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# **BMJ Open**

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

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24	Abstract
25	Objective: The Person Empowered Asthma Relief (PREPARE) study found that as-
26	needed inhaled corticosteroid supplementation combined with participants' usual
27	controller and rescue therapy reduced asthma exacerbations. Here we sought to
28	determine if treatment assignment to the Intervention (called PARTICS) vs Control
29	(Usual Care) had an impact on controller therapy based on clinicians' written
30	prescriptions. Design: Secondary data analysis. Setting: Practices treating asthma.
31	Participants: PREPARE study participants were included in this analysis.
32	Interventions: PREPARE study. Outcome Measures: For impact of the PARTICS
33	therapy on patients, each patient-month was assigned to a controller step based on a 6-
34	step classification scheme. An overall Linear Mixed Effect Model was completed for all
35	28 months of data and a Linear Mixed Effect Spline Model was completed for before
36	and after enrollment data to determine controller changes over a 28-month period (12
37	months prior to enrollment, the month of enrollment, and 15 months after enrollment)
38	between the two study arms. Results: This analysis included 713 participants. Of these,
39	49.1% were Usual Care patients and 50.9% were PARTICS patients. Throughout the
40	study, the majority of patients changed asthma controller medications in both arms. By
41	the end of the study, the Usual Care patients were at a significantly higher asthma
42	controller medication step (0.20 step higher) than the PARTICS patients. Conclusions:
43	Clinicians' prescribing patterns showed significant changes over time. Compared with
44	Usual Care patients, PARTICS patients were on lower doses of asthma controller
45	medications by the end of the study.
46	

#### 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.

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	62	INTRODUCTION
	63	Twenty-five million adults have asthma in the US.(1) Asthma exacerbations cause the
	64	largest number of lost days from school or work for children and young adults, one-third
)	65	of all days.(2, 3) Despite new medications,(4, 5) new drug regimens,(6-11) and the
	66	ongoing evolution of treatment guidelines(12-14) the number of people with asthma
-	67	exacerbations in the previous year has decreased only slightly over the past 20 years,
,	68	from 51.6% to 46.0%.(15, 16) Asthma is also a disease with a high degree of disparities
)	69	in outcomes. Blacks have exacerbation and death rates that are 2-2.5 times higher than
	70	Whites and Asians,(17) while Hispanics, particularly Caribbean Hispanics,(18, 19) have
-	71	2 times the rate of exacerbations and 1.5 times the death rate.(20, 21) Thus, there is an
)	72	ongoing need to expand and improve treatment approaches for individuals with asthma.
) 	73	
)	74	The paradigm concerning use of inhaled corticosteroids (ICS) only as a controller, i.e.,
	75	as a once or twice a day medication, has been evolving. The use of ICS-formoterol as
	76	both controller and rescue therapy (single maintenance and reliever therapy [SMART])
	77	is endorsed by multiple guideline groups across the world, include the US, GINA, and
)	78	UK guidelines.(12, 14, 22) Previous randomized controlled trials have also
	79	demonstrated that as-needed, stand-alone, ICS use in conjunction with short acting
	80	beta-agonist (SABA) for acute asthma symptom relief can improve asthma outcomes.(7,
) ,	81	23-29) The Person Empowered Asthma Relief (PREPARE) trial utilized a stand-alone
, ) )	82	ICS combined with participants' usual controller and rescue therapy in an approach
	83	called Patient Activated Reliever-Triggered ICS (PARTICS).(30)
-	84	
)		

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The PARTICS intervention decreased asthma exacerbations, improved asthma control and guality 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** 

1 2							
3 4	108						
5 6 7	109	The PREPARE study was a pragmatic, open label, patient level randomized trial					
8	110	designed to observe the effects of adding ICS to rescue therapy among AA/B and H/L					
2 3 4 5 6 7	111	adults with moderate-to-severe asthma.(31) In the PREPARE study, the					
13	112	Intervention/PARTICS group (hereafter, "PARTICS group") received additional ICS					
15	113	medication (donated by TEVA, beclomethasone 80 mcg) and was asked to use 1 puff o	f				
17	114	beclomethasone for every 1 puff of usual rescue inhaler and 5 puffs of beclomethasone					
19	115	for every 1 rescue nebulization, in addition to usual care. The control group received					
22	116	usual care (hereafter, "UCare group"), described previously.(31) Exacerbations were					
24	117	tracked using patient-reported outcomes that were adjudicated using EHR data and					
26	118	patient interviews. The sub-study detailed here covers the prescriber side of asthma					
28 29 30 31 32 33 34 35 36	119	controller medications, as recorded in the EHRs of the primary asthma treating clinician					
	120	(primary care, pulmonologist or allergist) for a subset of enrollees. To determine the					
	121	effect, we analyzed PREPARE participants' asthma controller medications over 28					
	122	months (12 months before enrollment into PREPARE, month of enrollment into					
38	123	PREPARE, and 15 months after enrollment).					
40	124	FHP Data Acquisition					
	125	EHR Data Acquisition					
44 45 46 47 48	126						
	127	Each site was asked to provide EHR data for each participant within the PREPARE					
49 50	128	study. The DARTNet Institute provided a set of instructions for each site including the					
51 52	129	variables needed from the EHR. Sixteen of the 19 participating sites provided data from					
53 54 55	130	their EHR or data warehouse. Requested information included care site information,					
55 56 57							
58 59			6				
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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 guality 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 

60

1 2		
- 3 4	153	Once the standardized data were received from DARTNet, the individual site files were
5 6	154	combined for analysis. DARTNet worked with the AAFP to review and modify, if
7 8 9	155	needed, existing "value sets" (i.e., list of codes associated with clinical concepts- either
10 11	156	specific medications, conditions, or procedures). Value sets were created that
12 13	157	segregated asthma medications as specifically needed for this analysis. Medications
14 15	158	were categorized on a monthly basis as active using the following rules:
16 17 18	159	Start date of medication: The month the prescription was written was considered
19 20	160	the start date/month.
21 22	161	End date of medication:
23 24 25	162	$\circ$ If an end date was provided, then it was used if it was 12 months or less
26 27	163	from the time the prescription was written.
28 29	164	$\circ$ If no end date was provided, then an end date of 12 months after the
30 31 32	165	prescription was written was used.
32 33 34	166	Dosage/quantity and refills provided were also used to determine if a 12-month
35 36	167	end date was appropriate or a shorter time span should be used due to how the
37 38	168	prescription was written.
39 40 41	169	Once each asthma medication for each patient had assigned months, all medications
42 43	170	were assigned to types of asthma medications (e.g., low/medium/high dose ICS, Long-
44 45	171	Acting Beta-Agonists (LABA), Long-Acting Muscarinic Antagonist (LAMA)). Using those
46 47 48	172	assigned types, all medications for each patient were collapsed into one record for each
49 50	173	month (patient-month). The medication types for each month were assigned to a
51 52	174	controller step based on highest ICS dose (i.e., low, medium, high) that they were
53 54 55	175	prescribed along with additional controller medications.
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1 2		
2 3 4	176	
5 6	177	Outcome Groupings
7 8 9	178	
10 11	179	Each patient-month was assigned to a controller step based on a six-step classification
12 13	180	scheme. The hierarchy of controller step levels (located in Supplemental Materials) was
14 15 16	181	based on Guideline Steps (hereafter referred to as step) outlined in the National Asthma
17 18	182	Education and Prevention Program (NAEPP) guidelines.(14) If a patient had no
19 20	183	medication used within the classification scheme, then the patient was assigned a "0"
21 22	184	for the month indicating the patient had no asthma controller medications prescribed to
23 24 25 26 27	185	him/her within a given month. The six-step classification scheme (plus "0" for no
	186	medication) was used as the dependent variable in the statistical models.
28 29	187	
30 31 32	188	Statistical Methods
33 34	189	
35 36	190	This analysis was a secondary data analysis. Descriptive and inferential statistics were
37 38 39	191	completed as appropriate. To start, changes in asthma controller medication were
40 41	192	determined by the starting and stopping of prescriptions according to the EHR data
42 43	193	rules. A change was the movement up or down in the step hierarchy. Then to model the
44 45	194	EHR data, Linear Mixed Effect Model (LME; overall model and a spline version) were
46 47 48	195	used with the assigned asthma controller medication step in each month as the
49 50	196	dependent variable; independent variable(s) varied depending on the model. A series of
51 52	197	LMEs were completed to determine the individual demographic variables that
53 54 55 56 57 58	198	contributed (p < 0.05) to the model. The dependent variable for all LMEs was the six-

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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

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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 🦯	P
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. Demogra	aphics and	l Comparisons	with Main Study (n	(%)).
	PART	ICS (n = 363)	UCare (n = 350)	Sig with Main Stuc
Overall (n = 713)	36	63 (50.9%)	350 (49.1%)	0.722
Female	29	97 (81.8%)	292 (83.4%)	0.295
Non-Hispanic/Bla	ack 21	6 (59.5%)	217 (62.0%)	<0.001
				1
Changes in Asth	ma Contro	ller Medicatior	Prescriptions	
As noted in Table	3, asthma	controller medic	ation prescription ch	anges, without regar
to the change dire	ection, occu	rred over time (	before and after enro	Ilment; comparison
two time points) fo	or both the l	JCare and PAR	TICS groups. Chang	es included addition
withdrawal of inha	lers or med	lications, biolog	ics, and leukotriene i	nhibitors, as well as
	e of all med	lications. Howev	ver, changes were st	atistically similar, so
changes in dosag				
0 0	ged controll	er medications	with similar frequenc	y over the various tir
0 0	-	er medications	with similar frequenc	y over the various ti
poth groups chang	-	er medications	with similar frequenc	y over the various tir

Overall (n = 713)

PARTICS (n =

363)

UCare (n = 350)

6

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 t		
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 i		
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 Splin		
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.		
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Parameter	Estimate	Standard	95% CI	t
		Error		
	-2 Restricted Lo	 og Likelihood: 24	603.78	
	Month: F(1, 568	-		
		19.00) = 0.01; p		
	Site: F(14, 549	9.00) = 8.47; p <	0.001	
De	ecade of Birth: F	(4, 549.00) = 2.6	0; 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		Refe	rence	
	0.10	<u> </u>		0.04
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

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p-value < 0.05	9			
Born: 1990s & 2000s	No.	Re	ference	
Born: 1980s	0.20	0.23	[-0.26, 0.65]	0.84
Born: 1970s	0.10	0.22	[-0.34, 0.54]	0.43
Born: 1960s	0.16	0.22	[-0.27, 0.58]	0.73
Born: 1940s & 1950s	0.52	0.22	[0.09, 0.94]	2.38*
Site 16		Ret	ference	
Site 15	-1.46	0.46	[-2.36, -0.55]	-3.16*
Site 14	0.25	0.28	[-0.30, 0.79]	0.89
Site 13	0.26	0.27	[-0.28, 0.79]	0.95

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).

 60

75					
76	Model After Enrollmen	it (one month al	fter through the	e 15 months after	r Enrollm
77	Table 5)				
78					
79	Table 5. Final After En	rollment LME R	esults.		
	Parameter	Estimate	Standard Error	95% CI	t
		-2 Restricted Lo	bg Likelihood: 33	3387.07	
		Month: F(1, 684	1.72) = 24.59; p	< 0.001	
		Group: F(1, 63	31.01) = 4.72; p	= 0.03	
		Site: F(15, 633	3.60) = 9.91; p <	0.001	
	Dee	cade of Birth: F(4	4, 631.09) = 3.83	3; p = 0.004	
	COVI	D 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		Refe	rence	
	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

Born: 1980s	0.30	0.20	[-0.09, 0.69]	1.49
Born: 1970s	0.24	0.19	[-0.13, 0.62]	1.27
Born: 1960s	0.00	0.18	[-0.36, 0.36]	0.01
Born: 1940s & 1950s	0.46	0.19	[0.10, 0.83]	2.49*
Site 16	0	Ref	erence	
Site 15	-1.36	0.45	[-2.24, -0.48]	-3.03*
Site 14	0.56	0.26	[0.05, 1.08]	2.17*
Site 13	-0.17	0.27	[-0.69, 0.35]	-0.64
Site 12	0.31	0.47	[-0.62, 1.23]	0.65
Site 11	0.59	0.29	[0.02, 1.15]	2.05*
Site 10	0.43	0.26	[-0.08, 0.94]	1.65+
Site 9	0.41	0.28	[-0.13, 0.95]	1.49
Site 8	0.43	0.39	[-0.34, 1.20]	1.09
Site 7	0.57	0.25	[0.08, 1.06]	2.30*

> 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.

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

e assigned steps differed significantly between the sites. Seven sites (Sites 2, 3, 4, 5, 1, 14) had significantly higher steps of asthma controller medications than patients m Site 16 (reference site). One site (Site 15) had significantly lower steps of asthma troller medications than patients from Site 16. The assigned steps differed nificantly with the patients' decade of birth. Patients born in the 1940s/1950s had nificantly higher levels of asthma controller medications than patients born in the 90s/2000s. Lastly, in the months when COVID-19 was not present (before April 20), both groups of patients had a significantly higher asthma controller medication el than after the COVID-19 pandemic began (Table 5).

# SCUSSION

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

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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

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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.

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355	Select sites provided their patients with significantly higher (or lower) asthma controller
356	medications than the reference site (Site 16). The differences could be accounted for by
357	different overall participant asthma severity across sites,(31) clinicians' prescribing
358	patterns, organizational policies, or environmental factors. Though all clinicians
359	providing asthma care for PREPARE participants completed the Asthma IQ
360	program(37) to help standardize care, this intervention would not affect baseline (or pre-
361	baseline) prescribing patterns, which were in place prior to the training. Further
362	exploration into the reasons for the differences is warranted.
363	
364	This sub-study shows that clinicians' prescribing patterns did change over time, and the
365	PARTICS patients were prescribed lower doses of asthma controller medications by the
366	end of the study.
367	
368	Acknowledgements: We would like to acknowledge all study participants for their time
369	and dedication. We would also like to acknowledge the PREPARE Operations Team
370	and Nancy Maher. We would also like to acknowledge the PREPARE site principal
371	investigators.
372	
373	Availability of Data: Data available upon reasonable request to the corresponding
374	author.
375	
376	Patient and Public Involvement: Patients and the public were not involved in the
377	design, conduct, reporting, and dissemination of this secondary data analysis.

1 2		
3 4	378	
5 6	379	Financial Support: Supported by a PCORI Award (PCS-1504-30283, to Dr. Israel), the
7 8 9	380	Gloria M. and Anthony C. Simboli Distinguished Chair in Asthma Research award (to
9 10 11	381	Dr. Israel), and by grants from the National Institute of Allergy and Infectious Diseases
12 13	382	(K23AI125785, to Dr. Cardet) and the American Lung Association–American Academy
14 15	383	of Allergy, Asthma, and Immunology (AI-835475, to Dr. Cardet). QVAR and QVAR
16 17 18	384	RediHaler inhalers were provided free of charge and funding for the AssistRx pharmacy
19 20	385	was provided by Teva Pharmaceuticals. NIOX VERO devices for measuring exhaled
21 22	386	nitric oxide were provided free of charge by Circassia Pharmaceuticals.
23 24 25	387	
26 27	388	Conflicts of Interest:
28 29	389	Elisabeth Callen: Dr. Callen receives support for other work (paid directly to her
30 31 22	390	institution) from Otsuka Pharmaceuticals, NIH, PCORI, HRSA, United Health
32 33 34	391	Foundation, SAMHSA, Merck, Eli Lilly, CDC, and Takeda.
35 36	392	Elliot Israel: Dr. Israel receives support for other work (paid directly to his institution)
37 38	393	from AstraZeneca, Avillion Mandala/Denali, Circassia, Gossamer Bio, NIH, Novartis,
39 40 41	394	and PCORI; he receives consulting fees from Allergy and Asthma Network, Amgen,
42 43	395	AstraZeneca, Avillion, GlaxoSmithKline, Merck, NHLBI, Novartis, Pneuma Respiratory,
44 45	396	Regeneron, Sanofi Genzyme, TEVA, and Cowen; he receives royalties from UpToDate
46 47 48	397	- Wolters Kluwer; he has been paid honoraria from TEVA, Cowen, and Westchester
49 50	398	Medical Center; he has been paid for expert testimony by Cambridge Medical Experts,
51 52	399	Danaher Lagnese, and SettlePou; he has been paid for Participation on a Data Safety
53 54 55	400	Monitoring Board or Advisory Board by Novartis; he is a member of the coordinating
55 56 57		
58		00

committed for National Asthma Education Prevention Program and he is on the editorial board for the Journal of Allery and Clinical Immunology and the Journal of Allergy & Clinical Immunology, in Practice; he owns stock in Nesos Corp; and he has received a study drug for an unrelated study from Genentech, Sun Pharmaceuticals, Laurel Pharmaceuticals, Om Pharmaceuticals, Nestle, CSL Behring, Glaxo, and Sanofi Regeneron. 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. **Anne Fuhlbrigge:** Dr Fuhlbrigge an unpaid consultant to Teva, AstraZeneca and Novartis pharmaceuticals for epidemiologic analyses related to asthma outcomes and a co-investigator for the PREPARE, funded through PCORI. Gabriela Gaona: declares no conflict of interest. Wilson Pace: Dr. Pace's organization has received funding via subcontracts from CDC, PCORI, NIH, Boehringer Ingelheim, ONC, Tabula Rasa Healthcare, and Astra-Zeneca; his organization received consulting fees for his work from Boehringer Ingelheim; his organization has received payment for expert testimony; he is on the Advisory Board (paid) for AT Still Research Foundation and an Advisory board and Executive Committee member (unpaid) for COPD Foundation 360 Network; he owns stock through trust in Johnson and Johnson, Eli Lilly, Novo-Nordisk, Pfizer, Novartis, Moderna, and Amgen; he received grant and writing support for an unrelated project from Boehringer Ingelheim; and is an unpaid members of Colorado Medicaid Provider Rate Review Committee.

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Brian Manning: declares no conflict of interest.	
Elizabeth Staton: declares no conflict of interest.	
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3 4	1	Supplemental Materials
5	2	
6	3	Hierarchy of Controller Step Levels
7	4	
8	5	Step 2
9	6	○ Low dose ICS
10	7	• Step 3
11	8	<ul> <li>Low dose ICS plus Leukotriene inhibitor</li> </ul>
12	9	<ul> <li>Medium dose ICS</li> </ul>
13	10	<ul> <li>Low dose ICS plus LABA OR LAMA</li> </ul>
14	11	• High dose ICS
15	12	• Step 4
16 17	13	<ul> <li>Medium dose ICS plus Leukotriene inhibitor</li> </ul>
18	14	<ul> <li>Low dose ICS plus LABA OR LAMA plus Leukotriene inhibitor</li> </ul>
19	15	<ul> <li>Low dose ICS plus LABA AND LAMA</li> <li>Low dose ICS plus LABA AND LAMA plus Low/astriang inhibitor</li> </ul>
20	16	<ul> <li>Low dose ICS plus LABA AND LAMA plus Leukotriene inhibitor</li> <li>High dose ICS plus Laukotriene inhibitor</li> </ul>
21	17	<ul> <li>High dose ICS plus Leukotriene inhibitor</li> <li>Madium dose ICS plus LABA OB LAMA</li> </ul>
22	18 10	<ul> <li>Medium dose ICS plus LABA OR LAMA</li> <li>Medium dose ICS plus LABA OR LAMA plus Louketrians inhibitor</li> </ul>
23	19	<ul> <li>Medium dose ICS plus LABA OR LAMA plus Leukotriene inhibitor</li> </ul>
24	20	Step 5
25	21	<ul> <li>Medium dose ICS plus LABA AND LAMA</li> <li>Medium dose ICS plus LABA AND LAMA plus Louketriops inhibitor</li> </ul>
26	22 23	<ul> <li>Medium dose ICS plus LABA AND LAMA plus Leukotriene inhibitor</li> <li>High dose ICS plus LABA OB LAMA</li> </ul>
27	23 24	<ul> <li>High dose ICS plus LABA OR LAMA</li> <li>High dose ICS plus LABA AND LAMA</li> </ul>
28	24 25	
29	26	
30 31	20 27	<ul> <li>High dose ICS plus LABA AND LABA plus Leukotriene inhibitor</li> <li>Step 6</li> </ul>
32	28	
33	29	<ul> <li>Biologics</li> <li>Daily Corticosteroids</li> </ul>
34	30	o Daily conticosteroids
35	31	Overall Model for All 28 Months (Supplemental Table 1; no corrections applied; no spline)
36	32	
37	33	The month before or after enrollment did show a significant increase over time (estimate: 0.039;
38	34	t = 9.315). The UCare patients were at a significantly higher asthma controller medication level
39	35	overall (difference: $0.191$ ; t = $2.327$ ). The assigned reclassified levels differed significantly
40	36	between the sites (F(15, 692.810) = 19.968; p = 0.000). Five sites (Sites 2, 3, 4, 5, 7) had
41	37	significantly higher steps of asthma controller medications than patients from Site 16. Two sites
42	38	(Sites 6, 15) had significantly lower steps of asthma controller medications than patients from
43 44	39	Site 16. The assigned reclassified levels differed significantly with the patients' decade of birth
44 45	40	(F(4, 692.014) = 5.135; p = 0.000). Patients born in the 1940s/1950s had significantly higher
46	41	levels of asthma controller medications than patients born in the 1990s/2000s (difference:
47	42	0.611; t = 3.803). Lastly, in the months were COVID-19 was not present (before April 2020), the
48	43	patients had a significantly higher asthma controller medication level than after the COVID-19
49	44	pandemic began (difference: 0.902; t = 14.118; Supplemental Table 1).
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Supplemental Table 1. Fin 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						
		l, 18759.68) = 199.				
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 Site 2	-0.44 1.14	0.34	[-1.11, 0.24] [0.55, 1.73]	-1.27 3.80*		
Site 3	1.14	0.23	[1.05, 1.96]	6.49*		
Site 3	0.91	0.23	[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	0.61	Refer		2.00*		
Born: 1940s & 1950s Born: 1960s	0.61	0.16	[0.30, 0.93] [-0.11, 0.52]	<u>3.80*</u> 1.29		
Born: 1970s	0.21	0.10	[-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		Refer				
p-value < 0.05						
•						

# 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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Keywords:	Patients, Asthma < THORACIC MEDICINE, STATISTICS & RESEARCH METHODS

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3 4	1	An electronic health record data analysis on the impact of rescue triggered inhaled			
5 6	2	corticosteroids on controller therapy in Black and Latinx Individuals from a pragmatic,			
7 8 9	3	open label, patient level randomized trial			
9 10 11	4				
12 13	5	Elisabeth F. Callen, PhD <sup>1,2*</sup> , Elliot Israel, MD <sup>3</sup> , Juan Carlos Cardet, MD, MPH <sup>4</sup> , Anne			
14 15	6	L. Fuhlbrigge, MD, MS <sup>5</sup> , Brian K. Manning, MPH <sup>1,2</sup> , Gabriela Gaona, MPH, CPH <sup>2</sup> ,			
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51 52	22	Email: elisabeth.callen@dartnet.info			
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25	Abstract
26	Objective: The Person Empowered Asthma Relief (PREPARE) study found that as-
27	needed inhaled corticosteroid supplementation combined with participants' usual
28	controller and rescue therapy reduced asthma exacerbations for Black and Latinx
29	individuals. Here we sought to determine if treatment assignment to the Intervention
30	(called PARTICS) vs Control (Usual Care) had an impact on controller therapy based on
31	clinicians' written prescriptions. Design: Secondary data analysis of electronic health
32	record data of a pragmatic, open label, patient level randomized trial. Setting: Practices
33	treating asthma. Participants: PREPARE study participants - Black and Latinx
34	individuals with asthma. Interventions: Effects of adding ICS to rescue therapy among
35	Black and Hispanic adults with moderate-to-severe asthma. Outcome Measures: For
36	PARTICS therapy impact on patients, each month is the 28-month period (12 months
37	prior to enrollment, the month of enrollment, and 15 months after enrollment), a patient
38	was assigned to a controller step based on a 6-step classification scheme. A Linear
39	Mixed Effect Spline Model was completed for before and after enrollment data to
40	determine controller changes over a 28-month period between the two study arms.
41	Results: This analysis included 713 participants. Of these, 49.1% were Usual Care
42	patients and 50.9% were PARTICS patients. Throughout the study, the majority of
43	patients changed asthma controller medications in both arms. By the end of the study,
44	the Usual Care patients were at a significantly higher asthma controller medication step
45	(0.20 step higher) than the PARTICS patients. Conclusions: Clinicians' prescribing
46	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

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1 2		
2 3 4	50	Strengths and Limitations of This Study:
5 6	51	Strength: Long follow-up time using electronic health record analysis of
7 8 9	52	controller medications prescribed from 12 months before enrollment into the
9 10 11	53	Person Empowered Asthma Relief (PREPARE) study through 15 months after
12 13	54	enrollment.
14 15 16	55	• Strength: Even if data were missing, we were able to use all available data due to
17 18	56	the type of analysis we used – Linear Mixed Effect Model.
19 20	57	Limitation: EHR data have inherent missingness and can have gaps due to
21 22 23	58	infrequent visits and prescribing activities.
23 24 25	59	Limitation: Some individuals were on dual ICS inhalers not counting the study-
26 27	60	prescribed beclomethasone, and these individuals were assigned based on the
28 29 30	61	highest potency of any of the non-study prescribed ICS inhalers.
31 32	62	Limitation: In addition, not every site within PREPARE provided data, but we had
33 34	63	data from the majority of sites.
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# 64 INTRODUCTION

Twenty-five million adults have asthma in the US.<sup>1</sup> Asthma exacerbations cause the largest number of lost days (one-third of all days) from school or work for children and young adults.<sup>23</sup> Despite new medications,<sup>45</sup> new drug regimens,<sup>6-11</sup> and the ongoing evolution of treatment guidelines<sup>12-14</sup>, 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%.<sup>15 16</sup> 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,<sup>17</sup> while Hispanic individuals, particularly Caribbean Hispanic individuals,<sup>18</sup><sup>19</sup> have 2 times the rate of exacerbations and 1.5 times the death rate.<sup>20 21</sup> 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.<sup>12 14 22</sup> 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.<sup>7 23-29</sup> 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).<sup>30</sup>

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87 The PARTICS intervention in PREPARE decreased asthma exacerbations, improved 88 asthma control and guality of life, and reduced reliever use in African American/Black 89 (AA/B) and Hispanic/Latinx (H/L) adults with moderate to severe asthma, a group with 90 disproportionate asthma morbidity that has been difficult to reduce.<sup>30</sup> This research 91 92 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 93 assessments, in AA/B and H/L adults, integrated with rescue nebulizer therapy, required 94 no changes in a participant's current controller therapy, and appears to have fewer 95 insurance barriers than an ICS-formoterol based approach. Participants on PARTICS 96 also reported lower SABA use, both as a metered dose inhaler and via nebulizer, and 97 fewer controller refills as well as a self-reported reduction in controller ICS dosage.<sup>30</sup> 98 99 The objective of this paper is to report on a pre-specified PREPARE trial sub-analysis 100 using electronic health record (EHR) data to determine if treatment assignment (the 101 PARTICS intervention vs. usual care) had an impact on controller therapy through 102

103 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 104 105 period (12 months prior to enrollment, month of enrollment, and 15 months after 106 enrollment) between the two arms of the study.

- - 108 METHODS
- 109

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## **Brief Description of the PREPARE Study**

The PREPARE study was a pragmatic, open label, patient level randomized trial 112 designed to observe the effects of adding ICS to rescue therapy among AA/B and H/L 113 adults with moderate-to-severe asthma.<sup>31</sup> In the PREPARE study, the 114 Intervention/PARTICS group (hereafter, "PARTICS group") received additional ICS 115 medication (donated by TEVA, beclomethasone 80 mcg) and was asked to use 1 puff of 116 beclomethasone for every 1 puff of usual rescue inhaler and 5 puffs of beclomethasone 117 for every 1 rescue nebulization, in addition to usual care. The control group received 118 usual care (hereafter, "UCare group"), described previously.<sup>31</sup> Exacerbations were 119 tracked using patient-reported outcomes that were adjudicated using EHR data and 120 patient interviews. The sub-study detailed here covers the prescriber side of asthma 121 controller medications, as recorded in the EHRs of the primary asthma treating clinician 122 (primary care, pulmonologist or allergist) for a subset of enrollees. To determine the 123 effect, we analyzed PREPARE participants' asthma controller medications over 28 124 months (12 months before enrollment into PREPARE, month of enrollment into 125 126 PREPARE, and 15 months after enrollment). The PREPARE study and this sub-study were approved by the IRB (Partners Human Research Committee: 2016P001839/BWH) 127 128 and written informed consent was obtained from each participant at the time of 129 enrollment (recruitment period: November 2017 – April 2021). 130 **EHR Data Acquisition** 131

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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 CLICZ 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.

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5 6 7	157	EHR Data Cleaning
, 8 9	158	
10 11	159	Once the standardized data were received from DARTNet, the individual site files were
12 13	160	combined for analysis. DARTNet worked with the AAFP to review and modify, if
14 15 16	161	needed, existing "value sets" (i.e., list of codes associated with clinical concepts- either
17 18	162	specific medications, conditions, or procedures). Value sets were created that
19 20	163	segregated asthma medications as specifically needed for this analysis. Medications
21 22 23	164	were categorized on a monthly basis as active using the following rules:
24 25	165	Start date of medication: The month the prescription was written was considered
26 27	166	the start date/month.
28 29 30	167	End date of medication:
30 31 32	168	$\circ$ If an end date was provided, then it was used if it was 12 months or less
33 34	169	from the time the prescription was written.
35 36 27	170	$\circ$ If no end date was provided, then an end date of 12 months after the
37 38 39	171	prescription was written was used.
40 41	172	Dosage/quantity and refills provided were also used to determine if a 12-month
42 43	173	end date was appropriate or a shorter time span should be used due to how the
44 45 46	174	prescription was written.
47 48	175	Once each asthma medication for each patient had assigned months, all medications
49 50	176	were assigned to types of asthma medications (e.g., low/medium/high dose ICS, Long-
51 52 53	177	Acting Beta-Agonists (LABA), Long-Acting Muscarinic Antagonist (LAMA)). Using those
54 55 56 57 58	178	assigned types, all medications for each patient were collapsed into one record for each

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1 2			
2 3 4	179	month (patient-month). The medication types for each month were assigned to a	
5 6 7	180	controller step based on highest ICS dose (i.e., low, medium, high) that they were	
7 8 9	181	prescribed along with additional controller medications.	
10 11	182		
12 13	183	Outcome Groupings	
14 15 16	184		
17 18	185	Each patient-month was assigned to a controller step based on a six-step classification	
19 20 21	186	scheme. The hierarchy of controller step levels (located in Supplemental Materials) was	3
21 22 23	187	based on Guideline Steps (hereafter referred to as step) outlined in the National Asthma	а
24 25	188	Education and Prevention Program (NAEPP) guidelines. <sup>14</sup> If a patient had no	
26 27 20	189	medication used within the classification scheme, then the patient was assigned a "0"	
28 29 30	190	for the month indicating the patient had no asthma controller medications prescribed to	
31 32	191	him/her within a given month. The six-step classification scheme (plus "0" for no	
33 34	192	medication) was used as the dependent variable in the statistical models.	
35 36 37	193		
37 38 39	194	Statistical Methods	
40 41	195		
42 43	196	This analysis was a secondary data analysis. Descriptive and inferential statistics were	
44 45 46	197	completed as appropriate. To start, changes in asthma controller medication were	
47 48	198	determined by the starting and stopping of prescriptions according to the EHR data	
49 50	199	rules. A change was the movement up or down in the step hierarchy. Then to model the	
51 52 53	200	EHR data, Linear Mixed Effect Model (LME; overall model and a spline version) were	
54 55 56	201	used with the assigned asthma controller medication step in each month as the	
57 58 59		1	0

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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.<sup>33-35</sup> 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). 

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RESULTS

Demographics

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229	After cleaning EHR data obtained from each site, there were 713 participants (out of
230	1,201 participants randomized in PREPARE) included in these analyses. The remaining
231	patients in the PREPARE study (488) did not have their data included because the sites
232	did not provide EHR data. The breakdown of participants by site is in Table 1. Of these,
233	350 (49.1%) were in the UCare Group and 363 (50.9%) were in the PARTICS Group.
234	Most participants were female and Non-Hispanic/Black (Table 2 for comparisons with
235	the full study cohort). As the University of Puerto Rico, a major H/L enrolling site, was
236	not able to provide EHR data, the cohort of participants included in this analysis has a
237	lower percent of H/L participants than the full study (p<0.001; Table 2).

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

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

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Site 9       48         Site 10       58         Site 11       42         Site 12       9         Site 13       71         Site 14       70	
Site 11     42       Site 12     9       Site 13     71	
Site 12         9           Site 13         71	
Site 13 71	
Site 14 70	1
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Site 15 13	
Site 16 37	

27 241 

# 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

# 244 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

~	abanges in decage of all modications. However, abanges were statistically similar, as
	changes in dosage of all medications. However, changes were statistically similar, so
b	both groups changed controller medications with similar frequency over the various tim
р	periods included in Table 3.
Т	Table 3. Changes in Asthma Medications Over Time (n (%)).
	PARTICS (n =
	Overall (n = 713) UCare (n = 350) 363)
	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%)
N	Modelling of Electronic Health Record Data
A	After models with the individual demographic variables were completed (model include
ir	in supplemental materials for reference), each model contained the assigned step each
n	month as the dependent variable and the month, the group (PARTICS or UCare), the
s	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
Т	The patients decade of birth and OOVID TO concellent contributed significantly to the
ir	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 th

differences between before and after Enrollment and to determine the effect of the

200						
266	intervention using prescribers' written prescriptions. The next two models detail the LME					
267	with Spline accounting for before Enrollment (Table 4) and after Enrollment (Table 5).					
268						
269	Model for Before Enro	llment (12 mont	hs prior throu	gh one month b	efore	
270	Enrollment; Table 4)					
271						
272	Table 4. Final Before E	Enrollment LME	Results.			
	Parameter	Estimate	Standard	95% CI	t	
			Error			
		-2 Restricted Lo	g Likelihood: 24	1603.78		
		Month: F(1, 568.	00) = 198.82; p	< 0.001		
		Group: F(1, 54	9.00) = 0.01; p	= 0.94		
		Site: F(14, 549	.00) = 8.47; p <	0.001		
	De	ecade of Birth: F(	4, 549.00) = 2.6	0; 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+	

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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		Refe	rence		

\* 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

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: $F(1, 9448.26) = 29.68$ ; $p < 0.001$		Enrollment took place e	ntirely before the			
279       assigned steps differed significantly between the sites.         280       Four sites (Sites 2, 3, 5, 7) had significantly higher steps of asthma controller         281       Four sites (Sites 2, 3, 5, 7) had significantly higher steps of asthma controller         282       medications compared with patients from Site 16 (reference site). One site (Site 15) had         283       significantly lower steps of asthma controller medications than patients from Site 16.         284       The assigned steps differed significantly with the patients' decade of birth. Patients bor         285       in the 1940s/1950s had significantly higher levels of asthma controller medications that         286       patients born in the 1990s/2000s (Table 4).         287       Model After Enrollment (one month after through the 15 months after Enrollment         289       Table 5.         290       Table 5. Final After Enrollment LME Results.         291       Table 5. Final After Enrollment LME Results.         292       -2 Restricted Log Likelihood: 33387.07         293       Month: F(1, 684.72) = 24.59; p < 0.001	70			start of the CO	VID-19 pandemi	c.) The
280         281       Four sites (Sites 2, 3, 5, 7) had significantly higher steps of asthma controller         282       medications compared with patients from Site 16 (reference site). One site (Site 15) had         283       significantly lower steps of asthma controller medications than patients from Site 16.         284       The assigned steps differed significantly with the patients' decade of birth. Patients bor         285       in the 1940s/1950s had significantly higher levels of asthma controller medications that         286 <b>Model After Enrollment (one month after through the 15 months after Enrollment</b> 287 <b>Table 5. Final After Enrollment LME Results.</b> 288 <b>Parameter</b> Estimate         290 <b>Table 5. Final After Enrollment LME Results.</b> 291 <b>Table 5. Final After Enrollment LME Results.</b> 292 <b>Table 5. Final After Enrollment LME Results.</b> 293 <b>Table 5. Final After Enrollment LME Results.</b> 294 <b>Covertion:</b> F(1, 681.72) = 24.59; p < 0.001	.79	assigned steps differed	significantly betw	veen the sites.		
282       redications compared with patients from Site 16 (reference site). One site (Site 15) has significantly lower steps of asthma controller medications than patients from Site 16.         283       significantly lower steps of asthma controller medications than patients from Site 16.         284       The assigned steps differed significantly with the patients' decade of birth. Patients bor         285       in the 1940s/1950s had significantly higher levels of asthma controller medications tha         286       patients born in the 1990s/2000s (Table 4).         287       288         288       Model After Enrollment (one month after through the 15 months after Enrollment         289       Table 5. Final After Enrollment LME Results.         290       291         291       Table 5. Final After Enrollment LME Results.         292       -2 Restricted Log Likelihood: 33387.07         293       -2 Restricted Log Likelihood: 33387.07         294       Month: F(1, 684.72) = 24.59; p < 0.001	80					
282       medications compared with patients from Site 16 (reference site). One site (Site 15) has significantly lower steps of asthma controller medications than patients from Site 16.         283       Significantly lower steps of asthma controller medications than patients from Site 16.         284       The assigned steps differed significantly with the patients' decade of birth. Patients bor         285       in the 1940s/1950s had significantly higher levels of asthma controller medications that         286 <b>Model After Enrollment (one month after through the 15 months after Enrollment</b> 287 <b>Table 5. Final After Enrollment LME Results.</b> 290 <b>Table 5. Final After Enrollment LME Results.</b> 291 <b>Table 5. Final After Enrollment LME Results.</b> 292 <b>Context</b> 293 <b>Context</b> 294 <b>Context</b> 295 <b>Context</b> 296 <b>Context</b> 297 <b>Context</b> 298 <b>Context</b> 299 <b>Context</b> 290 <b>Context</b> 291 <b>Context</b> 292 <b>Context</b> 293 <b>Context</b> 294 <b>Context</b> 295 <b>Context</b> 296 <b>Context</b>	281	Four sites (Sites 2, 3, 5,	7) had significar	ntly higher steps	of asthma contr	oller
283       significantly lower steps of asthma controller medications than patients from Site 16.         284       The assigned steps differed significantly with the patients' decade of birth. Patients bor         285       in the 1940s/1950s had significantly higher levels of asthma controller medications that         286       patients born in the 1990s/2000s (Table 4).         287       Model After Enrollment (one month after through the 15 months after Enrollment         288       Table 5)         290       Table 5. Final After Enrollment LME Results.         Parameter       Estimate       Standard       95% Cl       t         -2 Restricted Log Likelihood: 33387.07       Month: F(1, 684.72) = 24.59; p < 0.001	282	medications compared	with patients from	n Site 16 (refere	nce site). One si	te (Site 15) had
285       in the 1940s/1950s had significantly higher levels of asthma controller medications that         286       patients born in the 1990s/2000s (Table 4).         287       Model After Enrollment (one month after through the 15 months after Enrollment         288       Model After Enrollment (one month after through the 15 months after Enrollment         289       Table 5)         290       291         291       Table 5. Final After Enrollment LME Results.         Parameter       Estimate         28       Error         -2 Restricted Log Likelihood: 33387.07         Month: F(1, 684.72) = 24.59; p < 0.001	283	significantly lower steps	of asthma contro	oller medications	s than patients fr	om Site 16.
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 95% Cl t Fror -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	284	The assigned steps diffe	ered significantly	with the patients	s' decade of birth	n. Patients born
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Z89       Table 5)         290       291         Table 5. Final After Enrollment LME Results.         Parameter       Estimate       Standard       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: $F(1, 9448.26) = 29.68; p < 0.001$		Model After Enrollmen	it (one month af	ter through the	15 months after	er Enrollment:
290         Table 5. Final After Enrollment LME Results.         Parameter       Estimate       Standard       95% CI       t         -2 Restricted Log Likelihood: $33387.07$ -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: $F(1, 9448.26) = 29.68; p < 0.001$						,
Table 5. Final After Enrollment LME Results.         Parameter       Estimate       Standard       95% CI       t         -2 Restricted Log Likelihood:       3387.07         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: $F(1, 9448.26) = 29.68; p < 0.001$						
Parameter         Estimate         Standard         95% CI         t $Error$ $Error$ -2 Restricted Log Likelihood: 33387.07           Month: F(1, 684.72) = 24.59; p < 0.001		Table 5. Final After Fr				
Parameter       Estimate       Standard       95% CI       t         Error       -2 Restricted Log Likelihood: $33387.07$ -2 Restricted Log Likelihood: $33387.07$ Month: F(1, 684.72) = 24.59; p < 0.001	91	Table 5. Final After En	roliment LWE R	esults.		
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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: $F(1, 9448.26) = 29.68$ ; $p < 0.001$			-2 Restricted Lo	g Likelihood: 33	3387.07	
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			Month: F(1, 684	72) = 24.59; p ·	< 0.001	
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	44					
Decade of Birth: F(4, 631.09) = 3.83; p = 0.004 COVID Correction: F(1, 9448.26) = 29.68; p < 0.001			8.60) = 9.91; p <	0.001		
COVID Correction: F(1, 9448.26) = 29.68; p < 0.001		Decade of Birth: F(4, 631.09) = 3.83; p = 0.004				
Intercent (Baseline) 2.04 0.29 [1.48.2.60] 7.16*			D Correction: F(1	l, 9448.26) = 29	.68; p < 0.001	
		COVI				
50 51 52 53 54		81 82 83 84 85 86 87 88 88 89 90	<ul> <li>Four sites (Sites 2, 3, 5, medications compared visions is significantly lower steps difference in the 1940s/1950s had patients born in the 199</li> <li>Model After Enrollment Table 5)</li> <li>Table 5. Final After Enrol</li> </ul>	<ul> <li>Four sites (Sites 2, 3, 5, 7) had significant medications compared with patients from significantly lower steps of asthma control The assigned steps differed significantly in the 1940s/1950s had significantly high patients born in the 1990s/2000s (Table patients born in the 1990s/2000s (Table Model After Enrollment (one month af Table 5)</li> <li>Table 5. Final After Enrollment LME R</li> <li>Parameter Estimate</li> <li>-2 Restricted Low Month: F(1, 684 Group: F(1, 63) Site: F(15, 633)</li> </ul>	81Four sites (Sites 2, 3, 5, 7) had significantly higher steps82medications compared with patients from Site 16 (refere83significantly lower steps of asthma controller medications84The assigned steps differed significantly with the patient85in the 1940s/1950s had significantly higher levels of asth86patients born in the 1990s/2000s (Table 4).87Model After Enrollment (one month after through the89Table 5)909191Table 5. Final After Enrollment LME Results.92Parameter93Estimate94Standard94Enror95-2 Restricted Log Likelihood: 3396Month: F(1, 684.72) = 24.59; p97Group: F(1, 631.01) = 4.72; p98Site: F(15, 633.60) = 9.91; p	Four sites (Sites 2, 3, 5, 7) had significantly higher steps of asthma contr medications compared with patients from Site 16 (reference site). One si significantly lower steps of asthma controller medications than patients fr The assigned steps differed significantly with the patients' decade of birth in the 1940s/1950s had significantly higher levels of asthma controller me patients born in the 1990s/2000s (Table 4). Model After Enrollment (one month after through the 15 months after Table 5) Table 5. Final After Enrollment LME Results. Parameter Estimate Standard 95% CI Error -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

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Month	-0.05	0.01	[-0.06, -0.03]	-4.95*	
UCare	0.20	0.09	[0.02, 0.39]	2.17*	
PARTICS		Ref	erence		
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	

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42 43	30
44 45	30
46 47 48	30
48 49 50	30
51 52	31
53 54	31
55 56	
57 58	
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	Born: 1990s & 2000s		Refe	erence	
	No COVID-19	0.38	0.07	[0.24, 0.51]	5.45*
	COVID-19 Present Reference				
2	* p-value < 0.05				
3					
1	The UCare patients were	e at a significan	tly higher asthm	na controller medi	cation step
5	overall than the PARTIC	S patients acro	ss all time perio	ds for the time af	er Enrollment.
5	However, the months aft	er Enrollment c	lid show a signit	ficant decrease in	controller
7	intensity over time for bo	th groups, whic	h could be due	to the COVID-19	pandemic.
3	When compared to the N	lodel Before E	nrollment, the di	fference between	the UCare and
9	PARTICS patients with the	ne changes ove	er time indicate	that the PARTICS	patients had
)	significantly greater decr	ease in the inte	ensity of their co	ntroller therapy co	ompared to
1	UCare patients (Tables 4	and 5).			
2					
3	The assigned steps diffe	red significantly	y between the s	ites. Seven sites (	Sites 2, 3, 4, 5,
1	7, 11, 14) had significantly higher steps of asthma controller medications than patients				
5	from Site 16 (reference site). One site (Site 15) had significantly lower steps of asthma				
5	controller medications than patients from Site 16. The assigned steps differed				
7	significantly with the patients' decade of birth. Patients born in the 1940s/1950s had				
3	significantly higher levels of asthma controller medications than patients born in the				
Э	1990s/2000s. Lastly, in the months when COVID-19 was not present (before April				
D	2020), both groups of pa	tients had a sig	nificantly highe	r asthma controlle	er medication
-	level than after the COVI	D-19 pandemic	c began (Table 🤅	5).	

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2 3 4	312	
5 6	313	DISCUSSION
7 8 9 10 11 12 13	314	This study shows, through prescribers' written prescriptions, there was a greater
	315	decrease in asthma controller medication level over time (after Enrollment) in the
	316	PARTICS patients compared with the UCare patients with both groups starting at the
14 15	317	same asthma controller medication level. The decrease in intensity reduces, to some
16 17 18	318	degree, the expected increase in total ICS exposure that would result from adopting the
19 20	319	PARTICS strategy. The results in this sub-study complement and confirm the results in
21 22	320	the main effects paper that that shows that self-reported ICS-containing controller refills
23 24 25	321	were lower for participants assigned to PARTICS vs usual care. <sup>30</sup> Between this sub-
23 26 27 28 29 30 31 32	322	study and the main effects paper, the participants' reported and prescribers' EHR data
	323	indicate decreased asthma controller medication use over time for the PARTICS
	324	patients compared with the UCare patients, even with correcting for COVID-19. When
33 34	325	combined with the patient self-reported levels of controller ICS use and rescue ICS
35 36	326	fulfillment data from the main effects paper, this sub-study supports that PARTICS
37 38 39	327	improves outcomes at the population level, as the intensity of ICS controller therapy
40 41	328	dropped as well as self-reported controller ICS use. Treating clinicians were free to
42 43	329	adjust asthma medications as deemed necessary during the study. Primary asthma
44 45	330	treating clinicians were not provided the monthly Asthma Control Test scores that were
46 47 48	331	collected for research purposes, but patients may have been more aware of their
49 50	332	asthma symptoms through repeated completion of this instrument. For many patients
51 52	333	the primary asthma treating clinician was not the research prescribing clinician, but the
53 54 55	334	treating clinician would have been aware of the study medication. While it is not
56 57		

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and

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,<sup>30</sup> though total ICS use considering both controller and rescue use likely increased to some degree.

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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.<sup>36</sup> 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.<sup>36</sup> 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,<sup>31</sup> clinicians' prescribing patterns, organizational policies, or environmental factors. Though all clinicians providing asthma care for PREPARE participants completed the Asthma IQ program<sup>37</sup> 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.

2 3 4	380	
5 6 7	381	Acknowledgements: We would like to acknowledge all study participants for their time
8 9	382	and dedication. We would also like to acknowledge the PREPARE Operations Team
10 11 12	383	and Nancy Maher. We would also like to acknowledge the PREPARE site principal
13 14	384	investigators.
15 16 17	385	
17 18 19	386	Availability of Data: Data available upon reasonable request to the corresponding
20 21	387	author.
22 23 24	388	
25 26	389	Patient and Public Involvement: Patients and the public were not involved in the
20 27 28	390	design, conduct, reporting, and dissemination of this secondary data analysis.
29 30	391	
31 32 33	392	Financial Support: Supported by a PCORI Award (PCS-1504-30283, to Dr. Israel), the
34 35	393	Gloria M. and Anthony C. Simboli Distinguished Chair in Asthma Research award (to
36 37	394	Dr. Israel), and by grants from the National Institute of Allergy and Infectious Diseases
38 39 40	395	(K23AI125785, to Dr. Cardet) and the American Lung Association–American Academy
40 41 42	396	of Allergy, Asthma, and Immunology (AI-835475, to Dr. Cardet). QVAR and QVAR
43 44	397	RediHaler inhalers were provided free of charge and funding for the AssistRx pharmacy
45 46 47	398	was provided by Teva Pharmaceuticals. NIOX VERO devices for measuring exhaled
47 48 49	399	nitric oxide were provided free of charge by Circassia Pharmaceuticals.
50 51	400	
52 53 54 55 56 57 57	401	Conflicts of Interest:
58 59 60		23 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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1 2		
2 3 4	402	Elisabeth Callen: Dr. Callen receives support for other work (paid directly to her
5 6	403	institution) from Otsuka Pharmaceuticals, NIH, PCORI, HRSA, United Health
7 8	404	Foundation, SAMHSA, Merck, Eli Lilly, CDC, and Takeda.
9 10 11	405	Elliot Israel: Dr. Israel receives support for other work (paid directly to his institution)
12 13	406	from AstraZeneca, Avillion Mandala/Denali, Circassia, Gossamer Bio, NIH, Novartis,
14 15	407	and PCORI; he receives consulting fees from Allergy and Asthma Network, Amgen,
16 17 18	408	AstraZeneca, Avillion, GlaxoSmithKline, Merck, NHLBI, Novartis, Pneuma Respiratory,
19 20	409	Regeneron, Sanofi Genzyme, TEVA, and Cowen; he receives royalties from UpToDate
21 22	410	- Wolters Kluwer; he has been paid honoraria from TEVA, Cowen, and Westchester
23 24	411	Medical Center; he has been paid for expert testimony by Cambridge Medical Experts,
25 26 27	412	Danaher Lagnese, and SettlePou; he has been paid for Participation on a Data Safety
28 29	413	Monitoring Board or Advisory Board by Novartis; he is a member of the coordinating
30 31	414	committed for National Asthma Education Prevention Program and he is on the editorial
32 33 34	415	board for the Journal of Allery and Clinical Immunology and the Journal of Allergy &
35 36	416	Clinical Immunology, in Practice; he owns stock in Nesos Corp; and he has received a
37 38	417	study drug for an unrelated study from Genentech, Sun Pharmaceuticals, Laurel
39 40	418	Pharmaceuticals, Om Pharmaceuticals, Nestle, CSL Behring, Glaxo, and Sanofi
41 42 43	419	Regeneron.
44 45	420	Juan Carlos Cardet: Dr Cardet reports receiving honoraria from AstraZeneca, Chiesi,
46 47	421	GSK, Genentech, and Sanofi for work on advisory boards and delivering lectures on
48 49	422	asthma pathobiology and management.
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and

**Anne Fuhlbrigge:** Dr Fuhlbrigge an unpaid consultant to Teva, AstraZeneca and Novartis pharmaceuticals for epidemiologic analyses related to asthma outcomes and a co-investigator for the PREPARE, funded through PCORI. Gabriela Gaona: declares no conflict of interest. **Wilson Pace:** Dr. Pace's organization has received funding via subcontracts from CDC, PCORI, NIH, Boehringer Ingelheim, ONC, Tabula Rasa Healthcare, and Astra-Zeneca; his organization received consulting fees for his work from Boehringer Ingelheim; his organization has received payment for expert testimony; he is on the Advisory Board (paid) for AT Still Research Foundation and an Advisory board and Executive Committee member (unpaid) for COPD Foundation 360 Network; he owns stock through trust in Johnson and Johnson, Eli Lilly, Novo-Nordisk, Pfizer, Novartis, Moderna, and Amgen; he received grant and writing support for an unrelated project from Boehringer Ingelheim; and is an unpaid members of Colorado Medicaid Provider Rate Review Committee. Brian Manning: declares no conflict of interest. Elizabeth Staton: declares no conflict of interest.

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3	1	Supplemental Materials
4	2	
5	3	Hierarchy of Controller Step Levels
6 7	4	
8	5	Step 2
9	6	<ul> <li>Low dose ICS</li> </ul>
10	7	Step 3
11	8	<ul> <li>Low dose ICS plus Leukotriene inhibitor</li> </ul>
12	9	<ul> <li>Medium dose ICS</li> </ul>
13	10	<ul> <li>Low dose ICS plus LABA OR LAMA</li> </ul>
14	11	○ High dose ICS
15	12	• Step 4
16	13	<ul> <li>Medium dose ICS plus Leukotriene inhibitor</li> </ul>
17	14	<ul> <li>Low dose ICS plus LABA OR LAMA plus Leukotriene inhibitor</li> </ul>
18	15	<ul> <li>Low dose ICS plus LABA AND LAMA</li> </ul>
19	16	<ul> <li>Low dose ICS plus LABA AND LAMA plus Leukotriene inhibitor</li> </ul>
20	17	<ul> <li>High dose ICS plus Leukotriene inhibitor</li> </ul>
21	18	<ul> <li>Medium dose ICS plus LABA OR LAMA</li> </ul>
22	19	<ul> <li>Medium dose ICS plus LABA OR LAMA plus Leukotriene inhibitor</li> </ul>
23	20	• Step 5
24	21	<ul> <li>Medium dose ICS plus LABA AND LAMA</li> </ul>
25	22	<ul> <li>Medium dose ICS plus LABA AND LAMA plus Leukotriene inhibitor</li> </ul>
26	23	<ul> <li>High dose ICS plus LABA OR LAMA</li> </ul>
27 29	24	<ul> <li>High dose ICS plus LABA AND LAMA</li> </ul>
28	25	<ul> <li>High dose ICS plus LABA OR LAMA plus Leukotriene inhibitor</li> </ul>
29 30	26	<ul> <li>High dose ICS plus LABA AND LABA plus Leukotriene inhibitor</li> </ul>
30 31	20	<ul> <li>Step 6</li> </ul>
32	28	
33	20	
34	30	<ul> <li>Daily Corticosteroids</li> </ul>
35	31	Overall Model for All 28 Months (Supplemental Table 1; no corrections applied; no spline)
36	32	
37	33	The month before or after enrollment did show a significant increase over time (estimate: 0.039;
38	34	t = 9.315). The UCare patients were at a significantly higher asthma controller medication level
39	35	overall (difference: 0.191; t = 2.327). The assigned reclassified levels differed significantly
40	36	between the sites (F(15, 692.810) = $19.968$ ; p = $0.000$ ). Five sites (Sites 2, 3, 4, 5, 7) had
41	37	significantly higher steps of asthma controller medications than patients from Site 16. Two sites
42	38	(Sites 6, 15) had significantly lower steps of asthma controller medications than patients from
43	39	Site 16. The assigned reclassified levels differed significantly with the patients' decade of birth
44	40	(F(4, 692.014) = 5.135; p = 0.000). Patients born in the 1940s/1950s had significantly higher
45	41	levels of asthma controller medications than patients born in the 1990s/2000s (difference:
46	42	0.611; t = $3.803$ ). Lastly, in the months were COVID-19 was not present (before April 2020), the
47	43	patients had a significantly higher asthma controller medication level than after the COVID-19
48 40	44	pandemic began (difference: 0.902; t = 14.118; Supplemental Table 1).
49 50	45	pandemic began (difference: 0.902, t = 14.110, Supplemental Table 1).
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3.24\*

9.32\*

2.33\*

-1.27

3.80\*

6.49\*

3.49\*

5.24\*

-4.25\*

3.02\*

0.13

1.11

0.19

0.43

-0.58

-0.33

0.78

-4.05\*

3.80\*

1.29

1.54

1.80 +

14.19\*

Supplemental Table 1. Fin	1	<b>U</b>			
Parameter	Estimate	Standard Error	95% CI		
		og Likelihood: 736			
		0.37) = 86.77; p <			
		91.99) = 5.41; p =			
		.81) = 19.97; p <			
	ecade of Birth: F(4				
	D Correction: F(1, 0.78	0.24			
Intercept (Baseline) Month	0.78	0.24	[0.31, 1.25]		
UCare	0.04	0.00	[0.03, 0.05]		
PARTICS	0.19		[0.03, 0.35] rence		
Site 1	-0.44	0.34	[-1.11, 0.24]		
Site 1	1.14	0.34	[0.55, 1.73]		
Site 3	1.51	0.23	[1.05, 1.96]		
Site 3	0.91	0.26	[0.40, 1.42]		
Site 5	1.22	0.20	[0.76, 1.68]		
Site 6	-0.93	0.23	[-1.36, -0.50]		
Site 7	0.66	0.22	[0.23, 1.08]		
Site 8	0.04	0.33	[-0.61, 0.69]		
Site 9	0.27	0.24	[-0.21, 0.74]		
Site 10	0.05	0.23	[-0.41, 0.50]		
Site 11	0.11	0.25	[-0.38, 0.60]		
Site 12	-0.24	0.41	[-1.04, 0.57]		
Site 13	-0.07	0.23	[-0.51, 0.37]		
Site 14	0.17	0.23	[-0.27, 0.62]		
Site 15	-1.43	0.35	[-2.13, -0.74]		
Site 16			rence		
Born: 1940s & 1950s	0.61	0.16	[0.30, 0.93]		
Born: 1960s	0.21	0.16	[-0.11, 0.52]		
Born: 1970s	0.26	0.17	[-0.07, 0.58]		
Born: 1980s	0.31	0.17	[-0.03, 0.65]		
Born: 1990s & 2000s		Refei	rence		
No COVID-19	0.90	0.06	[0.78, 1.03]		
COVID-19 Present		Refei	rence		
* p-value < 0.05					

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4.26\*

2.30\*

1.35

1.11

4.79\*

5.08\*

2.26\*

3.82\*

-0.87

-0.08

-1.56

4.82\*

0.78

3.50\*

0.19

-1.38

6.34\*

-0.53

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2.97\*

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1.49

3.51\*

Supplemental Table 2. LM			1.07550.44	
All V	ariables (-2 Restri	•		
Month: F(1, 694.89) = 5.31; p = 0.02				
		(5.15) = 1.81; p =		
		l.21) = 18.76; p =		
	•	01.07) = 0.16; p =		
	ecade of Birth: F(4	•	•	
	Race/Ethnicity: F(	, , .	•	
COV	Language: F(1, 695.91) = 2.22; p = 0.14 COVID Correction: F(1, 12122.12) = 12.28; p = 0.			
Intercept (Baseline)	4.57	1.07	[2.46, 6.67]	
Month	0.03	0.01	[0.00, 0.05]	
UCare	0.41	0.30	[-0.19, 1.00]	
PARTICS	0.11	Refer		
Site 1	1.43	1.29	[-1.10, 3.96]	
Site 2	5.35	1.12	[3.16, 7.53]	
Site 3	4.43	0.87	[2.72, 6.15]	
Site 4	2.42	1.07	[0.32, 4.53]	
Site 5	3.71	0.97	[1.80, 5.61]	
Site 6	-0.74	0.85	[-2.41, 0.93]	
Site 7	-0.07	0.83	[-1.69, 1.55]	
Site 8	-1.88	1.21	[-4.24, 0.49]	
Site 9	4.93	1.02	[2.93, 6.94]	
Site 10	0.75	0.96	[-1.14, 2.65]	
Site 11	3.53	1.01	[1.55, 5.52]	
Site 12	0.30	1.55		
Site 13	-1.29	0.94	[-2.74, 3.33]	
Site 14			[-3.14, 0.55]	
Site 15	6.08 -0.75	0.96	[4.20, 7.96] [-3.56, 2.06]	
Site 16	-0.75	Refer		
Male	0.16	0.40		
	0.10		[-0.63, 0.95]	
Female Born: 1940s & 1950s	1.77	Refer		
	0.40	0.60 0.59	[0.60, 2.95] [-0.75, 1.56]	
Born: 1960s Born: 1970s			-	
Born: 1980s	0.60	0.61	[-0.61, 1.80]	
	0.20	0.63	[-1.04, 1.45]	
Born: 1990s & 2000s	-0.37	Refer 0.47		
Hispanic Nan Uianania	-0.37		[-1.29, 0.55]	
Non-Hispanic	0.00	Refer		
English	0.82	0.55	[-0.26, 1.89]	
Spanish	0.50	Refer		
No COVID-19	0.59	0.17	[0.26, 0.92]	
COVID-19 Present		Refer	ence	