their asthma and asthma medications. There are two scales in the BMQ: one that assesses patients' beliefs about the necessity of controller (i.e., ICS) medication for managing their asthma (Necessity scale), and another scale which measures worries and concerns about possible negative consequences of using their medication (Concerns scale). The BMQ is a validated instrument has been widely used in asthma and other chronic illnesses and has been shown to be a robust predictor of adherence with chronic therapy. (Menckeberg 2008)

Patient Health Questionnaire (PHQ)-2

The PHQ-2 asks two questions that screen for depression and has been shown to be a valid and reliable measure. The PHQ-2 has up to 97 percent sensitivity and 67 percent specificity in adults, with a 38 percent positive predictive value and 93 percent negative predictive value (Whooley, 1997).

Dose counter data for rescue ICS and SABA

Vanguard specific questions:

- Satisfaction with therapy (intervention only)
- Assessment of enrollment process
- Assessment of receiving 1st inhaler—intervention only
- Assessment of monthly questionnaire process
- Assessment of QVAR refill process—intervention only
- Overall assessment of study participation
- Which inhalers are you using for rescue?
- If you have seen your clinician, did you discuss your rescue medicines?
- Did seeing your clinician result in you making any changes in recommendations from those given by the study materials?
- Is the pouch helpful?
- Do you carry the pouch with you outside of the house?

- How frequently do you carry the pouch with you outside the house?
- Have you talked to any other person about your rescue inhalers—such as family, friends, others with asthma?
- Did they give you any different advice?
- Did that change what you are taking for rescue inhalers? If so, how?

Discrimination Scale

The short version of the 'Everyday Discrimination Scale' consists of 5-questions with answer choices that range in a Likert scale. It has an alpha = 0.77 and has been used in tested in multiple other chronic diseases, such as cardiovascular disease. Its results have been used in those disease to support a positive association between degrees of perceived discrimination and prevalence of chronic disease. This scale has not been used in a large-scale study of African-American/Black and Hispanic/Latino patients, and therefore, our results would be novel. These could help determine the underpinnings of the increased asthma-related morbidity and mortality rates observed in these communities.

Payer's Scale

Health system use metrics of patient's overall health status and health related quality of life when determining which therapies to recommend or include in their pharmacy benefits. We have included questions commonly considered important in the decisions to facilitate our dissemination activities at completion of this trial.

COVID-19 Questionnaire (short)

It has been reported that COVID-19 is disproportionately affecting minority populations in terms of its direct effects related to the frequency and the morbidity of those infected. To understand the effect on our at risk PREPARE study population of African American/Blacks and Hispanic/Latinos, we have developed and added a short questionnaire, to the current monthly surveys for our study patients regarding COVID19:

- Have they been diagnosed with COVID-19
- Did they have a test
- Symptoms
- Psychosocial – (job, ability to get asthma meds, etc.)

(b) Questionnaires administered, by study phase and visit

1. Vanguard [Complete]

Tool or domain	Baseline	1 week	6 weeks	12 weeks
Eligibility	X			
Demographics	X			
Co-morbidities	X			
Asthma medications	X			X
Exacerbations	X			X
Smoking status	X			X

Lost days of work or school	X			X
Beliefs about Medications Questionnaire—asthma	X			
Health Literacy-Brief Form	X			
PHQ-2	X			
MARS-5 adherence	X			
Perceived stress	X			
Asthma Symptom Utility Index	X			X
Asthma APGAR (control)	X			X
Asthma Control Test	X			X
Ask-12 (adherence likelihood)				
Vanguard telephone interview questions:				
Inhaler dose counter # Usual rescues Maintenance (non-pouch) QVAR (intervention)		X	X	X
Address change		X	X	
Satisfaction with therapy (intervention only)				X
Assessment of enrollment process		X		
Assessment of monthly questionnaire process			X	X
Assessment of QVAR refill process—intervention only		X	X	X
Overall assessment of study participation				X

2. Full Study

Tool or domain	Baseline	Monthly	Final Survey
Eligibility	X		
Demographics	X		
Co-morbidities	X		
Asthma medications	X	X	X
Exacerbations	X	X	X
Smoking status	X	X	X
Lost days of work or school	X	X	X
Beliefs about Medications Questionnaire—asthma	X		
Health Literacy-Brief Form	X		
PHQ-2	X		
MARS-5 adherence questions	X		X
Perceived Stress Index	X		
Asthma Symptom Utility Index	X	X	X
Asthma APGAR (control)	X	X	X
Asthma Control Test	X	X	X
Payers Scale	X		
Everyday Discrimination Scale (SHORT)	X		
Satisfaction with therapy (intervention only)			X
Refill information		X	X
Address change		X	
Permission to contact for additional questions related to PREPARE			X
Permission to contact for future studies			X
COVID-19 questionnaire (SHORT)		X	X

3. Unbiased and systematic data collection:

Vanguard:

- To maximize compliance and reduce bias, these questionnaires *can be completed through various ways matched to participant preference and literacy level*--mailed questionnaire, email, text, telephone, smart-phone, and website. Our patient partners emphasized that such varied techniques are necessary to assure that we do not bias our results to those interested in responding via specific modality. We will also reimburse participants $20/questionnaire to compensate patients for their time for completing each questionnaire. Trial staff will follow up with participants who do not complete their monthly questionnaires. We used these techniques in the BELT trial in which we enrolled >1,000 AA patients and achieved >75% survey completion using only paper and phone techniques. Patients will be notified to complete monthly survey by their method of choice. If patient has requested a paper survey, it is mailed to him/her. If the patient has not completed the survey in 7 days a reminder is sent

(post card). If the patient has not completed the survey in 7 more days then patient is added to central research team queue to be contacted directly either by phone, email or text. The patient will stay on this list until the survey has been completed/received.

- Additional questionnaires asking about the study process will be administered (as shown above). Procedurally, participants enrolled in the Vanguard assigned to the treatment arm will be asked at 6 weeks to request an ICS refill. Participants will either be asked verbally or get a post card at enrollment to call to test the system for requesting an ICS refill. Further, they will be asked to call for ICS refills when their ICS inhaler reaches the 100 (out of 120) remaining puff threshold. This is to facilitate refill requests being placed during the short Vanguard process. In addition, we will track patients' usage of their inhalers with a sensor made by Propeller Health. Patients in the intervention group will have a sensor attached to both the rescue medication and ICS that they will keep in the pouch provided to them. The patients in the control group will receive a sensor to track usage of their rescue medication (a pouch is provided for the patient to carry their rescue inhaler). The sensor system includes a hub that will be plugged in at the patient's home and will transmit data to a secure database at Propeller Health. Once a month the data will be sent to the data coordinating center. Otherwise, there will not be other procedural or data collection differences between the full study and the Vanguard process.

- Full study differences**:** There will be no additional questionnaires as described in the first paragraph above**.** All follow-up will be via phone as outlined in the previous section, "Follow Up Intensity."

4. Medications and reimbursement

Vanguard: We will use a real-life distribution system (Teva's specialty pharmacy, Shared Solutions through electronic scripts in the EHR). Teva will collaborate with us to implement the study and distribute and monitor drug disbursement. Shared Solutions Pharmacy will act as our central pharmacy. Therefore will *de facto* be able to demonstrate that the delivery is feasible, sustainable, and scalable across the United States.

There will be no cost for the ICS inhaler. The Teva pharmaceutical company has agreed to donate ICS (beclomethasone diproprionate HFA, QVAR. Patients will order refills from Teva's specialty pharmacy, Shared Solutions.

Full study differences: The QVAR inhaler will change to the QVAR® RediHaler™

5. Fractional exhaled nitric oxide (FeNO) test:

During the study visit, we will ask participants to exhale into a machine that determines nitric oxide gas levels in their breath. This procedure was not conducted in the Vanguard phase, and will only be conducted during the full study.

6. Blood draw (Eosinophils):

During the enrollment visit, we will ask each participant if s/he agrees to have blood drawn.

The blood draw is to determine Eosinophil counts which are known to be associated with response to Inhaled Corticosteroids. The test used will be a complete blood count with differential (CBC with differential). The amount of blood needed for this test is 3 mL, collected in a purple top tube. This will be the only blood draw for the participant throughout the study. This procedure will only be conducted during the full study.

E. Participant and Patient Retention

Vanguard: Participant retention will be monitored through the monthly survey process. During the survey completion process no attempt will be made to alter a participant's medication use, whether in the intervention or enhanced usual care arms. Participants will receive two automated reminders followed by in person follow up in an attempt to complete the monthly surveys. Participants will be asked to provide a contact person that is likely to know how to contact the patient should their phone or address change. The local site staff will also be asked to help locate patients lost to contact. At regular intervals across the study a small number of gift items will be provided to a randomly selected individual that has completed the last three monthly questionnaires. Patients will also be paid $20 for their time in completing the each of the monthly questionnaires, as well as once at the end of the Vanguard when patients return their sensor, using the ClinCard research debit card system. If patients receive overages on their smartphone bills as a result of answering the questionnaires, they will receive $5 per questionnaire on their ClinCard. In addition retention in the Vanguard process will be assisted with multiple brief phone contacts to assess study processes.
These contacts will not take place in the full study as they would represent a type of case management and thus an intervention in their own right.

- Full study differences: Patients who fill out their monthly survey within 6 days of receiving their first reminder on day 26, will be entered into a lottery/raffle. They will have a chance to win one of three $100 prizes each month. Sites located in Florida will not participate in the lottery due to state restrictions.

  In addition, we will be implementing a few additions to focus on patient retention and engagement during the study. We will:
  - send an appreciation card semi-annually to patients to keep in contact with them.
  - send a quarterly text message reminder (to all patients who have enabled text message reminders) about their treatment arm to encourage adherence to their medications and remind them about completing their monthly surveys.
  - send announcements via text message about winners of the lottery prizes (excluding any personal information), to help motivate patients to complete their surveys in a timely manner.

  Exact text for these outreach methods are uploaded as separate attachments.

- Data Collection and Quality

Vanguard: there will be some additional questions in the monthly surveys otherwise the system will be identical.

1. Database Design and Administration

The electronic data capturing system PEERS will be designed and programmed by the University of Colorado Denver, Department of Family Medicine (UCDFM). The data collection system will be reviewed by the study team, undergo User Acceptance Testing (UAT) and Quality Assurance (QA) before being made available for data entry.
Throughout the study, the system will be monitored both by UCDFM and the Statistical DCC at Duke Clinical Research Institute (DCRI), with quality issues being identified, logged, and action plans developed.

Access to the data collection system and database should be strictly controlled and well documented. Personnel at UCDFM and the Statistical DCC of DCRI will have no right to delete or change data. Only the site and central site users will have this ability. Data cleaning will be done by automatic or manually created queries to the site users who will need to confirm and change data in response. All the data changes will be tracked by the system and stored in a database audit trail which can be accessed as needed.

Our database will include the following major covariates: age, gender, prior corticosteroid bursts in past year (Y/N), ICS/LABA prescription, and current smoking (Y/N). Age and gender will be self- reported and can be checked against medical records. Corticosteroid bursts in the past year are subject to recall issues. However, patient-reported bursts have been shown to correlate with the likelihood of prospective
bursts (Miller 2007).

In addition, where available we will search the patient's prescription records for bursts of prednisone. With regards to smoking, while imperfect we will use the validated questions used in national surveys in section 7 of the CDC Behavioral Risk Factor Surveillance System (CDC 2013). ICS/LABA use will be confirmed through the medical record.

No complex data linkages will be required for this project. All patients will be consented, so we can link records using 'clear text' methods. Furthermore, all existing health data will come from the sites, and thus will be linked prior to being transferred to the research team. Given the small number of patients per site, if any concerns were to arise, questionable linkages can be manually checked. We will use EHR data to supplement the evaluation of asthma care by participating clinicians. This will include a limited de- identified data set related to asthma diagnosis and care (e.g. rates of controller therapy for patients with persistent asthma and rates of use of oral steroids for asthma exacerbations in the non-enrolled patients) for all patients for the practice with asthma and linking of EHR data to study participants for similar assessed. In addition, to determine if COVID 19 has an impact on asthma and asthma care we will extract COVID PCR and/or serology data when available. Pharmacy fulfillment data will be cross-checked by date of birth. For the general population of asthma patients, no record linkages are planned.

Outcomes will primarily be identified through monthly patient questionnaires. The responses to these questionnaires will serve as a trigger to undertake further review of medical records data. Discrete EHR data may be misleading in a study of this nature.

Exacerbations will be identified from patient reported data in the monthly questionnaires. That data will include acute increases in asthma symptoms that result in an asthma related

hospitalization or being given a prescription for oral steroids during an asthma related emergency room visit, clinic visit or telephone consultation. The occurrence of the hospitalization or visit and the prescribing of oral steroids will be confirmed by querying the patient's EHR. Most of our sites have confirmed that ED and hospital visits areusually included within their EHR. However, if the information is not available, e.g. hospitalization not document in the clinic record or patient self treating with oral steroids previously prescribed for home use, the information will be confirmed by a call to the patients by a study nurse or coordinator requesting more specifics such as the exact date and the name of the prescription and duration of use or the name and duration of stay at a hospital.

All exacerbations will be reviewed by a team of 3 physicians blinded to the patient study assignment. A study nurse or coordinator will obtain the documents required for review and make sure that any information related to study arm assignment, intervention or enhanced usual care, is redacted. Drs. Pace, Carroll and Cardet will do the initial review. If all 3 agree that it is or is not an exacerbation that decision will be accepted. If they do not have unanimous agreement, the event and all information will be sent to the adjudication team, Drs. Israel, Fuhlbrigge and Yawn to make a final decision. All physicians assessing or adjudicating exacerbations will be blinded to randomization.

The Policy Stakeholder Group requested additional data elements for secondary analyses-- total number of asthma related visits made to the enrolling site, ED visits, hospitalizations, and total asthma medication usage. The Policy Stakeholder Group was interested in how PARTICS might affect visits not associated with an exacerbation and thus not captured with our original data collection plan. In addition to asking patients o their monthly questionnaires, we will also ask all sites to provide site-generated billing data for their patients from one year prior to the date of consent 12 to15 months following consent (depending on when the patient was enrolled). It will be adjusted for a 12 month rate. Thus, we will be able to compare between-groups visit frequencies as well as within-group visit frequencies over time. The impact on total asthma medication could influence the ease of acceptance of this strategy during dissemination.

Full study differences: The additional questionnaires used in the Vanguard (as noted above in pages 38-39) will not be included in the Full study monthly questionnaires.

2. Data Monitoring and Site Auditing

The PEERS system will be programmed such that patient intake, baseline and monthly questionnaire data is required to be completed prior to advancing to the next section. Thus, patients who complete the consent, enrollment, baseline and monthly data collection processes should have complete data. All outcome data will be selected from radio button or pick list questions and thus data will be codified at the time of capture. The PEERS system will also provide an administrative section for each site as well as the local research team. This section will provide patient contact information following consent. Allow messaging between the sites and the AAFP NRN staff and allow study staff to collect patient data using a computer assisted survey process when needed. Sites are primarily being asked to enroll patients. The eligibility criteria will be built into the consent process. The enrollment rate will be tracked using the administrative processes for the AAFP NRN within PEERS. If a site uses a paper method for any consents then an administrative page will be created to allow the local site to complete the eligibility criteria after consent is obtained. These sites will be monitored by a daily PEERS report to the central AAFP NRN staff. If a site appears to be struggling with recruitment the AAFP NRN staff may make a site visit to see if they can assist with rethinking the recruitment

process.

3. Methodology for Collecting Patient Consent and Questionnaire Data

The Patient Engaged Electronic Reporting System (PEERS) has been developed and enhanced over the past 15 years by the University of Colorado, Department of Family Medicine (CUDFM.) The system is licensed to the DARTNet Institute and will be customized and provided to the study through a purchased services agreement between the AAFP and DARTNet. The system is a HIPAA compliant, multi-modal, fully localized patient data collection and study management system. The system is used for both clinical care and research. The system is a table driven data collection system with advanced within questionnaire data management as well as between questionnaire data management. Many of the advanced features will not be necessary for this project.

At enrollment, following consent, patients will provide all available contact methods (phone number, email, text) and will receive reminders on all methods provided. All messages are HIPAA compliant (no clinical information is included) and provide a link the appropriate login system (browser/mobile browser for email or text message and interactive voice response system for phone messages.) Patients may move between data collection systems as they wish.

PEERS is hosted in the CUDFM data center (which also serves as the HIPAA compliant data center for all DARTNet activities.) This center is secured environment with 24 hour police monitoring, password controlled entry that is monitored as well as both local and central police alerts for open/ajar doors. The entire center is located behind the University of Colorado Palo Alto firewall with advanced intrusion detection software and monthly remote server auditing for security. The data environment is located behind a second, research/clinical firewall maintained by the CUDFM informatics staff. All data transmissions for end users are encrypted. The CUDFM maintains daily incremental back-ups, weekly system images and monthly full file level back-ups. Off- site and cloud back-up storage is maintained with a 12-month rotation system.

4. Database Lock

The study database will be locked after the data are reviewed by both CUDFM and the DCRI statistical team to ensure that the datasets provided for analyses are complete and accurate. The final datasets will be exported into SAS and provided to the DCRI statistical team through a secured website.

F. Engagement Plan

1. Stakeholder Groups

Patients, patient advocacy groups, providers, including pharmacists, professional societies, healthcare policy experts, and content experts have all been engaged from the beginning in formulating our question, identifying the study groups (AA and H/L adults), selecting the intervention (PARTICS) and the Asthma IQ, choosing outcomes (exacerbations and missed work and school days), and suggesting the exploratory aims and analyses for this PREPARE study. Our stakeholders, especially our patient partners and their advocates have been, and will be, integral parts of the study of the study team. Below, we describe their involvement in planning the proposal up to now, review how the study governance includes them going forward using the Vanguard cycle as an example, and explain their proposed

involvement in the subsequent parts of the study including data interpretation, results presentation and dissemination. We have been working with 6 stakeholder groups. Three separate groups were created for patients including AA partners, H/L partners, and advocacy groups. The patient partners have been working with us over the past year. We have also included provider groups (those participating in the study), professional society stakeholders from the major lung and allergy societies, health policy partners (including insurance, national pharmacy, population management, and Center for Medicare/Medicaid Services representatives), and clinical trial specialists including those with experience recruiting AA and H/L populations.

2. Organizational Participation of the Stakeholders

The patients and other stakeholder groups are tightly interwoven into the study governance. They represent 8 out of 9 groups (8 out of 13 individuals) on the Executive Committee that meets monthly to monitor and govern the study. In addition, each of the stakeholder groups has a specific co-Investigator liaison on the Operations Committee (OC) (responsible for supervising operations). These liaisons are responsible for managing interactions with each stakeholder group. Due to the importance of the patient voice in this research, we are employing Ms. Rodriguez-Louis, an AA/Hispanic asthma educator as a specific manager of these interactions assisted by Dr. Fagan, an expert in community outreach. A Spanish interpreter (Hebbert) has been provided, if desired by any H/L stakeholder. Ms. Rodriguez-Louis will be a member of the Executive Committee as well as the Operations Committee. All stakeholders will be invited and reimbursed for attending the 2 day study start-up meeting to engage all participants and to hear patient voices. In addition, there will be a 2-day meeting in year 5 for the whole team to work on analysis, interpretation and development of understandable messages. Before and between the in-person meetings, the groups will meet regularly by conference call and webinar to assure they are fully engaged in following the study progress and dealing with problems that arise in the conduct of any study. Further, we are not only incorporating the voice our patient stakeholders in our study, we are actually incorporating actual patient subject voice into designing our study as described in our Vanguard study process. During the final 2 years, our stakeholders will spend considerable time helping us develop the dissemination goals and strategies that they have already begun to consider. All partners and stakeholders are compensated for their time and attendance at equal rates. Patient input will be channeled through two different mechanisms throughout this trial. Dr. Juan Carlos Cardet, a native of Puerto Rico, and Ms. Jacqueline Rodriquez, an African-American educator, will be the Operations Committee representatives to the H/L and AA patients. With the assistance of our patient facilitators, they will meet regularly and an on ad hoc basis (frequency will depend on the phase of the study with their respective groups to seek their feedback and communicate their input for the Operations Committee. Additionally, the groups will have direct representation on the Executive Committee of the study. Suzanne Madison, Margie Lorenzi, and Barbara Kaplan will respectively represent the AA, H/L, and patient advocacy committees to the Executive Committee. The Executive Committee sets the policy for the entire study, approves all protocols, approves all budgets and extraordinary expenditures, established new committees, and reviews all publications and communications. Additionally, all committees and subcommittees to be established will either include representatives of the patient stakeholder committees, e.g., dissemination, or include specific liaisons who will be responsible for meeting with, and channeling, stakeholder input.

G. Project Milestones and Timeline

Work in the first nine months will focus on obtaining initial IRB approvals, developing training materials, and preparing the data collection systems, the patient contact systems, and reminder systems for surveys.
From Q3 of Year 1 – 1st month of Year 2, we will enroll the Vanguard cohort, extensively evaluate and work with our stakeholders to interpret the data from the Vanguard assessments. The Vanguard data will be important in the stakeholders' work to finalize the protocol, and modify and finalize patient and clinician education materials.
At the end of year one and in Q1 of year 2 site recruitment will be completed, training and IRB approval of the final protocol will occur.
The first patient will be enrolled at the end of Q1 of Year 2, and enrollment will end during Q1 Year 4 with follow up of last patient completed by Q1, year 5.
For Vanguard 5 months after the contract, and complete it within 6 months Throughout the period of patient enrollment and follow up, we will work with our patient and other stakeholders to address implementation issues such as slow recruitment, incomplete patient retention, problems with training materials, low response to monthly surveys and other issues that arise. The patients will help identify and resolve barriers around these issues and help us modify processes as required.
In year 4, Dr. Yawn will begin working with the stakeholder groups to finalize dissemination goals and specific strategies to facilitate widespread uptake of PARTICS (See Dissemination and Implementation).

Data cleaning and analysis will occur in Q~~2~~ 4of Year 5.
Interpretation of the results as well as manuscript preparation and final crafting of understandable patient messaging and other early dissemination activities will be finalized in Q3 and Q4 of year 5 with a final face to face stakeholders' meeting in Q3 or 4 of year 5.

A final report of the study will be completed in month 60.

III. Study Outcomes and Statistical Analysis

A. Patient-centeredness of PREPARE outcomes

This study is designed to use real-world patient-reported outcomes (exacerbations, asthma control, quality of life, missed activities) that are of demonstrated importance to patients, providers, payers, and policy makers. Below we describe the patient-centeredness of our primary and major secondary outcomes.

B. Primary Outcome

Vanguard: We will be doing multiple assessments about the implementation and operationalization of the study processes. We will use descriptive statistics and qualitative analyses. Questionnaires administered to participants are included in the appendix.

Full study differences: We will be analyzing questionnaire data to address our hypotheses. There will be no assessments with regards to study processes as in the Vanguard phase.

Rate of asthma exacerbations per year is the primary outcome of this trial. It has been argued that exacerbations are the most important asthma outcome, because they constitute the greatest risk to patients, and are a cause of anxiety to patients and their families. All of our patient partners agreed that exacerbations have major impacts on their lives and would be

interested in using PARTICS if it would prevent or significantly reduce exacerbations. In addition to their effects on patients, exacerbations result in a great stress on health care providers (Lane 2006, Skrepnek 2004, Andersson 2003) and are of high importance to payers and health care policy makers. Exacerbations increase the risk of asthma mortality (Jorgensen 2003) and generate the greatest cost to the health care system (Reddel 2009, Lane 2006). Asthma exacerbations are recognized as a common clinical manifestation in patients with all levels of asthma severity (Pauwels 1997, O'Byrne 2001). National consensus guidelines have defined an asthma exacerbation as a worsening of asthma reported by the patient of a degree that requires treatment with corticosteroids (Revicki 1998).
The standardization of how we define asthma exacerbations was the focus of both an ERS/ATS Task Force (Reddell 2009) and a workshop sponsored by the NIH (Fuhlbrigge 2012).

Our primary outcome, the rate of asthma exacerbations per year, is defined as the number of exacerbations, emergency room visits, or hospitalizations requiring oral or parenteral corticosteroids, per patient per year. It will be captured by subject self-report via a monthly asthma exacerbations questionnaire (AEQ). Reports will be substantiated by verification in the EHR or direct patient interview. Multiple clinical trials demonstrate convergent validity with other measures of asthma-related health status (Busse 2011, Peters 2010, Lemanske 2010) and their responsiveness to intervention (O'Byrne 2005). We previously developed, tested, and used the AEQ as part of the BELT trial, in which we enrolled >1,000 AA patients. The AEQ is sensitive but not specific, meaning it overestimates the number of true exacerbations and therefore requires confirmation, but is not likely to miss exacerbations. Therefore, we will use the medical records or, if necessary, contact all patients whose form suggested an exacerbation to confirm. We will categorize these exacerbations as to whether they resulted in a hospitalization or emergency department visit. Using all sources of data available, an independent group of physicians (who are blinded about patient's randomized treatment) will adjudicate and classify all possible asthma exacerbation events to determine if an exacerbation is truly a primary endpoint event. All adjudications will be based on a document with pre-specified rules for adjudication.

C. Secondary Outcomes

1. Asthma Control: Asthma Control Test (ACT) score

Asthma control represents the degree to which impairment (impact of asthma on patient's daily life) is minimized and the goals of therapy are met. The National Asthma Education and Prevention Program's Expert Panel Report 3 (NAEPP 2007), of which Drs. Israel and Yawn were members or reviewers, 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. With the input of our stakeholders we will use the ACT (rather than the ACQ) for monthly outcome measures of asthma control. The Asthma Control Test (ACT) (described in D.III.8) measures asthma control— attainable only by patient report—and was developed to have low patient burden (Nathan 2004). Scores from the ACT allow providers to rapidly determine whether a patient's asthma is controlled or not (Nathan 2004). The ACT is self-reported and has been validated in multiple settings (office setting, mail, & by telephone) (D.III.8-Validation of Scales).

The ACT is easy to use, patient completed, and assesses the frequency of shortness of breath, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. The ACT has been evaluated in independent study population

samples and can be self-administered in person or at home (Schatz 2007a), by telephone (Schatz 2007b) and by mail (Schatz 2007c). The ACT has been recommended by the NAEPP and the NIH Asthma outcome workshop (NAEPP 2007, Cloutier 2012) because of the extensive validation data for these tools, using the widest range of criterion and construct measures, including demonstration of responsiveness to therapy and a minimal clinically important difference (MCID). The MCID is defined as the smallest difference in a given score of interest which patients perceive as beneficial and which would support a change in the patient's management (Jaeschke 1989). The MCID for the ACT has been defined as 3 for individuals over time and between populations (Schatz 2009) and cut-off values for uncontrolled asthma: ACT ≤ 19 (Nathan 2004), and "very poorly controlled" asthma: ACT ≤ 15 have been established. (Schatz 2006, Nathan 2004). Asthma APGAR will be used as a secondary assessment of control to see if the three questions with a shorter time reference and therefore less risk of recall bias can be used to replace the ACT. (Rank, MCP 2014).

2. Preference Based Quality of Life: Asthma Symptom Utility Index (ASUI)

The ideal outcome measure for any comparative effectiveness analysis captures the risks and benefits for each of the interventions from the patient's point of view. The use of a preference-based instrument, the Asthma Symptom Utility Index (ASUI), captures this important information (Revicki 1998). The measure is entirely patient experience focused. To develop this measure, patients were asked to assign a relative value to different health states. The ASUI has two important features that highlight its importance to patients: 1) the ASUI captures the tradeoff of the positive and negative aspects of interventions from the patient's point of view, and 2) the ASUI measures the severity and impact of asthma symptoms. For asthma, the type and severity of asthma symptoms can differ between individuals or differ in a given individual over time. In addition, certain symptoms may be more troublesome than others to patients, and certain treatments might be more or less desirable. Whereas a patient with severe asthma might not appear to improve in terms of having significant symptom free days, s/he might improve in the severity and or frequency of the symptoms, something that is not captured by symptom-free day scales. The ASUI is probably the symptom scale most frequently used in asthma studies including large multicenter clinical trials (Boushey 2005). The ASUI's psychometric properties are well documented and support the reliability and construct validity of the instrument, including internal consistency reliability and test-retest reliability. The minimum clinically important difference has been determined as 0.09 points (Bime 2012).

3. Days Lost from Work or School or Usual activities

As highlighted by our patient partners in our focus groups, days lost from work and school are a great concern for asthma patients**.** At the request of the patient partners, we have included this outcome measure. Days lost from work and school will be collected using a validated questionnaire developed and utilized as part of the National Health Interview Survey (NHIS 2014). If a patient does not work or go to school they are asked a question about days he/she was unable to carry out usual activities due to asthma. Our patient partners felt that this was a very important outcome that they would be interested in.

4. FeNO

Fractional exhaled nitric oxide (FeNO): Exhaled nitric oxide gas will be measured during the study visit. Asthma is an inflammatory disease of the lung. The PREPARE trial relies on the fact that in many cases asthmatic inflammation is of the eosinophilic (or Type 2) form of inflammation.

Corticosteroids are particularly effective in targeting Type 2 inflammation. While inhaled corticosteroids (ICS) were initially thought to be a therapy for all asthmatics, studies now suggest that up to half of asthmatics may have non-type 2 inflammation and thus may be less responsive to ICS (Woodruff 2009). Thus, it is possible that PARTICS may be most beneficial for a particular group of patients – those with Type 2 mechanisms of inflammation.

5. Blood draw/Eosinophils

Peripheral blood eosinophils may identify asthmatics that are most responsive to Patient Activated Reliever-Triggered Inhaled CorticoSteroid (PARTICS). Eosinophil counts can be calculated by a complete blood count with differential. We will determine whether peripheral blood eosinophil count serves as an effect modifier of the relationship between treatment (PARTICS vs. usual care) and the study's primary outcome (number of asthma exacerbations per year). We will stratify participants based on a pre-specified peripheral blood eosinophil count threshold of 300/uL. This threshold is based on a frequently-used cutoff for 'eosinophil-high' status in the anti-eosinophil therapy literature (Giannetti 2016).

D. Exploratory Outcomes

1. Asthma deteriorations:

Asthma deteriorations are defined as episodes of increased asthma symptoms for two or more days which resulted in patient determined increases in usual asthma medications without hospitalization, emergency department visit or prescription of oral steroids. In the previous mentioned BELT study (Wechsler 2015), we found that some patients chose not to seek medical care despite significant levels or length of increased symptoms due to transportation or financial barriers or health beliefs. However, these individuals did report increased use of the medications previously prescribed for their asthma. Evaluating both exacerbations and deteriorations may provide a more complete picture of the impact of the intervention on changes in asthma control and acute increases in symptoms.

2. The Asthma Medication Ratio (AMR)

This is a metric used by HEDIS to assess quality of asthma care in healthsystems. It is calculated as the rate of controller therapy refills over the controller therapy plus the rescue therapy refills over a period of one year. In a subset of enrolled patients, we will use the available pharmacy reported fill data from the patient's health care system plus the ICS fill data from Teva for the intervention group to calculate AMR in the enhanced usual care and intervention arms.

3. Asthma APGAR:

The Asthma APGAR has been validated against the ACT in White children and adults but has not been validated against the ACT in African American or Hispanic Latino populations. We will use this opportunity to assess the validation to consider whether or not this brief control assessment could be used in African American/Black or Hispanic/Latino populations.

4. Total health care utilization and asthma-related healthcare utilization:

To assess the potential impact of use of PARTICS on the patient's health care utilization

will be evaluated during the follow up months of the study for all enrolled patients and comparing those in the enhanced usual care with those in the intervention group. We will also collect utilization data for the 12-month period before enrollment to assess changes in health care utilization within the enhanced usual care and within the intervention group for the period prior to enrollment and the annualized total health care utilization for the enrollment period.

Utilization will be based on review of the patient's insurance claims record for those sites with access to insurance data and health care system's billing data and EHR for all visits and procedures at any site (e.g. outpatient, urgent care, emergency department, hospital-based) for integrated delivery systems. For those clinics that are part of a system that includes pharmacy fulfillment data and/or insurance claims data, we will include all prescription medications that the patient obtained from the pharmacy.

Asthma-related health care utilization will be considered to include all visits and procedures which include asthma as a diagnosis in the outpatient and urgent care setting and for which asthma is a first or second diagnosis for emergency department or hospitalizations. While this is not likely to be completely accurate picture of the amount of time spent on asthma during particularly out-patient visits, it is a conservative estimate and unlikely to involve a systematic difference in billing procedures between the two study arms or before and during study enrollment.

5. Medication Data:

For patients randomized to the intervention group, the amount of QVAR use (estimated in total refills per period) due to PARTICS treatment will be reported by summary tables. Information on all other medication use will be available only in subset of patients for whom pharmacy fulfillment data is available from their health system. When available, the total number of dispensed inhalers for all of the patients' usual maintenance medications and usual rescue medications will be reported in summary tables.
No formal statistical tests are planned.

E. Biostatistical Analysis, Statistical Design, and Sample Size

Vanguard data validation

The data transfer process will be tested in the Vanguard study. Data collected from Vanguard process will be transferred from the Patients Engaged Electronic Reporting System (PEERS) developed by the University of Colorado, Department of Family Medicine (CUDFM) to DCRI. The verification of data transfer integrity will be performed at DCRI according to DCRI SOP.

Unexpected data inconsistencies within and between data sources will also be examined and reported. It will help to determine if additional data queries or validation rules will need to be developed to ensure the data quality in the full study.

Randomization data from PEERS system will be compared with the original randomization scheme generated by DCRI to make sure the PEERS system randomization data match the randomization scheme created by DCRI. The randomization slots actually used by Vanguard patients will also be examined to make sure the randomization process works as

planned in the Vanguard study.

Data collected through Vanguard process will be summarized by randomized treatment using appropriate descriptive statistics. Descriptive summaries of the continuous variables will be presented in terms of mean, standard deviation and percentiles (e.g., median, 25th and 75th percentiles), while discrete variables will be summarized in terms of frequencies and percentages. Due to the small sample size of the Vanguard study, no formal statistical tests will be performed.

Data report will focus on the Vanguard specific questions that survey about the study enrollment process, intervention process, monthly questionnaire process, and medication refill process. In addition, the screen failure data, patients' adherence barrier data from ASK-12, reasons of patients' drop-out or premature discontinuation, data on missed visits will also be carefully examined and reported. These data will help the study team to identify the barriers of patient enrollment, treatment compliance, and patient and physician adherence.

Full study differences: Formal statistical analyses will be performed.

1. Overview

Statistical analysis will be performed at the Statistical Data Coordinating Center at Duke Clinical Research Institute (DCRI). The study will use a randomized, parallel design to test the addition of PARTICS to provider-educated care as compared to continuation of provider-educated care. All major treatment comparisons between the randomized groups in this trial will be performed according to the principle of "intention- to-treat" (ITT); that is, subjects will be analyzed according to the treatment arm they were randomized to regardless of their compliance with the study medication.

Data collected in this study will be documented using summary tables with appropriate descriptive statistics for continuous variables and binary variables.
Annualized rates of count outcomes will be summarized using the annualized mean occurrence based on the Poisson model. In addition, survival curves will be constructed for all time to event endpoints using Kaplan-Meier methods.

Unless otherwise specified, the statistical analyses procedures for comparisons of the two groups will be as follows: 1) Two-sample t test or Kruskal-Wallis test for continuous parameters; 2) Chi-square test of independence for binary comparisons unless the number of events is less than 10, in which case Fisher's exact test will be used; 3) Cochran Mantel-Haenszel Modified Ridit Scores for non-time-to-event categorical variables with >2 categories (nominal variables will be compared using the General Association p-value; ordinal variables will be compared using the Row Mean Score p- value); 4) Andersen-Gill adaptation of Cox regression for time-to-event variables with more than one occurrence. 5) Log- rank test for first occurrence of time-to-event variables. All statistical tests and/or confidence intervals, as appropriate, will be performed at α=0.05 (2-sided) unless specified otherwise. SAS statistical software (version 9.1 or higher) will be used in analyses, unless otherwise noted.

2. Background Data and Baseline Characteristics:

Baseline demographic and clinical characteristics, including age, gender, socioeconomic status (SES), ethnic groups (Hispanic/Latino or African American), smoking status, BMI, medical

history/comorbidities, asthma history, and asthma medication use (e.g., ICS/LABA use vs. ICS use) will be summarized for each randomized treatment arm of the study. Asthma exacerbations during the 12 months prior to randomization will also be reported.

In addition, data on patients' attitude towards ICS (by the Beliefs about Medications Questionnaire - BMQ), healthy literacy level (by S-TOFHLA questionnaire), depression level (by Patient Health Questionnaire—PHQ-2), treatment adherence likelihood (by ASK-12 questionnaire) will also be tabulated by randomized treatment groups.

Asthma exacerbations, Asthma Control Test (ACT) scores, lost days of work or schools within one month prior to randomization will also be reported using summary tables.

Only descriptive statistics will be reported for the baseline data. Continuous variables will be presented in terms of mean, standard deviation, and percentiles (e.g., median, 25th and 75th percentiles), while discrete variables will be summarized in terms of frequencies and percentages.

3. Treatment Compliance

Treatment Compliance will be monitored throughout the study. Numbers of patients non-compliant with treatment or crossing-over will be documented using counts and rates over time.

Sensitivity analyses will be performed for patients who have treatment cross- overs.

The primary analysis will be based on an Intention-to-treat analysis, but we will also conduct a Per Protocol analysis with available data.

4. Statistical Analysis for Primary Outcome

The primary aim of the study is to determine the impact of PARTICS on asthma outcomes in a minority population consisting of African American and Hispanic/Latino adults. The primary outcome of this study will be the intensity of asthma exacerbations during the months of follow-up between those patients randomized to addition of PARTICS to provider-educated care vs. those who continue with provider-educated care alone.

Rate of asthma exacerbations per year will be reported for two treatment groups. Annualized rates of count outcomes will be summarized using the annualized mean occurrence based on the Poisson model.

Exacerbations rates during follow-up will be compared using the Andersen-Gill adaptation of time-to-event Cox proportional hazards model with robust standard errors to account for potential multiple occurrences of the outcome in each patient (Andersen Gill, 1982). This model was selected over the more commonly used time to first event Cox model for two reasons. First, we believe that total experience during follow-up matters more to patients than the onset of the first exacerbation. Second, the power is increased when multiple events can be included. The covariates in the primary comparison will include: study center (to account for any geographic variation in patterns of care), h/o exacerbations in the past year (y/n), on ICS/LABA prior to randomization (Y/N), race/ethnicity, smoking status (as defined for subgroups), age, BMI (body mass index), and gender since all may influence the rate of exacerbations or the response to corticosteroids. The primary effect will be based on the randomized treatment arm indicator

variable.

Time from randomization to first asthma exacerbation will be compared using the log-rank test. In addition, survival curves will be constructed for this time-to-event endpoint using Kaplan-Meier method.

5. Secondary Outcome Analyses

Secondary outcome variables include asthma symptom utility index (ASUI), asthma control as measured by the Asthma Control Test, and the number of days lost from work or school. For outcomes measured as continuous variables, a linear mixed model will be employed to compare the treatment arms. The dependent variable will be change from the baseline value. The model will use data from all available assessments and the predictors (included as fixed- effects) will include randomized treatment arm, continuous time of assessment as a linear and quadratic term and the interactions of the treatment arm with the time variables. Independent random-effects will be included for intercept and time variables. The model will adjust for all the variables adjusted for in the primary analysis.

6. Subgroup Analysis

Subgroup analyses for the primary efficacy outcome will be performed on the ITT population in order to explore whether the treatment effect is consistent across subgroups. Our goal is to determine the impact of PARTICS on asthma exacerbations in two pre-specified main subgroups determined by 1) race/ethnic group (African American vs. Hispanic/Latino) and 2) smoking status [i.e., participants who are previous (>10 pack- years)/current (or within 1 year) smokers vs. those who have not smoked (in the past year and <10py)] 3) patients with high FeNO vs. low and 4) patients with high eosinophil counts vs. low. Based on our prior experience, about 50% of our population will be smokers or ex- smokers.

Subgroup analyses to evaluate variation in treatment effect will be performed on the basis of tests for interaction using the same Andersen-Gill version of the Cox proportional hazards model as used in the primary analysis. The model will be including terms for treatment arm, subgroup, and treatment by sub-group interaction and adjust for all variables included in the primary model. Additionally, treatment effects within each categorical subgroup will be examined separately using analogous Andersen-Gill model. Event rates by treatment arm and hazard ratios with 95% confidence intervals will be reported for each subgroup.
Forest plots will be generated displaying the estimated hazard ratios and 95% confidence intervals for each subgroup will be presented. Variation in treatment effect will be assessed on the basis of tests for interaction in the Andersen-Gill version of the Cox proportional hazards model described above. Treatment effects estimated within each categorical subgroup will be considered exploratory/hypothesis generating. Thus, no adjustment for multiple testing will be employed.

Additional exploratory subgroup analyses will be performed investigating the effect of the following factors: 1) modality in which questionnaires have been returned; 2) patients' attitude towards ICS from the validated BMQ (skeptical (low necessity, high concerns), indifferent (low necessity, low concerns), ambivalent (high necessity, high concerns), accepting (high necessity, low concerns)); 3) presence of depressive symptoms (yes/no); 4) health literacy status (low or marginal versus high); and 5) patient adherence barriers from the validated ASK12 questions 1,2,3 and 11 related to measures of inconvenience, forgetting and

cost.

7. Exploratory Analyses

In addition to the exploratory subgroup analyses mentioned above, we will also explore whether patient characteristics such as BMI, ICS/LABA use vs. ICS use, co- morbidity (such as history of heart disease, cancer, stroke, diabetes, chronic kidney disease, COPD/emphysema/chronic bronchitis, HIV/AIDS, and hypertension), and prior exacerbations (e.g., exacerbation within 12 months prior to randomization) affect the apparent effectiveness of PARTICS by examining the interaction of these factors with treatment. In addition, we will explore whether self-perceived discrimination affect outcomes regardless of treatment assignment.

The effect of provider adherence and patient adherence on the effectiveness of the PARTICS intervention will also be investigated. We will collect information from patients regarding their medication use and have added “non-invasive” ways to monitor what actually happens after they are randomized to either the enhanced usual care group or the intervention group. To this end, we will collect and incorporate the following into our descriptive information and into our exploratory analyses: 1) Information on the refills of the ICS in PARTICS “non-invasively” through the renewals at the pharmacy; 2) Information on PARTICS “adherence” by cross-referencing the ICS data above with patient monthly report of usage on their questionnaires and SABA pharmacy fulfillment data if available; 3) Information on PARTICS effects on other asthma medication use by comparing medication use between the intervention and non-intervention groups by examining monthly self-report and cross- referencing to pharmacy fulfillment data; 4) Measure of provider compliance with guidelines, by assessing whether providers adjust medications according to NAEPP guidelines. We will obtain this information “non-invasively” by examining EHR medication prescribing information at asthma related visits (none required by study). For each of these visits, we will refer to the patient’s self-reported asthma control score of the prior month (provided by the patient monthly questionnaire). We will examine medication prescribing at that visit from the EHR to assess the frequency with which providers stepped up, or stepped-down, care according to guideline recommendations (NAEPP, 2007); Patient adherence and provider adherence between the two treatment groups will be compared.

The analyses on the exploratory outcomes will also be performed. The rate on asthma deteriorations will be reported by treatment groups. The composite endpoint of asthma deteriorations or exacerbations will be analyzed using the same Andersen-Gill version of the Cox proportional hazards model as used in the primary analysis. The Asthma APGAR data will be analyzed using the same mixed model approach as described above in the Asthma Control Test (ACT) score analyses.

Data on the Asthma Medication Ratio (AMR) during the follow-up months, the total health care utilization (i.e., total number of visits made to the enrolling sites, total number of ED visits, and total number of hospitalizations), and asthma related health care utilization (i.e., number of visits made to the enrolling sites, number of ED visits, and number of hospitalizations for which asthma is a first or second diagnosis) will be summarized. Differences between two randomized treatment groups on these variables will be compared using either t-test or Kruskal-Wallis test if full follow-up is available on everyone or Poisson or Negative Binomial regression models with time as an offset to account for differential duration of follow-up.

8. Sample Size and Power Considerations

Sample size and power calculations were performed using PASS software (Hintze 2011), using the similarity of inference between the Andersen-Gill models and Poisson regression.

For the primary efficacy outcome, power calculations were based on an estimated primary event intensity of 0.4 per year (0.5 per 15 months) in the control arm (as seen in the BELT study), 15 months of follow-up for each individuals with an annualized rate of uniform loss to follow-up of 25% (31.25% in 15 months of follow-up) and a two-sided significance level of 0.05. With these assumptions, 1200 up to patients (600 per arm) yields 80% power to declare a reduction of 23.5% in the intensity of exacerbations as statistically significant. Even if the event rate were lower at .35 we would still have 80% power to detect a 25% difference. This difference is clinically meaningful and is well within the 25-50% (and more likely 40-50%) (O'Byrne 2006, Rabe 2006, Buhl 2012, Papi 2013, Calhoun 2012)) reductions noted with such studies.

For subgroup analysis, using these same assumptions, with group size of 600 (300/arm), at a power level of 80% we would be able to detect an expected change of 32%, still well within the noted effects.

Power for secondary outcome comparisons were also calculated. Based on results observed in the BELT study, we expect the standard deviations in ASUI scores to be 0.23 in each arm. Thus, we will have 80% power to detect a difference of 0.04 in ASUI scores between treatment arms. Assuming standard deviations of 4.9 in each treatment arm on the ACT questions score, we will have 80% power to detect a difference of 0.96 in ACT scores.

9. Interim Analysis

It is anticipated that our independent safety officer will review the accumulating data at approximately 6-month intervals. Interim data analyses of the key safety and outcome data will be performed in a blinded fashion for each of these data reviews. The primary objective of these analyses will be to evaluate the accumulating data. Our independent safety officer will review the clinical outcome rates, patient recruitment, compliance with the study protocol, reasons and patterns of the missing data, adverse event rates and other factors that reflect the overall progress and integrity of the study.

Before each independent safety officer review session, a blinded summary safety data report will be provided to the safety officer. The extracted data files and the analysis programs for each independent safety officer report will be archived and maintained at the Statistical Data CC for the life of the study.

We will monitor the event rate as it accumulates in a blinded fashion to help us determine if we will achieve sufficient power. We will also review the baseline characteristics of enrolled participants to make sure we have enrolled the population defined in the protocol.

10. Addressing missing data

Every effort will be undertaken to limit premature discontinuations and ascertain completeness of data collection. Based on patient partner and patient advocate feedback, we are providing multiple methods of delivering the forms and multiple ways for participants to respond, including mail, email, telephone, text, smartphone app, website, and voice- response systems. We will also implement procedures designed to retain patients and increase responses. We will reimburse participants for completing forms with levels that our patient advisors felt would encourage completion. For any positive responses regarding exacerbations, we will call to verify and, where available, obtain medical records. We will also use the systems we used in our prior BELT study with AA participants to monitor missing data. Forms that are >10 days delayed result in attempts to re-contact the participant through all available consented modalities.

In concert with intent-to-treat principles, we will continue to attempt to obtain information on patients who failed to return questionnaires. Sites will have access to medical records, claims data and prescription refills. Thus, unless the patient has withdrawn consent, we will be able to continue collecting information on the primary outcome through these alternative means. We will obtain the following information for dropouts: 1) reason for dropping out; 2) primary determiner of dropout; 3) degree of participation. We will use a traditional consort diagram to track the randomized patients. Full sample size will be presented in all tables and figures with clear annotation of the numbers used for each analysis.

For the primary analysis (Andersen-Gill model) subjects discontinuing the study prematurely will be censored at the time of discontinuation. This approach might lead to biased results if discontinuation does not occur at random. Thus, two sensitivity analysis will be undertaken to examine the sensitivity of inference when data is missing at random and not at random: 1. Inverse probability weighting. In this approach, contribution of each subject to the risk set calculated at time t will be inversely weighted by the estimated probability of remaining uncensored up to time t. This probability will be estimated using a Cox proportional hazards model fitted to time to censoring with variables potentially prognostic of both, failure and censoring, both baseline and time- dependent (such as most frequent major protocol deviations, certain AEs etc.), entered as covariates. In order to reduce potentially high variability of the resulting treatment effect estimators due to sampling variability in weights, the weights will be “stabilized” by multiplication of probabilities of remaining uncensored up to time t estimated using baseline covariates only. 2. Pattern-mixture approach. As per Little 2012. we will assume that for participants who drop out, the hazard of an outcome deviates from that of participants who do not drop out by an offset--r1 for treatment and r0 for placebo. We will then explore the effect of this deviation on the findings for various choices of the offsets in the two study groups. If the treatment effect is qualitatively maintained for the range of offsets that are considered to be clinically plausible, then the findings will be considered to be robust.

In other analyses, missing data will be handled by using multiple imputation. Ten imputed data sets will be generated with imputation methods based on the regression or Monte Carlo framework. Final results will be based on averages from the ten imputed data sets with appropriate estimator employed of the variance. The variables included in the imputation model as covariates will be pre-specified.

IV. Research team

A. Overview

Our team of academic researchers combines expertise in asthma and asthma care, designing and implementing clinical trials and pragmatic studies in primary care settings, engaging patient partners, and other invested stakeholders. Three team members participated in the NAEPP 2007 asthma guidelines (Israel, Yawn, Fuhlbrigge), and all have worked in asthma research for many years. Germane to this trial, Israel, Yawn, Pace, Pencina, and Fuhlbrigge have collaborated on a large-scale asthma trial in 17 diverse practice settings in which they recruited more than 1,000 AA participants (BELT trial). Dr.
Israel is a recognized expert in asthma clinical trial design. He brings together collaborators with expertise in: 1) asthma clinical epidemiology and outcomes measurement (Fuhlbrigge); 2) execution of practice-based trials in asthma practitioner- based settings (Yawn, Pace); 3) organizational infrastructure and telecommunication- based patient outreach and data handling (Pace); 3) understanding barriers to adherence in asthma (Dr. Rand) 4) experienced engagement facilitators and asthma educators (Rodriguez-Louis, Fagan); 5) an investigator who is a native of Puerto Rico (Cardet); and 6) trial analytics (Pencina). Teva pharmaceuticals has agreed to provide almost $1 million of drug (QVAR® RediHaler™ (beclomethasone dipropionate HFA) and Teva has agreed to handle drug distribution and provide pharmacist stakeholders. Below we briefly describe the expertise of the primary researchers.

B. Clinical Coordinating Center at Brigham and Women's Hospital

The primary research facility is the Brigham and Women’s Hospital (Harvard).

C. Practice Based Research Networks: American Academy of Family Physicians (AAFP) National Research Network (NRN):

The AAFP NRN is one of the largest practice-based research networks in the country which has focused primarily on pragmatic clinical trials (PCTs) for the past seven years. The AAFP NRN will serve as the clinical coordinating center for this project.
Network studies have resulted in over 90 publications in the past 14 years with a number of papers under review and in development. The AAFP NRN has received funding from NIH, AHRQ, CDC, and numerous foundations and industry sources. Virtually every PBRN study involves multiple clinical locations with pilots often engaging 8 to 12 sites and full PCTs engaging 20 to 40 sites, thus the AAFP NRN staff routinely supports multi- site trials. The AAFP NRN experience includes the Americans In Motion-Healthy Interventions trial, a 3-year, multi-million dollar trial examining the impact of the AIM-HI approach on improving diet, exercise and emotional well-being on weight, physical fitness, psychological health as well as physiologic and metabolic parameters in over 650 obese individuals cared for in 24 family medicine offices across 15 states (Pace 2013). A second project conducted with the Olmsted Medical Center Research Office (incorporated into the AAFP NRN sub-contract for this project) supported 30 family medicine offices in recruiting, treating and tracking over 2200 recently post-partum women for depression symptoms for a year after enrollment (Yawn 2012). This study was only the second to demonstrate improved outcomes with the treatment of post- partum depression. Finally, the entire research core recently completed the BELT study which tracked 1100 African American individuals with asthma for up to 18 months across 20 sites. The AAFP NRN, in conjunction with the core study team, have demonstrated their ability to effectively coordinate large, multi-site PCTs. The AAFP NRN has demonstrated its ability to coordinate multiple clinical sites for a number of large projects.

D. Johns' Hopkins Adherence Center

Dr. Cynthia Rand is a nationally known expert in the area of medication adherence and the barriers that exist to improving treatment adherence. Dr. Rand has been involved previously in a number of asthma studies and will join the research team to guide the work with patient stakeholders and the clinical sites to address identified barriers to adherence to the patient reliever-activated use of ICS.

E. Data Coordinating Center and Statistical Analysis at Duke (Duke Clinical Research Institute (DCRI))

(DCRI) is a not-for-profit academic research organization (ARO) located in Durham, NC, created by Duke University. DCRI will provide analytic and statistical support and manuscript writing support. DCRI's mission is to facilitate greater academic involvement in clinical research by serving as a leading center of clinical data management and analysis. Dr. Michael Pencina has extensive experience in designing and performing epidemiological studies and clinical trials and is currently a Professor of Mathematics/Statistics, Biostatistics and Epidemiology at Duke University. Dr. Pencina was the lead biostatistician for the BELT study and has led analysis of a number of other asthma related trials. DCRI has provided methodological and data analytic support for hundreds of large clinical trials. DCRI will also manage the reports and responses to the independent safety officer. Drs. Israel and Pencina have a long and productive working relationship.

F. Clinical Sites

Montefiore/Albert Einstein PBRN NYCRNG recruiting estimate 100 patients

Has worked with the entire research team on the previously described BELT grant demonstrating their ability to recruit patients with asthma for a project of this nature. This site utilizes primarily FQHCs as clinical sites with both African American and Latino populations. The group has been involved in a number of large trials, including ACCORD and ALL-HAT. The research team and the clinical sites are experienced in conducting clinical trials and have a proven track record of working well within multi-site clinical trials.

The Department of Family Medicine at University of Florida Gainesville recruiting estimate 100 patients

The Department has practice sites in several communities, providing training in urban and rural medicine and health care for underserved areas in the State. Dr. Ku-Lang Chang was a co-investigator in the BELT study. He successfully recruited African American individuals with moderate to severe asthma and will serve as site PI for this study. The Department and Dr. Chang have also been involved in a number of phase III and IV drug trials. There are several clinical sites that are used. They have identified just under 1000 potentially eligible patients from the EHR.

The MetroHealth System, recruiting estimate 100 patients –

A large FQHC that covers Cleveland and delivers care at 16 locations mainly through primary care offices, but does have both adult and pediatric pulmonary clinicians.
MetroHealth is an integrated healthcare delivery system affiliated with Case Western Reserve University and is the primary safety-net healthcare provider in northeast OH with over 1 million outpatient visits per year and over 500 physicians. The MetroHealth System consists of one

tertiary care medical center and over 20 satellite clinics throughout Northeast OH. The site is working with the AAFP NRN on a comparative effectiveness grant from Health Resources and Services Administration (HRSA) looking at atypical anti-psychotics in children, hypertension in children and obesity. The site has both large African American and Latino populations. The MetroHealth System takes care of thousands of people with asthma in primary care, pediatric and adult asthma clinics run by pulmonologist and clinics run by allergy and immunology physicians. The site has identified 1900 African Americans and Latinos with asthma on an ICS.

The Departments of Internal and Family Medicine at University of North Carolina Chapel Hill (UNC) recruiting estimate 200 patients –

Dr. Tamera Coyne Beasley will lead recruitment activities for this project through Internal Medicine, Family Medicine and Pulmonary sites. UNC has worked extensively with Dr. Pace through AHRQ Task Orders as well as a partner in the DARTNet Institute Collaborative. As a large, research oriented institution UNC has extensive experience in participating in and running large research trials. In fact, the investigative team at UNC just completed a PCORI asthma study for which they recruited over 100 adult patients. The UNC patient population for this project is predominately African American. EHR data has identified over 2800 potentially eligible African American and Latino individuals.

Mount Sinai Divisions of Pulmonary Medicine and General Internal Medicine, recruiting estimate 100 patients

They are parts of a major research institution where both the co-investigators and clinical sites have directed or participated in numerous research projects involving patient consent. Dr. Wisnivesky has been the PI and currently serves as the PI for a number of pulmonary related projects. Dr. Wisnivesky has focused his research on asthma medication adherence barriers, barriers to ICS use and health literacy related to asthma therapy (Ponieman 2009, Sofianou 2013). He has been involved in a number of clinical trials and successfully recruited patients with asthma for these trials. Dr. Wisnivesky and Dr. Israel have been colleagues for years but this will be the first research project they have conducted together.

Division of Allergy and Immunology at the University of Puerto Rico, recruiting estimate 100 patients –

The Division of Allergy and Immunology at the University of Puerto Rico is the project lead and has been involved in three asthma projects over the past eight years recruiting from approximately 1250 patients for each project, including a genome wide association project related to asthma and a study of ethnic differences in bronchodilator responsiveness (Galanter 2008, Naqvi 2007). The Division also provides patient care in five other local community primary care practices and will utilize these sites as needed to supplement patient enrollment. Dr. Nazario and Dr. Cardet are colleagues that have known each other for some time.

University of Alabama Birmingham recruiting estimate 100 patients –

It has and has worked with the AAFP NRN on several projects over the past four years including studying novel approaches to ease the burden of collecting patient consent (Mudano 2013), Cities for Life (http://www.aafpfoundation.org/online/foundation/home/programs/education/citiesforlife.h tml), a community wide project to improve patient use of community resources for lifestyle changes,

and the EDGE project. UAB is a large research oriented institution which conducts numerous patient consented studies in any given year. Dr. Trevor recently completed a study of use of pulmonary rehabilitation for patients with asthma (Trevor, in press) as the PI. She has also been a co-investigator in studies with Dr. Israel and other industry studies she has run out of the UAB clinical system. Dr. Trevino leads the Asthma Clinic for the Adult Pulmonary Division. She has reached out to the UAB Department of Family Medicine which will recruit patients as well. The population is predominately African American and the adult pulmonary clinic cares for over 1500 potentially eligible patients with the Department of Family Medicine adding to this total.

University of Illinois, Chicago recruiting estimate 50 patients –

UIC is a major academic research institution. The PI for this project, Dr. John Hickner, has worked with Dr. Pace and Dr. Yawn on a number of previous projects, including a project with Dr. Israel to examine the impact of primary office spirometry (Yawn 2007). Other projects with Dr. Pace include two patient safety reporting projects funded by AHRQ and a recent international project to examine the needs of primary care clinicians for point of care lab testing. Dr. Hickner a previous director of the AAFP NRN and has been involved in a large number of clinical trials. His site will utilize Family Medicine, Internal Medicine and Pulmonary clinics if required for patient recruitment.

Emory University recruiting estimate 50 patients –

Emory is a major academic research institution. Dr. Lutz, the PI for this project, was the Director of the Ambulatory Sentinel Practice Network (ASPN), the precursor network to the AAFP NRN. Dr. Pace has worked with Dr. Lutz since his time at the University of Colorado stretching back over 20 years. Dr. Lutz has directed a number of large clinical trials while with ASPN including an HIV surveillance trial and an international otitis media trial (Calonge 1991, Froom 1990).

Howard University recruiting estimate 100 patients–

Howard is one of the original predominately Black Medical Schools in the US and has worked closely with Georgetown to advance clinical research. Patients for this project will be recruited through the Department of Community and Family Medicine and their affiliated clinical locations across Washington, DC and Maryland. The DC Primary Care Research Network (DCPrimNet) includes 44 clinical sites with over 14,000 clinical visits per week. The network will provide sites for this project and has completed four previous research projects.

University of South Florida recruiting estimate 100 patients –

The University of South Florida Allergy and Immunology Clinical Research Center is a nationally recognized center of excellence in asthma research. They have proven themselves to be able to successfully recruit for multiple previous studies. Dr. Casale was the PI on a recent project with the AAFP NRN (Dr. Pace co-I) studying the impact of the Asthma IQ system on quality of care. Dr. Casale and Dr. Israel are also close colleagues. Dr. Casale and the USF team have been involved in a large number of clinical trials, recent studies include an evaluation of tiotropium versus LABA in asthma (Kerstjens 2015), and studies of TLR9 agonists for asthma therapy (Casale 2015).

University of Central Florida recruiting estimate 20 patients –

UCF is a new medical school and does not have an extensive research history. UCF is interested in getting started in participating in clinical trials, given the local population with the second highest number of individuals from Puerto Rico living in the surrounding area in the US, the research team has invited them to participate as a clinical site. With the small enrollment number the site has agreed to accept a lower start-up payment and the total cost per patient recruited is not any higher than other sites. Dr. Pasarica has participated on clinical trial research teams as part of her PhD activities. This site will recruit from the faculty practice as well as clinical faculty practices in the Kissimmee area. The AAFP NRN staff is very familiar in supporting and helping primarily clinical sites become successful research sites and will provide extensive support to the PI and study coordinator at this site.

University of Mississippi recruiting estimate 65 patients –

The UMMC is a research oriented academic medical center with a culture of conducting clinical trials. Dr. Marshall, site PI, has been involved in a number of previous asthma studies and his center has proven its ability to recruit patients in previous work. Past trials include a placebo controlled study of omalizumab (Novartis, Marshall, G), an NIH study on mindfulness and asthma (5R21AT002938-02 Pbert) and DoD study on improved decision support (USM-MRCSSC-12162005-68D/NNS06AA68D Faruque). Dr. Marshall and Dr. Israel are colleagues but have not worked together in a research capacity previously.

G. Back-up sites

Given the budget structure for this project where the majority of a site's budget is dependent on successful recruitment there was a logical limit to the number of clinical sites that could be included. With 1200 patients required for appropriate power we have budgeted for up to 1385 patients being consented. This will allow for some patients who are found to not be eligible after being enrolled and patient drop-out within the first month of the study.
The budget for enrolling patients is fixed and will follow the sites that are successful in their enrollment. To be sure this project successfully meets its enrollment goal (the biggest single problem in most clinical trials) we have also budgeted to be able to on-board 2 additional sites should enrollment fall short. There are currently two other medical systems that have expressed interest in participating that we were not able to include at this time. Jacobi Medical Center in New York City was a component of our last application and Wayne State University asked to be included in this application. Both locations have been told that if there are any enrollment problems they will be added to the clinical performance sites.

H. Site Management and Monitoring

This study will be completed at multiple sites serving a variety of functions. The primary research facility is the Brigham and Women's Hospital (Harvard) with clinical site coordinating support from the American Academy of Family Physicians National Research Network, data coordinating center (DCC) and statistical support from the Duke Clinical Research Institute and the clinical enrollment site all around the Eastern and Southern US. Please note that sites are primarily paid by actual enrollments. Enrollment will be competitive. While submitted budgets are based on anticipated enrollment, payments will be made based on actual enrollments. Site capacities vary from 20 patients to 200 patients, thus site budgets vary greatly. The smallest site is receiving a lower start- up amount so the per patient cost at this site is actually slightly

lower than two other sites. The number of patients available per site is shown below and also in the Performance Sites and Resources section.
American Academy of Family Physicians National Research Network (AAFP NRN) will be engaged to support these study sites for successful completion of the Asthma IQ program by all enrolling clinicians, as well as issues of site implementation support. They will also be responsible for the systems to collect monthly patient reported outcome data including confirmation of asthma exacerbations through contact with the clinic sites or the enrolled patient. The study sites will be responsible for patient enrollment procedures including informed consent, collection of patient baseline data and providing prescription for ICS to be sent to the central pharmacy for those randomized to PARTICS. Clinical sites will enter their collected data onto the AAFP NRN's maintained study database.
The clinical sites will provide continuing asthma care to all enrolled patients as they deem appropriate incorporating the on-line instructional component of the Asthma IQ asthma management system.

I. Research Staff--Site Interactions

Drs. Pace, Israel and Yawn have conducted a number of clinical trials together over the past 12 years as outlined in sections above. 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 the plan to deal with recruitment challenges. The sites provide extensive feedback to the research team and adjustments to the protocol may be made. For this project this 2 day meeting will also include the all stakeholder groups outlined in Engagement and Appendix. 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. Informed consent is practiced and ideas for distance consent will be reviewed.

Typically a few months before the in person meeting the AAFP NRN staff will begin working with each site's study coordinator to complete any local IRB submissions that are required. Given the new emphasis on ceding IRB approval if at all possible we will definitely initially ask each local IRB to consider ceding to the Harvard 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 interactions more meaningful at the face to face meeting.

After the face-to-face meeting 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 IHC system, on web-based video consent processes, another review of enrollment criteria, how to interface with Teva 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, Carroll and Yawn) will contact and talk with each site PI to be sure he or she is comfortable with all processes. (Dr. Carroll is the current Director of the AAFP NRN and experienced in clinical trials.)

After recruitment begins the AAFP NRN staff will schedule weekly meetings with each site study coordinator and help them trouble shoot any issues that arise as well as maintain communication between sites. The senior staff will touch base with the site PIs at least monthly for the first 4 to 6 months and then may spread these contacts out if the site is having no issues

and is effectively recruiting for the study. 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 list serve 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.

Finally, travel funds have been included in years 2 to 4 for site visits to provide on- site support and review for sites that are experiencing problems or if enrollment concerns are expressed by the AAFP NRN or local site staff. This combination of support and tracking has proven very successful over time and is routine operating procedure for all AAFP NRN supported studies.

V. Drug supplies

Teva Pharmaceuticals will provide free inhaled corticosteroids (QVAR® RediHaler™ beclomethasone dipropionate HFA), and has agreed to act as our central pharmacy and set up electronic prescriptions for electronic health records, and to have two pharmacists (one serving predominantly H/L customers and the other AA customers) participate. The Vice President of Retail Sales will be one of our stakeholders. Teva has agreed to provide almost $1 million of drug and has agreed to handle drug distribution and provide pharmacist stakeholders.

VI. Patient Partners/Stakeholder Feedback

A. African-American Patient Partners

Through our patient engagement facilitators, we met with this focus group twice and we held conference calls with this group as well to assure that we had heard their feedback. Their feedback has been important to us and has caused us to alter important parts of the grant. These patients have agreed to participate throughout the grant. They have provided biosketches and letters of agreement. As outlined in Engagement, this group will meet as often as biweekly depending on the phase of the Grant (e.g., Increased during Vanguard planning and interpretation, and less during study conduct). Ms. Rodriguez-Louis, from the operations committee, is responsible for meeting with them regularly to obtain feedback and assure involvement. Additionally, Ms. Suzanne Madison, will serve as their representative on the Executive Board, which sets all policies for the study and approves protocols and committees. She will also report back to this committee. All committee members are compensated at the same rate as stakeholders of all committees.

B. Hispanic/Latino Patient Partners

With the assistance of a Spanish translator, we also met with this focus group twice and we held conference calls with the potential members. These patients have agreed to participate as outlined, including attending the face-to-face initial meeting and the concluding-interpretation- dissemination meeting. They have provided biosketches and letters of agreement. This patient group will also meet as often as biweekly depending on the phase of the grant (e.g., increased during Vanguard planning and interpretation, and less during study conduct). Dr. Cardet, from the operations committee, a Puerto Rican native with immediate family on the island, is responsible for meeting with them regularly, with the assistance of facilitators and translators, to obtain feedback and assure involvement. Additionally, Ms. Margi Lorenzi, will serve as their representative on the Executive Board. She

will also report back to this committee.
These committee members are compensated at the same rate as stakeholders of all committees.

C. Patient Advocacy

Two of the major organizations involved in Asthma Patient advocacy have agreed to join us**.** Ms. Kaplan will represent advocacy to the Executive Committee (EC). Dr. Yawn will be their liaison to the Operation Committee (OC).

D. Healthcare Providers

We have included representatives of the provider groups participating in the studies as well as pharmacists and staff. Dr. Wisnivesky will represent this group. He has extensive experience dealing with both AA and H/L populations in his venue in NYC. Dr. Yawn will be their liaisons to the OC.

E. Professional Societies

We have included representatives of the major lung, allergy, and family medicine professional societies. Our members include past-presidents of these societies. Dr. Finn, past-president of the American Thoracic Society, with a particular interest in outcome disparities, will represent this group to the EC. Dr. Israel will be their liaison to the OC.

F. Health Policy Experts

We have included a broad range of policy experts including medical officers of health insurance units, a member of the Center of Medicaid Services, and population management experts. Dr. Westfall will represent the group to the EC and Dr. Fuhlbrigge will be their OC liaison.

G. Expert Scientific Advisors

We have included experts in asthma clinical trial design and the Operational lead of the AA BELT study. We have also included Drs. Burchard and Celedon who have extensive experience recruiting and retaining H/L populations with asthma. Dr. Israel will be their liaison to the operations committee and Dr. Wechsler will be their representative.

VII. Protection from Risk, Adverse Events, Asthma Exacerbations, and Safety Monitoring

A. Human Subjects Involvement and Characteristics

1. Human Subject Enrollment

Human subjects will be involved in the proposed study. One thousand two hundred and ten 1210 African American (AA) and Hispanic/Latino (H/L) adults, ages 18 years and older will be enrolled in this study. Up to 20% of Hispanic adults consider themselves Black/Hispanic (see **section XII, Table 1**). Any potential subject identifying themselves as both Black and Hispanic will be included in the Hispanic group. All enrollees will have a clinical history consistent with asthma and a prescription for an inhaled corticosteroid (ICS), either as a stand-alone controller medication or in combination with a long-acting beta-agonist (LABA). If they

meet the enrollment criteria (see **section II.C.1 Eligibility Criteria** XII, Table 2)**,** they will be randomized to one of two treatment options, either standardized provider educated care or standardized provider educated care plus as needed combination ICS+short-acting beta-agonist (SABA) (PARTICS) for acute symptoms.

African American and Hispanic/Latino adults with asthma experience a disproportionate rate of asthma exacerbation compared to other racial/ethnic groups. We will be examining the comparative effectiveness of PARTICS among AA and H/L men and women ages 18 years and older with a clinical diagnosis of asthma; no patients from other racial or ethnic groups will be enrolled. Detailed inclusion and exclusion criteria are listed in section **II.C.1 Eligibility Criteria.**

The data collected from the subjects in this study (basic demographic and monthly information on asthma control and exacerbations) will be entered into a database maintained by the University of Colorado Department of Family Medicine (UC- DFM) and then de-identified and stored on local server for later data cleaning and secure transfer to Dr. Michael Pencina at Duke University for data analysis. The majority of study sites have been identified and included in this application (See **Sites and Resources).** The American Academy of Family Physicians National Research Network (AAFP NRN) will be engaged to support these study sites for successful completion of the Asthma IQ program by all enrolling clinicians, as well as issues of site implementation support. They will also be responsible for the systems to collect monthly patient reported outcome data including confirmation of asthma exacerbations through contact with the clinic sites or the enrolled patient. The study sites will be responsible for patient enrollment procedures including informed consent, collection of patient baseline data and providing prescription for ICS to be sent to the central pharmacy for those randomized to PARTICS. Clinical sites will enter their collected data onto the AAFP NRN's maintained study database. The clinical sites will provide continuing asthma care to all enrolled patients as they deem appropriate incorporating the on-line instructional component of the Asthma IQ asthma management system.

2. Sources of Materials

One blood specimen will be collected at enrollment for a CBC with differential. Data on all subjects will be collected and entered into the AAFP NRN's Integrated Health Connect (ICH) study database. This database includes identifiable information as it is directly accessed by the study patients and utilized by the research staff to track all enrolled patients. When data are transferred to Dr. Pencina at Duke for analysis, study patients will be identified by a unique identifier without any patient names or addresses. Site study coordinators and the research staff at the AAFP NRN, in the course of following and collecting data from the subjects, will have access to the subjects' personal information and may have access to medical records for confirmation of exacerbations, emergency room visits and hospitalizations. The data captured in the IHC database will include information on race/ethnicity and sex, relevant medical history, asthma medication usage, asthma- related quality of life, information on co-morbid conditions, asthma control, missed school and work days and asthma symptoms, and asthma exacerbations. Whenever feasible, the subjects will enter their own information directly into an online survey utility both during the enrollment process and for the monthly surveys. When needed, support from the coordinator or a voice assist system will be available at enrollment with comparable support for the monthly survey completion. Support for these utilities will be provided by the UC-DFM, an AAFP NRN partner, and will meet all HIPAA privacy and security requirements including strong passwords and secure URLs. These data will then be transferred into the study database at the U of Colorado Denver Department of Family Medicine. The data to be collected and the manner of de-identification will be discussed with the enrolled patients

as part of the informed consent process.

B. Risks to Human Subjects

1. Change in medications

We are adding prn SABA/ICS (PARTICS) to the patient's current therapy. All other changes in patient medications will be made by the patient's personal clinician. Thus, we are not introducing any new medication class to patients' regular daily controller therapy regimen. At baseline, patients will either be on ICS/LABA combination, or on ICS monotherapy, and will be asked to continue their current therapy.

Patients randomized to the intervention arm will be given a prescription filled by central pharmacy and delivered to the patient for an extra ICS inhaler (beclomethasone dipropionate/QVAR® RediHaler™). Included with the ICS inhaler will be a Velcro band to attach to their SABA rescue inhaler to facilitate easy access to both "rescue" medications. Patients will be instructed to take an inhalation of ICS whenever they take a puff of SABA for acute symptom relief but not when the SABA is used as exercise pretreatment. To minimize the risk of overuse of ICS, subjects who are currently having an asthma exacerbation will be considered to be uncontrolled on their current therapy and will be asked to see their physician to re-evaluate treatment options before enrolling in the study. Shared Solutions will contact the central staff if a patient calls for a third refill of QVAR® RediHaler™ (beclomethasone dipropionate HFA) in a month. The central staff will notify the site and the provider will be alerted. All subjects will be informed that the alternative to participation in the trial is to continue their baseline asthma therapies.

2. Inhaled Corticosteroids Risks

All subjects will already have been on daily ICS maintenance therapy prior to enrollment in the study. ICS therapy is currently commonly used for asthma but not approved for use as rescue therapy—ICS as rescue therapy is what the intervention group will be asked to do (PARTICS). Participants assigned to the intervention group will be provided with the ICS beclomethasone dipropionate (QVAR® RediHaler™ (beclomethasone dipropionate HFA)) and asked to use one puff of it for every puff of albuterol used for rescue. Overall corticosteroid dosing may be increased in the intervention group, especially in the short term. However, data from efficacy studies of the PARTICS approach suggest that total inhaled corticosteroid dose will actually decrease as providers decrease the ICS dose due to improved patient control. Additionally, since we are targeting a group that has a high risk of exacerbation (1/3 or more based on our prior studies) for many subjects the total yearly dose of corticosteroids will be decreased even further due to avoidance of oral corticosteroid bursts resulting from the decreased rate of asthma exacerbations with PARTICS.

All subjects will be informed that beclomethasone dipropionate/QVAR® RediHaler™ (beclomethasone dipropionate HFA) can most commonly produce:

- hoarseness,
- throat irritation, and
- yeast infection of the mouth or throat (known as thrush or oral candidiasis,

We will advise participants to rinse their mouths with water and spit the water with each inhaler

use in order to avoid these side effects. We will inform participants that other less common risks with use of beclomethasone dipropionate/QVAR® RediHaler™ (beclomethasone dipropionate HFA) may occur, although many of these side effects usually occur when corticosteroids are taken orally, not inhaled, and have been reported in children. These include:

- Osteoporosis
- Glaucoma
- Cataracts
- Adrenal gland suppression

Pregnancy is not a contraindication to asthma controller therapy, including ICS. Improved asthma control has been shown to be associated with improved pregnancy outcomes. We will advise all women to seek maternity care as soon as they are aware of the possibility of pregnancy and to inform their physician or nurse midwife of their participation in this study.

We will advise participants to consult with their doctor or nurse about any changes to their asthma treatment regimen, and to discuss with their doctor or nurse if they think they may be experiencing any effects due to using beclomethasone dipropionate/QVAR® RediHaler™.

3. Asthma Questionnaires Risks

There are no risks associated with questionnaires and patients will be reimbursed for their time in the amount of $20 for each of the monthly surveys they return and $50 for completion of the enrollment process and demographic questionnaires at baseline.

4. Procedural Risks

Fractional exhaled nitric oxide (FeNO) testing: Exhaled nitric oxide gas will be measured during the study visit. This procedure involves exhaling into a device that measures FeNO. The associated risks are minimal. It is possible that a participant could become lightheaded from blowing into the machine, but this is uncommon since participants are instructed to not blow forcefully into the machine.

Blood eosinophil count: a blood draw of 3mL, or less than one teaspoon, will be taken from participants during the study visit, and a complete blood count with differential will be performed on the sample. The associated risks are minimal. It is possible that the participant will have some light bruising at the blood draw site, which will subside in a few days.

We will not conduct any other study specific procedures aside from data collection and medical record review.

5. Blood Draw Risks:

The patients will be asked if s/he is willing to have 3 mL's of blood drawn during enrollment to process a CBC w/differential. The blood draw is minimal risk. However, the blood draw may cause a small amount of pain or bruising. Rarely, people faint when their blood is drawn.

C. Adequacy of Protection Against Risks

1. Recruitment and Informed Consent

At study start-up, the research team will work with the Operations Committee and patient partners to draft an Informed Consent Template. Our goal will be to make the informed consent documents very brief while providing the patients with the information required to determine their desire to participate in the study and meet the requirements of all involved IRBs. Informed consent form will be uniform throughout the sites except as required by a site's IRB. We will work with sites to attempt to use a central IRB for all sites where this is feasible. We will work on multiple approaches to completion of informed consent to facilitate enrollment. Some patients will be consented online, using a study consent form URL and a web (visual) conference between the subject and the study staff who will review all study details similar to an in-person visit.

If a site's IRB requires modifications to the consent forms, a separate URL for that site will be provided which will then link the participants to the central IHC system. All subjects will be provided with the informed consent form/web site when the study site investigators have determined they may be an acceptable candidate for randomization. The form, the aims of the study, the data collection, follow-up requirements, and all potential risks and benefits of the study will be discussed with the subject by qualified study site personnel. Informed consent will be obtained before any study data is collected. Documentation of this process will be required, the subject will e-sign the informed consent document or sign a paper consent form if required by the local IRB. Electronic signatures will be maintained by the IHC system and documentation of each enrolled patient's consent will be provided to the AAFP NRN by each site obtaining it. Paper consent forms will be maintained at the site as part of the subject's research records (which may be separate from their medical records) as well as a copy provided to the AAFP NRN and to the patient. No subjects will be enrolled without documentation of informed consent and no waivers of this process will be sought or granted due to the use of the addition of a medication in the intervention. The IHC system has been used for many studies with online consent approved by over 15 IRBs across the country.

2. Risk of asthma exacerbation

This study is directed toward the reduction of asthma exacerbations. Acute management of subjects' asthma is not changed or mandated by the study and will be handled by the patient's chosen clinician in their usual manner. Training clinicians with the Asthma IQ instructional component as support for standardized provider educated care has been shown to improve asthma control and may be associated with decreased risk of exacerbations. The use of PARTICS (combined ICS+SABA) for acute symptom relief is intended to further reduce the risk of exacerbations and no data have been published to show that the use of combined acute relief medications increases exacerbation potential. Data collection will include assessment of exacerbations, with confirmation through communication with the patient's primary site of asthma care. Due to the pragmatic nature of the study, no additional interventions will be provided unless the patient has an allergic reaction to the components of the ICS used for this study. If such is the case both the patient and their care site will be notified to assure they have information on the exact medication to which the apparent allergic reaction occurred and the patient's participation in the study will be discontinued since no other options for a different type of ICS are available within the study.

3. Risk of excess inhaled corticosteroid use

As mentioned in the risk section, we anticipate, based on the efficacy data, that ICS use will actually decrease over the course of the study. Patients will be cautioned about steroid side effects and told to report them to their physician. We will also work with our sites, patients, and providers to review additional precautions.

4. Adverse Event Monitoring

(a) Asthma-Related Adverse Events:

Data collection will include assessment of exacerbations, with confirmation through communication with the patient's primary site of asthma care. Due to the pragmatic nature of the study, no additional interventions will be provided unless the patient has an allergic reaction to the components of the ICS used for this study.

(b) Non-Asthma Adverse Events

We won't monitor these due to the nature of pragmatic trials like this one. However, adverse events due to concurrent illnesses other than asthma may be grounds for termination from the trial if the illness is considered significant by the investigator or the patient's personal physician or other clinician or if the patient is no longer able to participate effectively in the study. Patients experiencing minor intercurrent illnesses may
continue in the study. Examples of minor intercurrent illnesses include acute rhinitis, sinusitis, upper respiratory infections, urinary tract infections, and gastroenteritis.
Because this is a pragmatic trial, no restrictions on medications for treatment of these conditions will be made.

(c) Serious Adverse Events:

These are events that meet any of 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. Also includes any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above.

5. Management of Asthma Exacerbations

This study is directed toward the reduction of asthma exacerbations. Acute management of subjects' asthma is not changed or mandated by the study and will be handled by the patient's chosen clinician in their usual manner. Training clinicians with the Asthma IQ instructional component as support for standardized provider educated care has been shown to improve asthma control and may be associated with decreased risk of exacerbations. The use of PARTICS (combined ICS+SABA) for acute symptom relief is intended to further reduce the risk of exacerbations and no data have been published to show that the use of combined acute relief medications increases exacerbation potential.
Data collection will include assessment of exacerbations, with confirmation through communication with the patient's primary site of asthma care. Due to the pragmatic nature of the study, no additional interventions will be provided unless the patient has an allergic reaction to the components of the ICS used for this study. If such is the case both the patient and their care site will be notified to assure they have information on the exact medication to which the

apparent allergic reaction occurred and the patient's participation in the study will be discontinued since no other options for a different type of ICS are available within the study.

6. Data and Safety Monitoring Plan

We will appoint an independent safety officer from the Division of Pulmonary and Critical Care Medicine from Brigham and Women's Hospital who has no other role in the PREPARE trial. This independent safety officer will be presented data in a blinded manner, and review safety data twice annually.

The PI of the study will be informed of serious adverse events as soon as they occur and will notify the central IRB at Partners within 5 working days/7 calendar days.

7. Risk to Data Confidentiality

Potential risks to data confidentiality will be mitigated by requirements for the de-identification of study data before secure transfer from the University of Colorado data collection site to Duke and by security protocols for the IHC patient-reported outcomes data capture systems. All users of the IHC system will be tracked and only provided access in a secure fashion following established UC-DFM Standard Operating Procedures for this process. The IHC system is an enterprise level system that handles multiple research and clinical data collection processes across thousands of individuals simultaneously. This project will be totally isolated from all other ongoing research activities. Patients will only have access to their personal information, questionnaires appropriate for their current research activities and the educational video(s) associated with their arm of the study. Site research staff will only have access to the patients enrolled by their site. AAFP NRN staff will have access to patient contact data for all patients, as well as reports indicating questionnaire status for each individual. The IHC system will automatically lock the monthly questionnaire for three weeks following completion by an individual assuring that we do not have duplicate completion of one month's questionnaire. 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 these data.

8. Inclusion of Women and Minorities

Only African American and Hispanic/Latino adults ages 18 years and older with asthma will be enrolled in this study, as the proposed research question focuses on the treatment of asthma specifically in this population. Based on past research experience and evidence from the medical literature, the researchers feel that this population is at significantly higher risk from asthma than other racial and ethnic groups and that further study in this specific population is needed. Therefore, no other racial/ethnic groups will be enrolled.
Women will be enrolled with no exclusion for pregnancy if determined acceptable by the woman's maternity care clinician(s). Statistics for studies of this type indicate that the percentage of women within the population to be enrolled will be approximately 60%. The study will seek to enroll approximately 50% of subjects of African American self- reported race and approximately 50% of Hispanic/Latino self-reported ethnicity with the provision as stated above that those reporting themselves to be Black and Hispanic will be enrolled in the H/L group. Enrollment of one group may be slowed or stopped if recruitment is faster or recruitment goals

are met for this group. The expected enrollment is detailed in the section XII, Table 1.

9. Inclusion of Children/Adolescents

Patients ages 18 to 21 will be included in this study. While they are labeled as “children” for study inclusion criteria by the National Institutes of Health and the Department of Health and Human Services, no special requirements for informed consent or parental permissions or safety concerns exist for this study among those aged 18 to 21 at all sites, except for the University of Puerto Rico—UPR requires assent of children ages 18 to 21 plus consent of a legal guardian.

D. Potential Benefits and Importance of the Knowledge to be Gained

1. Benefits to Human Subjects and Others

We believe there may be a potential benefit to those patients randomized to the PARTICS arm but this is still unknown. The potential benefit would be decreased numbers of exacerbations (asthma episodes that require oral steroid bursts or hospitalizations) and possibly decreased symptoms and reduced need for extra asthma medications. It is also possible that implementation of the Asthma IQ training for standardized provider educated care may improve rates of asthma control and this benefit could accrue to patients *in both arms* of the study.

Asthma has been resistant to various approaches to improve outcomes. Most approaches to date have focused in improving clinician implementation of current clinical guidelines and improving patient adherence with these treatment guidelines but when successful have been complex and difficult to widely disseminate. A few projects have worked at the community level to improve environmental conditions, but are also difficult to disseminate widely.

The approach studied in this project puts the patient in control of the level of additional use of ICS controller medications. The potential for benefit to society and individuals with asthma in general is very significant as the PARTICS represents a new approach to asthma therapy. Current asthma controller therapy follows a rigid, provider- prescribed approach. This study will examine the potential benefits of a patient controlled approach added to typical use of daily controller medications. Multiple studies and quality improvement projects have attempted to reduce asthma exacerbations, a theoretically ambulatory care-sensitive condition, with little long term improvement in outcomes. Any chance to determine a method to close this gap in care and learn how better to treat these subjects in clinical practice presents a clear benefit to African American and Hispanic/Latino adults with asthma.

Our proposed study seeks to inform a key health decision for people with asthma and clinicians who treat it-- should asthma patients use, and providers prescribe, a controller medication to be used each time a reliever is used in order to reduce asthma exacerbations? The PREPARE trial can help with that decision by assessing the ability of PARTICS to reduce exacerbation occurrences, reduce days lost from school or work, and reduce the consumption of ICS – all outcomes of high importance to patients.

This health decision is particularly pertinent among AAs and H/Ls, who bear a disproportionate burden of asthma morbidity and are less likely to receive, choose, or be able to comply with guideline-driven care. If the study shows that the PARTICS approach reduces exacerbations and/or improves other outcomes important to patients, then this approach can easily be adopted by patients and their providers in the context of current care since it is intuitive and

takes advantage of current patient-driven patterns of reliever inhaler use.

2. Knowledge to be Gained

PREPARE will teach us whether a PARTICS strategy can reduce asthma exacerbations in a real-world setting with high-risk populations as has been demonstrated in efficacy studies. It will also teach us whether the PARTICS approach can be implemented in health care systems that treat substantial numbers of minority patients. Although PARTICS- type strategies have been shown to significantly reduce exacerbations in carefully controlled efficacy studies by nearly 50% it's unclear patients will accept this strategy in real life outside the realm of an efficacy clinical trial.
PREPARE will also teach us whether the rationale for the PARTICS approach is better understood and accepted by patients than current standards of care, and whether it can reduce potential barriers to asthma self-management, such as beliefs about medication, cost, forgetting medication, health literacy and depression. While our preliminary data suggests significant benefit of the PARTICS strategy across a diverse population, this trial will teach us whether particular subgroups of patients show a greater benefit from this approach.

VIII. Data Sharing and Trial Information

A. ClinicalTrials.gov

This pragmatic trial requires registration on clinicaltrials.gov and registration will be done prior to enrollment of the first patient, during the first year of the project.

B. Data Sharing Plan

During the course of the PREPARE study, the Executive Committee (EC), which includes patients, patient advocates, and representatives of other stakeholder committees will establish a Data Sharing Committee (DSC) that will include at least two patient representatives. The DSC will develop a PREPARE Data Sharing Plan to be approved by the EC. This plan will include a detailed description of a post-project Data Request Process.
Complete, cleaned de-identified copies of the final datasets will be maintained at a secure location to be determined by the Steering Committee. These datasets will be made available as outlined in the PREPARE Data Sharing Plan via the established Data Request Process within one year of completion of the study. Specifics of this plan will be proposed by the Data Coordinating Center and ratified by the Executive Committee and at minimum will include the following provisions:

A specific Data Request form will be created that will need to be completed by all applicants requesting data and submitted to the PREPARE Data Sharing Committee. Required information to be provided on the Data Request form will include:

--Details on the requesting individual(s) and their affiliated organization
--Detailed specification of required data
--Intended use of the data
--Timeline for receipt of the data

Applicants will need to provide funds to cover the costs of retrieving the data and

fulfilling the specifications of the request. The costs of the requests will be based on the number of hours to fulfill the request and the specific billing rate of the statistician performing the task. Data requests will require approval by a majority of the Data Request Committee, including the Principal Investigators.

The PREPARE Data Sharing Committee will remain active following the end of the study and will meet periodically to review and evaluate specific data requests. Requests for data will need to come through one of the Data Sharing Committee members who, upon receiving the request, will schedule a meeting to review the request. Requests may be fully approved, conditionally approved, or denied, or additional information may be requested based upon specific criteria established in the

PREPARE Data Sharing Plan. The PREPARE Data Sharing Committee decisions will be communicated in writing to the requesting individual and can be communicated verbally by the contacted Data Sharing Committee member as well. If approved, de- identified SAS datasets will be prepared in accordance with the data specifications requested. In addition to providing the above described data sharing resources, a complete copy of the de- identified datasets, along with the data dictionary will be placed in the public archives.

IX. Nebulizer Qualitative Sub study

Background: Preliminary data show a high rate of consistent nebulizer use in the overall study (~45%), regardless of treatment assignment. Most of the published research on nebulizer use is focused on the pediatric population. Given the significant proportion of participants who report using a nebulizer regularly in our PREPARE trial this exploratory sub-study represents an opportunity to add to the published literature on the topic of nebulizer usage in Hispanic and African American adults.

Aim: This qualitative sub-study is to help us understand preferences, practices, and decision-making about nebulizer use among a sample of African American and Hispanic/Latino asthmatic adults.

Recruitment: a random sample of 40 patients who report using a nebulizer for rescue on their baseline questionnaire and report using a nebulizer in the past 4 weeks for rescue on at least one monthly survey will be interviewed. We will include 20 AAs, 10 Usual Care, 10 Intervention; 20 H/L, 10 Usual Care, 5 Spanish speaking; 10 Intervention, 5 Spanish speaking. We will exclude patients from two PREPARE sites not covered by Partners' IRB: Atrium and UIC.

All site PIs and/or Medical Directors will be contacted and asked permission for us to offer participation in this nebulizer sub-study to current PREPARE participants who self-report nebulizer use (as noted above).

A random sample of 300 participants will be contacted by mail. We will send opt-out letters with an opt-in clause (uploaded as separate attachment) and an information sheet (uploaded as separate attachment) explaining the sub-study and asking them to contact us if they did not wish to be offered participation in this sub-study. Participants will be informed that calls will be recorded for study purposes and will request verbal consent prior to the interviews starting (phone script uploaded as separate attachment). When participants are reached, they will be

offered the option being interviewed at the time of scheduling a more convenient date/time for the sub-study interview. Research staff trained in qualitative research will conduct a 30 min telephone-based interview (interview uploaded as a separate attachment).

Each participant will be called a maximum of 5 times with at least two of those times being an evening call. Messages will include a study specific call-back number and scripted message (message script uploaded as separate attachment).

X. COVID-19 Sub study

Background: The PREPARE study has produced riveting data/manuscripts regarding the COVID-19 pandemic and its impact on this disproportionately affected population of African American/Black and Hispanic/Latinx adults with asthma. First, a clinical communication published in May 2021 finding a 40% reduction in asthma exacerbations from January - August 2020 compared to January - August 2019 (during COVID-19) has had an overwhelming impact on researchers and the community. The finding was highlighted by several news agencies including the Atlantic. Additionally, a second manuscript has been accepted by JACI in Practice. Although we sampled only a subset of patients in the study, the findings showed that this population experienced changes in the quality of their asthma care and had increased socioeconomic stressors as a result of the COVID-19 pandemic and may be hesitant or unwilling to receive a COVID-19 vaccine.

The patient partners, stakeholders and research team agree that there is much more to be learned about this population with regards to COVID-19. In specific, we would like to better understand what might have contributed to the reduction in asthma exacerbations that we are measuring as our primary outcome. This involves understanding what practices have been undertaken by our population and, in order to make recommendations, to understand some of the attitudes toward COVID-19-induced modifications.

Aims: The aims of the sub study are to 1) explore subject behavioral changes which may have resulted in decreased exacerbations following the Covid19 pandemic. 2) explore patients' attitudes towards measures to prevent the spread of Covid19 (mask wearing, vaccine, etc.) and 3) investigate patient preferences towards telehealth vs. in person asthma clinic visits.

Methods: A COVID-19 questionnaire will be sent to PREPARE patients who agreed to be contacted after exiting the study. Approximately 1,000 agreed to future contact. The REDCAP, HIPPA compliant, questionnaire link will be sent via email and/or text and follow up of non responders will be by phone. As in the full study, to compensate patients for their time, we will pay patients $25 for completing the questionnaire. Payment will be made through the BWH ADVARRA system.

Each participant will be called a maximum of 5 times with at least two of those times being an evening call. Messages will include a study specific call-back number and scripted message (message script uploaded as separate attachment).

List of Abbreviations

AA: African Americans
AAAAI: Academy of Allergy Asthma and Immunology AAFP: American Academy of Family

Physicians ACT: Asthma Control Test
AEQ: Asthma Exacerbation Questionnaire AMR: Asthma Medication Ratio
ARO: academic research organization ATS: American Thoracic Society
ASK-12: Adherence Starts with Knowledge-12 ASUI: Asthma Symptom Utility Index
BELT: Anticholinergic vs Long-Acting β-Agonist in Combination With Inhaled Corticosteroids in Black Adults With Asthma: The BELT Randomized Clinical Trial.
BMQ: Beliefs about Medication Questionnaire CCPC: Disease Control and Prevention
DCC: Data Coordinating Center
DCRI: Duke Clinical Research Institute EC: Executive Committee
ED: emergency department EHR: electronic health record
ERS: European Respiratory Society H/L: Hispanic/Latinos
ICS: inhaled corticosteroids LABA: long-acting beta-2 agonists
MCID: minimal clinically important difference
NAEPP: National Asthma Education and Prevention Program NIH: National Institutes of Health
NRN: National Research Network OC: Operations Committee
PARTICS: Patient Activated Reliever-Triggered Inhaled CorticoSteroid PCORI: Patient-Centered Outcomes Research Institute
PCT: pragmatic clinical trial
PEERS: Patient Engaged Electronic Reporting System PHQ-2: Patient Health Questionnaire
PREPARE: Patient Empowered Strategy to Reduce Asthma Morbidity in Highly Impacted Populations
QA: Quality Assurance
SABA: short-acting beta-agonist SES: socioeconomic status UAT: User Acceptance Testing
UCDFM: University of Colorado Denver, Department of Family Medicine.

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XII. FIGURES

Figure 1. PREPARE Overall Study Structure

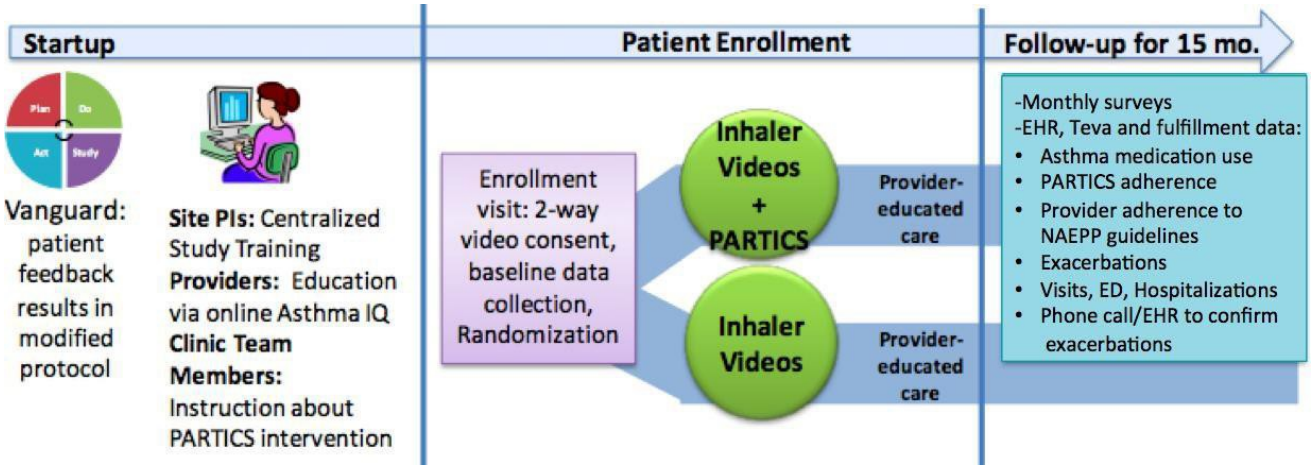


Figure 2. PREPARE Participant Flow Diagram

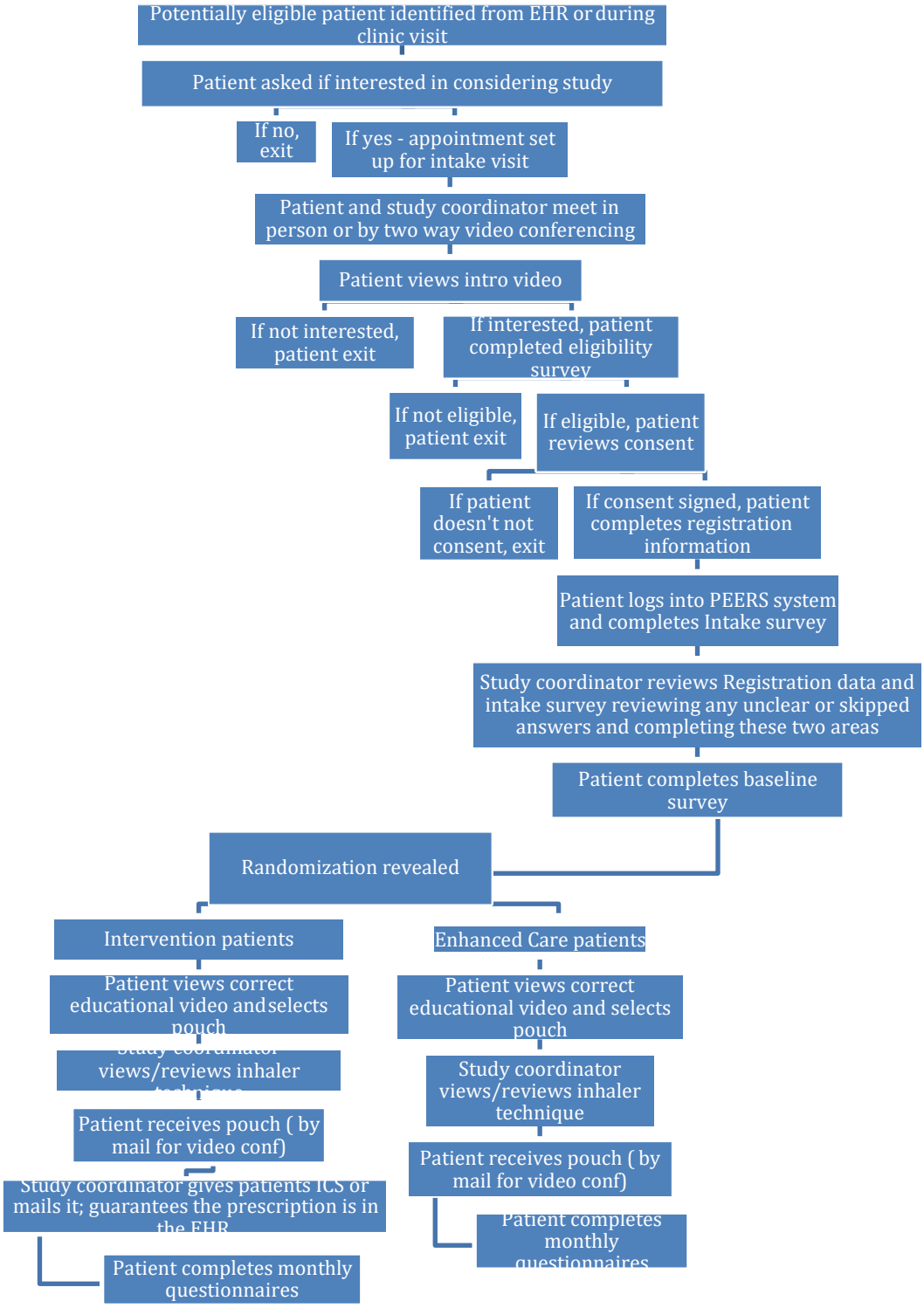
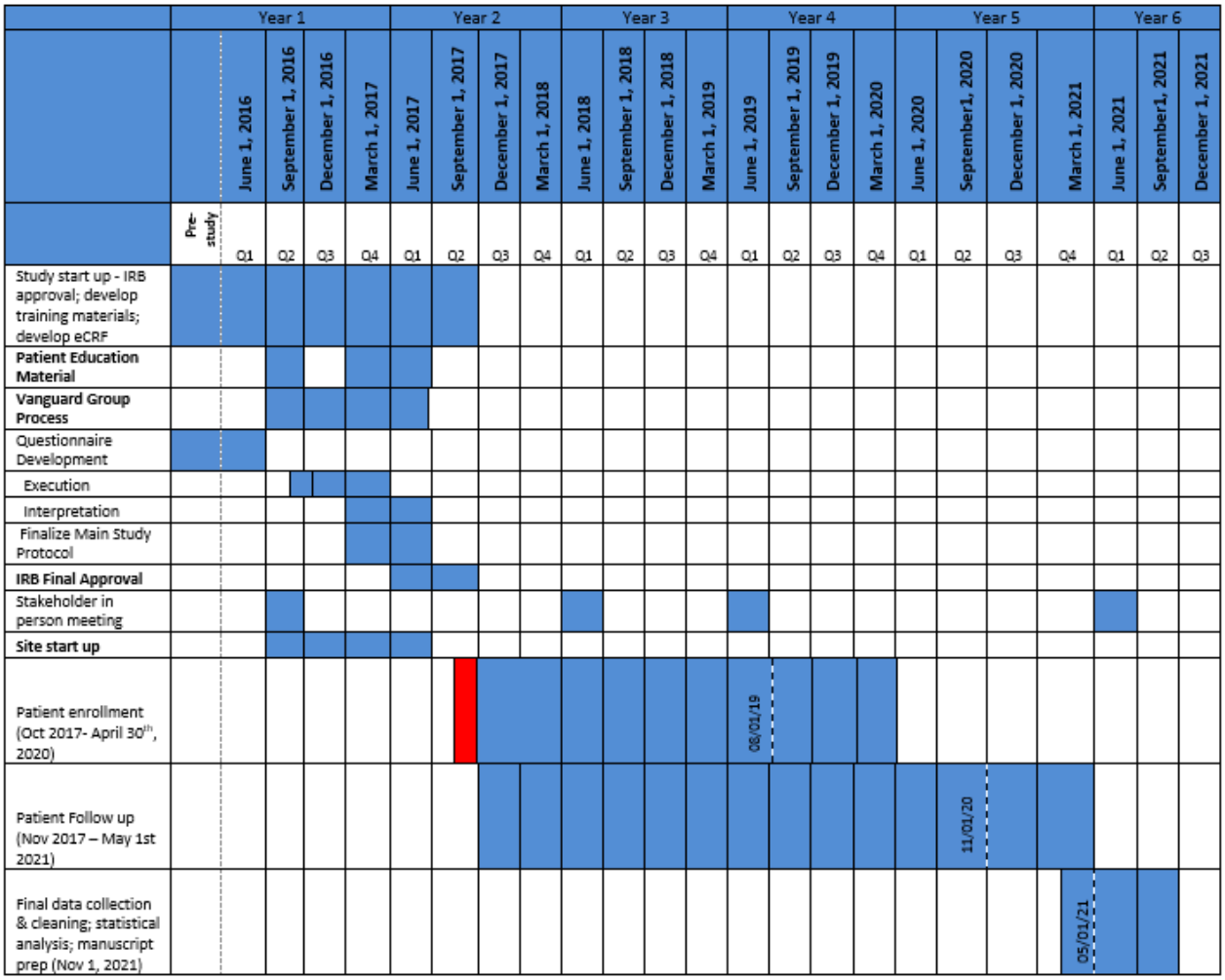


Figure 3. Project Milestones and Timeline



XIII. Tables

Table 1: Estimated Final Racial/Ethnic and Gender Enrollment Table

Race	Male (N)	Female (N)	Total (N)
American Indian/Alaska Native			
Asian			
Black/African American	300	380	680
Hawaiian/Pacific Islander			
White	170	250	420
Multirace	40	60	100
Ethnicity	**Male (N)**	**Female (N)**	**Total (N)**
Hispanic (Latino/Latina)	250	350	600
Non-Hispanic	195	405	600

XIV. APPENDIX

A. Vanguard Interview Questions: Qualitative Interview - 12 weeks [complete]

Instructions to interviewer: Please ask each of the questions to each person/interview you do.

Each question has the core concept bolded; the core concept is the general topic of a piece of the study we are interested in. After each core concept is an open-ended question. Please start with these and give the participant time to answer them before diving in to the prompt/probe questions. Based on the participant's answer to the open- ended question, it may not be necessary to ask each and every prompt/probe question. The prompt and probe questions are listed as guidance for you but it may not be necessary to ask them all. Please use your own judgment on this.

Refer to the accompanying Tip Sheet for Interviewing (at the end of these questions) prior to your interviews if needed to help you prepare for the interview.

Hello, am I speaking with [participant's name]? My name is [Victoria] and I am a part of the PREPARE study team.

Thank you for being available to speak with me today. I really appreciate it.

This interview will probably take about 20 minutes. Is this still a good time for you?

[Check also that connection is good, no background noise, and audiorecorder working properly].

Is it OK if I audiorecord this call? That would really help me be sure I remember everything you say and give my full attention to our conversation.

The purpose of today's interview is to learn more about your experience being a part of this study. Your ideas and feedback about ways we can improve our work for the future are very important to us. Please feel free to share your opinions as honestly and openly as you can. There are no "right" or "wrong" answers here.

If you have any specific questions or concerns that come up in our discussion that I cannot answer, I will be sure to give you the contact information that you need to get those answers from other research team members.

For enhanced usual care and intervention patients at 12 weeks:
I would like to start off asking your general impression of being a part ofthis study?
What worked for you? What didn't work for you?
What would you tell a friend with asthma about this study?

If you didn't have to do these interviews would you consider doing this again for up to 15 months?

Do you think the payments for completing the questionnaires was reasonable?

1. What can you tell me about any of the educational materials you saw or were provided as part of the study? Thinking back to the **study video's** that you saw when you enrolled in the study. Have you watched any of the study video's again since you were enrolled?

    - If yes -> which video's did you watch again? (intro video, study video, inhaler video) *only intervention patients saw the study video*
        - What made you decide to watch the [use answer from previous] video again? Was it helpful? Did you watch it more than once? Did you show the video to any friends or family?
    - If No --> Why did you not watch them again? (too long? Too boring? Just forgot? --> too long/too boring etc- Any suggestions on improvements? Just forgot -->Anything we could do to remind you that they are available)

    Thinking back to the **study packet** you received when you enrolled in the study. Have you looked through the packet again since you were enrolled?

    - If yes -> What did you go to the packet to look for?
        - Where you able to find the information you needed? Was it helpful? Did you show the packet to any friends or family?

    - If No --> Why did you not look at it again? (too long? Too boring? Just forgot? --> too long/too boring etc- Any suggestions on improvements? Just forgot -->Anything we could do to remind you that it is available)

    Did you ever look at the **website** for the study?

    If yes -> What did you go to the website to look for?

        - Where you able to find the information you needed? Was it helpful? Did you show the website to any friends or family?
    - If No --> Why did you not look at it? (too long? Too boring? Just forgot? --> too long/too boring etc- Any suggestions on improvements? Just forgot -->Anything we could do to remind you that it is available)

2. Now I'd like to ask you about your experience with the **monthly questionnaire**. (this is the survey that you completed every month with questions about your asthma and inhaler usage).

    Open-ended question: How was the experience overall? Option-tell me about your overall experience with the monthly questionnaires. Can you walk me through it as it happened for you?

    Did you get any reminders to complete your questionnaires? Did the reminder message come when you expected it?
    If it didn't come when you expected it, can you tell me more about that? Was it helpful? Why or why not?
    Tell me about any difficulties you had completing the questionnaire.

    How easy or hard were the questions to answer?

    Were there any questions that seemed to repetitive (as if you were being asked the same thing over and over again)

Would it have helped if someone read the questions to you?

What is your opinion on the length of the questionnaire? (Was it too long, too short, or just right?)

Was there anything we didn't ask that you think would be important for us to know?

3. Now I'd like to ask you some questions about your **inhalers/puffers**.

   How many quick reliever/albuterol inhaler canisters do you currently have and use? Do you usually keep separate or different quick relief inhalers in multiple places like the car, work, home?

   Do you remember how many refills of your quick reliever/albuterol you have gotten since the start of the study?

   What do you usually call your albuterol inhaler?

For usual care only:

Did you fill in the medicine log when you got the new inhaler?

Yes --> Was it hard to remember to do this? What could we do to make this easier?

No --> What could we do to make it easier?

Do you have any ideas on other ways (besides the medicine log) you could keep track of your inhalers during a longer study? Would a periodic reminder via text message/ phone call/ email help? Would a sticker on your pouch have helped you remember?

1. Do you use a nebulizer? If no go on if Yes
   Have you used your **nebulizer** in the past week? (about how many times?) _____Past two weeks? (about how many times?) _____
2. **Overall**, how do you feel your asthma has been since you started the study? Tell me about how you feel compared to before you started the study. Has there been any change? What if anything is different for you? Have you noticed any changes in your health?
3. Are there things that you think we should change or improve about this study? Please give us any ideas you may have.
4. Do you have any concerns or questions for me about the study?

For intervention only:

1. Now I'd like to ask you some questions about your study medicine **QVAR.** How many refills of QVAR have you gotten since the start of the study? Any difficulties with the refills?
2. Now let's talk about the part of the study that asks you to use the study medication **QVAR.**

   2a. Open-ended question: How was it taking an additional medication? Prompts/probes:

   2b. Was it hard to remember to use the QVAR® with the albuterol/quick reliever?
   If yes --> Is there anything that you think we could do that would help you remember?

   2C. How often do you think you used both inhalers together puff for puff?

   For example if you took 4 puffs of albuterol/quick reliever you then took 4 of QVAR®?

   2D. Did you fill in the medicine log when you got the new inhaler?

Yes --> Was it hard to remember to do this? What could we do to make this easier?

No --> What could we do to make it easier?

Do you have any ideas on other ways (besides the medicine log) you could keep track of your inhalers during a longer study? Would a periodic reminder via text message/ phone call/ email help? Would a sticker on your pouch have helped you remember?

3. Have you used your **nebulizer** in the past week? (about how many times?) _____Past two weeks (about how many times? _____
   If yes --> did you use your QVAR after using the nebulizer?
   If yes -> how many puffs did you use?
   If no (or not 5 puffs) -> why did you not use 5 puffs of QVAR (hard to remember, too many puffs, etc). What could we do to make it easier to remember or less scary?
4. During the study, did you make a **visit for your asthma to a healthcare provider**? This includes your regular asthma doctor or someone covering for your regular doctor, urgent care and Emergency department.

   If yes - did you mention the PREPARE study to them?

   - If yes- tell me more about that, what did they have to say? Did they have questions? Were you able to answer those questions?
   - If No- tell me why not? What could we have done to make it easier to remember to tell providers about the PREPARE study?

   - Did you show them your stickers, yellow card, or any other information about the study?
     - If yes- tell me more about that? Did they look at them? Ask any questions? Was the card/sticker/website helpful?
     - If no- tell me why not? What could we have done to make it easier to remember to share your card/sticker?
   - Did the provider talk with you about how you were taking the QVAR?
     - If yes- tell me more about that ? Did they adjust your dose? Did they tell you take it differently than you had been taking it? Did they seem concerned about how you were taking the QVAR?

   If No- skip to next question.
5. Do you think that using the **2 inhalers** medicines was better for you asthma?
   - If yes- can you give me an example of why you thought it was better?
     - If it were an option would you continue to use the two medications together?
   - If no- tell me why you didn't think the extra inhaler helped?
     - If it were an option would you continue to use the two medications together?
6. **Overall**, how do you feel your asthma has been since you started the study? Tell me

about how you feel compared to before you started the study. Has there been any change? What if anything is different for you? Have you noticed any changes in your health?

7. Are there things that you think we should change or improve about this study? Please give us any ideas you may have.
8. Do you have any concerns or questions for me about the study?