NIH Collaboratory Grand Rounds

Friday, June, 17, 2022

PREPARE – Person Empowered Asthma Relief

A Successful, Pragmatic, Primarily Remote Trial in Black and Latinx Population with Asthma: Challenges and Successes

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The NEW ENGLAND JOURNAL of MEDICINE

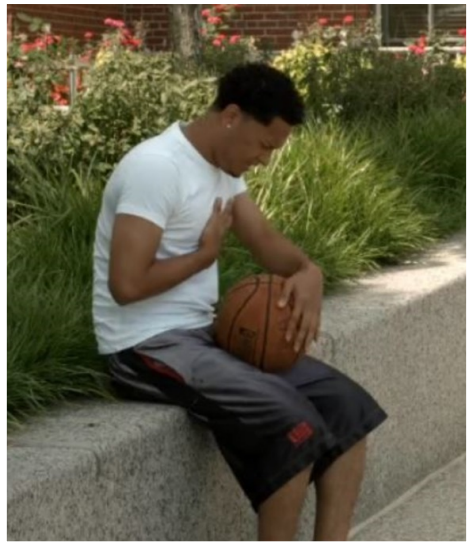
ORIGINAL ARTICLE

Reliever-Triggered Inhaled Glucocorticoid in Black and Latinx Adults with Asthma

E. Israel, J.-C. Cardet, J.K. Carroll, A.L. Fuhlbrigge, L. She, F.W. Rockhold, N.E. Maher, M. Fagan, V.E. Forth, B.P. Yawn, P. Arias Hernandez, J.M. Kruse, B.K. Manning, J. Rodriguez-Louis, J.B. Shields, B. Ericson, A.D. Colon-Moya, S. Madison, T. Coyne-Beasley, G.M. Hammer, B.M. Kaplan, C.S. Rand, J. Robles, O. Thompson, M.E. Wechsler, J.P. Wisnivesky, M.D. McKee, S.P. Jariwala, E. Jerschow, P.J. Busse, D.C. Kaelber, S. Nazario, M.L. Hernandez, A.J. Apter, K.-L. Chang, V. Pinto-Plata, P.M. Stranges, L.P. Hurley, J. Trevor, T.B. Casale, G. Chupp, I.L. Riley, K. Shenoy, M. Pasarica, R.A. Calderon-Candelario, H. Tapp, A. Baydur, and W.D. Pace

Israel et al. N Engl J Med. 2022 Apr 21;386(16):1505-1518

Burden of disease from asthma in Black and Latinx adults



- Black and Latinx patients bear disproportionate burden
  - >2x rates of ER visits and asthma-related deaths relative to Whites
  - Puerto Ricans have >4x asthma-related death rate relative to Whites

- Efforts to reduce this burden are expensive and mostly unsuccessful

https://minorityhealth.hhs.gov, Press et al. *J Gen Intern Med*. 2012

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As-needed inhaled corticosteroid strategies

- While inhaled corticosteroids (**ICS**) are the cornerstone of asthma controller therapy strategies, adherence to them is low (25%)
- Data show that as-needed ICS use guided by asthma symptom-triggered beta-agonist use can improve asthma outcomes
- Patient empowering
- Low burden on providers
- Feedback from patient partners

Apter JACI 2011; Williams JACI 2010; Boushey 2005, Papi 2007, Calhoun 2012 NHLBI Expert Panel Review 4, 2020;

Reduced Rates of Exacerbation and Other Pt-Centered Outcomes with PARTICS as c/w Enforced NAEPP

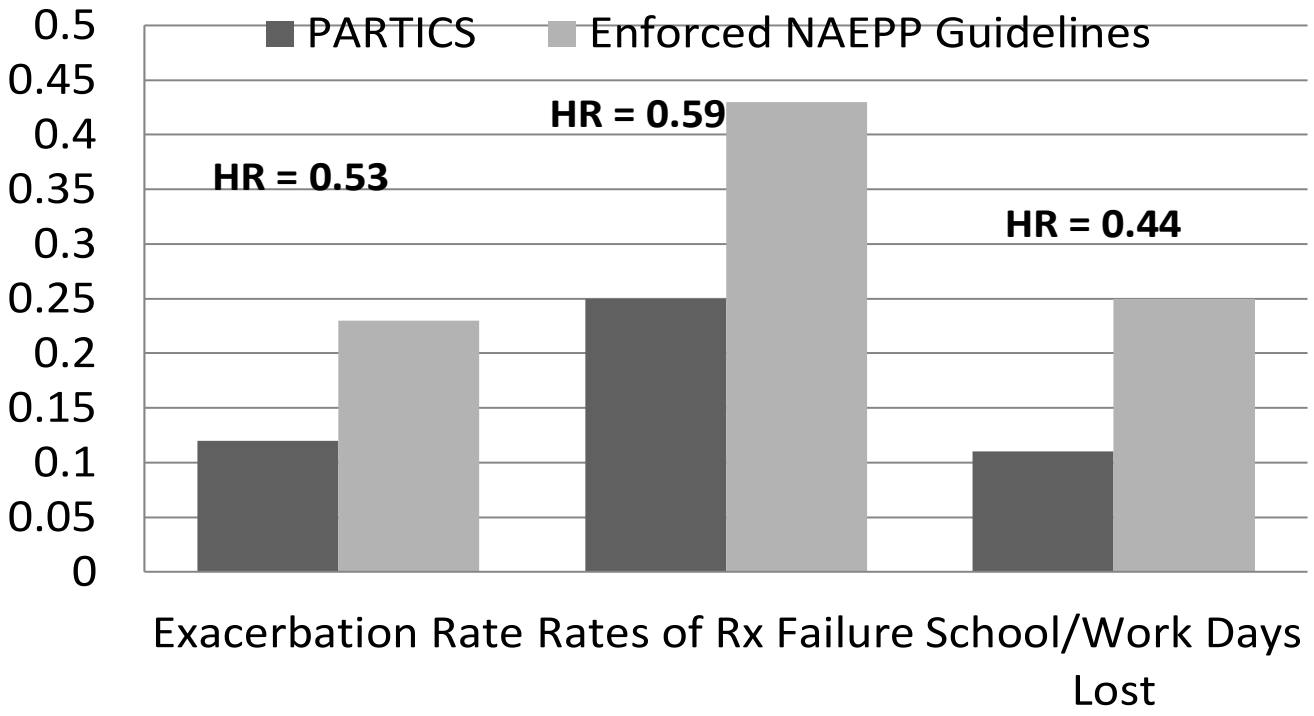

Fig B-2. Yearly rates of events in a non-pragmatic study where NAEPP guideline ICS use was enforced (90% adherence as c/w ~25% adherence in pragmatic studies). HR=Hazard Ratios (which represent a 47%, 41%, and 56% reduction in events with PARTICS. (Adapted from Calhoun 2012)

PREPARE study overview

- **Design**: randomized (1:1), open-label, pragmatic clinical trial
- **Population**: 1,201 Black and Latinx adults w moderate to severe persistent asthma, on ICS w either an ACT <20 or an exacerbation in the past year
- **Pragmatic Population**
  - Self identified populations
  - Doctor diagnosis of asthma (excluded if doctor diagnosis of COPD w/h/o smoking
  - No limit on smoking hx or current smoking
  - No limitations on co-morbidities except for other lung diseases

PREPARE study overview

- **Pragmatic/Patient-Centered Intervention**: 1 clinic/study visit
  - Randomized to PARTICS (Patient Activated Reliever Triggered ICS) or continued usual care
  - All watched a video on optimal asthma care (English or Spanish)
  - PARTICS given a ICS inhaler and watched video on using it **in addition to** underlying therapy
    - instructed to take 1 puff of ICS every time they used their beta-agonist and 5 puffs when they used a nebulizer WITHOUT CHANGING THEIR UNDERLYING THERAPY
  - Refill of PARTICS inhaler (not underlying therapy) by 1-800 number
- **Remote F/U for 15 months**
  - Monthly surveys to all patients
  - Last patient enrolled in March 2020 (pre-COVID) and followed through pandemic

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Outcomes

- **Primary Outcome:** rate of asthma exacerbations/year determined by monthly survey, verified and adjudicated
- **Additional pre-specified outcomes:**
  - Asthma Control Test (**ACT**)
  - Asthma Symptom Utility Index (**ASUI**)
  - Days lost from work/school/usual activities
- Exploratory/Post-hoc Outcomes
  - ED visits
  - Hospitalizations
  - Medication use

STUDY RESULTS

Procedural

- Recruited 1201 patients
- 90% survey completion rate
- 4% data loss

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Baseline Characteristics

Baseline Characteristic	PARTICS+UC (n=600)	UC (n=601)	Total (N=1201)
Race and ethnicity, %			
African American/Black (AA/B)	50.5	49.9	50.2
Hispanic/Latinx (H/L)	49.5	50.1	49.8
Both AA/B and H/L	6.3	4.3	5.3
Age (years), mean (SD)	48.3 (13.5)	47.0 (13.9)	47.7 (13.7)
Sex assigned at birth, % female	84.7	82.7	83.7
BMI in obese range (≥30.0), %	70.2	67.1	68.8
Smoking status, %			
Current smoker	11.5	12.3	11.9
Former smoker	9.0	7.7	8.3
In smoking environment	27.5	30.1	28.8
Maintenance asthma medications, %			
ICS without ICS/LABA	28.5	28.1	28.3
ICS/LABA	71.3	71.7	71.5
Biologic	2.8	3.2	3.0
Nebulizer use			
Reported use of nebulizer, %	68.0	65.9	66.9
# Quick-reliever nebs/week in those using nebs, mean (SD)	2.7 (4.6)	3.0 (4.8)	2.9 (4.7)
Number of comorbid conditions, %			
0	27.7	31.8	29.7
≥1	72.4	68.2	70.0
FeNO, ≥30 ppb, % of subset	29.5	30.7	30.1
Abs eos ≥300 cells/μL, % subset	25.5	27.7	26.6
Hx asthma exacerbation in past yr, %	73.3	71.0	72.2
Asthma Control Test (ACT), mean (SD)	14.7 (4.4)	14.5 (4.5)	14.6 (4.4)
≤15, %	55.3	56.2	55.8
Asthma Symptom Utility Index (ASUI), mean (SD)	0.67 (0.22)	0.67 (0.21)	0.67 (0.21)
Patient Health Questionnaire (PHQ-2) mean (SD)	1.6 (1.7)	1.8 (1.8)	1.7 (1.8)
Depressive (PHQ-2 score ≥3), %	24.8	28.1	26.5

- Characteristics well balanced across treatment arms
- Majority obese
- Many current or former smokers, and in smoking environments
- >2/3 regularly using nebs
- >2/3 with comorbidities

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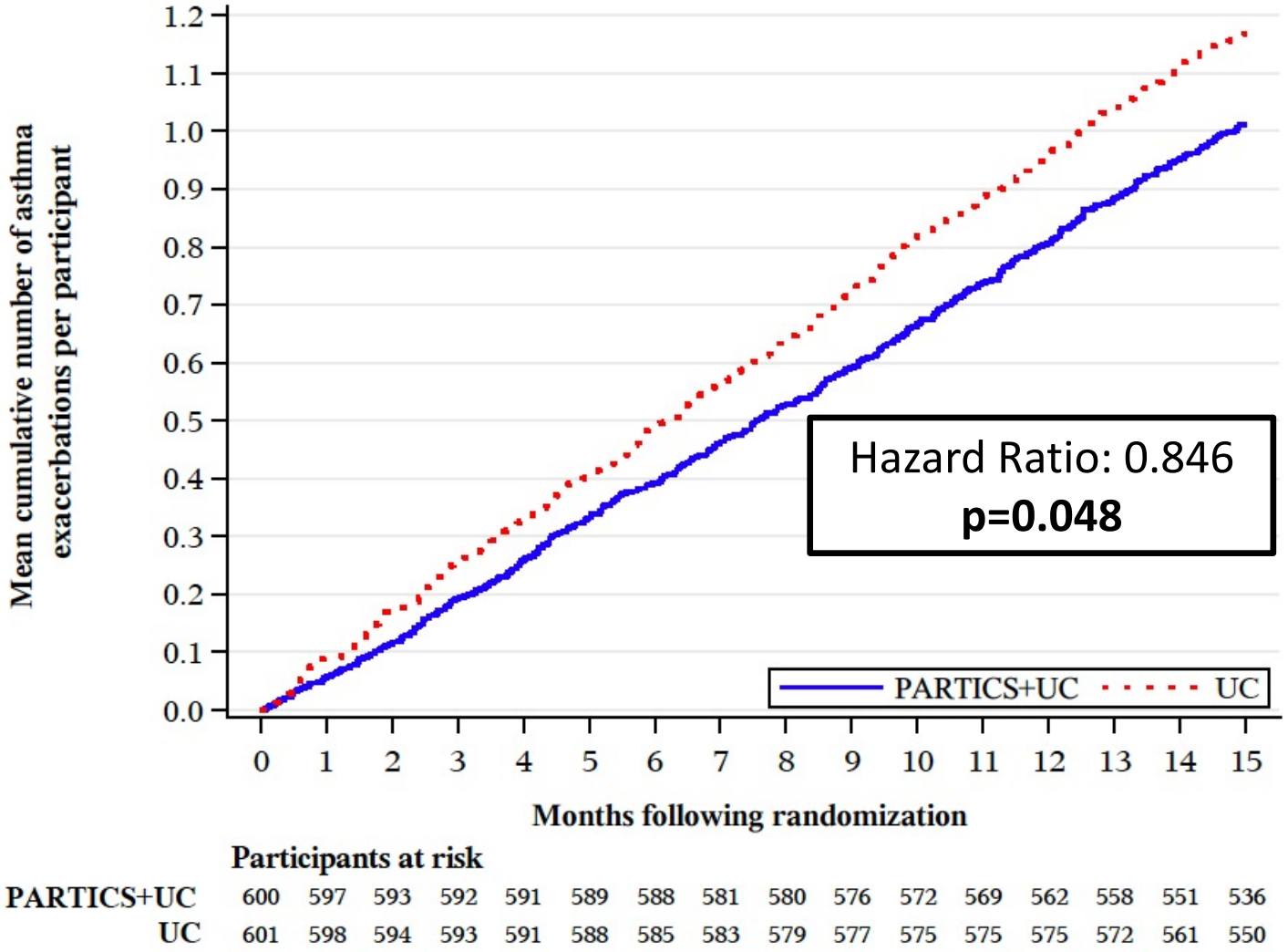
PARTICS reduces asthma exacerbations



- **PARTICS** reduced severe exacerbations by 0.13/person/year
- This is **equal or greater** than the reduction in severe exacerbations seen in **SMART** studies cited by NAEPP (0.12/patient/year, weighted by sample size and duration)

PARTICS: **P**atient **A**ctivated **R**eliever **T**riggered **ICS**

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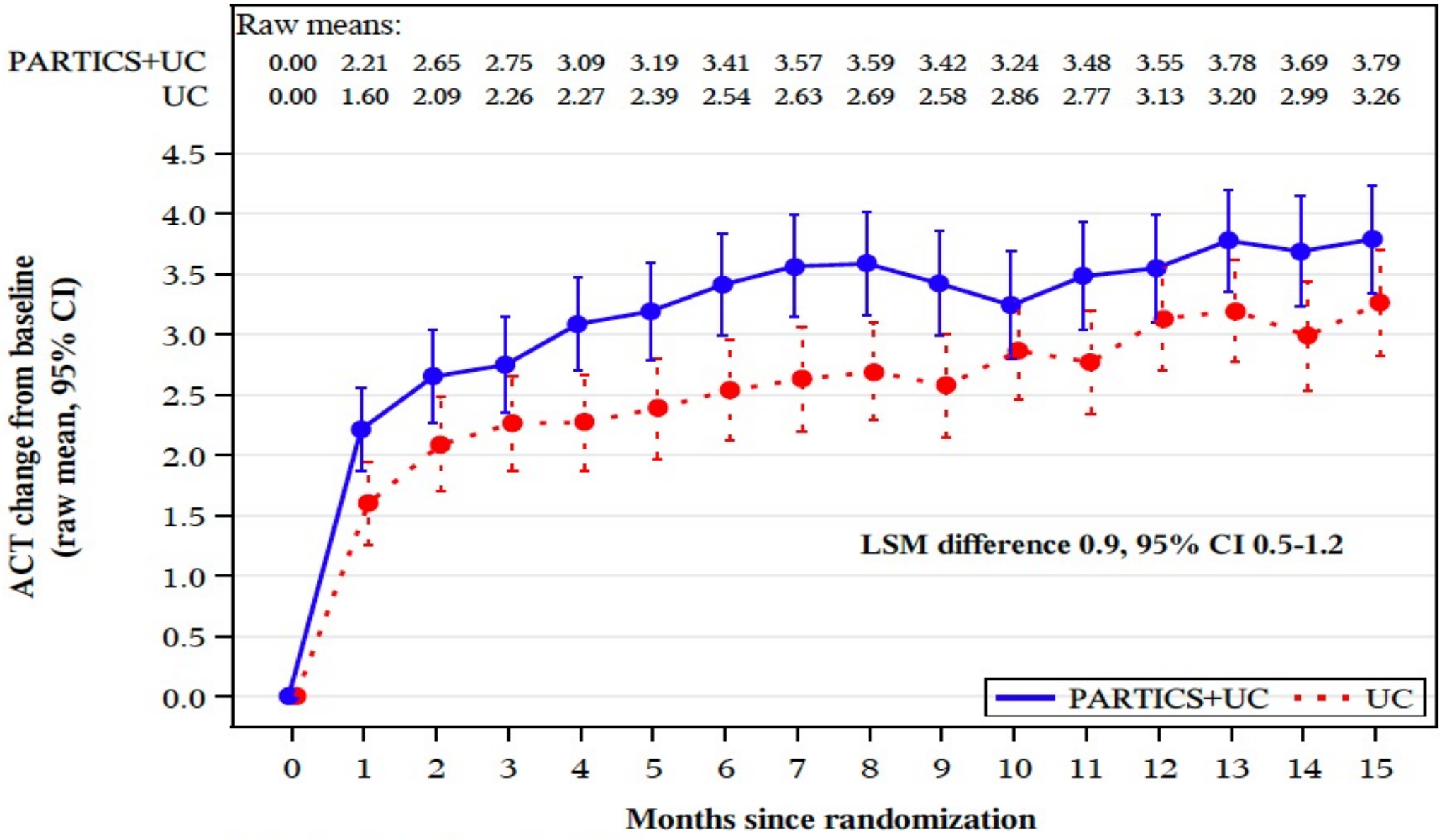
PARTICS Improved Asthma Control



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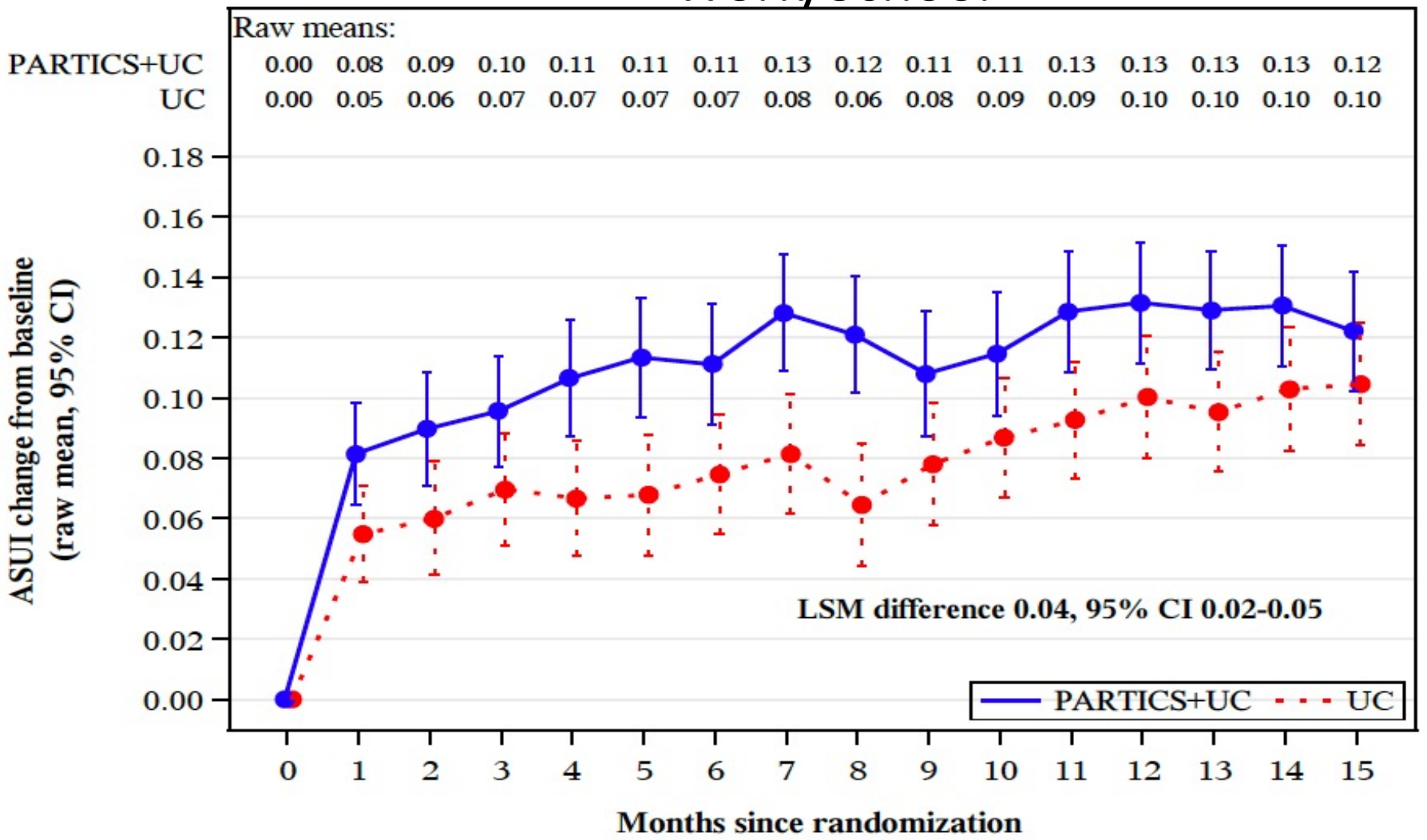
PARTICS Improved Quality of Life and Reduced Days Lost from Work/School



	PARTICS+UC (n=600)	UC (n=601)	Between-groups Comparison	P-value
Days lost from work/school /usual activities	13.4	16.8	RR: 0.80	**0.013**

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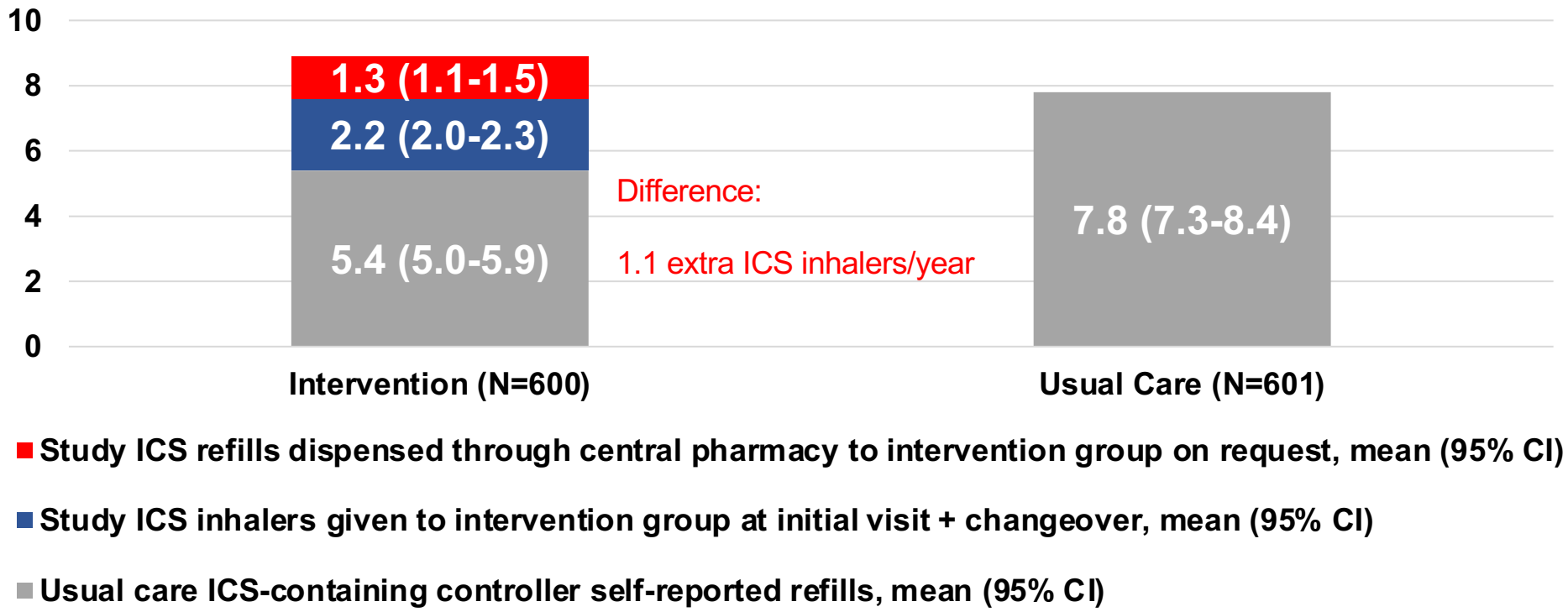
PARTICS Users Reported Mean 1.1 Extra Controller Cannister/Yr



SMART average 4.5/year

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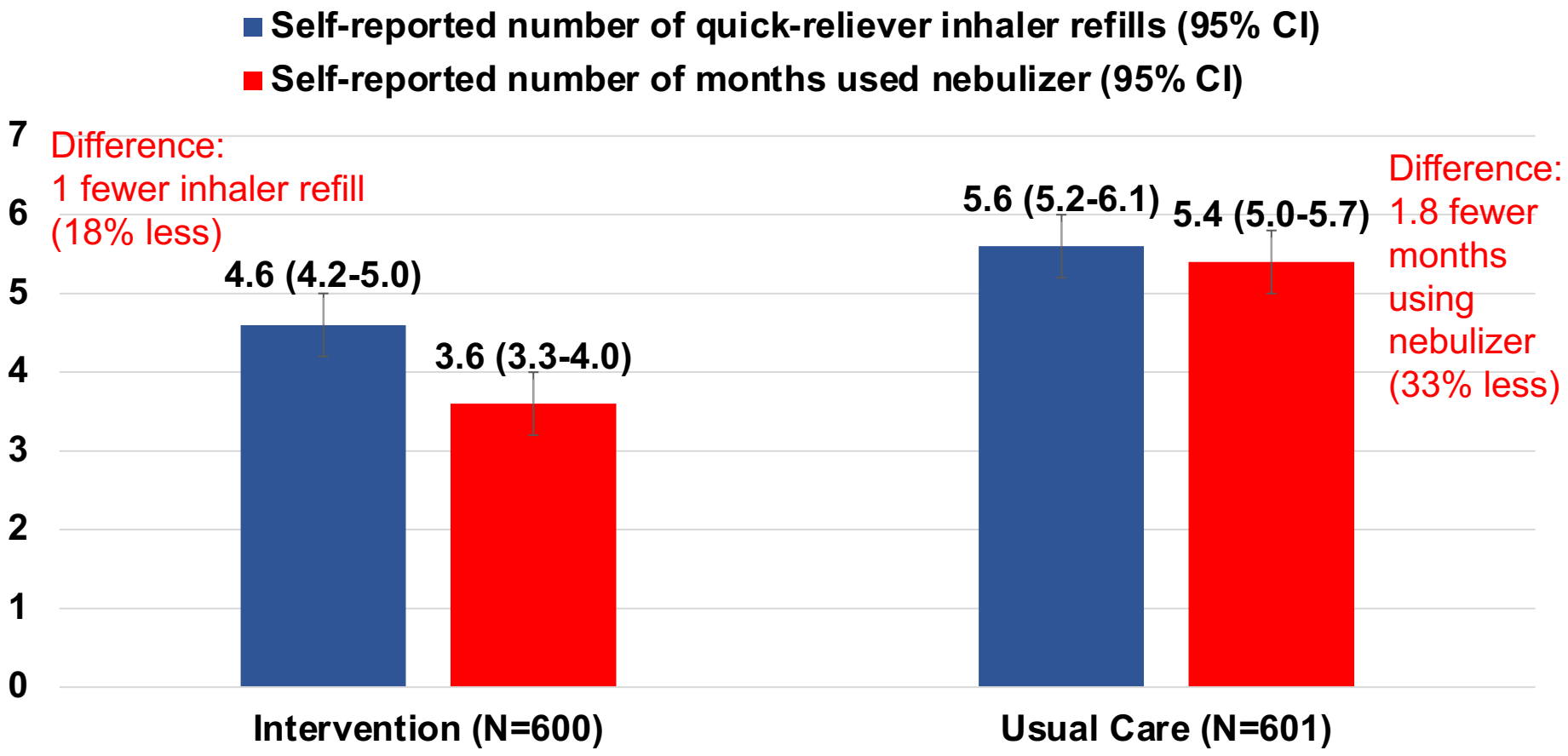
PARTICS Reduced Reliever Therapy Use



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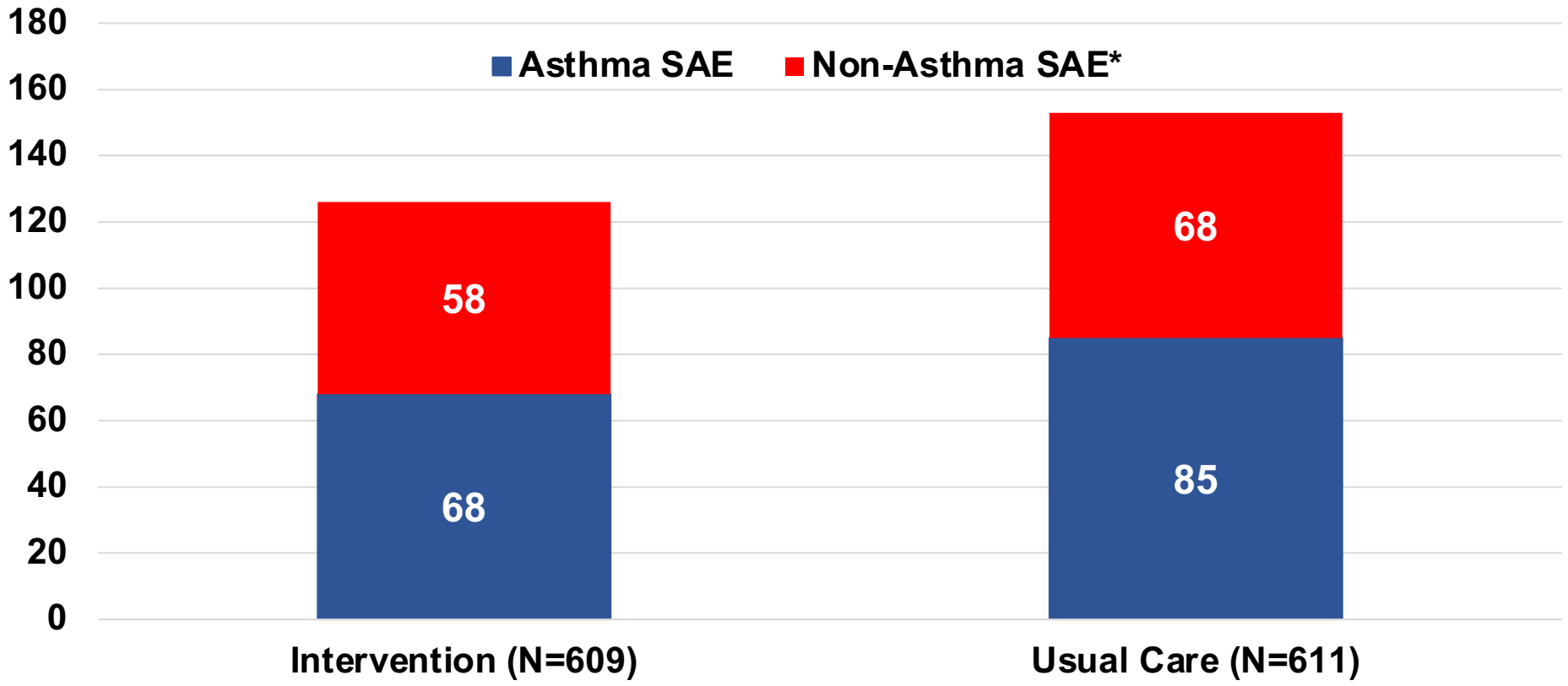
Number of Asthma and Non-Asthma Serious Adverse Events Were Numerically Reduced with PARTICS



* Severe adverse effects (**SAE**) include cardiac events, gastrointestinal disorders, hematology/oncology, immune system disorders, infections and infestations, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, nervous system disorders, psychiatric disorders, renal/urinary disorders, reproductive system and breast disorders, respiratory, thoracic, mediastinal disorders, skin and subcutaneous tissue disorders, substance abuse, vascular disorders and unclassified.

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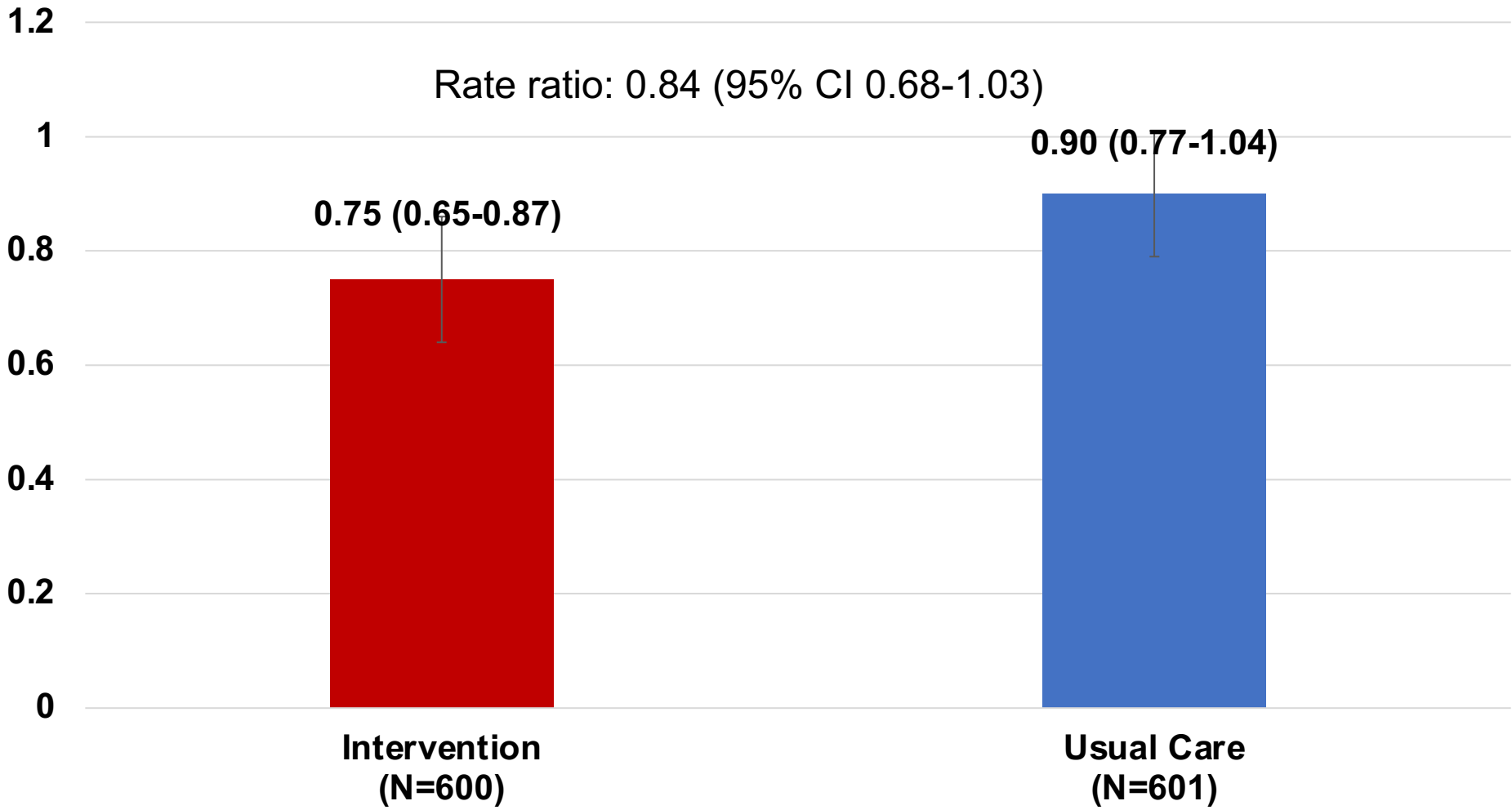
PARTICS Numerically Reduced ER/UC Visits for Asthma



ER: emergency room; **UC**: urgent care

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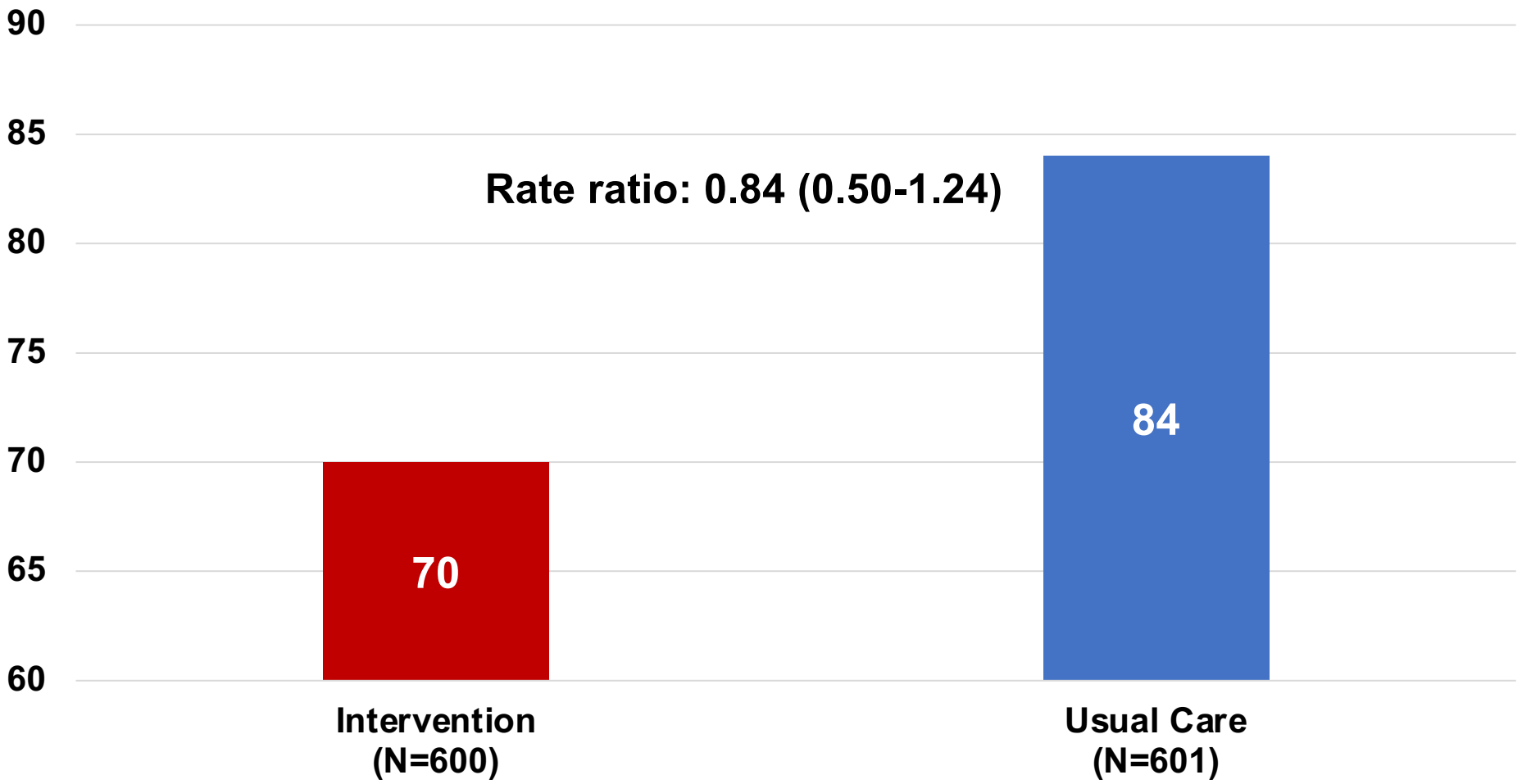
PARTICS Numerically Reduced Hospitalizations for Asthma



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How Did We Get There?

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Key Stakeholder Groups with Participaton on Exec Committee

- Patient Partner Advisors: N=17 (AA/B=8; H/L=9)
- Site Co-Investigators: N=19
- Expert Scientific Advisors: N=6
- Patient Advocacy Stakeholders: N=4
- Health Policy Stakeholders: N=6
- Professional Society Stakeholders: N=6

Executive Committee

- Patient Partner Representatives (H/L and AA/B)
- Scientific Stakeholder Advisor Representative
- Health Policy Stakeholder Representative
- Healthcare Representative
- Professional Society Representative
- PI Chair, Co-PI Chair, CRO PI, Co-PI (asthma outcomes expert)
- Project Director, Engagement Project Manager, Asthma Educator
- PCORI project officer, senior program associate and contract manager

Anticipated Issues

- Difficulty recruiting the populations
  - Patient advisors
    - People who look and talk like us
      - Videos
      - Brochures
    - Practices that treat us
    - Simplifying messages
    - Using specific Spanish vernacular
    - Adequate payment for survey completion
    - Immediate payment for survey completion
    - Appreciation notes from investigators in May Asthma awareness month and November around Thanksgiving
    - First 3 rules of studies: KISS,KISS,KISS
  - Patient advisors reviewed ALL patient facing material

Unanticipated Issues

- Scientific advisors – Nebulizer use
  - Added 5 puffs/nebulizer use
  - 67% of our patients ended up reporting nebulizer use

Findings from Vanguard

Challenge and Solution/s

- Challenge
  - Patients do not typically use the words “rescue” and “maintenance” inhaler
- Solution:
  - At enrollment, the study coordinator asked what the patient called their SABA and put the information into the data collection system for it to prepopulate within inhaler question.
  - Included all ICS names in ICS questions
  - Better explanation in instructional video

Challenge and Solution/s cont'd

- Challenge
  - Timely survey response (within 15 days) was low
- Solutions
  - Reimbursement for time to fill out the survey
  - A monetary prize incentive for completing within 7 days
  - A one-click link access to the online survey
  - Reminders at 26, 28 and 30 days; paper survey sent out on day 30; Central staff begin calling on day 32*
  - Participants choose how to fill out the monthly survey
    - 68% online completion
    - 28% by phone online completion
    - 3% by mail online completion
    - 1% used multiple options

*There were 9,244 call attempts to follow up with 901 participants (75% of the cohort) on 6195 surveys (~ 33% of overall surveys)

Challenge and Solution/s cont'd

- Challenge
  - Intervention patients understood taking ICS when they take SABA, however, not all patients understood using on a 1:1 basis
- Solutions
  - Reinforced information in video; specifics 1:1, 2:2 showed examples
  - Teach back with Study Coordinator

Challenge and Solution/s cont'd

- Challenge
  - Patients did not understand how to report dose counter number; or refills – because they did not understand the question
- Solutions
  - KISS
  - Eliminated dose counter strategy
  - Revised the question to ask if and when they switched to a new inhaler
  - Prepopulated the question with the name they call the inhaler
  - Prepopulated when they last filled out survey with date

Challenge and Solution/s cont’d

- Challenge
  - Patients complained the survey was too long
- Solutions
  - Eliminated several survey instruments
  - Shortened some non-standardized questions

In Study Adaptation: Low Self-Reported Use of Nebulizer Intervention

- Consultation with patient partners

  Pointed out that patients may not have the ICS inhaler with them when they use a neb

  - Provided an additional ICS and pouch to put on the nebulizer
  - Updated video with in depth instruction
  - Added the wording “the machine” after nebulizer in the survey so they understood the question more clearly
  - Gave out magnets with the information to take a puff of ICS for every puff of a rescue inhaler and 5 puffs each time they used their nebulizer

Patient Partner Advisors Involvement Challenges

- The majority had no research background
- Most of the research team and stakeholders from professional groups had not worked with patients as advisors
- Inclusion of 2 Spanish speaking only patient stakeholders to be representative of the population being enrolled

Addressing Challenges

- Dedicated and Professional Engagement Personnel as Part of Operations Team
  - 1 full time bi-lingual engagement project manager
  - Part time asthma educator who worked in the community with patient advisors
  - Consultant nurse leader of patient experience and patient advisory councils
- Education of patient partners on study design principles and statistics
- Compensation at level of consultants – hourly rate
- Continuous involvement in decisions from study design to analysis
- All invited to yearly in-person board meetings
  - Pre-meeting for patient partners only explaining major issues to be discussed
  - Patient partners embedded at each table and each breakout group

Addressing Challenges

- On committees, such as the executive, questionnaire, publications, website, etc.
- There were 2 calls each month one in English and one and Spanish

  In-person meetings included a translator and all materials were in English and Spanish
  - Feedback on all suggested action items
  - If suggestions were made and could not be instituted, there was a clear explanation why (such as wording in the consent form, changes to standardized questionnaires)

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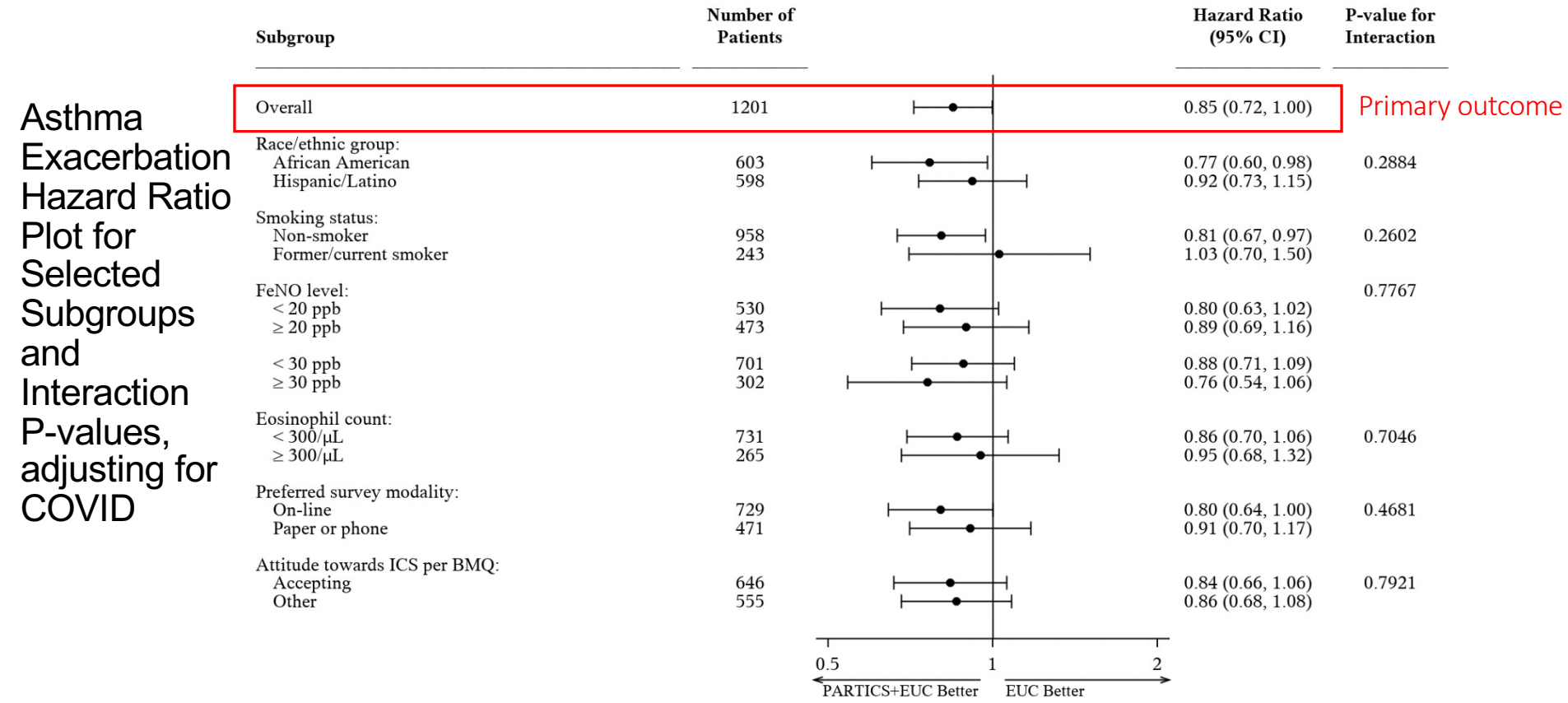
Publications

- E. Israel, et al. *Reliever-Triggered Inhaled Glucocorticoid in Black and Latinx Adults with Asthma*. N Engl J Med. 2022 Apr 21;386(16):1505-1518. doi: 10.1056/NEJMoa2118813.
- J.C. Cardet, et al. *Caribbean Latinx with moderate-severe asthma bear greater asthma morbidity than other Latinx.* J Allergy Clin Immunol, In Press
- J. C. Cardet, et al. *Socioeconomic status associates with worse asthma morbidity among Black and Latinx adults.* J Allergy Clin Immunol. 2022 May 18:S0091-6749(22)00661-3. doi: 10.1016/j.jaci.2022.04.030
- A. Apter, et al. *Nebulizer Use by Black and Latinx Patients with Moderate to Severe Persistent Asthma*. J Allergy Clin Immunol Pract 2021. DOI: 10.1016/j.jaip.2021.10.016
- J. Carroll, et al. *Socioeconomic Impact of COVID19 & Willingness to be Vaccinated in African American/Black and Hispanic/Latinx Asthmatic Adults*. National Medical Association (NMA), 2021; DOI: 10.1016/j.jnma.2021.12.010
- Salciccioli, J, et al. *Effect of Covid19 on asthma exacerbation*. J Allergy Clin Immunol Pract, 2021; DOI: 10.1016/j.jaip.2021.04.038
- E. Israel, et al. *A randomized, open-label, pragmatic study to assess reliever-triggered inhaled corticosteroid in African American/Black and Hispanic/Latinx adults with asthma: Design and methods of the PREPARE trial*. Contemporary Clinical Trials, 2021; DOI:10.1016/j.cct.2020.106246
- J.C. Cardet, et al. *Adherence to adding inhaled corticosteroids to rescue therapy in a pragmatic trial with adults with asthma: A pilot study.* Ann Allergy Asthma Immunol. 2020;124(5):487-493.e1. DOI:10.1016/j.anai.2019.12.027

Backup Slides

Heterogeneity of PARTICS Effect on Asthma Exacerbation Rates

Asthma Exacerbation Hazard Ratio Plot for Selected Subgroups and Interaction P-values, adjusting for COVID



A priori defined significant interaction p-values at <0.15

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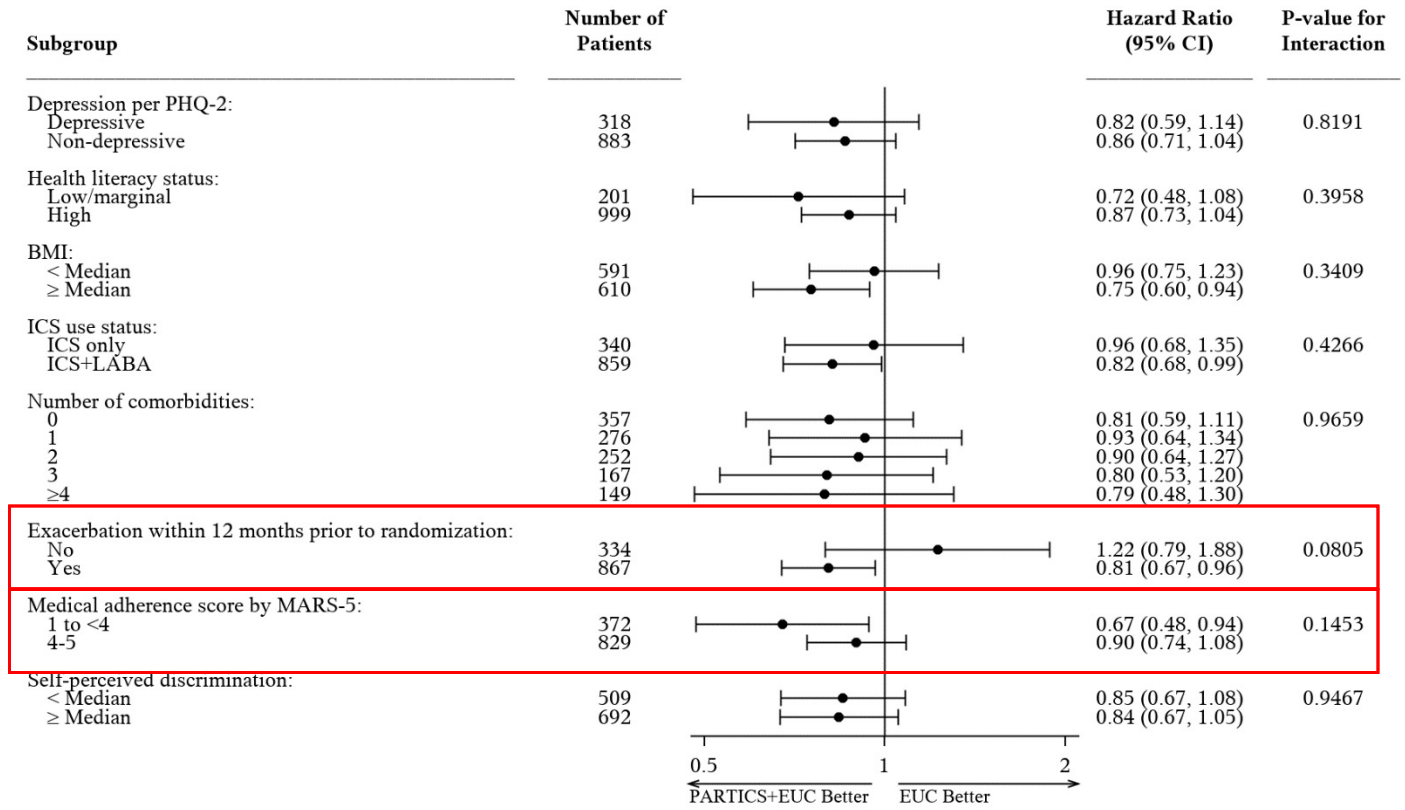

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PARTICS COMPARED TO SMART

PARTICS

- Nebulizer allowed
- Exacerbation in past year OR ACT <20
- Bronchodilation at entry - not required
- Mean reduction in exacerbations/per year = 0.13
- Reduction in Exacerbations if Restricted to Prior Exacerbation only – 0.22
- Reduction in Exacerbations if restricted to bronchodilators at entry - ??
- Asthma Control – Improved
- Extra Controller Use (Cannisters/yr) – 1.1

SMART

- Nebulizer not allowed
- Exacerbation in past year
- Bronchodilation at entry - required
- Mean reduction in exacerbations/per year = 0.12
- Reduction in Exacerbations if Restricted to Prior Exacerbation only – 0.12
- Reduction in Exacerbations if restricted to bronchodilators at entry - 0.12
- Asthma Control – Variable
- Extra Controller Use (Cannisters/yr) –4.5