

Journal Pre-proof

Adherence to Adding Inhaled Corticosteroids to Rescue Therapy in a Pragmatic Trial with Adults with Asthma– a Pilot Study

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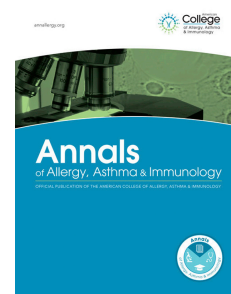
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1. Inhaled corticosteroids
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5. Asthma treatment guidelines
6. Effectiveness research

Abbreviations: **ACT:** Asthma Control Test®; **ICS:** inhaled corticosteroids; **LABA:** long-acting beta-agonist; **PARTICS:** Patient-Activated Reliever-Triggered ICS; **PEERS:** Patient Engaged Electronic Reporting System; **PREPARE:** PeRson EmPowered Asthma RELief pragmatic trial; **PCORI:** Patient-Centered Outcomes Research Institute; **SABA:** short-acting beta-agonist

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Abstract

Background:

Underuse of guideline-recommended inhaled corticosteroids (ICS) controller therapy is a risk factor for greater asthma burden. ICS concomitantly-used with rescue inhalers [Patient-Activated Reliever-Triggered ICS ('PARTICS')] reduced asthma exacerbations in efficacy trials, but whether PARTICS is effective in pragmatic trials is unknown.

Objective:

We conducted this pilot to determine the feasibility of executing a large-scale pragmatic PARTICS trial and to improve study protocols.

Methods:

Four sites recruited 33 Hispanic or Black persistently asthmatic adults, randomized them ~3:1 to intervention or usual care, and followed them for 12 weeks. All participants received asthma guideline-based educational videos; intervention participants received video-based instructions on implementing PARTICS plus usual medications. The study involved one randomization visit and monthly questionnaires. Timely questionnaire responses (+/-2 weeks) were monitored. Participants underwent qualitative phone interviews to assess self-reported adherence to PARTICS and understand barriers to completing study procedures.

Results:

Timely questionnaire response rates were 61%, 64%, 70% at 4, 8 and 12 weeks, respectively. Self-reported adherence to PARTICS was 76% [95%CI 58-94%(n=21)], 88% [95%CI 72-100%(n=16)], and 62% [95%CI 36-88%(n=13)] at weeks 1, 6, and 12, respectively. Barriers to completing study procedures included difficulties with questionnaire access, remembering to use ICS and rescue inhalers together, and obtaining refills. Only 22% of participants recognized their short-acting bronchodilator as "reliever" or "rescue".

Conclusion:

Recruitment was feasible within the allocated period. Adherence to PARTICS was incomplete, questionnaire completion was suboptimal, and common rescue inhaler nomenclature usage was limited. We have modified the full study protocol to attempt to improve adherence to PARTICS and minimize barriers to study procedures.

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1 Introduction

2
3 The high burden of disease in asthma, with substantial morbidity, mortality¹ and societal
4 costs², is disproportionately prevalent in African-American and Hispanic populations³. Underuse
5 of guideline-recommended asthma controller therapy is a risk factor for worse disease
6 outcomes⁴. Although daily inhaled corticosteroids (**ICS**) are the pillars of controller therapy
7 guidelines,⁵ adherence to daily ICS is low—only 25-60% of prescribed doses are used^{6,7}. Low
8 adherence to daily ICS regimens may stem from their prescription for *daily* use vs. the *episodic*
9 nature of asthma symptoms. Patients tend not to use medicines unless symptom-motivated⁸. To
10 date, improving the adherence to daily ICS therapy without employing resource-intensive
11 interventions has been difficult⁹. However, one way to increase patients' ICS intake may be to
12 prescribe these for as-needed, symptom-triggered use.

13 Current guidelines also instruct patients to use inhaled short-acting beta-agonist
14 bronchodilators (**SABA**; i.e. rescue inhalers, e.g. albuterol) as-needed for asthma symptom
15 worsening. As-needed ICS use is not currently supported by US healthcare delivery systems
16 despite robust evidence demonstrating reductions in asthma morbidity when used in combination
17 with long-acting beta-agonist (**LABA**) bronchodilators (i.e. "SMART" therapy—"Single
18 (inhaler) Maintenance And Reliever Therapy", which is the use of the inhaled corticosteroid
19 budesonide combined in a single inhaler with the long-acting, quick-onset beta-agonist
20 formoterol as both controller and rescue therapy)¹⁰. Further, among patients with mild persistent
21 asthma, ICS and SABA combined in a single inhaler and used as needed for rescue therapy
22 (without regular controller therapy) showed equal asthma exacerbation rates as guideline-driven
23 and enforced regular ICS controller therapy plus as needed SABA¹¹. Finally, using ICS
24 concomitantly with rescue SABA (Patient-Activated Reliever-Triggered ICS; a '**PARTICS**'

strategy) reduced asthma exacerbations nearly by 50% (but not statistically significantly) compared with guideline-driven care in an efficacy trial¹². However, efficacy trials allow for substantial researcher oversight, leading to greater than normal adherence rates to guideline-driven regimens (>90%). Further, efficacy trial participants represent <5% of asthmatic patients¹³. These features limit the external validity of efficacy trial findings.

Conversely, pragmatic trials are designed for study result generalizability and implementation¹⁴. Pragmatic trials allow less researcher oversight over study processes meant to improve adherence. It is unknown whether PARTICS is effective in pragmatic trials mimicking real-world conditions. Additionally, a PARTICS strategy has not been tested in highly-impacted minority asthmatic populations, which are commonly underrepresented in efficacy trials¹⁵. The Patient-Centered Outcomes Research Institute (**PCORI**)-funded PeRson EmPowered Asthma RElief (**PREPARE**) pragmatic trial will address whether PARTICS can improve asthma outcomes relative to guideline-driven standard of care in African-American and Hispanic participants with asthma. This large-scale multi-centered study entails study processes including participant education, communication with participants and their clinicians, drug delivery, and outcome ascertainment (see ‘Methods’ section below). Many of these processes had not been previously tested in other trials. Therefore, we proposed—and PCORI supported—conducting a pilot study to determine our pragmatic trial’s feasibility, and to use these results to improve its protocol.

Methods

Between February and July 2017, four community clinical sites recruited 33 African-American and Hispanic patients with persistent asthma aged 18-75 years who were currently prescribed ICS controller therapy (with or without other controller therapies, e.g. LABA). These

sites represent others in the currently ongoing full PREPARE study in terms of geography, health system and practice size diversity. Eligible participants either had to be prescribed ICS/LABA, or ICS alone and have uncontrolled asthma (Asthma Control Test (**ACT**®) score<20) or 1+ asthma exacerbations in the year prior to enrollment. Participants were then randomized 3:1 to the PARTICS intervention or ‘enhanced usual care’ and followed for 12 weeks (**Figure 1**). Participants randomized to the PARTICS intervention were provided with QVAR® (beclomethasone dipropionate HFA, 80 microgram/puff) inhalers and shown how to request QVAR® refills by phone at any point during the study. These participants were instructed to use one puff of QVAR® for every one puff of rescue inhaler used as needed, and 5 puffs of QVAR® for every one rescue nebulization used as needed—which is the PARTICS strategy. We did not specify a maximum number of QVAR® puffs they could use, but reviewed the signs and symptoms of asthma exacerbations and explained what to do and how to seek medical care to treat such events. Participants assigned to the PARTICS strategy were asked to continue their regular controller therapy, which required either ICS or ICS/LABA use, but may have also included other regular controller therapy drugs such as leukotriene receptor antagonists or long-acting muscarinic antagonists, among others. All participants were instructed to adhere to any changes in controller therapy that their clinician prescribed throughout the course of the study. Clinicians managing these participants’ care in the community were asked to complete the American Academy of Allergy, Asthma and Immunology Asthma IQ® education program for Continued Medical Education credit to standardize and enhance ‘usual care’ to guideline-recommended care prior to enrolling participants. Two Spanish-only speaking participants were directly enrolled into the intervention arm to test the Spanish language version of our study materials (**Figure 2**).

All participants received guideline-based educational videos on recognizing and treating asthma symptoms (all materials were available in English and Spanish). An introductory video prior to randomization explained the study question, design, interventions, and on recognizing and treating asthma symptoms. One segment of this video is based on an American Lung Association video that describes features of asthma as a disease, and also delves into the definition of ‘rescue’ and ‘controller’ therapy for asthma, emphasizing the need for controller therapy to be used daily as prescribed by clinicians. Additional pre-randomization videos show patients demonstrating how to use MDI and diskus inhalers (these introductory videos can be found at https://www.youtube.com/channel/UC1A_Gak_r5XZ6tx_olcIgsQ). After randomization to either the PARTICS or enhanced usual care groups, all participants also received an inhaler storage pouch to increase adherence to asthma medications in both trial arms (**Supplementary Figure 1**). Both groups viewed videos instructing them to carry their study pouch with their inhalers with them at all times. Each group was shown a video either on how to implement PARTICS in addition to usual controller medications, or how to continue using their controller therapy as prescribed. A patient advisory committee reviewed all materials administered to participants and the study design itself to ensure patient-centeredness.

The study involved a single visit during which patients consented to participation, completed baseline questionnaires (see online repository), followed by randomization using the Patient Engaged Electronic Reporting System (**PEERS**) system®, a HIPAA-compliant electronic participant data capturing system. Monthly questionnaires were administered through computers, tablets, or smart phone using PEERS®, as well as mail, or telephone, based on participants’ preference. Participants were compensated for attending their study visit (\$50) and for completing monthly questionnaires (\$20) using a ‘P’ (debit) card. Timely questionnaire

96 responses (due date +/-2 weeks) were monitored. Participants underwent qualitative phone
97 interviews at 1, 6 and 12 weeks post-enrollment to ask about their experiences with the consent,
98 randomization, and data collection processes, understanding of study procedures and
99 expectations, understanding of PARTICS (intervention participants), and suggestions for
100 improvement. Self-reported adherence to PARTICS was defined by answering affirmatively to
101 the question “Are you using ICS and rescue inhalers together?” during qualitative phone
102 interviews. All study sites obtained central IRB approval (through Partners Human Research
103 Committee). Written informed consent was obtained from all patients prior to participation in
104 this study. No formal statistical tests were performed due to the pilot’s small sample size.
105

Results

The key findings of this study were that participant recruitment was feasible in the allotted 12-week timeframe, that questionnaire completion was suboptimal, that adherence to PARTICS was incomplete, and that several barriers hindered completion of study procedures, as elaborated below.

Participant recruitment

We recruited comparable proportions of African-American and Hispanic participants into both treatment arms as planned, completing the study in the allocated 6-month time period. Overall, participants were mostly female, >40 years old, obese (mean BMI >30), and had uncontrolled asthma (mean ACT® score <20), requiring a median >14 rescue puffs/month (**Table 1**).

Assessing questionnaire data acquisition

Timely questionnaire responses among all participants (n=33) were 61% (95% CI 44%-78%), 64% (95% CI 48%-80%), 71% (95% CI 54%-86%) at weeks 4, 8, and 12, respectively (**Table 2**). Timely questionnaire responses may have varied more for participants assigned to 'enhanced usual care' (between 22%--78%) compared with participants assigned to PARTICS (between 63%--75%). Among all participants, the percent of questionnaires not completed were 39%, 36%, 30% at 4, 8, and 12 weeks, respectively; 24% of all participants did not complete >1 questionnaire. Importantly, 78% of participants assigned to enhanced usual care did not complete their week 4 questionnaire.

Evaluating adherence

In phone interview, participants' report of adherence to PARTICS was 76% [95% CI 58-94% (n=21)], 88% [95% CI 72-100% (n=16)], and 62% [95% CI 36-88% (n=13)] at weeks 1, 6, and 12, respectively (**Figure 3**). Although some use of ICS with rescue SABA was self-reported in all, not all participants used both inhalers in ~1:1 ratio as instructed.

Qualitative findings: participants' experiences in the study and suggestions for improvement

Overall, participants commented favorably and expressed satisfaction with study recruitment procedures, the informed consent process, study videos, and the enrollment/baseline data collection process. Participants reported having difficulty with log-in access to electronic questionnaires (22% of interviewees), infrequent use of the terms "rescue" and "maintenance" to describe inhalers (22% of PARTICS-assigned interviewees), remembering to use ICS and rescue inhalers together (20% of PARTICS-assigned interviewees), and obtaining ICS refills (19% of PARTICS-assigned interviewees).

Based on these data, we addressed the key issues identified during our pilot study and modified the full protocol as described below and in **Table 3**.

Protocol changes to improve adherence

Our strategies to improve adherence to PARTICS were aimed either at participants or their clinicians. Those aimed at participants included PREPARE trial stickers reminding them of the PARTICS strategy, placed in their medication pouch and in the Velcro joining their ICS inhaler with their rescue inhaler; reminder messages sent through the PEERS® system: (1) a message window that appears with monthly survey completion, (2) quarterly text messages sent

to participants' smart phones; and scheduled phone calls one month after study enrollment with a scripted message for study coordinators. Strategies aimed at their clinicians included having PARTICS appear as a 'research prescription' in the participants' electronic medical record and sending letters to clinicians reinforcing the PREPARE trial and the PARTICS concept and reminding clinicians of their patient's enrollment in the study.

We also determined from qualitative interviews that some participants began using <1:1 ratio of ICS:rescue inhalers. To address this issue, educational videos were edited to better communicate the 1:1 concept. Study coordinators are now also instructed to ask enrollees for a 'teach-back' of the PARTICS method.

Protocol changes to facilitate timely and complete questionnaire data acquisition

The PREPARE trial's primary outcome will be number of asthma exacerbations treated with systemic corticosteroids (3+ days of oral, or 1+ days of intravenous or intramuscular, corticosteroids administered by a clinician for the treatment of asthma) ascertained by monthly questionnaires. The trial's success thus depends on our ability for questionnaire data acquisition. However, we found that roughly one third of all monthly questionnaires were not completed; this rate was even greater for the week 4 questionnaire for the usual care group, where 78% of questionnaires were not completed. In order to maximize the likelihood of participants completing their monthly questionnaires in a timely fashion, we have created text reminders to be sent several days prior to the questionnaire due date. We also have scheduled a phone call one month after enrollment to confirm that our reminders are being received, and reinforce the importance of completing surveys. Finally, we have created a lottery system where participants who submit timely questionnaire responses enter to win a \$100 prize. Since we found during

qualitative interviews that log-in access to electronic questionnaires was difficult for some, we now have allowed participants an opt-in option to 1-click access surveys. This option bypasses the log-in screen, but introduces the risk of losing participant data confidentiality by exposing their asthma diagnosis (otherwise not revealing any other protected health information).

Protocol changes to minimize barriers to study procedures

Through qualitative interviews, we identified that most participants found the initial visit to be too long. We determined that a protracted baseline visit could compromise participant recruitment during the study. Therefore, we decided simplify the questionnaire, considering that some questions were redundant with other data already being collected. Similarly, fewer than half of all participants correctly completed their medication log, and most found it tedious. Thus, we no longer ask participants to complete a medication log in the full study. We also appreciated from these interviews that many participants do not recognize the term ‘rescue’ inhaler. In response, we now record the name each participant uses for his/her rescue inhaler and use that personalized nomenclature in all questionnaire materials (a programmatic PEERS® feature).

Finally, we discovered that our screening algorithms based on our eligibility criteria permitted us to enroll a participant with COPD, despite COPD being exclusionary. We revised our protocol to exclude participants with lung diseases other than asthma, or asthmatic participants treated with biologics or systemic corticosteroids who are consequently less likely to respond to PARTICS.

Discussion

We performed this pilot study to determine the feasibility of a pragmatic trial testing a

PARTICS strategy across diverse clinical settings throughout the United States. Our results show that recruitment of our target population is achievable, and that the PEERS system® can facilitate the consenting process, baseline data collection, randomization, monthly questionnaire delivery and data collection, and reminder message distribution. Further, our results show that dissemination of a PARTICS strategy is possible but requires facilitation.

We found that study participants conceptually understood PARTICS (using ICS with as-needed rescue inhaler in response to asthma symptoms). However, self-reported adherence to PARTICS during the 12-week study period was incomplete, suggesting that additional reminders may be necessary to maintain adequate adherence levels to PARTICS. Consequently, we have implemented new methods to remind participants and their clinicians of the PARTICS strategy, including electronic messages, stickers, a coordinator call one month after enrollment, and electronic medical record and letter notifications to clinicians about their patient's enrollment in the full study. Our findings are limited by a small sample size and need to be corroborated in the large-scale full PREPARE study. We also identified several issues that prompted us to improve the messaging of our PARTICS strategy and our ability to collect monthly questionnaire data. One such issue was the difficulty some participants had with accessing the online questionnaires. In response we have allowed an opt-in option to 1-click access surveys, which as previously noted introduces the risk of loss of data confidentiality by exposing their asthma diagnosis (but otherwise not revealing any other protected health information). However, we worked with our center's privacy office to establish that participants opting for the 1-click access would not experience a significant privacy risk, particularly when doing so through a cellular phone. Based on this finding we therefore encouraged the full study cohort to enroll using cellular phones.

Our protocol modifications raise the question about pragmatism vs. efficacy in clinical

224 trials. But in consultation with pragmatic trial experts, we understand that our above-described
225 interventions are pragmatic because of their real-world feasibility, while adding rigor to our
226 study design. An important balance between rigor and pragmatism needs to be attained in
227 pragmatic trial design, because a lack of rigor will bias any study towards the null hypothesis
228 even if there is actually a benefit to be obtained from an intervention—a scenario which would
229 not yield valuable results. Conversely, as previously stated, pragmatic clinical trials can yield
230 more impactful results that better inform clinicians and patients about the effectiveness of an
231 intervention when used in real-world settings compared to the perhaps more rigorous but
232 contrived settings of efficacy trials. We believe that the protocol modifications suggested in this
233 manuscript have increased our ability to rigorously address the study question of the full
234 PREPARE protocol while maintaining a pragmatic design. Another reason we believe our study
235 design is consistent with real-world settings is that pharmaceutical companies are currently
236 developing ICS-SABA dual-drug inhalers—when available, these drugs will facilitate the real-
237 world delivery of both drugs simultaneously, simplifying ‘PARTICS’. We anticipate that
238 adherence to our PARTICS strategy is likely to be less adhered to than a similar strategy using a
239 single inhaler ICS/SABA combination. However, no ICS/SABA combination inhaler is currently
240 available in the US, and the FDA does not permit ICS/formoterol to be marketed for as needed
241 use. The full PREPARE study design attempts to encourage the simultaneous use of the two
242 different inhaler classes while using commercially-available formulations. Given that, an
243 important reason to have conducted this Vanguard pilot study was to document the degree of
244 adherence to PARTICS, which we expected and indeed found to be incomplete, and to
245 understand the barriers inherent in our pragmatic study design that led to incomplete adherence.
246 We have thus presented lessons learned from this pilot that could be useful to other asthma

investigators in trying to maximize adherence to approaches analogous to PARTICS in the setting of a pragmatic trial design.

There are a few important distinctions between our PARTICS approach and those approaches used in prior studies with single inhaler combination ICS/SABA¹¹ or ICS/formoterol used as needed for rescue^{10, 16, 17}. We have recruited participants with persistent asthma but of varied asthma severity (mild, moderate, and severe persistent asthma) and thus varied and complex controller therapy regimens. In contrast to other studies, ours did not ask participants to replace their baseline controller therapy regimens with PARTICS. Our study asked these participants to *supplement* their rescue therapy with as needed ICS (QVAR®), but to keep their controller therapy as prescribed by their clinicians—which could also change throughout the trial as directed by their clinician. We do not know whether PARTICS is superior, equivalent, or inferior to controller therapy plus as needed ICS/formoterol for rescue. However, we do know that our American healthcare system has been unable to incorporate the so-called SMART therapy approach of using ICS/formoterol inhalers as both controller and rescue therapy despite global asthma guidelines supporting it⁵. One potential reason for the inability of our healthcare system to incorporate this approach is concerns with excessive LABA use. Large, international ICS/LABA trials reassured us that twice daily use of ICS/LABA is safe compared to daily controller therapy with ICS alone^{18, 19}. However, these trials did not investigate the safety of ICS/LABA used as needed and thus potentially many more times per day than twice. Our PARTICS strategy may thus be more amenable to our American healthcare system to incorporate since it supplements rescue therapy with ICS—which we hypothesize will be effective in reducing asthma exacerbations—without incurring the potential concerns of excessive LABA use. Our study also has a distinct racial/ethnic composition relative to prior

studies in that we enrolled Hispanic and African-American patients, who bear a disproportionate burden of disease. This pilot study has improved the full PREPARE study to better address our hypothesis within our unique patient population.

Our results suggest that pilot studies can be very useful in identifying and correcting issues that could be detrimental to large-scale pragmatic trials in asthma. The methodological issues we identified included suboptimal questionnaire completion, incomplete adherence to the PARTICS intervention, and barriers to completion of study procedures. These barriers included difficulties with questionnaire access, remembering to use ICS and rescue inhalers together (PARTICS), obtaining refills, and with incorporating common rescue inhaler nomenclature. We modified the full PREPARE study protocol with the changes suggested in this manuscript. Pilot studies can incorporate and test strategies based on patient engagement and their real-world experiences.

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Tables

Table 1: Baseline characteristics by treatment assignment

CHARACTERISTIC	Enhanced usual care (n=9)	PARTICS (n=24)
Gender (proportion (%) women)	9/9 (100%)	16/24 (67%)
Age in years (mean (SD))	43.7 (13.6)	48.5 (12.1)
BMI in kg/m² (mean (SD))	34.3 (6.0)	33.4 (8.8)
Race/ethnicity (proportion (%))		
African American	5/9 (56%)	13/24 (54%)
Hispanic	4/9 (44%)	11/24 (46%)
Household income <\$35k (proportion (%))	5/9 (55%)	16/24 (67%)
Smoking status		
Non-smoker (proportion (%))	8/9 (89%)	17/24 (71%)
Former smoker (proportion (%))	0/9 (0%)	4/24 (17%)
Current smoker (proportion (%))	1/9 (11%)	3/24 (13%)
Clinical history (year prior to enrollment):		
ED/urgent care (1+, proportion (%))	3/9 (33%)	12/24 (50%)
Hospitalizations (1+, proportion (%))	2/9 (24%)	3/24 (12%)
Work or school days missed due to asthma (1+, proportion (%))	4/9 (44%)	9/24 (38%)
Asthma controller therapy (proportion (%))		
ICS only	1/9 (11%)	3/24 (13%)
ICS/LABA or ICS/LAMA	8/9 (89%)	21/24 (88%)
Diagnosed with asthma age < 22 years (proportion (%))	8/9 (88%)	15/24 (63%)
ACT score (median (25th, 75th pctl.))	19 (15, 20)	18 (15, 21)
Inhaler usage		
Total number of rescue puffs/month (median (25 th , 75 th pctl.))	14 (5, 45)	15 (3,40)
Always carry rescue inhaler (% yes)	7/9 (78%)	18/24 (75%)
Extra ICS with uncontrolled asthma (% yes)	3/9 (33%)	11/24 (46%)

Table 2: Timeliness of monthly questionnaire completion

Timing of questionnaire completion	Enhanced usual care (n=9)	PARTICS (n=24)
Month 1		
Within 7 days of the expected date	2/9 (22%)	12/24 (50%)
Within 15 days of the expected date	2/9 (22%)	18/24 (75%)
No completion	7/9 (78%)	6/24 (25%)
Month 2		
Within 7 days of the expected date	4/9 (44%)	8/24 (33%)
Within 15 days of the expected date	6/9 (67%)	15/24 (63%)
No completion	3/9 (33%)	9/24 (38%)
Month 3		
Within 7 days of the expected date	5/9 (56%)	12/24 (50%)
Within 15 days of the expected date	7/9 (78%)	16/24 (67%)
No completion	2/9 (22%)	8/24 (33%)

Table 3: Modifications to full study protocol based on pilot study results

Issue identified during pilot study	Modification to full study protocol
• Incomplete adherence to PARTICS	• Created notifications to both clinicians and participants about the PREPARE trial and about PARTICS • Added more PREPARE stickers to participant package
• Untimely questionnaire responses (15+ days late)	• Created reminders at days 26, 28, 30 • Scheduled 2 phone calls prior to day 35 • Scheduled phone call on day 27 to corroborate reminders are received • Started lottery system rewarding timely survey responses
• Participants infrequently use “rescue” or “maintenance” inhaler nomenclature	• Adopted participants’ own nomenclature for inhalers throughout questionnaires • Changed terms to “quick relief” and “daily medicine” in consent form • Modified instructional videos
• Low completion frequency of medicine log (<50%)	• Discontinued using medicine log
• Consent/enrollment process is too long	• Deleted unessential questions (ASK12)
• Difficulty accessing electronic questionnaire	• Allowed opt out option to 1-click access
• Idea of ICS with SABA is understood, but not 1:1 ratio	• Reinforced ratio in videos (1:1, 2:2, etc.) • Teach back with study coordinator • Labels in pouch indicate 1:1
• Enrolled participants with COPD	• Added eligibility criteria to exclude participants unlikely to benefit from PARTICS—those with COPD and other lung diseases; and those who regularly use biologics or systemic corticosteroids

Journal Pre-proof

Figures

Figure 1. Pilot study schema

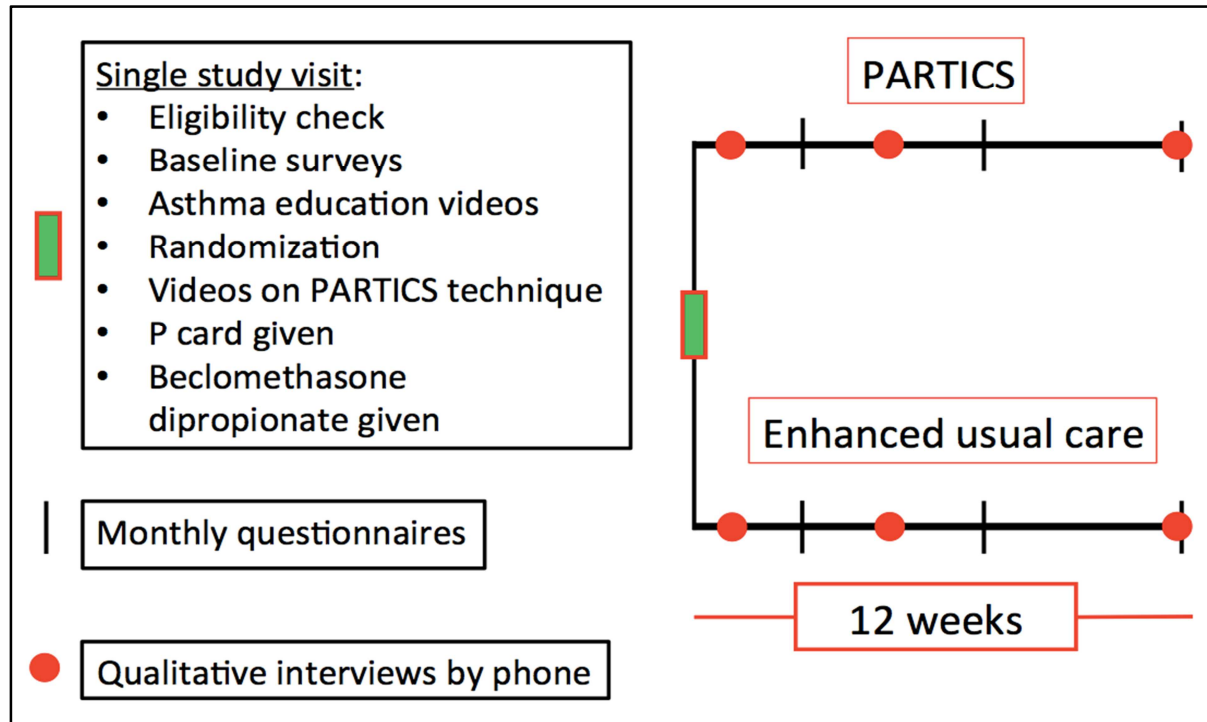


Figure 2. Pilot study CONSORT diagram

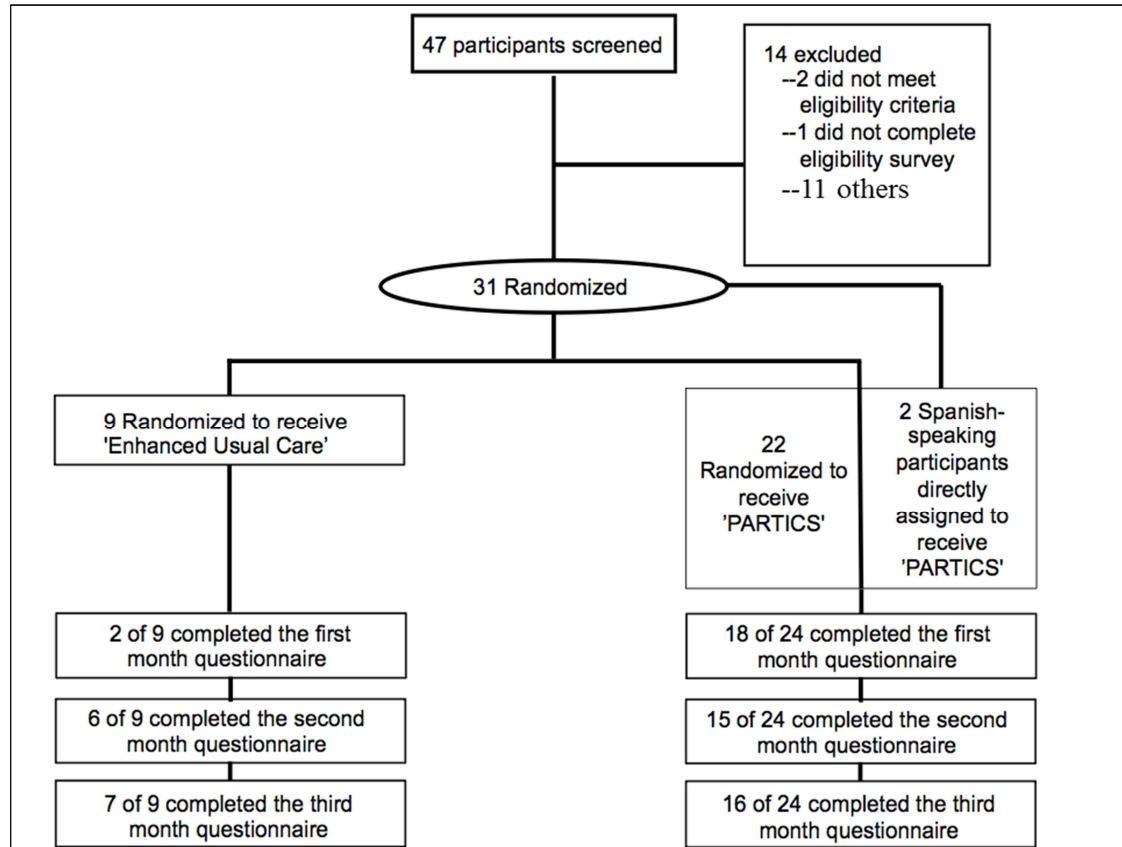


Figure 3: Self-reported adherence to PARTICS

