

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

#### Title (Provisional)

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

#### Authors

Callen, Elisabeth; Israel, Elliot; Cardet, Juan Carlos; Fuhlbrigge, Anne L; Manning, Brian; Gaona, Gabriela; Staton, Elizabeth; Pace, Wilson D

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### VERSION 1 - REVIEW

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Reviewer	1
Name	Kew, Kayleigh M.
Affiliation	Freelance
Date	26-Jun-2024
COI	I have previously published in this area during my employment with Cochrane, but have no actual or potential conflicts or biases relating to the research.

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All the best with your research. This is an interesting analysis that, with some amendments, I believe can add to the wider literature around rescue triggered ICS for asthma.

#### General points

This is an interesting and largely well reported study that could add to the literature around ICS as reliever therapy for people with asthma. However, the overall objective of the study is confused and the focus seems to be on pre-enrolment variation by decade of birth and site rather than a subgroup analysis investigating the impact of race on treatment effect. I would like to see clarification of the main purpose of the study that either justifies the focus or realigns it to the original objective. If there is a study protocol, was the objective to:

- Look into variation in prescribing patterns and what drives them? (in which case the pre-enrolment focus makes sense, but this is not what is indicated in the Abstract objective)
- Investigate racial differences in the effect of the intervention? (as indicated by the title, but this is lost to other investigations in the paper)

- Compare the impact of PARTICS vs Usual care on prescribing patterns using EHR data (in which case, the focus should be on the post-enrollment effect, not pre-enrollment, and the black/hispanic question should be listed as a secondary aim)

The title should then be amended to better reflect the study design and rationale depending on the above.

## Abstract

There should be a clearer explanation of the objective of the study (see general points - no mention of black/hispanic focus), intervention and alternative strategies. *Participants: PREPARE study participants* and *Interventions: PREPARE study* is not sufficient – this should include basic demographics and details of intervention vs comparison.

Design should include the design of the original study and there needs to be a methods section to explain more clearly what sort of secondary analysis was done - some of this seems to be under *Outcome measures* but it is difficult to follow (patient-month assignment to asthma steps, linear mixed effect model...). Following section notes that it is an EHR analysis – this needs to be mentioned in the abstract.

## Strengths and Limitations

First two bullets are summaries of the study rather than strengths. These could be better presented as long follow-up, large sample size etc, or expanded to tell the reader something about the generalizability of the sample or what it adds to the wider literature.

## Background

I am not an asthma specialist but the background gives a good and clear overview of current practice and the grounding of the question, including the rationale for focusing on black and hispanic/latinx patients as an at-risk group.

## Methods

This section is clear with a good use of subheadings, both in terms of the original study and the EHR acquisition, cleaning and analysis.

Outcome groupings are well defined, with supplemental materials and referenced to NAEPP.

Linear mixed effect models are not my area of expertise, but I would like to see justification for the methods used to choose and include demographic variables in the model which seems post-hoc and potentially open to bias. These analyses are 'not shown' (line 248) and should be included for transparency in the supplementary materials.

## Results

The small number of hispanic/latinx participants due to the Puerto Rico site not providing data, and overall data completeness (713/1201; 59%) is an unfortunate but major limitation.

Table 1 is not important for the main text and can be moved to supplemental materials (counts of pps used in the EHR data by site)

The disaggregation by site seems to be a red herring throughout the results. It is useful to know there was significant site variation, especially where this could have been impacted by missing site data (Table 2 is particularly useful for this; Demographics and Comparisons with main study), but the

focus should be on the comparison between treatment groups as per the proposed objective of the study. What the reader needs to understand is how far randomization held, i.e. whether the pre-enrolment site variation balanced out between intervention groups.

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<b>Reviewer</b>	<b>2</b>
<b>Name</b>	<b>Zairina, Elida</b>
<b>Affiliation</b>	<b>Universitas Airlangga, Pharmacy Practice</b>
<b>Date</b>	<b>22-Jul-2024</b>
<b>COI</b>	<b>I have no competing interest</b>

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Thank you for giving me the opportunity to review this study. This study was part of the main study RCT and the results was based on secondary analysis from secondary data. This study analyzed the impact of rescue-triggered ICS on controlled therapy in Black and Latinx individuals with asthma. This sub study shows that clinicians' prescribing patterns did change over time, and the PARTICS group was prescribed lower doses of asthma controller medications by the end of the study.

I have a few concerns regarding the following that would be better if the author can add into the discussion part of the paper.

- 1, The title was include patients from black and Latin individuals but I have seen no particular reason why this group is particular compare to the other population.
- 2, Are the main study include patients from this group only? Although this was a secondary analysis, the description of population needs to be described / explained.
3. The justification why site 16 was used as reference needs to be explained.

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## VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Comments to the Author:

This is an interesting and largely well reported study that could add to the literature around ICS as reliever therapy for people with asthma. However, the overall objective of the study is confused and the focus seems to be on pre-enrolment variation by decade of birth and site rather than a subgroup analysis investigating the impact of race on treatment effect. I would like to see clarification of the main purpose of the study that either justifies the focus or realigns it to the original objective.

*Language throughout the manuscript has been updated.*

If there is a study protocol, was the objective to:

- Look into variation in prescribing patterns and what drives them? (in which case the pre-enrolment focus makes sense, but this is not what is indicated in the Abstract objective)
- Investigate racial differences in the effect of the intervention? (as indicated by the title, but this is lost to other investigations in the paper)
- Compare the impact of PARTICS vs Usual care on prescribing patterns using EHR data (in which case, the focus should be on the post-enrollment effect, not pre-enrollment, and the black/hispanic question should be listed as a secondary aim)

*It's the third bullet. Pre-enrollment data is included to show that the two groups were the same prior to the start of the intervention.*

The title should then be amended to better reflect the study design and rationale depending on the above.

*The title has been modified.*

#### Abstract

There should be a clearer explanation of the objective of the study (see general points - no mention of black/hispanic focus), intervention and alternative strategies. Participants: PREPARE study participants and Interventions: PREPARE study is not sufficient – this should include basic demographics and details of intervention vs comparison.

*More explanation has been added to the abstract.*

Design should include the design of the original study and there needs to be a methods section to explain more clearly what sort of secondary analysis was done - some of this seems to be under Outcome measures but it is difficult to follow (patient-month assignment to asthma steps, linear mixed effect model...). Following section notes that it is an EHR analysis – this needs to be mentioned in the abstract.

*The abstract has been reworked to update this language.*

#### Strengths and Limitations

First two bullets are summaries of the study rather than strengths. These could be better presented as long follow-up, large sample size etc, or expanded to tell the reader something about the generalizability of the sample or what it adds to the wider literature.

*The Strengths and Limitations have been updated.*

#### Background

I am not an asthma specialist but the background gives a good and clear overview of current practice and the grounding of the question, including the rationale for focusing on black and hispanic/latinx patients as an at-risk group.

*Thank you.*

#### Methods

This section is clear with a good use of subheadings, both in terms of the original study and the EHR acquisition, cleaning and analysis.

*Thank you.*

Outcome groupings are well defined, with supplemental materials and referenced to NAEPP.

*Thank you.*

Linear mixed effect models are not my area of expertise, but I would like to see justification for the methods used to choose and include demographic variables in the model which seems post-hoc and potentially open to bias. These analyses are 'not shown' (line 248) and should be included for transparency in the supplementary materials.

*We have added a combined model to the supplemental materials that demonstrates this without overly burdening the reader with multiple tables to interpret.*

## Results

The small number of hispanic/latinx participants due to the Puerto Rico site not providing data, and overall data completeness (713/1201; 59%) is an unfortunate but major limitation.

*We do indicate in the limitation section that we acknowledge not every site providing data is a limitation.*

Table 1 is not important for the main text and can be moved to supplemental materials (counts of pps used in the EHR data by site)

*Table 1 is important as it indicates the breakdown by site and can be considered demographic information. We left Table 1 in for that reason.*

The disaggregation by site seems to be a red herring throughout the results. It is useful to know there was significant site variation, especially where this could have been impacted by missing site data (Table 2 is particularly useful for this; Demographics and Comparisons with main study), but the focus should be on the comparison between treatment groups as per the proposed objective of the study. What the reader needs to understand is how far randomization held, i.e. whether the pre-enrolment site variation balanced out between intervention groups

*The discussion has been updated to make this clearer.*

Reviewer: 2

Comments to the Author:

Thank you for giving me the opportunity to review this study. This study was part of the main study RCT and the results was based on secondary analysis from secondary data. This study analyzed the impact of rescue-triggered ICS on controlled therapy in Black and Latinx individuals with asthma. This sub study shows that clinicians' prescribing patterns did change over time, and the PARTICS group was prescribed lower doses of asthma controller medications by the end of the study.

*Thank you.*

I have a few concerns regarding the following that would be better if the author can add into the

discussion part of the paper.

1, The title was include patients from black and Latin individuals but I have seen no particular reason why this group is particular compare to the other population.

*Lines 69-71 in the introduction highlight why Black and Hispanic/Latinx individuals were chosen for the original PREPARE study (and thus this study). [“Black individuals have exacerbation and death rates that are 2-2.5 times higher than White individuals and Asian individuals,(17) while Hispanic individuals, particularly Caribbean Hispanic individuals, (18, 19) have 2 times the rate of exacerbations and 1.5 times the death rate.(20. 21)”]*

2, Are the main study include patients from this group only? Although this was a secondary analysis, the description of population needs to be described / explained.

*Yes, the individuals included in this sub-study came from the original study. Table 2 provided the demographic information for the sub-population used in this sub-study. Additionally, the first sentence in the EHR Data Acquisition section indicates the data came from the PREPARE study: “Each site was asked to provide EHR data for each participant within the PREPARE study.”*

3. The justification why site 16 was used as reference needs to be explained.

*For each variable, one “category” has to be used as a reference. All variables have a reference category specified. An explanation has also been added in the Statistical Methods section.*

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## VERSION 2 - REVIEW

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<b>Reviewer</b>	<b>1</b>
<b>Name</b>	<b>Kew, Kayleigh M.</b>
<b>Affiliation</b>	<b>Freelance</b>
<b>Date</b>	<b>02-Oct-2024</b>
<b>COI</b>	

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The extent of revision to this article does not go far enough to address the concerns raised about the lack of clarity about the main purpose of the study, its relation to the original study, and the methods used. Reporting is not clear enough to understand the story of the study and its contribution to the literature beyond what was known already.

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<b>Reviewer</b>	<b>2</b>
<b>Name</b>	<b>Zairina, Elida</b>
<b>Affiliation</b>	<b>Universitas Airlangga, Pharmacy Practice</b>
<b>Date</b>	<b>18-Oct-2024</b>

COI

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I have no further comments