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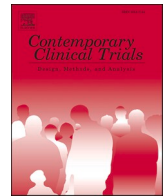# A randomized, open-label, pragmatic study to assess reliever-triggered inhaled corticosteroid in African American/Black and Hispanic/Latinx adults with asthma: Design and methods of the PREPARE trial

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A B S T R A C T

Background: Asthma prevalence, morbidity, and mortality disproportionately impact African American/Black (AA/B) and Hispanic/Latinx (H/L) communities. Adherence to daily inhaled corticosteroid (ICS), recommended by asthma guidelines in all but the mildest cases of asthma, is generally poor. As-needed ICS has shown promise as a patient-empowering asthma management strategy, but it has not been rigorously studied in AA/B or H/L patients or in a real-world setting.

Design and Aim

The PeRson EmPowered Asthma RElief (PREPARE) Study is a randomized, open-label, pragmatic study which aims to assess whether a patient-guided, reliever-triggered ICS strategy called PARTICS (Patient-Activated Reliever-Triggered Inhaled CorticoSteroid) can improve asthma outcomes in AA/B and H/L adult patient populations. In designing and implementing the study, the PREPARE research team has relied heavily on advice from AA/B and H/L Patient Partners and other stakeholders.

Methods

PREPARE is enrolling 1200 adult participants (600 AA/Bs, 600H/Ls) with asthma. Participants are randomized to PARTICS + Usual Care (intervention) versus Usual Care (control). Following a single in-person enrollment visit, participants complete monthly questionnaires for 15 months. The primary endpoint is annualized asthma exacerbation rate. Secondary endpoints include asthma control; preference-based quality of life; and days lost from work, school, or usual activities.

Discussion

The PREPARE study features a pragmatic design allowing for the real-world assessment of a patient-centered, reliever-triggered ICS strategy in AA/B and H/L patients. Outcomes of this study have the potential to offer powerful evidence supporting PARTICS as an effective asthma management strategy in patient populations that suffer disproportionately from asthma morbidity and mortality.

1. Introduction

In the United States, 25 million people (19 million adults) have asthma, which annually accounts for 1.8 million emergency department (ED) visits, 9.8 million clinic visits, 189,000 hospitalizations [1], and annual costs totaling over $80 billion [2]. Nearly half of adults with asthma report experiencing at least one asthma exacerbation annually [1]. Asthma exacerbations result in significant morbidity and mortality, with over 3400 annual asthma-attributed deaths [1]. Additionally, asthma exacerbations drive a large portion of asthma-related health care costs [2–4].

African American/Black (AA/B) and Hispanic/Latinx (H/L) populations bear a disproportionate share of asthma morbidity and mortality [1,5]. When compared with Caucasians, asthma prevalence is 35% higher in AA/Bs and approximately 100% higher in H/Ls [1,6–8]. When adjusted for prevalence, relative to Caucasians, AA/Bs and H/Ls

experience higher rates of asthma-related ED visits and hospitalizations [9–14] and approximately double the death rate [1,15].

The 2007 National Asthma Education and Prevention Program (NAEPP) guidelines recommend regular use of an inhaled corticosteroid (ICS) in all but the mildest cases [16]. Unfortunately, implementation of NAEPP guidelines has been inadequate [17], especially for AA/B and H/L patients [18,19]. Clinicians may not prescribe ICS, and patients may not adhere to daily ICS use when prescribed. Patients fill on average only 3 months' worth of asthma controller therapies (such as ICS) per year [20–23]. Low adherence to daily ICS regimens may reflect patients' experience of the episodic nature of asthma symptoms and perceived need for therapy [24]. Unfortunately, while intensive programs to improve adherence may have some effect, they remain expensive and difficult to scale-up [25].

Difficulties with adherence to regular ICS has led to investigations of as-needed ICS. A study of as-needed ICS triggered by symptoms in

patients with mild asthma showed that exacerbation rates were no different between those who used symptom-based versus regular ICS [26]. Subsequently, studies of ICS use triggered by short-acting β₂-agonist (SABA) use showed similar results [27,28]. In all of these studies, as-needed ICS use resulted in significantly less total ICS exposure. Subsequent studies with combination ICS and the long-acting β₂-agonist (LABA) formoterol have produced similar findings [29–32]. However, studies of a reliever-triggered ICS strategy have not been conducted in AA/B or H/L populations and, except for one [32], have not been conducted in real-world settings.

An as-needed ICS strategy (in addition to regular controller therapy or not) has several potential real-world benefits, including mitigating adherence-related challenges and reducing burden on healthcare professionals, which may reduce implementation barriers. We therefore investigated a reliever-triggered ICS strategy, which we call PARTICS (Patient-Activated Reliever-Triggered Inhaled CorticoSteroid), in which the patient uses ICS each time he or she uses a reliever medication such as SABA (e.g., albuterol). In the PeRson EmPowered Asthma RElief (PREPARE) study, funded by the Patient-Centered Outcomes Research Institute (PCORI), our aim is to assess whether the PARTICS strategy can improve asthma outcomes in AA/B and H/L adult patient populations in a real-world setting.

2. Study procedures

2.1. Study overview and goal

The PREPARE study is a randomized, open-label, pragmatic trial in AA/B and H/L adults with asthma. The goal is to determine whether PARTICS improves outcomes important to patients, health care professionals, and the health care system in AA/B and H/L populations disproportionately impacted by asthma. The primary endpoint of the trial is the annualized rate of asthma exacerbations requiring systemic steroid therapy or hospitalization. This endpoint was selected due to its relevance and importance to all stakeholders involved in the planning of this study, including AA/B and H/L adults with asthma and/or caregivers of individuals with asthma (our "patient partners"), patient advocates (members of patient advocacy societies), asthma researchers, healthcare professionals, and health system and policy leaders.

2.2. Protocol development

The PREPARE protocol was designed to adhere to PCORI Methodology Standards [33] with regards to patient centeredness, data integrity and analytical rigor; and as a pragmatic trial, as judged by PRagmatic Explanatory Continuum Indicator Summary (PRECIS) criteria [34]. In developing the PREPARE protocol, the investigators consulted with numerous stakeholders, including our patient partners, health care professionals, leaders of professional societies, patient advocacy groups, health policy leaders, pharmacists, and representatives of pharmaceutical companies—all of whom offered broad input in study design, implementation, and commitments for dissemination.

In the initial stages of protocol development, conference calls with patient partners and other stakeholders were held at least monthly to develop the study materials and processes and ensure that PREPARE remained patient-centered and of low burden to study participants. Patient partners and stakeholders are an integral part of the team and have been involved in all aspects of planning and decision-making, throughout the entire study (Table 1).

2.3. Study participants and sites

PREPARE is enrolling 1200 adult (age 18–75) participants with asthma, who self-identify as AA/B ($n = 600$) or H/L ($n = 600$). Recruitment began in November 2017 and was completed in March 2020. Participants are recruited from 19 clinical organizations

Table 1
Frequency of in-person meetings and conference calls for various stakeholder groups.

	Protocol development	Enrollment and follow-up	Data analysis[b]
Patient Partners	Up to bi-monthly	Monthly	Monthly
Patient Advocates	Quarterly	Quarterly	Monthly
Other Professional Stakeholders	Up to monthly	Quarterly	Quarterly
Executive Committee[a]	Monthly	Monthly	Monthly

[a] The Executive Committee governs the study and is comprised of investigators and representatives of stakeholder groups, including AA/B patient partners, H/L patient partners, patient advocates, healthcare professionals, professional societies, health policy leaders, and clinical trials experts.
[b] To contribute to data analysis, stakeholders listed will see preliminary data tables and be involved in discussions of implications of results.

(Supplement 1), representing a diverse range in practice size, health system type, geographic distribution, and specialty (allergy/immunology, pulmonology, and family medicine/internal medicine, with the majority being primary care clinics). The American Academy of Family Physicians National Research Network (AAFP NRN) serves as our site coordinating center, managing site training and ongoing site support.

Enrolled participants are centrally randomized 1:1 to one of two study arms: PARTICS + Usual Care (intervention) versus Usual Care (control). Planned duration of follow-up is 15 months. Participants attend one in-person visit to enroll in the study, provide baseline demographics, and view pre-recorded videos which provide a detailed overview of the PREPARE study, education on asthma, and for those in the intervention arm, instructions on how to use PARTICS. Following the single in-person enrollment visit, all participants receive one follow-up telephone call within the first month after enrollment to ensure comfort filling out the monthly questionnaires and to reinforce study procedures. Participants then complete study questionnaires each month for 15 months (Fig. 1). Data collected from these 15 monthly questionnaires will be used to determine patient outcomes. Participants are compensated 50 dollars for the enrollment visit, and 20 dollars for each completed questionnaire. Randomization, patient intake, informed consent, baseline data collection, and monthly survey data collection are completed using the Patient Engaged Electronic Reporting System (PEERS®), a Health Insurance Portability and Accountability Act (HIPAA)-compliant electronic data capture and study management system developed by the University of Colorado Department of Family Medicine.

2.4. Intervention: PARTICS

Participants randomized to the PARTICS intervention are provided a pressurized metered-dose inhaler (pMDI) containing the ICS beclomethasone dipropionate hydrofluoroalkane (HFA) 80 µg (QVAR® prior to December 2018, QVAR® RediHaler™ thereafter; Teva Respiratory, LLC), and are instructed to use one puff of ICS for every puff of reliever inhaler used as needed, and 5 puffs of ICS for every reliever nebulizer treatment used as needed. Participants view a video, co-developed with our patient partners, that gives education on asthma and explains how and why to use the PARTICS medications (video available upon request). We provide a medication pouch for the participants' PARTICS inhalers, and a Velcro® band to attach the ICS and reliever inhalers to one another.

2.5. Control

Participants randomized to the Usual Care arm do not have any required changes to their asthma therapy. All participants watch an enrollment video concerning asthma (for participants in the control arm, PARTICS-related instructions are removed). To maintain a similar
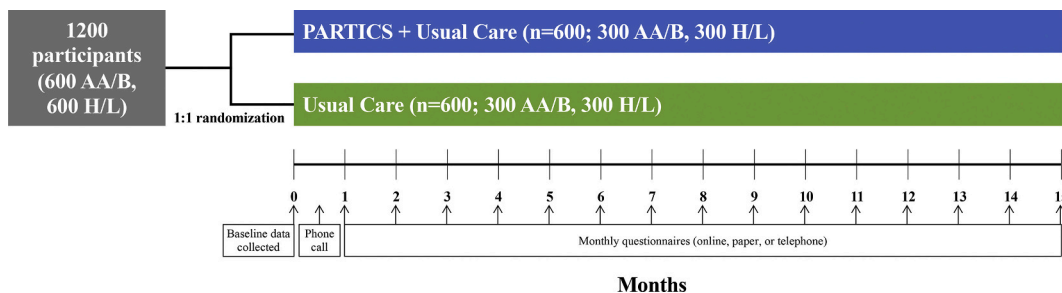
Fig. 1. PREPARE study design.
AA/B: African American/Black; H/L: Hispanic/Latinx.

degree of engagement with participants in the intervention versus the control arm, we have standardized communications and intensity of contact as much as possible. When an additional point of contact with the PARTICS group was required (e.g., sending out new beclomethasone inhalers due to the changeover to QVAR® RediHaler™), we added a point of contact with the control group as well (e.g., sending out new medication pouches and reminding participants to have their reliever medication with them at all times).

2.6. Adaptive protocol modifications

In the early stages of PREPARE, we noticed that participant adherence to the PARTICS intervention (which is self-reported in the monthly questionnaires) was suboptimal in those participants using nebulized reliever therapy. Of these participants, 72% reported using concomitant ICS with their nebulized reliever all or most of the time. Furthermore, while the PARTICS intervention is 5 puffs of ICS with every rescue nebulization, only 20% of participants reported using 4–5 puffs, and 70% reported using 1–2 puffs. In consultation with patient partners and stakeholders, we made adaptive modifications to the protocol and the enrollment videos to reinforce the PARTICS strategy with participants in the intervention arm. PARTICS instructions were added to a splash screen at the end of each monthly survey, emphasizing the ratios of 1:1 ICS to reliever inhaler and 5:1 ICS to reliever nebulization. Participants in the intervention arm receive a magnet printed with the PARTICS instructions, and quarterly text messages reminding them of the PARTICS strategy. Finally, those who report using a nebulizer receive a second QVAR® and a Velcro® pouch (used to attach the QVAR® to the nebulizer) equipped with a PREPARE trial sticker as a visual reminder. After these adherence interventions, 82% of nebulized rescue therapy users now report using concomitant ICS all or most of the time, and 63% report using 4–5 puffs.

These additional reminders and points of contact with the intervention group were balanced with additional reminders and points of contact with the control group. A splash screen message was added to each monthly survey reminding control participants to use their daily asthma controller medications even in the absence of asthma symptoms. Participants in the control arm receive a magnet with a message reminding them to keep their reliever inhaler with them at all times and receive quarterly text messages reminding them to take their asthma medicines every day.

2.7. Standardizing usual care

In order to reduce variation in asthma management across study sites, all clinicians enrolling participants into either the intervention or the control arm were required to complete the educational component of the Asthma IQ asthma management system [35], either online or by attending an in-person presentation. The Asthma IQ system was jointly developed by the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American Academy of Family Physicians

(AAFP). The educational component takes approximately 20 min to complete and reviews the existing NAEPP Expert Panel Report-3 [36] guidelines for diagnosis and management of asthma.

2.8. Study endpoints and assessments

Primary and secondary study endpoints were determined with all stakeholders. They are outlined in Table 2. In consideration of minimizing the burden to study participants and investigators, all data are collected via monthly questionnaires, completed by the study participants either online (via smartphone, desktop or laptop), by phone interview or by mail. The questionnaires require approximately 10 min to complete.

2.9. Primary endpoint

The primary endpoint of the trial is the annualized asthma exacerbation rate which, as mentioned previously, was selected based on input from our patient partners and other stakeholders. In this study, an asthma exacerbation is defined as an incidence of asthma worsening that requires 72 h or more of oral or parenteral steroids, or hospitalization. An ED visit or urgent care visit without receipt of at least 72 h of oral or parenteral steroids is not considered an exacerbation.

Possible exacerbations are captured by participant self-report via a monthly Asthma Exacerbation Questionnaire (AEQ; Supplement 2). These self-reported events (possible asthma exacerbations) are verified in the Electronic Health Record (EHR) or, if necessary, by participant telephone interview. All possible asthma exacerbation events are adjudicated by a group of clinicians blinded to participant randomization status, based on pre-specified rules for adjudication, using all sources of data available. Only the verified and adjudicated asthma exacerbations will be included in the data analyses.

2.10. Secondary endpoints

The secondary endpoints are level of asthma control; preference-based quality of life; and days lost from work, school or usual activities. All secondary endpoints are assessed at baseline and then monthly

Table 2
Study endpoints and related assessments.

Primary endpoint	Assessment
Asthma exacerbation rate (annualized)	Self-reported via monthly Asthma Exacerbation Questionnaire (AEQ), then verified and adjudicated
Secondary endpoints	Assessments
Asthma control	Asthma Control Test (ACT), assessed at baseline and monthly
Preference-based quality of life	Asthma Symptom Utility Index (ASUI), assessed at baseline and monthly
Days lost from work, school, or usual activities	Self-reported via monthly questionnaire

for 15 months.

Asthma control is assessed using the Asthma Control Test (ACT), which is a patient self-administered tool for assessing level of asthma control [37]. The ACT is a validated, 5-item questionnaire that assesses asthma symptoms, rescue medication use, daily functioning, and overall perception of asthma control, with a 4-week recall. Scores on each item range from 1 to 5 and the total score ranges from 5 to 25. An ACT score > 19 indicates well-controlled asthma.

Preference-based quality of life is assessed using the Asthma Symptom Utility Index (ASUI). The ASUI is a validated, 10-item questionnaire designed to assess four asthma symptoms (cough, wheeze, dyspnea, and nocturnal awakening) and side effects from asthma medications over a 2-week recall period [38]. The frequency and severity of each item are assessed on a 4-point Likert scale. The items are then weighted according to patient preferences, and the summary score is a continuous scale ranging from 0 (worst possible symptoms) to 1 (no symptoms).

Data regarding days lost from work, school, and usual activities are collected using a validated questionnaire developed and utilized as part of the National Health Interview Survey (NHIS) [39]. Study participants who do not work or go to school are asked about days they are unable to carry out usual activities due to asthma.

Several important covariates are also assessed, as detailed in the Statistical Analysis section. Two of these, fractional exhaled nitric oxide (FeNO) and blood eosinophils, were added as assessments as an adaptive modification to the study protocol, in response to the increased focus on asthma phenotyping and biomarker analysis. FeNO is analyzed at baseline using a NIOX® device (generously provided by Circassia Limited), which non-invasively measures the amount of nitric oxide in exhaled breath. Blood eosinophils are analyzed via complete blood count (CBC) with differential at baseline, if the participant agrees to a blood draw. If not, a historic blood eosinophil measurement value within a year prior to baseline may be used.

2.11. Developing the protocol

We conducted a 3-month pilot study, supported by PCORI, to test the feasibility of the larger pragmatic PREPARE trial, and to use the results to improve PREPARE's protocol. We enrolled 16 AA/B and 17H/L participants from four sites that represented the geographic, health system and practice size diversity of the 19 PREPARE study sites. Participants had a single enrollment visit, viewed instructional videos and then answered monthly questionnaires at Months 1, 2, and 3; they also

underwent qualitative phone interviews at 1, 6, and 12 weeks. The key findings of the pilot study, which have been detailed previously [40], were that questionnaire completion was suboptimal (60–70% completed within 15 days) and that there were gaps in understanding of the asthma medication terminology used in the questionnaires. These 33 participants did not enroll in the full PREPARE trial and are not included in the 1200 PREPARE participants.

A face-to-face meeting was held with our patient partners, other stakeholders and the operations group to discuss strategies to improve survey completion rates and understanding of inhaler terminology, without sacrificing the pragmatic nature of the study. We shortened the survey; incentivized timely survey response with a monthly lottery for a $100 prize (except in Florida where this is prohibited); provided the option of one-click access to surveys (no log-in required); added reminders using the PEERS® system via text message, phone message and email; and reinforced the importance of filling out the monthly surveys during the follow-up telephone call during Month 1. Because we learned that participants use many different terms for their inhalers, and might not recognize the terms "reliever", "rescue", "controller", or "maintenance", we ask participants at baseline what names they use for their inhalers, and then personalize their surveys by referring to their inhalers by those names.

2.12. Accommodations for low literacy

To ensure that literacy or language barriers do not interfere with trial recruitment or data collection, all written trial material is available in English or Spanish and was designed for a low-literacy audience. For those with difficulty reading, the investigators have made available, if needed, oral materials for consent, video-based introductory instructions (English: https://youtu.be/4XXOW3I4aOg; Spanish: https://youtu.be/4IsW5N7kOno), and in-person telephone-based monthly survey completion (all in both English and Spanish). Videos contain members of the ethnic group with which the participant self-identifies.

2.13. Participant eligibility

Due to their stringent eligibility criteria, efficacy trials generally represent only about 5% of adult patients with asthma [41,42]. In contrast, we have set broad eligibility criteria (Table 3), including allowing enrollment of past or current smokers. We do exclude patients

Table 3
Eligibility criteria.

Inclusion criteria	Exclusion criteria

• Physician-diagnosed asthma for at least 1 year
• Age 18–75 years
• African American/Black or Hispanic/Latinx based on self-identification
• Ability to provide informed consent
• Clinical history consistent with asthma for >1 year
• Prescribed daily ICS with or without additional maintenance therapies
• ACT score of ≤19 *OR* a patient-reported history of ≥1 asthma exacerbation in the past year requiring systemic corticosteroid use
	• Life expectancy <1 year
	• Known allergy to beclomethasone dipropionate
	• Chronic Obstructive Pulmonary Disease (COPD) or other chronic lung disease other than asthma, with the exception of the following:
	  • Diagnosis of COPD in a never smoker without any other lung disease or any other disease that might cause airway obstruction
	  • Diagnosis of COPD in a former smoker with normal pulmonary function tests (PFTs)[a] after the patient quit smoking
	  • Diagnosis of COPD in a current smoker with normal PFTs[a] in the past 24 months
	  • Diagnosis of COPD in a current or former smoker with obstruction on PFTs, but normal diffusing capacity in the past 24 months *AND* demonstrated forced expiratory volume in one second (FEV_1) reversibility to bronchodilator of 12% or more at any time
	• Asthma exacerbation in the past month requiring use of systemic corticosteroid; visit to the doctor's office, ED or urgent care; or overnight hospitalization
	• Regular systemic corticosteroid use (daily or every other day) for any reason
	• Use of biologics for asthma (injection or infusion), unless the patient has been on a stable dose of a biologic for at least 6 months *AND*:
	  • Had an asthma exacerbation at least 2 months after starting the biologic, *OR*
	  • Has a current ACT score of ≤19
	• Bronchial thermoplasty within the past 6 months
	• Another person living in the same household already enrolled in the study

[a] Normal PFTs defined as: FEV_1 > 80% predicted, FEV_1/forced vital capacity (FVC) ≥70%, and diffusing capacity for carbon monoxide (DLCO) ≥80% predicted.

with known Chronic Obstructive Pulmonary Disease (COPD), unless they meet the lung function and smoking history criteria outlined in Table 3. Since the PARTICS strategy is patient-activated, and repeated observation of the strategy in a household might lead to adopting PARTICS behaviors, we do not enroll more than one study participant per household.

Since the primary outcome of the study is asthma exacerbations, we enrolled patients at risk of exacerbation by requiring that participants have either poorly controlled asthma (ACT score of ≤ 19) or a history of at least one asthma exacerbation requiring systemic corticosteroid in the past year.

2.14. Concomitant asthma medications

In keeping with the pragmatic nature of this study, all participants in both study arms continue their current asthma medications after enrollment and for the duration of the study. With the exception of regular oral corticosteroid (OCS), all other asthma controller therapies are permitted. Patients on biologics may be eligible for the study if they have been on a stable dose for at least 6 months and either had an exacerbation within the last year but no earlier than 2 months after starting the biologic or are still symptomatic (ACT score ≤ 19). Clinicians are permitted to modify the participant's asthma medication regimen as they see fit.

2.15. Management of risks to human participants

While previous studies have indicated that the PARTICS strategy reduces ICS exposure [26–28], it is possible that participants assigned to the PARTICS group may experience increased ICS exposure, particularly in the short-term. Participants are monitored for excess ICS use (defined as requesting ≥ 3 QVAR® refills in 1 month). All participants are informed of potential side effects of ICS and told to report them to their healthcare professional and are also advised to rinse their mouth with water after each ICS dose.

Due to the pragmatic nature of this study, non-serious adverse events are not systematically monitored. However, serious adverse events are monitored and, if study-related, reported to the principal investigator (PI) as soon as they occur, and to the central Investigational Review Board (IRB) within 5 working days. A serious adverse event is defined as any event that results in death, hospitalization, persistent/significant disability, or congenital anomaly/birth defect; or is otherwise life-threatening. An independent safety officer who has no involvement in the PREPARE trial reviews safety data in a blinded manner (death and asthma-related hospitalization data are unblinded) twice annually.

This study is being carried out in accordance with The Declaration of Helsinki. Informed consent is obtained for all participants, and participant privacy rights are rigorously observed. The study protocol was approved by the Partners Healthcare IRB and was approved by IRBs at all participating sites via reliant review.

3. Statistical analysis

3.1. Overview

Statistical analysis is performed at the Statistical Data Coordinating Center at Duke Clinical Research Institute (DCRI), using SAS statistical software Version 9.4 or higher (SAS Institute Inc., Cary, NC). Data from PEERS® are transferred to DCRI for analysis, a process which was tested in the above-mentioned pilot study.

In the final analysis, all major treatment comparisons between the randomized groups will be performed using the intention-to-treat (ITT) population. The ITT population will exclude 19 participants from one study site that did not comply with protocol entry criteria and study procedures and was closed. Participants in the ITT population will be analyzed according to their randomized treatment arm. All randomized

participants are included in the safety analysis.

Statistical comparison by treatment groups in the primary analysis will be performed using two-sided significance tests. A significance level of 0.05 will determine statistical significance for the primary analysis. If the analysis of the primary endpoint does not yield a p-value <0.05, the subgroup analyses of the primary endpoint data and the analyses of the secondary endpoints will all be considered exploratory.

3.2. Sample size and power calculations

To determine the desired effect size for the primary outcome, we consulted our patient partners regarding the percent reduction in exacerbations that they felt would motivate them to use an additional as-needed inhaler. Our patient partners told us that a reduction by a quarter in asthma exacerbation rates would be meaningful for them, and we powered the study accordingly. We felt that an enrollment of 1200 participants was feasible, and thus needed to extend beyond the initially planned 12 months of follow-up in order to appropriately power the study. Thus, for the primary efficacy outcome, power calculations were based on an estimated primary event intensity of 0.4 exacerbations per year (0.5 per 15 months) in the control arm, 15 months of follow-up for each individual 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 participants (600 per arm) yielded 80% power to declare a reduction of 23.5% in the rate of exacerbations as statistically significant. We did not factor adherence directly into the model, as this is a pragmatic study, but did inflate the sample size to allow for dropouts and low adherence.

Sample size and power calculations were performed using PASS software [43], using the similarity of inference between the Andersen-Gill models and Poisson regression.

3.3. Randomization and blinding

Participants are centrally randomized, stratifying by site and race/ethnicity (AA/B versus H/L), using the PEERS® system. Participants are randomized in a 1:1 ratio of intervention (PARTICS + Usual Care) to control (Usual Care). In keeping with the spirit of a pragmatic trial, the study participants and investigators are not blinded to the treatment assignment. However, in order to reduce selection bias, the randomization scheme is kept confidential from all investigators. The randomization scheme is generated by an unblinded statistician at DCRI and is implemented by an authorized party who has no involvement in the conduct of the study.

3.4. Primary endpoint analysis

The timing and frequency of asthma exacerbations during follow-up in the two randomized treatment arms will be compared using the Andersen-Gill adaptation of the time-to-event Cox proportional hazard model with robust standard errors to account for multiple occurrences of the outcome in each participant. This comparison will be stratified by race/ethnic group: AA/B and H/L (participants who self-identify as both AA/B and H/L will be classified as H/L, in accordance with our patient partners' recommendation). The following baseline characteristics, which may influence the rate of exacerbations or the response to ICS, will be adjusted for in the primary analysis model: age, sex, smoking status, body mass index (BMI), geographic region, season of randomization, history of exacerbations in the past year, and use of ICS/LABA prior to randomization.

Several secondary analyses of primary endpoint data will be performed. Comparison between the two groups of the count of asthma exacerbations during follow-up will be performed using the Poisson model. If overdispersion of data is noticed, negative binomial regression will be used. Time from randomization to first asthma exacerbation between the two treatment arms will be compared using the log-rank

test, and survival curves will be constructed using the Kaplan-Meier method. Sensitivity analyses will be performed: first, to test whether the change of ICS from QVAR® to QVAR® RediHaler™ has a significant effect on the effectiveness of PARTICS; second, to evaluate the effect of protocol and treatment compliance by constructing and analyzing treatment and protocol compliance estimands; and third, using the modified intention-to-treat (mITT) population to analyze the primary endpoint. The mITT population will include all participants in the ITT population minus those who meet any of the following criteria: (1) did not have an exacerbation in the year prior to randomization and had an ACT score of ≥20 at enrollment; (2) were not taking ICS at enrollment; or (3) have COPD and did not meet the COPD inclusion criteria.

3.5. Covariate analysis

The heterogeneity of treatment effect among various participant characteristics will be studied by examining the interaction of several different covariates with the randomized treatment group using the Andersen-Gill model. These covariates are detailed in Table 4.

The covariates that are adjusted for in the primary analysis model, listed above, will also be included in the models when we examine each interaction of interest. If the covariate of interest is already on the list of covariates that are included in the model, this covariate is included in the model only once. Covariates that will be both included in the model and tested for interaction with treatment are bolded in Table 4.

Some covariates listed in Table 4 will be analyzed as continuous variables in the models that examine the interaction between the variable and the treatment. The linearity of this interaction will be assessed by fitting a flexible model using a restricted cubic spline transformation of the continuous variable. If nonlinearity is detected, the significance of the interaction between the nonlinear components of the spline function and the treatment will then be tested. These continuous covariates will be used to categorize participants into subgroups only when subgroup data need to be graphically displayed.

3.6. Secondary endpoint analysis

ACT and ASUI will be analyzed as continuous variables, using mixed model with repeated measures (MMRM) to compare treatment effects. The response variable will be change in ACT score or ASUI score from baseline at all 15 monthly 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 covariates included in the primary analysis model. Of note, we present the ACT with a slight variation from the published and validated version in that the order of questions 3 and 4 is reversed.

Days lost from work, school, and usual activities will be analyzed using Poisson or negative binomial regression models (if overdispersion of data is noticed), with time as an offset to account for differential duration of follow-up.

4. Discussion and conclusion

4.1. Discussion

The design of the PCORI-funded PREPARE study was informed by several key factors: PCORI's Methodology Standards, the PRECIS criteria for designing pragmatic clinical trials, the outcomes of the pilot study, and most importantly, the ongoing guidance of our collaborative partners and stakeholders. These include patient partners (AA/B and H/L adults with asthma and/or caregivers), patient advocacy groups, healthcare professionals, scientific experts, professional medical societies, health policy experts, insurers, and representatives of pharmaceutical companies. The insights and suggestions of our collaborative

Table 4
Planned covariate analyses.

Parameter	Analysis
Race/ethnic group	African American/Black versus Hispanic/Latinx
Smoking status	**Current (has smoked within 1 year) and former smokers (≥10 pack-years and has not smoked within 1 year) versus non-smokers (≤10 pack-years and has not smoked within 1 year)**
Fractional exhaled nitric oxide (FeNO)	High versus low FeNO at baseline, based upon two different thresholds [≥20 parts per billion (ppb) versus <20 ppb, and ≥ 30 ppb versus <30 ppb]
Blood eosinophil count	High versus low blood eosinophil count at baseline (≥300 cells/μL versus <300 cells/μL)
Questionnaire modality	Paper/telephone versus online (defined as ≥80% of monthly questionnaires completed online)
Attitude toward ICS	As a continuous variable based on the differential between the Necessity and Concern subscales of the Asthma-Specific Beliefs about Medicine Questionnaire (BMQ)[a]
Depressive symptoms	Presence of depressive symptoms [Patient Health Questionnaire (PHQ-2)[b] score ≥ 3] versus absence (PHQ-2 score < 3)
Health literacy status	Low/marginal versus high based on the Brief Health Literacy Scale (BHLS)[c]
Body mass index (BMI)	**As a continuous variable**
Medication use at baseline	**ICS/LABA versus ICS**
Comorbidities	Presence versus absence at baseline of heart disease, cancer, stroke, diabetes, chronic kidney disease, COPD, Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS), and hypertension
Exacerbation history	**Presence versus absence of an asthma exacerbation within 12 months prior to randomization**
Self-perceived discrimination	As a continuous variable based on the short version of the Everyday Discrimination Scale[d]
Self-reported medication adherence	As a continuous variable based on the Medication Adherence Report Scale (MARS-5)[e]

[a] The Asthma-Specific BMQ has 2 scales: the Necessity Scale (measures patients' beliefs about the necessity of ICS for managing asthma) and the Concerns Scale (measures patients' concerns about negative consequences of using ICS). A higher score on the Necessity Scale combined with a lower score on the Concerns scale indicates a more accepting attitude toward ICS.

[b] PHQ-2 asks two questions that screen for depression. Each question has a score ranging from 0 to 3. The total PHQ-2 score ranges from 0 to 6, with higher scores indicating greater presence of depressive symptoms.

[c] The BHLS consists of 3 items. The scores on items 1 and 3 range from 1 to 4; the score on item 2 ranges from 1 to 5. Higher scores indicate higher subjective health literacy. A participant is considered to have high health literacy if he/she receives a score of 4 on items 1 and 3, and a score of 4 or 5 on item 2. Otherwise the participant is considered to have low/moderate health literacy.

[d] The short version of the Everyday Discrimination Scale has 5 items with each item's score ranging from 1 to 6. The total score ranges from 5 to 30, with higher scores indicating a higher degree of perceived discrimination.

[e] The MARS-5 is a 5-item questionnaire that measures patients' self-reported medication adherence. Each item has a score ranging from 1 to 5. Total scores range from 1 to 25, with higher scores indicating higher self-reported adherence.

partners will be essential to interpretation of study outcomes and dissemination of study results.

A key feature of the PREPARE study is its pragmatic design, which will allow for real-world assessment of the efficacy of the PARTICS treatment strategy (Fig. 2). The study is enrolling from both primary care and asthma specialty practices, allows for the inclusion of many patients typically excluded from asthma studies (e.g., smokers) and has few exclusions for comorbidities, thus supporting broad applicability. The intervention imposes minimal burden on practice sites and requires minimal patient instruction. If needed, the short PARTICS instructional videos are readily accessible on the internet. Thus, if successful, the intervention could be easily implemented.

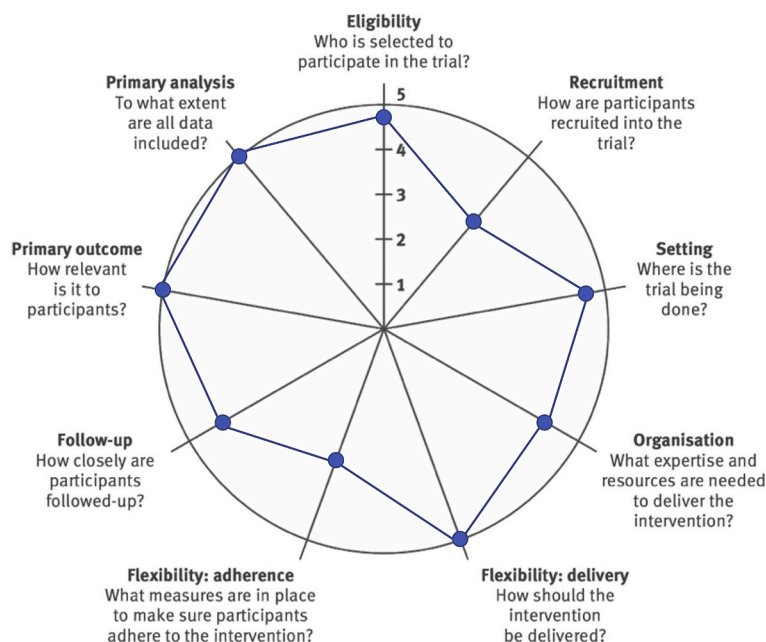The PARTICS strategy and the PREPARE study have received broad

Fig. 2. PREPARE PRECIS diagram.

and enthusiastic stakeholder support, for several reasons. First, the study's focus on AA/B and H/L patients addresses an important gap in asthma care: the disproportionate asthma morbidity among AA/B and H/L populations. In general, efforts to increase guideline-directed care in asthma tend to be complex and time- and resource-consuming, but still do not achieve substantial improvements in treatment outcomes [25]. Such efforts to improve asthma management have been particularly challenging among AA/B and H/L populations [44,45]. The PARTICS strategy is relatively easy to implement and in line with current patient patterns of medication use—which makes it patient-empowering, intuitive, provider-friendly, sustainable and scalable. Additionally, PARTICS has the potential to reduce total corticosteroid exposure by reducing the use of oral or parenteral corticosteroids associated with exacerbations; as this is a cause of concern for many of our patient partners and healthcare professional stakeholders, this would be a well-received outcome. Further, the PARTICS strategy offers an asthma management approach that reduces the clinician and patient resources necessary to reduce asthma morbidity (i.e., less clinician instruction time, less need for intensive programs to improve adherence to daily ICS, less cost for inhalers potentially due to less inhaler use), which is particularly relevant in many communities of color where resources may be limited.

Lastly, the outcomes measured have importance to multiple consumers and providers in the healthcare system. The primary outcome measure chosen for inclusion in PREPARE was carefully selected considering both stakeholder input and PCORI criteria. According to our patient partners, asthma exacerbations have dramatic adverse effects on their quality of life, resulting in states of health that cause distress, severely limit their activities, and result in loss of income or require personal financial expenditures. In addition, asthma exacerbations are associated with progressive decline in lung function [46] and cost the healthcare system billions of dollars annually [3,4]. Thus, the primary outcome measure of asthma exacerbations is of utmost importance to all stakeholders. The secondary outcome measures of asthma control, preference-based quality of life, and days lost from work or school will all be assessed using validated and well-documented patient-reported outcome measures, and reflect outcomes that our patient partners have indicated as important to them.

While as-needed use of ICS is not currently approved by the United States Food & Drug Administration (FDA), the PREPARE stakeholders

have explicitly and unanimously agreed that, should the PARTICS strategy result in reduced asthma exacerbation rates, they would support the adoption of this strategy as part of routine asthma management. Of note, at least one pharmaceutical company is developing a combination ICS/SABA preparation for approval in the United States. Additionally, the World Health Organization (WHO) Global INitiative for Asthma (GINA) 2020 asthma guidelines recommend as-needed low-dose ICS/formoterol (over as-needed SABA) as the preferred reliever for adult patients with asthma [46]. We applaud these recommendations. However, the study populations in the studies forming the basis of the GINA recommendations included very few individuals of color and several studies have suggested that AA/B and H/L populations may respond differently to asthma interventions [47–52]. Further, populations of color may have belief systems (e.g., negative beliefs about ICS [53]) and healthcare access which may impact the applicability of certain interventions. Prior to the adoption of an as-needed ICS strategy for AA/B and H/L populations, a pragmatic study such as PREPARE, to demonstrate that such an approach is applicable to these populations, is urgently needed.

There are several limitations to the PREPARE study. First, study participants are unblinded to their treatment assignment. While it is somewhat unlikely that the lack of participant blinding will have a large effect on exacerbations requiring steroids, it is possible that beliefs related to PARTICS efficacy may impact our secondary outcome measures, all of which are patient-reported. Second, the PARTICS + Usual Care group is provided with an additional ICS inhaler that the Usual Care group does not receive. Indeed, it is possible that participants in the PARTICS arm may use their study-provided ICS in ways other than intended, which could result in improvements merely related to increased availability of ICS. We discussed this with our healthcare professional and insurance partners, who agreed they would be willing to support the use of as-needed ICS should the study results be positive, despite this limitation. Further, considering the generally poor adherence to ICS documented in the literature [20–23], it is unlikely that most of our participants would use extra ICS. Lastly, by providing ICS and SABA in separate canisters, it is possible that our study will underestimate the effect of PARTICS due to participant non-adherence with the PARTICS strategy. A combination inhaler containing ICS and SABA in a single canister would eliminate the issue of participants forgetting to take their ICS each time they take their SABA; as mentioned above,

combination ICS/SABA products are being developed for the US market. We recognize this issue and, as mentioned, chose to depart from strict PRECIS criteria for pragmatic studies by reminding PARTICS participants on a monthly basis to use their as-needed ICS and SABA together. By introducing these measures to improve adherence, we reduced the pragmatic nature of the PREPARE trial protocol with regards to the flexibility of the intervention. However, we felt that deviating from the PRECIS pragmatic design in order to reinforce using ICS with SABA made sense and was acceptable given the impending availability of a combination ICS/SABA inhaler in the United States.

4.2. Conclusion

In summary, PREPARE is a 15-month pragmatic, randomized, parallel-group study of a patient-centered asthma intervention in patient populations that suffer disproportionately from asthma morbidity and mortality. We are enrolling 1200 adult AA/B and H/L patients and assessing whether the PARTICS strategy, when added on to usual care, can reduce deleterious asthma outcomes of great concern to patients and other stakeholders. The design of this study has been heavily informed by A/A and H/L patient partners, patient advocates, and other key stakeholders in healthcare, while also meeting the rigorous requirements of PCORI-funded research and aligning as much as possible with PRECIS criteria for a pragmatic clinical trial. Outcomes of this study have the potential to offer powerful evidence supporting PARTICS as an effective asthma management strategy for reducing morbidity in these populations.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2020.106246.

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