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Impact of rescue triggered inhaled corticosteroids on controller therapy in Black and Latinx Individuals

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Abstract

Objective: The Person Empowered Asthma Relief (PREPARE) study found that as-needed inhaled corticosteroid supplementation combined with participants' usual controller and rescue therapy reduced asthma exacerbations. Here we sought to determine if treatment assignment to the Intervention (called PARTICS) vs Control (Usual Care) had an impact on controller therapy based on clinicians' written prescriptions. **Design:** Secondary data analysis. **Setting:** Practices treating asthma. **Participants:** PREPARE study participants were included in this analysis. **Interventions:** PREPARE study. **Outcome Measures:** For impact of the PARTICS therapy on patients, each patient-month was assigned to a controller step based on a 6-step classification scheme. An overall Linear Mixed Effect Model was completed for all 28 months of data and a Linear Mixed Effect Spline Model was completed for before and after enrollment data to determine controller changes over a 28-month period (12 months prior to enrollment, the month of enrollment, and 15 months after enrollment) between the two study arms. **Results**: This analysis included 713 participants. Of these, 49.1% were Usual Care patients and 50.9% were PARTICS patients. Throughout the study, the majority of patients changed asthma controller medications in both arms. By the end of the study, the Usual Care patients were at a significantly higher asthma controller medication step (0.20 step higher) than the PARTICS patients. **Conclusions**: Clinicians' prescribing patterns showed significant changes over time. Compared with Usual Care patients, PARTICS patients were on lower doses of asthma controller medications by the end of the study.

Strengths and Limitations of This Study:

- This paper presents the results of an electronic health record analysis of controller medications prescribed from 12 months before enrollment into the Person Empowered Asthma Relief (PREPARE) study through 15 months after enrollment.
- The results show, from a provider perspective, that the patients enrolled in PREPARE and assigned to the intervention arm were using less asthma controller medications by the end of the study than patients assigned to the control arm.
- Limitations: EHR data have inherent missingness and can have gaps due to infrequent visits and prescribing activities. Some individuals were on dual ICS inhalers not counting the study-prescribed beclomethasone, and these individuals were assigned based on the highest potency of any of the non-study prescribed ICS inhalers. In addition, not every site within PREPARE provided data, but we had data from the majority of sites.

INTRODUCTION

Twenty-five million adults have asthma in the US.(1) Asthma exacerbations cause the largest number of lost days from school or work for children and young adults, one-third of all days.(2, 3) Despite new medications,(4, 5) new drug regimens,(6-11) and the ongoing evolution of treatment guidelines(12-14) the number of people with asthma exacerbations in the previous year has decreased only slightly over the past 20 years, from 51.6% to 46.0%.(15, 16) Asthma is also a disease with a high degree of disparities in outcomes. Blacks have exacerbation and death rates that are 2-2.5 times higher than Whites and Asians,(17) while Hispanics, particularly Caribbean Hispanics,(18, 19) have 2 times the rate of exacerbations and 1.5 times the death rate.(20, 21) Thus, there is an ongoing need to expand and improve treatment approaches for individuals with asthma.

The paradigm concerning use of inhaled corticosteroids (ICS) only as a controller, i.e., as a once or twice a day medication, has been evolving. The use of ICS-formoterol as both controller and rescue therapy (single maintenance and reliever therapy [SMART]) is endorsed by multiple guideline groups across the world, include the US, GINA, and UK guidelines.(12, 14, 22) Previous randomized controlled trials have also demonstrated that as-needed, stand-alone, ICS use in conjunction with short acting beta-agonist (SABA) for acute asthma symptom relief can improve asthma outcomes.(7, 23-29) The Person Empowered Asthma Relief (PREPARE) trial utilized a stand-alone ICS combined with participants' usual controller and rescue therapy in an approach called Patient Activated Reliever-Triggered ICS (PARTICS).(30)

The PARTICS intervention decreased asthma exacerbations, improved asthma control and quality of life, and reduced reliever use in African American/Black (AA/B) and Hispanic/Latinx (H/L) adults with moderate to severe asthma, a group with disproportionate asthma morbidity that has been difficult to reduce.(30) This research extended the general concept of using ICS with all rescue beta-agonist use, whether long- or short-acting. It also demonstrated effectiveness, through changes in validated assessments, in AA/B and H/L adults, integrated with rescue nebulizer therapy, required no changes in a participant's current controller therapy, and appears to have fewer insurance barriers than an ICS-formoterol based approach. Participants on PARTICS also reported lower SABA use, both as a metered dose inhaler and via nebulizer, and fewer controller refills as well as a self-reported reduction in controller ICS dosage.(30)

The objective of this paper is to report on a pre-specified PREPARE trial sub-analysis using electronic health record (EHR) data to determine if treatment assignment (the PARTICS intervention vs. usual care) had an impact on controller therapy through clinicians' written prescriptions. The analysis compares changes in controller intensity (e.g., low, medium, or high ICS dose) as determined by EHR data over a 28-month period (12 months prior to enrollment, month of enrollment, and 15 months after enrollment) between the two arms of the study.

METHODS

Brief Description of the PREPARE Study

The PREPARE study was a pragmatic, open label, patient level randomized trial designed to observe the effects of adding ICS to rescue therapy among AA/B and H/L adults with moderate-to-severe asthma.(31) In the PREPARE study, the Intervention/PARTICS group (hereafter, "PARTICS group") received additional ICS medication (donated by TEVA, beclomethasone 80 mcg) and was asked to use 1 puff of beclomethasone for every 1 puff of usual rescue inhaler and 5 puffs of beclomethasone for every 1 rescue nebulization, in addition to usual care. The control group received usual care (hereafter, "UCare group"), described previously.(31) Exacerbations were tracked using patient-reported outcomes that were adjudicated using EHR data and patient interviews. The sub-study detailed here covers the prescriber side of asthma controller medications, as recorded in the EHRs of the primary asthma treating clinician (primary care, pulmonologist or allergist) for a subset of enrollees. To determine the effect, we analyzed PREPARE participants' asthma controller medications over 28 months (12 months before enrollment into PREPARE, month of enrollment into PREPARE, and 15 months after enrollment).

EHR Data Acquisition

Each site was asked to provide EHR data for each participant within the PREPARE study. The DARTNet Institute provided a set of instructions for each site including the variables needed from the EHR. Sixteen of the 19 participating sites provided data from their EHR or data warehouse. Requested information included care site information,

patient visits, medications, diagnostic codes, and procedures. Each participating site provided a pilot data pull that was standardized to the Observational Medical Outcomes Partnership Common Data Model v5.4 (OMOP CDM v5.4) and reviewed for data quality. Data quality concerns were communicated back to the sites; in some cases, new data were submitted. After all patients from a given site had exited the study, that site re-pulled their data and sent it to DARTNet for data standardization. (Note: One site, Site 6, did not provide data for their patients from before their enrollment into PREPARE.)

EHR Data Standardization

DARTNet utilized its standard procedures (python scripts and SQL coding) to transform the data received from each site into the OMOP CDM v5.4.(32) Briefly, data were loaded into a receiving database. As data were moved into the final OMOP data model, known taxonomies were auto-mapped to source OMOP concept IDs and a “standard” OMOP concept ID. Source data using idiosyncratic codes were hand-mapped and processed through to the OMOP data model. Data quality reports were evaluated for all relevant sets of conditions, medications, procedures, and measures. Final data were sent to the American Academy of Family Physicians (AAFP) for cleaning and analysis.

EHR Data Cleaning

Once the standardized data were received from DARTNet, the individual site files were combined for analysis. DARTNet worked with the AAFP to review and modify, if needed, existing "value sets" (i.e., list of codes associated with clinical concepts- either specific medications, conditions, or procedures). Value sets were created that segregated asthma medications as specifically needed for this analysis. Medications were categorized on a monthly basis as active using the following rules:

- Start date of medication: The month the prescription was written was considered the start date/month.
- End date of medication:
    - If an end date was provided, then it was used if it was 12 months or less from the time the prescription was written.
    - If no end date was provided, then an end date of 12 months after the prescription was written was used.
- Dosage/quantity and refills provided were also used to determine if a 12-month end date was appropriate or a shorter time span should be used due to how the prescription was written.

Once each asthma medication for each patient had assigned months, all medications were assigned to types of asthma medications (e.g., low/medium/high dose ICS, Long-Acting Beta-Agonists (LABA), Long-Acting Muscarinic Antagonist (LAMA)). Using those assigned types, all medications for each patient were collapsed into one record for each month (patient-month). The medication types for each month were assigned to a controller step based on highest ICS dose (i.e., low, medium, high) that they were prescribed along with additional controller medications.

Outcome Groupings

Each patient-month was assigned to a controller step based on a six-step classification scheme. The hierarchy of controller step levels (located in Supplemental Materials) was based on Guideline Steps (hereafter referred to as step) outlined in the National Asthma Education and Prevention Program (NAEPP) guidelines.(14) If a patient had no medication used within the classification scheme, then the patient was assigned a “0” for the month indicating the patient had no asthma controller medications prescribed to him/her within a given month. The six-step classification scheme (plus “0” for no medication) was used as the dependent variable in the statistical models.

Statistical Methods

This analysis was a secondary data analysis. Descriptive and inferential statistics were completed as appropriate. To start, changes in asthma controller medication were determined by the starting and stopping of prescriptions according to the EHR data rules. A change was the movement up or down in the step hierarchy. Then to model the EHR data, Linear Mixed Effect Model (LME; overall model and a spline version) were used with the assigned asthma controller medication step in each month as the dependent variable; independent variable(s) varied depending on the model. A series of LMEs were completed to determine the individual demographic variables that contributed ($p < 0.05$) to the model. The dependent variable for all LMEs was the six-

step classification scheme described above. If a demographic variable was considered to have contributed, then the variable was included in the final models discussed below. We also included a COVID-19 correction variable to account for any possible changes in asthma controller medications that occurred due to the COVID-19 pandemic (i.e., 0=No COVID-19 pandemic present; 1=COVID-19 pandemic present). Due to the nature of the data and the autocorrelation present, the covariance matrix used was a Heterogeneous First-Order Autoregressive to account for the previous month's influence. LMEs were used due to the ability to cluster to the person/patient, the acceptance of potentially missing data, and that it also works for data that violate any distributional assumptions.(33-35) An overall LME was completed for all 28 months of data (located in the Supplemental Materials) and a LME with Spline was completed for before and after enrollment data. For the final LMEs, the random variables were intercept, clustered to the patient. The fixed variables were patient-month, group (PARTICS/UCare), site, decade of birth, and COVID-19 correction. An alpha of 0.05 was used. All analyses were completed using SAS 9.4 (Cary, NC).

RESULTS

Demographics

After cleaning EHR data obtained from each site, there were 713 participants (out of 1,201 participants randomized in PREPARE) included in these analyses. The remaining patients in the PREPARE study (488) did not have their data included because the sites

did not provide EHR data. The breakdown of participants by site is in Table 1. Of these, 350 (49.1%) were in the UCare Group and 363 (50.9%) were in the PARTICS Group. Most participants were female and Non-Hispanic/Black (Table 2 for comparisons with the full study cohort). As the University of Puerto Rico, a major H/L enrolling site, was not able to provide EHR data, the cohort of participants included in this analysis has a lower percent of H/L participants than the full study ($p<0.001$; Table 2).

Table 1. Counts of Participants used in the EHR Data by Site (n = 713).

Site	Count
Site 1	14
Site 2	21
Site 3	58
Site 4	34
Site 5	57
Site 6	79
Site 7	86
Site 8	16
Site 9	48
Site 10	58
Site 11	42
Site 12	9
Site 13	71
Site 14	70

Site 15	13
Site 16	37

Table 2. Demographics and Comparisons with Main Study (n (%)).

	PARTICS (n = 363)	UCare (n = 350)	Sig with Main Study
Overall (n = 713)	363 (50.9%)	350 (49.1%)	0.722
Female	297 (81.8%)	292 (83.4%)	0.295
Non-Hispanic/Black	216 (59.5%)	217 (62.0%)	<0.001

Changes in Asthma Controller Medication Prescriptions

As noted in Table 3, asthma controller medication prescription changes, without regard to the change direction, occurred over time (before and after enrollment; comparison of two time points) for both the UCare and PARTICS groups. Changes included addition or withdrawal of inhalers or medications, biologics, and leukotriene inhibitors, as well as changes in dosage of all medications. However, changes were statistically similar, so both groups changed controller medications with similar frequency over the various time periods included in Table 3.

Table 3. Changes in Asthma Medications Over Time (n (%)).

	Overall (n = 713)	PARTICS (n = 363)	UCare (n = 350)

12 Months Prior to Enrollment – Enrollment Month			
Changes Occurred	451 (63.3%)	219 (60.3%)	232 (66.3%)
Enrollment Month – 15 Months After Enrollment			
Changes Occurred	491 (68.9%)	247 (68.0%)	244 (69.7%)
Enrollment Month – 12 Months After Enrollment			
Changes Occurred	477 (66.9%)	239 (65.8%)	238 (68.0%)

Modelling of Electronic Health Record Data

After models with the individual demographic variables were completed (not shown), each model contained the assigned step each month as the dependent variable and the month, the group (PARTICS or UCare), the site, the patients' decade of birth, and COVID-19 correction as independent variables. After the final overall model (located in the Supplemental Materials), a spline was introduced to determine the differences between before and after Enrollment and to determine the effect of the intervention using prescribers' written prescriptions. The next two models detail the LME with Spline accounting for before Enrollment (Table 4) and after Enrollment (Table 5).

Model for Before Enrollment (12 months prior through one month before Enrollment; Table 4)

Table 4. Final Before Enrollment LME Results.

Parameter	Estimate	Standard Error	95% CI	t
-2 Restricted Log Likelihood: 24603.78 Month: F(1, 568.00) = 198.82; p < 0.001 Group: F(1, 549.00) = 0.01; p = 0.94 Site: F(14, 549.00) = 8.47; p < 0.001 Decade of Birth: F(4, 549.00) = 2.60; p = 0.04				
Intercept (Baseline)	2.80	0.30	[2.20, 3.39]	9.20*
Month	0.15	0.01	[0.13, 0.17]	14.10*
UCare	0.01	0.11	[-0.20, 0.22]	0.08
PARTICS	Reference			
Site 1	-0.10	0.46	[-1.00, 0.81]	-0.21
Site 2	1.12	0.38	[0.38, 1.86]	2.98*
Site 3	1.21	0.28	[0.65, 1.76]	4.29*
Site 4	0.62	0.32	[-0.01, 1.25]	1.93+
Site 5	1.50	0.28	[0.95, 2.06]	5.33*
Site 6	N/A	N/A	N/A	N/A
Site 7	0.72	0.27	[0.20, 1.24]	2.72*
Site 8	0.11	0.41	[-0.70, 0.92]	0.28
Site 9	0.43	0.29	[-0.15, 1.01]	1.46
Site 10	-0.18	0.29	[-0.75, 0.40]	-0.61
Site 11	0.10	0.31	[-0.51, 0.72]	0.33
Site 12	-0.84	0.48	[-1.80, 0.11]	-1.74+

Site 13	0.26	0.27	[-0.28, 0.79]	0.95
Site 14	0.25	0.28	[-0.30, 0.79]	0.89
Site 15	-1.46	0.46	[-2.36, -0.55]	-3.16*
Site 16	Reference			
Born: 1940s & 1950s	0.52	0.22	[0.09, 0.94]	2.38*
Born: 1960s	0.16	0.22	[-0.27, 0.58]	0.73
Born: 1970s	0.10	0.22	[-0.34, 0.54]	0.43
Born: 1980s	0.20	0.23	[-0.26, 0.65]	0.84
Born: 1990s & 2000s	Reference			

* p-value < 0.05

The UCare and PARTICS patients were at approximately the same step before enrollment. The months before Enrollment did show a significant decrease in controller intensity over time (months were inputted as negative value). (Note: The data for before Enrollment took place entirely before the start of the COVID-19 pandemic.) The assigned steps differed significantly between the sites.

Four sites (Sites 2, 3, 5, 7) had significantly higher steps of asthma controller medications compared with patients from Site 16 (reference site). One site (Site 15) had significantly lower steps of asthma controller medications than patients from Site 16. The assigned steps differed significantly with the patients' decade of birth. Patients born in the 1940s/1950s had significantly higher levels of asthma controller medications than patients born in the 1990s/2000s (Table 4).

Model After Enrollment (one month after through the 15 months after Enrollment; Table 5)

Table 5. Final After Enrollment LME Results.

Parameter	Estimate	Standard Error	95% CI	t
-2 Restricted Log Likelihood: 33387.07 Month: F(1, 684.72) = 24.59; p < 0.001 Group: F(1, 631.01) = 4.72; p = 0.03 Site: F(15, 633.60) = 9.91; p < 0.001 Decade of Birth: F(4, 631.09) = 3.83; p = 0.004 COVID Correction: F(1, 9448.26) = 29.68; p < 0.001				
Intercept (Baseline)	2.04	0.29	[1.48, 2.60]	7.16*
Month	-0.05	0.01	[-0.06, -0.03]	-4.95*
UCare	0.20	0.09	[0.02, 0.39]	2.17*
PARTICS	Reference			
Site 1	-0.37	0.39	[-1.13, 0.40]	-0.94
Site 2	1.40	0.33	[0.75, 2.05]	4.20*
Site 3	1.57	0.26	[1.05, 2.09]	5.97*
Site 4	1.31	0.29	[0.74, 1.89]	4.49*
Site 5	0.96	0.26	[0.44, 1.48]	3.63*
Site 6	-0.03	0.25	[-0.52, 0.45]	-0.14

Site 7	0.57	0.25	[0.08, 1.06]	2.30*
Site 8	0.43	0.39	[-0.34, 1.20]	1.09
Site 9	0.41	0.28	[-0.13, 0.95]	1.49
Site 10	0.43	0.26	[-0.08, 0.94]	1.65+
Site 11	0.59	0.29	[0.02, 1.15]	2.05*
Site 12	0.31	0.47	[-0.62, 1.23]	0.65
Site 13	-0.17	0.27	[-0.69, 0.35]	-0.64
Site 14	0.56	0.26	[0.05, 1.08]	2.17*
Site 15	-1.36	0.45	[-2.24, -0.48]	-3.03*
Site 16	Reference			
Born: 1940s & 1950s	0.46	0.19	[0.10, 0.83]	2.49*
Born: 1960s	0.00	0.18	[-0.36, 0.36]	0.01
Born: 1970s	0.24	0.19	[-0.13, 0.62]	1.27
Born: 1980s	0.30	0.20	[-0.09, 0.69]	1.49
Born: 1990s & 2000s	Reference			
No COVID-19	0.38	0.07	[0.24, 0.51]	5.45*
COVID-19 Present	Reference			

* p-value < 0.05

The UCare patients were at a significantly higher asthma controller medication step overall than the PARTICS patients across all time periods for the time after Enrollment. However, the months after Enrollment did show a significant decrease in controller intensity over time for both groups, which could be due to the COVID-19 pandemic.

When compared to the Model Before Enrollment, the difference between the UCare and PARTICS patients with the changes over time indicate that the PARTICS patients had significantly greater decrease in the intensity of their controller therapy compared to UCare patients (Tables 4 and 5).

The assigned steps differed significantly between the sites. Seven sites (Sites 2, 3, 4, 5, 7, 11, 14) had significantly higher steps of asthma controller medications than patients from Site 16 (reference site). One site (Site 15) had significantly lower steps of asthma controller medications than patients from Site 16. The assigned steps differed significantly with the patients' decade of birth. Patients born in the 1940s/1950s had significantly higher levels of asthma controller medications than patients born in the 1990s/2000s. Lastly, in the months when COVID-19 was not present (before April 2020), both groups of patients had a significantly higher asthma controller medication level than after the COVID-19 pandemic began (Table 5).

DISCUSSION

This study shows, through prescribers' written prescriptions, there was a greater decrease in asthma controller medication level over time (after Enrollment) in the PARTICS patients compared with the UCare patients. The decrease in intensity reduces, to some degree, the expected increase in total ICS exposure that would result from adopting the PARTICS strategy. The results in this sub-study complement and confirm the results in the main effects paper that that shows that self-reported ICS-containing controller refills were lower for participants assigned to PARTICS vs usual

care.(30) Between this sub-study and the main effects paper, the participants' reported and prescribers' EHR data indicate decreased asthma controller medication use over time for the PARTICS patients compared with the UCare patients, even with correcting for COVID-19. When combined with the patient self-reported levels of controller ICS use and rescue ICS fulfillment data from the main effects paper, this sub-study supports that PARTICS improves outcomes at the population level, as the intensity of ICS controller therapy dropped as well as self-reported controller ICS use. Treating clinicians were free to adjust asthma medications as deemed necessary during the study. Primary asthma treating clinicians were not provided the monthly Asthma Control Test scores that were collected for research purposes, but patients may have been more aware of their asthma symptoms through repeated completion of this instrument. For many patients the primary asthma treating clinician was not the research prescribing clinician, but the treating clinician would have been aware of the study medication. While it is not possible to determine if the drop in controller ICS dose, at the population level, was in response to the added as needed ICS, the increase in controller ICS dosage for the control patients would suggest changes were more likely to be based on asthma control and not perceived total steroid burden.

While the results of this sub-study confirm the results of the main effects paper, there are limitations. EHR data have inherent missingness and can have gaps due to infrequent visits and prescribing activities. In particular, assumptions concerning the length of time a prescription was active were made to determine an active medical regimen. While this may have affected the exact level for a given individual, the

assumptions were evenly applied across both groups. Further, some individuals were on dual ICS inhalers not counting the study-prescribed beclomethasone, and these individuals were assigned based on the highest potency of any of the non-study prescribed ICS inhalers. Again, while this may have affected the ICS level of an individual, the approach was evenly applied at all times across both groups. Thus, neither of these processes would bias the results for either of the study arms. In addition, not every site within PREPARE provided data, but we had data from the majority of sites. This reduction in ICS controller intensity in the PARTICS group was accompanied with a significant reduction in annualized exacerbation rates in this group,(30) though total ICS use considering both controller and rescue use likely increased to some degree.

The results show that there were significant changes over time (after Enrollment) as well as significant differences between the PARTICS and UCare groups, participating sites, participants' decades of birth, and the COVID-19 correction. In the spline regressions, the UCare and PARTICS patients were comparable before enrollment, and differences occurred after enrollment in PREPARE. This effect is consonant with our reported reduction in exacerbations in the PREPARE cohort during the COVID pandemic.(36) The significant effect due to COVID-19 could be due to a variety of factors including changes in lifestyles that occurred such as working from home and a reduction in air pollution due to fewer cars on the road.(36) This effect could be further studied using air pollution data around the patents' dwellings.

Select sites provided their patients with significantly higher (or lower) asthma controller medications than the reference site (Site 16). The differences could be accounted for by different overall participant asthma severity across sites,(31) clinicians' prescribing patterns, organizational policies, or environmental factors. Though all clinicians providing asthma care for PREPARE participants completed the Asthma IQ program(37) to help standardize care, this intervention would not affect baseline (or pre-baseline) prescribing patterns, which were in place prior to the training. Further exploration into the reasons for the differences is warranted.

This sub-study shows that clinicians' prescribing patterns did change over time, and the PARTICS patients were prescribed lower doses of asthma controller medications by the end of the study.

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Conflicts of Interest:

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Supplemental Materials

Hierarchy of Controller Step Levels

- Step 2
  - Low dose ICS
- Step 3
  - Low dose ICS plus Leukotriene inhibitor
  - Medium dose ICS
  - Low dose ICS plus LABA OR LAMA
  - High dose ICS
- Step 4
  - Medium dose ICS plus Leukotriene inhibitor
  - Low dose ICS plus LABA OR LAMA plus Leukotriene inhibitor
  - Low dose ICS plus LABA AND LAMA
  - Low dose ICS plus LABA AND LAMA plus Leukotriene inhibitor
  - High dose ICS plus Leukotriene inhibitor
  - Medium dose ICS plus LABA OR LAMA
  - Medium dose ICS plus LABA OR LAMA plus Leukotriene inhibitor
- Step 5
  - Medium dose ICS plus LABA AND LAMA
  - Medium dose ICS plus LABA AND LAMA plus Leukotriene inhibitor
  - High dose ICS plus LABA OR LAMA
  - High dose ICS plus LABA AND LAMA
  - High dose ICS plus LABA OR LAMA plus Leukotriene inhibitor
  - High dose ICS plus LABA AND LABA plus Leukotriene inhibitor
- Step 6
  - Biologics
  - Daily Corticosteroids

Overall Model for All 28 Months (Supplemental Table 1; no corrections applied; no spline)

The month before or after enrollment did show a significant increase over time (estimate: 0.039; t = 9.315). The UCare patients were at a significantly higher asthma controller medication level overall (difference: 0.191; t = 2.327). The assigned reclassified levels differed significantly between the sites (F(15, 692.810) = 19.968; p = 0.000). Five sites (Sites 2, 3, 4, 5, 7) had significantly higher steps of asthma controller medications than patients from Site 16. Two sites (Sites 6, 15) had significantly lower steps of asthma controller medications than patients from Site 16. The assigned reclassified levels differed significantly with the patients' decade of birth (F(4, 692.014) = 5.135; p = 0.000). Patients born in the 1940s/1950s had significantly higher levels of asthma controller medications than patients born in the 1990s/2000s (difference: 0.611; t = 3.803). Lastly, in the months were COVID-19 was not present (before April 2020), the patients had a significantly higher asthma controller medication level than after the COVID-19 pandemic began (difference: 0.902; t = 14.118; Supplemental Table 1).

Supplemental Table 1. Final LME Results.

Parameter	Estimate	Standard Error	95% CI	t
-2 Restricted Log Likelihood: 73628.74 Month: F(1, 740.37) = 86.77; p < 0.001 Group: F(1, 691.99) = 5.41; p = 0.02 Site: F(15, 692.81) = 19.97; p < 0.001 Decade of Birth: F(4, 692.01) = 5.14; p < 0.001 COVID Correction: F(1, 18759.68) = 199.32; p < 0.001				
Intercept (Baseline)	0.78	0.24	[0.31, 1.25]	3.24*
Month	0.04	0.00	[0.03, 0.05]	9.32*
UCare	0.19	0.08	[0.03, 0.35]	2.33*
PARTICS	Reference			
Site 1	-0.44	0.34	[-1.11, 0.24]	-1.27
Site 2	1.14	0.30	[0.55, 1.73]	3.80*
Site 3	1.51	0.23	[1.05, 1.96]	6.49*
Site 4	0.91	0.26	[0.40, 1.42]	3.49*
Site 5	1.22	0.23	[0.76, 1.68]	5.24*
Site 6	-0.93	0.22	[-1.36, -0.50]	-4.25*
Site 7	0.66	0.22	[0.23, 1.08]	3.02*
Site 8	0.04	0.33	[-0.61, 0.69]	0.13
Site 9	0.27	0.24	[-0.21, 0.74]	1.11
Site 10	0.05	0.23	[-0.41, 0.50]	0.19
Site 11	0.11	0.25	[-0.38, 0.60]	0.43
Site 12	-0.24	0.41	[-1.04, 0.57]	-0.58
Site 13	-0.07	0.23	[-0.51, 0.37]	-0.33
Site 14	0.17	0.23	[-0.27, 0.62]	0.78
Site 15	-1.43	0.35	[-2.13, -0.74]	-4.05*
Site 16	Reference			
Born: 1940s & 1950s	0.61	0.16	[0.30, 0.93]	3.80*
Born: 1960s	0.21	0.16	[-0.11, 0.52]	1.29
Born: 1970s	0.26	0.17	[-0.07, 0.58]	1.54
Born: 1980s	0.31	0.17	[-0.03, 0.65]	1.80+
Born: 1990s & 2000s	Reference			
No COVID-19	0.90	0.06	[0.78, 1.03]	14.19*
COVID-19 Present	Reference			

* p-value < 0.05

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An electronic health record data analysis on the impact of rescue triggered inhaled corticosteroids on controller therapy in Black and Latinx Individuals from a pragmatic, open label, patient level randomized trial

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Abstract

Objective: The Person Empowered Asthma Relief (PREPARE) study found that as-needed inhaled corticosteroid supplementation combined with participants' usual controller and rescue therapy reduced asthma exacerbations for Black and Latinx individuals. Here we sought to determine if treatment assignment to the Intervention (called PARTICS) vs Control (Usual Care) had an impact on controller therapy based on clinicians' written prescriptions. **Design:** Secondary data analysis of electronic health record data of a pragmatic, open label, patient level randomized trial. **Setting:** Practices treating asthma. **Participants:** PREPARE study participants - Black and Latinx individuals with asthma. **Interventions:** Effects of adding ICS to rescue therapy among Black and Hispanic adults with moderate-to-severe asthma. **Outcome Measures:** For PARTICS therapy impact on patients, each month is the 28-month period (12 months prior to enrollment, the month of enrollment, and 15 months after enrollment), a patient was assigned to a controller step based on a 6-step classification scheme. A Linear Mixed Effect Spline Model was completed for before and after enrollment data to determine controller changes over a 28-month period between the two study arms. **Results**: This analysis included 713 participants. Of these, 49.1% were Usual Care patients and 50.9% were PARTICS patients. Throughout the study, the majority of patients changed asthma controller medications in both arms. By the end of the study, the Usual Care patients were at a significantly higher asthma controller medication step (0.20 step higher) than the PARTICS patients. **Conclusions**: Clinicians' prescribing patterns showed significant changes over time. Compared with Usual Care patients,

PARTICS patients were on lower doses of asthma controller medications by the end of the study.

Strengths and Limitations of This Study:

- Strength: Long follow-up time using electronic health record analysis of controller medications prescribed from 12 months before enrollment into the Person Empowered Asthma Relief (PREPARE) study through 15 months after enrollment.
- Strength: Even if data were missing, we were able to use all available data due to the type of analysis we used – Linear Mixed Effect Model.
- Limitation: EHR data have inherent missingness and can have gaps due to infrequent visits and prescribing activities.
- Limitation: Some individuals were on dual ICS inhalers not counting the study-prescribed beclomethasone, and these individuals were assigned based on the highest potency of any of the non-study prescribed ICS inhalers.
- Limitation: In addition, not every site within PREPARE provided data, but we had data from the majority of sites.

INTRODUCTION

Twenty-five million adults have asthma in the US.[1] Asthma exacerbations cause the largest number of lost days (one-third of all days) from school or work for children and young adults.[2 3] Despite new medications,[4 5] new drug regimens,[6-11] and the ongoing evolution of treatment guidelines[12-14], the number of people with asthma exacerbations in the previous year has decreased only slightly over the past 20 years, from 51.6% to 46.0%.[15 16] Asthma is also a disease with a high degree of disparities in outcomes. Black individuals have exacerbation and death rates that are 2-2.5 times higher than White individuals and Asian individuals,[17] while Hispanic individuals, particularly Caribbean Hispanic individuals,[18 19] have 2 times the rate of exacerbations and 1.5 times the death rate.[20 21] Thus, there is an ongoing need to expand and improve treatment approaches for individuals with asthma.

The paradigm concerning use of inhaled corticosteroids (ICS) only as a controller, i.e., as a once or twice a day medication, has been evolving. The use of ICS-formoterol as both controller and rescue therapy (single maintenance and reliever therapy [SMART]) is endorsed by multiple guideline groups across the world, include the US, GINA, and UK guidelines.[12 14 22] Previous randomized controlled trials have also demonstrated that as-needed, stand-alone, ICS use in conjunction with short acting beta-agonist (SABA) for acute asthma symptom relief can improve asthma outcomes.[7 23-29] The Person Empowered Asthma Relief (PREPARE) trial utilized a stand-alone ICS combined with participants' usual controller and rescue therapy in an approach called Patient Activated Reliever-Triggered ICS (PARTICS).[30]

The PARTICS intervention in PREPARE decreased asthma exacerbations, improved asthma control and quality of life, and reduced reliever use in African American/Black (AA/B) and Hispanic/Latinx (H/L) adults with moderate to severe asthma, a group with disproportionate asthma morbidity that has been difficult to reduce.[30] This research extended the general concept of using ICS with all rescue beta-agonist use, whether long- or short-acting. It also demonstrated effectiveness, through changes in validated assessments, in AA/B and H/L adults, integrated with rescue nebulizer therapy, required no changes in a participant's current controller therapy, and appears to have fewer insurance barriers than an ICS-formoterol based approach. Participants on PARTICS also reported lower SABA use, both as a metered dose inhaler and via nebulizer, and fewer controller refills as well as a self-reported reduction in controller ICS dosage.[30]

The objective of this paper is to report on a pre-specified PREPARE trial sub-analysis using electronic health record (EHR) data to determine if treatment assignment (the PARTICS intervention vs. usual care) had an impact on controller therapy through clinicians' written prescriptions. The analysis compares changes in controller intensity (e.g., low, medium, or high ICS dose) as determined by EHR data over a 28-month period (12 months prior to enrollment, month of enrollment, and 15 months after enrollment) between the two arms of the study.

METHODS

Brief Description of the PREPARE Study

The PREPARE study was a pragmatic, open label, patient level randomized trial designed to observe the effects of adding ICS to rescue therapy among AA/B and H/L adults with moderate-to-severe asthma.[31] In the PREPARE study, the Intervention/PARTICS group (hereafter, "PARTICS group") received additional ICS medication (donated by TEVA, beclomethasone 80 mcg) and was asked to use 1 puff of beclomethasone for every 1 puff of usual rescue inhaler and 5 puffs of beclomethasone for every 1 rescue nebulization, in addition to usual care. The control group received usual care (hereafter, "UCare group"), described previously.[31] Exacerbations were tracked using patient-reported outcomes that were adjudicated using EHR data and patient interviews. The sub-study detailed here covers the prescriber side of asthma controller medications, as recorded in the EHRs of the primary asthma treating clinician (primary care, pulmonologist or allergist) for a subset of enrollees. To determine the effect, we analyzed PREPARE participants' asthma controller medications over 28 months (12 months before enrollment into PREPARE, month of enrollment into PREPARE, and 15 months after enrollment). The PREPARE study and this sub-study were approved by the IRB (Partners Human Research Committee: 2016P001839/BWH) and written informed consent was obtained from each participant at the time of enrollment (recruitment period: November 2017 – April 2021).

EHR Data Acquisition

Each site was asked to provide EHR data for each participant within the PREPARE study. The DARTNet Institute provided a set of instructions for each site including the variables needed from the EHR. Sixteen of the 19 participating sites provided data from their EHR or data warehouse. Requested information included care site information, patient visits, medications, diagnostic codes, and procedures. Each participating site provided a pilot data pull that was standardized to the Observational Medical Outcomes Partnership Common Data Model v5.4 (OMOP CDM v5.4) and reviewed for data quality. Data quality concerns were communicated back to the sites; in some cases, new data were submitted. After all patients from a given site had exited the study, that site re-pulled their data and sent it to DARTNet for data standardization. (Note: One site, Site 6, did not provide data for their patients from before their enrollment into PREPARE.)

EHR Data Standardization

DARTNet utilized its standard procedures (python scripts and SQL coding) to transform the data received from each site into the OMOP CDM v5.4.[32] Briefly, data were loaded into a receiving database. As data were moved into the final OMOP data model, known taxonomies were auto-mapped to source OMOP concept IDs and a “standard” OMOP concept ID. Source data using idiosyncratic codes were hand-mapped and processed through to the OMOP data model. Data quality reports were evaluated for all relevant sets of conditions, medications, procedures, and measures. Final data were sent to the American Academy of Family Physicians (AAFP) for cleaning and analysis.

EHR Data Cleaning

Once the standardized data were received from DARTNet, the individual site files were combined for analysis. DARTNet worked with the AAFP to review and modify, if needed, existing "value sets" (i.e., list of codes associated with clinical concepts- either specific medications, conditions, or procedures). Value sets were created that segregated asthma medications as specifically needed for this analysis. Medications were categorized on a monthly basis as active using the following rules:

- Start date of medication: The month the prescription was written was considered the start date/month.
- End date of medication:
    - If an end date was provided, then it was used if it was 12 months or less from the time the prescription was written.
    - If no end date was provided, then an end date of 12 months after the prescription was written was used.
- Dosage/quantity and refills provided were also used to determine if a 12-month end date was appropriate or a shorter time span should be used due to how the prescription was written.

Once each asthma medication for each patient had assigned months, all medications were assigned to types of asthma medications (e.g., low/medium/high dose ICS, Long-Acting Beta-Agonists (LABA), Long-Acting Muscarinic Antagonist (LAMA)). Using those assigned types, all medications for each patient were collapsed into one record for each

month (patient-month). The medication types for each month were assigned to a controller step based on highest ICS dose (i.e., low, medium, high) that they were prescribed along with additional controller medications.

Outcome Groupings

Each patient-month was assigned to a controller step based on a six-step classification scheme. The hierarchy of controller step levels (located in Supplemental Materials) was based on Guideline Steps (hereafter referred to as step) outlined in the National Asthma Education and Prevention Program (NAEPP) guidelines.[14] If a patient had no medication used within the classification scheme, then the patient was assigned a "0" for the month indicating the patient had no asthma controller medications prescribed to him/her within a given month. The six-step classification scheme (plus "0" for no medication) was used as the dependent variable in the statistical models.

Statistical Methods

This analysis was a secondary data analysis. Descriptive and inferential statistics were completed as appropriate. To start, changes in asthma controller medication were determined by the starting and stopping of prescriptions according to the EHR data rules. A change was the movement up or down in the step hierarchy. Then to model the EHR data, Linear Mixed Effect Model (LME; overall model and a spline version) were used with the assigned asthma controller medication step in each month as the

dependent variable; independent variable(s) varied depending on the model. A series of LMEs were completed to determine the individual demographic variables that contributed ($p < 0.05$) to the model. The dependent variable for all LMEs was the six-step classification scheme described above. If a demographic variable contributed significantly ($p<0.05$) to an LME containing month, group, site, and that demographic variable, then the variable was included in the final models discussed below. We also included a COVID-19 correction variable to account for any possible changes in asthma controller medications that occurred due to the COVID-19 pandemic (i.e., 0=No COVID-19 pandemic present; 1=COVID-19 pandemic present). For each variable included in the LMEs, the final category (e.g., Site 16 out of Sites 1-16) was used as a reference category. LMEs require a reference category for each categorical variable as a comparison for the other categories. Due to the nature of the data and the autocorrelation present, the covariance matrix used was a Heterogeneous First-Order Autoregressive to account for the previous month's influence. LMEs were used due to the ability to cluster to the person/patient, the acceptance of potentially missing data, and that it also works for data that violate any distributional assumptions.[33-35] An overall LME was completed for all 28 months of data (located in the Supplemental Materials) and a LME with Spline was completed for before and after enrollment data. For the final LMEs, the random variable was the intercept, clustered to the patient. The fixed variables were patient-month, group (PARTICS/UCare), site, decade of birth, and COVID-19 correction. An alpha of 0.05 was used. All analyses were completed using SAS 9.4 (Cary, NC).

RESULTS

Demographics

After cleaning EHR data obtained from each site, there were 713 participants (out of 1,201 participants randomized in PREPARE) included in these analyses. The remaining patients in the PREPARE study (488) did not have their data included because the sites did not provide EHR data. The breakdown of participants by site is in Table 1. Of these, 350 (49.1%) were in the UCare Group and 363 (50.9%) were in the PARTICS Group. Most participants were female and Non-Hispanic/Black (Table 2 for comparisons with the full study cohort). As the University of Puerto Rico, a major H/L enrolling site, was not able to provide EHR data, the cohort of participants included in this analysis has a lower percent of H/L participants than the full study ($p<0.001$; Table 2).

Table 1. Counts of Participants used in the EHR Data by Site (n = 713).

Site	Count
Site 1	14
Site 2	21
Site 3	58
Site 4	34
Site 5	57
Site 6	79
Site 7	86

Site 8	16
Site 9	48
Site 10	58
Site 11	42
Site 12	9
Site 13	71
Site 14	70
Site 15	13
Site 16	37

Table 2. Demographics and Comparisons with Main Study (n (%)).

	PARTICS (n = 363)	UCare (n = 350)	Sig with Main Study
Overall (n = 713)	363 (50.9%)	350 (49.1%)	0.722
Female	297 (81.8%)	292 (83.4%)	0.295
Non-Hispanic/Black	216 (59.5%)	217 (62.0%)	<0.001

Changes in Asthma Controller Medication Prescriptions

As noted in Table 3, asthma controller medication prescription changes, without regard to the change direction, occurred over time (before and after enrollment; comparison of two time points) for both the UCare and PARTICS groups. Changes included addition or withdrawal of inhalers or medications, biologics, and leukotriene inhibitors, as well as

changes in dosage of all medications. However, changes were statistically similar, so both groups changed controller medications with similar frequency over the various time periods included in Table 3.

Table 3. Changes in Asthma Medications Over Time (n (%)).

	Overall (n = 713)	PARTICS (n = 363)	UCare (n = 350)
12 Months Prior to Enrollment – Enrollment Month			
Changes Occurred	451 (63.3%)	219 (60.3%)	232 (66.3%)
Enrollment Month – 15 Months After Enrollment			
Changes Occurred	491 (68.9%)	247 (68.0%)	244 (69.7%)
Enrollment Month – 12 Months After Enrollment			
Changes Occurred	477 (66.9%)	239 (65.8%)	238 (68.0%)

Modelling of Electronic Health Record Data

After models with the individual demographic variables were completed (model included in supplemental materials for reference), each model contained the assigned step each month as the dependent variable and the month, the group (PARTICS or UCare), the site, the patients' decade of birth, and COVID-19 correction as independent variables. The patients' decade of birth and COVID-19 correction contributed significantly to the individual models which necessitates inclusion in the final model. After the final overall model (located in the Supplemental Materials), a spline was introduced to determine the

differences between before and after Enrollment and to determine the effect of the intervention using prescribers' written prescriptions. The next two models detail the LME with Spline accounting for before Enrollment (Table 4) and after Enrollment (Table 5).

Model for Before Enrollment (12 months prior through one month before Enrollment; Table 4)

Table 4. Final Before Enrollment LME Results.

Parameter	Estimate	Standard Error	95% CI	t
-2 Restricted Log Likelihood: 24603.78 Month: F(1, 568.00) = 198.82; p < 0.001 Group: F(1, 549.00) = 0.01; p = 0.94 Site: F(14, 549.00) = 8.47; p < 0.001 Decade of Birth: F(4, 549.00) = 2.60; p = 0.04				
Intercept (Baseline)	2.80	0.30	[2.20, 3.39]	9.20*
Month	0.15	0.01	[0.13, 0.17]	14.10*
UCare	0.01	0.11	[-0.20, 0.22]	0.08
PARTICS	Reference			
Site 1	-0.10	0.46	[-1.00, 0.81]	-0.21
Site 2	1.12	0.38	[0.38, 1.86]	2.98*
Site 3	1.21	0.28	[0.65, 1.76]	4.29*
Site 4	0.62	0.32	[-0.01, 1.25]	1.93+

Site 5	1.50	0.28	[0.95, 2.06]	5.33*
Site 6	N/A	N/A	N/A	N/A
Site 7	0.72	0.27	[0.20, 1.24]	2.72*
Site 8	0.11	0.41	[-0.70, 0.92]	0.28
Site 9	0.43	0.29	[-0.15, 1.01]	1.46
Site 10	-0.18	0.29	[-0.75, 0.40]	-0.61
Site 11	0.10	0.31	[-0.51, 0.72]	0.33
Site 12	-0.84	0.48	[-1.80, 0.11]	-1.74+
Site 13	0.26	0.27	[-0.28, 0.79]	0.95
Site 14	0.25	0.28	[-0.30, 0.79]	0.89
Site 15	-1.46	0.46	[-2.36, -0.55]	-3.16*
Site 16	Reference			
Born: 1940s & 1950s	0.52	0.22	[0.09, 0.94]	2.38*
Born: 1960s	0.16	0.22	[-0.27, 0.58]	0.73
Born: 1970s	0.10	0.22	[-0.34, 0.54]	0.43
Born: 1980s	0.20	0.23	[-0.26, 0.65]	0.84
Born: 1990s & 2000s	Reference			

* p-value < 0.05

The UCare and PARTICS patients were at approximately the same step before Enrollment. The months before Enrollment did show a significant decrease in controller intensity over time (months were inputted as negative value). (Note: The data for before

Enrollment took place entirely before the start of the COVID-19 pandemic.) The assigned steps differed significantly between the sites.

Four sites (Sites 2, 3, 5, 7) had significantly higher steps of asthma controller medications compared with patients from Site 16 (reference site). One site (Site 15) had significantly lower steps of asthma controller medications than patients from Site 16. The assigned steps differed significantly with the patients' decade of birth. Patients born in the 1940s/1950s had significantly higher levels of asthma controller medications than patients born in the 1990s/2000s (Table 4).

Model After Enrollment (one month after through the 15 months after Enrollment; Table 5)

Table 5. Final After Enrollment LME Results.

Parameter	Estimate	Standard Error	95% CI	t
-2 Restricted Log Likelihood: 33387.07 Month: F(1, 684.72) = 24.59; p < 0.001 Group: F(1, 631.01) = 4.72; p = 0.03 Site: F(15, 633.60) = 9.91; p < 0.001 Decade of Birth: F(4, 631.09) = 3.83; p = 0.004 COVID Correction: F(1, 9448.26) = 29.68; p < 0.001				
Intercept (Baseline)	2.04	0.29	[1.48, 2.60]	7.16*

Month	-0.05	0.01	[-0.06, -0.03]	-4.95*
UCare	0.20	0.09	[0.02, 0.39]	2.17*
PARTICS	Reference			
Site 1	-0.37	0.39	[-1.13, 0.40]	-0.94
Site 2	1.40	0.33	[0.75, 2.05]	4.20*
Site 3	1.57	0.26	[1.05, 2.09]	5.97*
Site 4	1.31	0.29	[0.74, 1.89]	4.49*
Site 5	0.96	0.26	[0.44, 1.48]	3.63*
Site 6	-0.03	0.25	[-0.52, 0.45]	-0.14
Site 7	0.57	0.25	[0.08, 1.06]	2.30*
Site 8	0.43	0.39	[-0.34, 1.20]	1.09
Site 9	0.41	0.28	[-0.13, 0.95]	1.49
Site 10	0.43	0.26	[-0.08, 0.94]	1.65+
Site 11	0.59	0.29	[0.02, 1.15]	2.05*
Site 12	0.31	0.47	[-0.62, 1.23]	0.65
Site 13	-0.17	0.27	[-0.69, 0.35]	-0.64
Site 14	0.56	0.26	[0.05, 1.08]	2.17*
Site 15	-1.36	0.45	[-2.24, -0.48]	-3.03*
Site 16	Reference			
Born: 1940s & 1950s	0.46	0.19	[0.10, 0.83]	2.49*
Born: 1960s	0.00	0.18	[-0.36, 0.36]	0.01
Born: 1970s	0.24	0.19	[-0.13, 0.62]	1.27
Born: 1980s	0.30	0.20	[-0.09, 0.69]	1.49

Born: 1990s & 2000s	Reference			
No COVID-19	0.38	0.07	[0.24, 0.51]	5.45*
COVID-19 Present	Reference			

* p-value < 0.05

The UCare patients were at a significantly higher asthma controller medication step overall than the PARTICS patients across all time periods for the time after Enrollment. However, the months after Enrollment did show a significant decrease in controller intensity over time for both groups, which could be due to the COVID-19 pandemic. When compared to the Model Before Enrollment, the difference between the UCare and PARTICS patients with the changes over time indicate that the PARTICS patients had significantly greater decrease in the intensity of their controller therapy compared to UCare patients (Tables 4 and 5).

The assigned steps differed significantly between the sites. Seven sites (Sites 2, 3, 4, 5, 7, 11, 14) had significantly higher steps of asthma controller medications than patients from Site 16 (reference site). One site (Site 15) had significantly lower steps of asthma controller medications than patients from Site 16. The assigned steps differed significantly with the patients' decade of birth. Patients born in the 1940s/1950s had significantly higher levels of asthma controller medications than patients born in the 1990s/2000s. Lastly, in the months when COVID-19 was not present (before April 2020), both groups of patients had a significantly higher asthma controller medication level than after the COVID-19 pandemic began (Table 5).

DISCUSSION

This study shows, through prescribers' written prescriptions, there was a greater decrease in asthma controller medication level over time (after Enrollment) in the PARTICS patients compared with the UCare patients with both groups starting at the same asthma controller medication level. The decrease in intensity reduces, to some degree, the expected increase in total ICS exposure that would result from adopting the PARTICS strategy. The results in this sub-study complement and confirm the results in the main effects paper that that shows that self-reported ICS-containing controller refills were lower for participants assigned to PARTICS vs usual care.[30] Between this sub-study and the main effects paper, the participants' reported and prescribers' EHR data indicate decreased asthma controller medication use over time for the PARTICS patients compared with the UCare patients, even with correcting for COVID-19. When combined with the patient self-reported levels of controller ICS use and rescue ICS fulfillment data from the main effects paper, this sub-study supports that PARTICS improves outcomes at the population level, as the intensity of ICS controller therapy dropped as well as self-reported controller ICS use. Treating clinicians were free to adjust asthma medications as deemed necessary during the study. Primary asthma treating clinicians were not provided the monthly Asthma Control Test scores that were collected for research purposes, but patients may have been more aware of their asthma symptoms through repeated completion of this instrument. For many patients the primary asthma treating clinician was not the research prescribing clinician, but the treating clinician would have been aware of the study medication. While it is not

possible to determine if the drop in controller ICS dose, at the population level, was in response to the added as needed ICS, the increase in controller ICS dosage for the control patients would suggest changes were more likely to be based on asthma control and not perceived total steroid burden.

While the results of this sub-study confirm the results of the main effects paper, there are limitations. EHR data have inherent missingness and can have gaps due to infrequent visits and prescribing activities. In particular, assumptions concerning the length of time a prescription was active were made to determine an active medical regimen. While this may have affected the exact level for a given individual, the assumptions were evenly applied across both groups. Further, some individuals were on dual ICS inhalers not counting the study-prescribed beclomethasone, and these individuals were assigned based on the highest potency of any of the non-study prescribed ICS inhalers. Again, while this may have affected the ICS level of an individual, the approach was evenly applied at all times across both groups. Thus, neither of these processes would bias the results for either of the study arms. In addition, not every site within PREPARE provided data, but we had data from the majority of sites. This reduction in ICS controller intensity in the PARTICS group was accompanied with a significant reduction in annualized exacerbation rates in this group,[30] though total ICS use considering both controller and rescue use likely increased to some degree.

The results show that there were significant changes over time (after Enrollment) as well as significant differences between the PARTICS and UCare groups, participating sites, participants' decades of birth, and the COVID-19 correction. In the spline regressions, the UCare and PARTICS patients were comparable before enrollment, and differences occurred after enrollment in PREPARE. This effect is consonant with our reported reduction in exacerbations in the PREPARE cohort during the COVID pandemic.[36] The significant effect due to COVID-19 could be due to a variety of factors including changes in lifestyles that occurred such as working from home and a reduction in air pollution due to fewer cars on the road.[36] This effect could be further studied using air pollution data around the patents' dwellings.

Select sites provided their patients with significantly higher (or lower) asthma controller medications than the reference site (Site 16). The differences could be accounted for by different overall participant asthma severity across sites,[31] clinicians' prescribing patterns, organizational policies, or environmental factors. Though all clinicians providing asthma care for PREPARE participants completed the Asthma IQ program[37] to help standardize care, this intervention would not affect baseline (or pre-baseline) prescribing patterns, which were in place prior to the training. Further exploration into the reasons for the differences is warranted.

This sub-study shows that clinicians' prescribing patterns did change over time, and the PARTICS patients were prescribed lower doses of asthma controller medications by the end of the study.

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Conflicts of Interest:

Elisabeth Callen: Dr. Callen receives support for other work (paid directly to her institution) from Otsuka Pharmaceuticals, NIH, PCORI, HRSA, United Health Foundation, SAMHSA, Merck, Eli Lilly, CDC, and Takeda.

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Juan Carlos Cardet: Dr Cardet reports receiving honoraria from AstraZeneca, Chiesi, GSK, Genentech, and Sanofi for work on advisory boards and delivering lectures on asthma pathobiology and management.

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Supplemental Materials

Hierarchy of Controller Step Levels

- Step 2
  - Low dose ICS
- Step 3
  - Low dose ICS plus Leukotriene inhibitor
  - Medium dose ICS
  - Low dose ICS plus LABA OR LAMA
  - High dose ICS
- Step 4
  - Medium dose ICS plus Leukotriene inhibitor
  - Low dose ICS plus LABA OR LAMA plus Leukotriene inhibitor
  - Low dose ICS plus LABA AND LAMA
  - Low dose ICS plus LABA AND LAMA plus Leukotriene inhibitor
  - High dose ICS plus Leukotriene inhibitor
  - Medium dose ICS plus LABA OR LAMA
  - Medium dose ICS plus LABA OR LAMA plus Leukotriene inhibitor
- Step 5
  - Medium dose ICS plus LABA AND LAMA
  - Medium dose ICS plus LABA AND LAMA plus Leukotriene inhibitor
  - High dose ICS plus LABA OR LAMA
  - High dose ICS plus LABA AND LAMA
  - High dose ICS plus LABA OR LAMA plus Leukotriene inhibitor
  - High dose ICS plus LABA AND LABA plus Leukotriene inhibitor
- Step 6
  - Biologics
  - Daily Corticosteroids

Overall Model for All 28 Months (Supplemental Table 1; no corrections applied; no spline)

The month before or after enrollment did show a significant increase over time (estimate: 0.039; t = 9.315). The UCare patients were at a significantly higher asthma controller medication level overall (difference: 0.191; t = 2.327). The assigned reclassified levels differed significantly between the sites (F(15, 692.810) = 19.968; p = 0.000). Five sites (Sites 2, 3, 4, 5, 7) had significantly higher steps of asthma controller medications than patients from Site 16. Two sites (Sites 6, 15) had significantly lower steps of asthma controller medications than patients from Site 16. The assigned reclassified levels differed significantly with the patients' decade of birth (F(4, 692.014) = 5.135; p = 0.000). Patients born in the 1940s/1950s had significantly higher levels of asthma controller medications than patients born in the 1990s/2000s (difference: 0.611; t = 3.803). Lastly, in the months were COVID-19 was not present (before April 2020), the patients had a significantly higher asthma controller medication level than after the COVID-19 pandemic began (difference: 0.902; t = 14.118; Supplemental Table 1).

Supplemental Table 1. Final LME Results with Significant Variables.

Parameter	Estimate	Standard Error	95% CI	t
-2 Restricted Log Likelihood: 73628.74 Month: F(1, 740.37) = 86.77; p < 0.001 Group: F(1, 691.99) = 5.41; p = 0.02 Site: F(15, 692.81) = 19.97; p < 0.001 Decade of Birth: F(4, 692.01) = 5.14; p < 0.001 COVID Correction: F(1, 18759.68) = 199.32; p < 0.001				
Intercept (Baseline)	0.78	0.24	[0.31, 1.25]	3.24*
Month	0.04	0.00	[0.03, 0.05]	9.32*
UCare	0.19	0.08	[0.03, 0.35]	2.33*
PARTICS	Reference			
Site 1	-0.44	0.34	[-1.11, 0.24]	-1.27
Site 2	1.14	0.30	[0.55, 1.73]	3.80*
Site 3	1.51	0.23	[1.05, 1.96]	6.49*
Site 4	0.91	0.26	[0.40, 1.42]	3.49*
Site 5	1.22	0.23	[0.76, 1.68]	5.24*
Site 6	-0.93	0.22	[-1.36, -0.50]	-4.25*
Site 7	0.66	0.22	[0.23, 1.08]	3.02*
Site 8	0.04	0.33	[-0.61, 0.69]	0.13
Site 9	0.27	0.24	[-0.21, 0.74]	1.11
Site 10	0.05	0.23	[-0.41, 0.50]	0.19
Site 11	0.11	0.25	[-0.38, 0.60]	0.43
Site 12	-0.24	0.41	[-1.04, 0.57]	-0.58
Site 13	-0.07	0.23	[-0.51, 0.37]	-0.33
Site 14	0.17	0.23	[-0.27, 0.62]	0.78
Site 15	-1.43	0.35	[-2.13, -0.74]	-4.05*
Site 16	Reference			
Born: 1940s & 1950s	0.61	0.16	[0.30, 0.93]	3.80*
Born: 1960s	0.21	0.16	[-0.11, 0.52]	1.29
Born: 1970s	0.26	0.17	[-0.07, 0.58]	1.54
Born: 1980s	0.31	0.17	[-0.03, 0.65]	1.80+
Born: 1990s & 2000s	Reference			
No COVID-19	0.90	0.06	[0.78, 1.03]	14.19*
COVID-19 Present	Reference			

* p-value < 0.05

Supplemental Table 2. LME Results with All Variables

All Variables (-2 Restricted Log Likelihood: 67558.41) Month: F(1, 694.89) = 5.31; p = 0.02 Group: F(1, 715.15) = 1.81; p = 0.18 Site: F(15, 721.21) = 18.76; p = 0.00 Gender: F(1, 701.07) = 0.16; p = 0.69 Decade of Birth: F(4, 717.97) = 4.24; p = 0.002 Race/Ethnicity: F(1, 739.73) = 0.62; p = 0.43 Language: F(1, 695.91) = 2.22; p = 0.14 COVID Correction: F(1, 12122.12) = 12.28; p = 0.00				
Intercept (Baseline)	4.57	1.07	[2.46, 6.67]	4.26*
Month	0.03	0.01	[0.00, 0.05]	2.30*
UCare	0.41	0.30	[-0.19, 1.00]	1.35
PARTICS	Reference			
Site 1	1.43	1.29	[-1.10, 3.96]	1.11
Site 2	5.35	1.12	[3.16, 7.53]	4.79*
Site 3	4.43	0.87	[2.72, 6.15]	5.08*
Site 4	2.42	1.07	[0.32, 4.53]	2.26*
Site 5	3.71	0.97	[1.80, 5.61]	3.82*
Site 6	-0.74	0.85	[-2.41, 0.93]	-0.87
Site 7	-0.07	0.83	[-1.69, 1.55]	-0.08
Site 8	-1.88	1.21	[-4.24, 0.49]	-1.56
Site 9	4.93	1.02	[2.93, 6.94]	4.82*
Site 10	0.75	0.96	[-1.14, 2.65]	0.78
Site 11	3.53	1.01	[1.55, 5.52]	3.50*
Site 12	0.30	1.55	[-2.74, 3.33]	0.19
Site 13	-1.29	0.94	[-3.14, 0.55]	-1.38
Site 14	6.08	0.96	[4.20, 7.96]	6.34*
Site 15	-0.75	1.43	[-3.56, 2.06]	-0.53
Site 16	Reference			
Male	0.16	0.40	[-0.63, 0.95]	0.40
Female	Reference			
Born: 1940s & 1950s	1.77	0.60	[0.60, 2.95]	2.97*
Born: 1960s	0.40	0.59	[-0.75, 1.56]	0.69
Born: 1970s	0.60	0.61	[-0.61, 1.80]	0.97
Born: 1980s	0.20	0.63	[-1.04, 1.45]	0.32
Born: 1990s & 2000s	Reference			
Hispanic	-0.37	0.47	[-1.29, 0.55]	-0.79
Non-Hispanic	Reference			
English	0.82	0.55	[-0.26, 1.89]	1.49
Spanish	Reference			
No COVID-19	0.59	0.17	[0.26, 0.92]	3.51*
COVID-19 Present	Reference			