PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Investigating Fractional Exhaled Nitric Oxide (FeNO) in Chronic Obstructive Pulmonary Disease (COPD) and Asthma-COPD Overlap (ACO): A Scoping Review Protocol
AUTHORS	Mostafavi-Pour-Manshadi, Seyed-Mohammad-Yousof; Naderi, Nafiseh; Barrecheguren, Miriam; Dehghan, Abolfazl; Bourbeau, Jean

VERSION 1 – REVIEW

REVIEWER	Jennifer DeLongpre and Peter Hahn Metro Health-University of Michigan Health
REVIEW RETURNED	21-Sep-2017

GENERAL COMMENTS	1) BACKGROUND SECTION: a) Background too long, information is redundant and not pertinent to the topic. Risk of getting to the objectives of the study in a delayed fashion. We recommend the review question and objective to be stated concisely and clearly. In this section, FeNO has been reported as being used clinically for the diagnosis of asthma. Based on ATS 2005 guidelines, we feel its role is restricted to asthma management in the following domains: 1) detecting eosinophilic airway inflammation, determining the likelihood of corticosteroid responsiveness, monitoring of airway inflammation to determine the potential need for corticosteroid and unmasking potential unsuspected nonadherence to corticosteroid therapy. Asthma diagnosis is a clinical diagnosis. FeNO has influenced asthma management not diagnosis in our opinion. b) One of the objectives stated was to study response of bronchodilators in COPD patients based on FeNO values. We question this objective as we are not aware of any role for FeNO in this domain [i.e. Assessing response to bronchodilators] c) The objective of studying relationship between FeNO & modifying factors is not mentioned in this section. However, it is mentioned late in the manuscript as a research question (#1) .What are the modifying factors that the group proposes to study?. Race, smoking, obstructive sleep apnea, co-existent sinusitis are some of the factors that can modify FeNO levels. Delineating the modifying factors can potentially reshape the search strategy and make it effective for the authors' objective(s). 2) Methods Section: Recommend not using prednisone in your research question. Recommend non-inhaled corticosteroids as a broader group rather than restrict to Prednisone/Prednisolone.

	2) Eligibility Section: What is the operational definition of COPD that the authors propose to uzse ? There is no clear study definition provided for COPD. Will the authors propose a preset definition prior to study review? What are the operational definitions for outcomes such as exacerbations etc.? 3) Information Source (Databases), Literature Search and Search Strategy Section The authors mention a “variety of keywords” and “database subject heading” and mention an example. We feel it is severely limited due to the addition of two AND joiners and usage of / symbol confusing the reader. For instance: “[COPD OR Chronic Obstructive Lung Disease OR Emphysema OR Chronic bronchitis OR ACO OR Asthma COPD Overlap Syndrome OR Concomitant asthma] AND [FeNO OR Fractional Exhaled Nitric Oxide] would be a more meaningful preliminary search strategy .A formal search strategy such as one done in PubMed should be provided as a separate table for the sake of clarity and free flowing nature of the manuscript. Other valid search strategies such as searching grey literature, using reference sections of manuscripts for additional literature have not been mentioned (snowballing, pearl growing strategies etc.)

REVIEWER	Toyib OLANIYAN, PhD University of Cape Town, South Africa
REVIEW RETURNED	29-Sep-2017

GENERAL COMMENTS	The authors did not adequately discuss the limitations of using 'a scoping review' methodology to address the research questions. Although, this kind of methodology is efficient for addressing a wide topic area, it would be difficult to inform new research area or address gaps in research without a proper quality assessment of the primary articles. Oftentimes, a poorly conducted primary article might flawed the result and conclusion from such study, thus misinforming the conclusion of the 'scoping review' itself. Using the authors word 'unfortunately this methodology in this context will only be able to address the breadth of the research area, but not the depth'.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1) BACKGROUND SECTION:

a) Background too long, information is redundant and not pertinent to the topic. Risk of getting to the objectives of the study in a delayed fashion. We recommend the review question and objective to be stated concisely and clearly. In this section, FeNO has been reported as being used clinically for the diagnosis of asthma. Based on ATS 2005 guidelines, we feel its role is restricted to asthma management in the following domains: 1) detecting eosinophilic airway inflammation, determining the likelihood of corticosteroid responsiveness, monitoring of airway inflammation to determine the potential need for corticosteroid and unmasking potential unsuspected nonadherence to corticosteroid therapy. Asthma diagnosis is a clinical diagnosis. FeNO has influenced asthma management not diagnosis in our opinion.

Response:

Thank you for your useful comments. We made changes and reformulated the background/introduction according to your comments as you can see in the manuscript with track changes. We shortened the introduction section to make it easier to reach the objectives in a timely fashion. We stated our questions/objectives more precisely and hopefully this reads better and more clearly in this revision. In addition, we revised the order of the objectives/questions to make them explicit. Also, we changed the term of the section 'background' to 'introduction', according to the PRISMA-P checklist. Regarding the FeNO role in asthma, in accordance with your suggestion, and also ATS guidelines, we kept 'management' and remove 'diagnosis'.

b) One of the objectives stated was to study response of bronchodilators in COPD patients based on FeNO values. We question this objective as we are not aware of any role for FeNO in this domain [i.e. Assessing response to bronchodilators]

Response:

You are absolutely right, there are studies on bronchodilators and FeNO in COPD but these studies are assessing the interaction of bronchodilators on the FeNO measurement. These studies have been removed from the question/objective and moved to the first question, .

c) The objective of studying relationship between FeNO & modifying factors is not mentioned in this section. However, it is mentioned late in the manuscript as a research question (#1) .What are the modifying factors that the group proposes to study?. Race, smoking, obstructive sleep apnea, co-existent sinusitis are some of the factors that can modify FeNO levels. Delineating the modifying factors can potentially reshape the search strategy and make it effective for the authors' objective(s).

Response:

According to your comment, the objective regarding FeNO and modifying factors has been added/completed to this section. We would like to investigate the modifying factors included but not limited to age, cigarette smoking, sex, glucocorticoids (ICS/GCS), bronchodilators, and exacerbations through our review.

2) Methods Section: Recommend not using prednisone in your research question. Recommend non-inhaled corticosteroids as a broader group rather than restrict to Prednisone/Prednisolone. Eligibility Section: What is the operational definition of COPD that the authors propose to uzse ? There is no clear study definition provided for COPD. Will the authors propose a preset definition prior to study review? What are the operational definitions for outcomes such as exacerbations etc.?

Response:
According to your suggestion, we omitted the term prenisolone and changed it to ‘non-inhaled/systemic corticosteroids’. As mentioned before, this research question was revised as well. Regarding the eligibility criteria, we intend to use the GOLD definition for the COPD defined by the post-bronchodilator ratio forced expiratory volume in 1 second over forced vital capacity (FEV1/FVC) below 0.7. Concerning the ACO, there is still no consensus and no validated definition; therefore, we are not able to define a unique definition for ACO. Actually, in this scoping review, we intend to identify different definitions used for identifying ACO in a variety of studies and report all of them. We have also provided the operational definition for exacerbation in the methodology section: < symptoms-based or event-based, i.e. requiring antibiotics or non-inhaled/systemic corticosteroids, emergency or hospital admission>. For the other outcomes as this is a scoping review, we will not limit to one definition and we will report all the operational definitions from the different studies that will be selected by our literature search. We expect to find different operational definitions such as sputum/blood eosinophilia, etc; thus, for the purpose of the scoping review, we do not want to limit to only one operational definition.

3) Information Source (Databases), Literature Search and Search Strategy Section
The authors mention a “variety of keywords” and “database subject heading” and mention an example. We feel it is severely limited due to the addition of two AND joiners and usage of / symbol confusing the reader.
For instance: “[COPD OR Chronic Obstructive Lung Disease OR Emphysema OR Chronic bronchitis OR ACO OR Asthma COPD Overlap Syndrome OR Concomitant asthma] AND [FeNO OR Fractional Exhaled Nitric Oxide] would be a more meaningful preliminary search strategy .A formal search strategy such as one done in PubMed should be provided as a separate table for the sake of clarity and free flowing nature of the manuscript. Other valid search strategies such as searching grey literature, using reference sections of manuscripts for additional literature have not been mentioned (snowballing, pearl growing strategies etc.)

Response:
Accordingly, we added OR/AND in their appropriate place to make these search strategy keywords more clear and precise. We have stated using the references of other studies in the abstract. Furthermore, we add this sentence to our methodology section as well. Gray literature is part of our excluding criteria. We added this exclusion criterion to the Table 1 in the methodology section. Table 2 for the sake of search strategy (Medline) has been added to the text. The updated search strategy on this database has been provided as a supplementary file.

Reviewer 2
The authors did not adequately discuss the limitations of using 'a scoping review' methodology to address the research questions. Although, this kind of methodology is efficient for addressing a wide topic area, it would be difficult to inform new research area or address gaps in research without a proper quality assessment of the primary articles. Oftentimes, a poorly conducted primary article might flawed the result and conclusion from such study, thus misinforming the conclusion of the 'scoping review' itself.
Using the authors word 'unfortunately this methodology in this context will only be able to address the breadth of the research area, but not the depth'.

Response:
We concur with the reviewer that scoping reviews should not be misinterpreted as a less rigorous version of a systematic review, when in fact they are a ‘different entity’ with a different set of purposes and objectives.

Scoping studies differ from systematic reviews in several ways:
1. Research question is more broadly defined;

2. Inclusion/exclusion developed post hoc at study selection stage;

3. Study selection includes all study types;

4. Data extraction: “Charts” data according to key issues, themes, etc.
The balance between breadth and depth of analysis is a challenge. However, the intent of our scoping review is to present an overview of the existing literature in a field of interest, i.e., FeNO in COPD, and as well synthesize and aggregate findings from different studies. We are presenting different themes, and a related question under each of these themes.
It is often said that the results of scoping reviews cannot be used to make recommendations for practice because quality of included studies is not assessed. We also recognize that some forms of quality assessment of all included studies would enable the identification of gaps in the evidence base and not just where research is lacking, and a better determination of the feasibility of a systematic review. However, the debate on the need for quality assessment in scoping review is still ongoing. It would be a huge challenge to assess quality among the wide range of study designs and a large volume of literature that will be included in the scoping review. This has been indicated as a limitation in the manuscript.
What everyone agrees on in a scoping review, it is to clearly report the processes and procedures undertaken as well as any limitations of the approach to ensure that readers have sufficient information to determine the value of findings and recommendations.

We have reviewed and made the appropriate changes in the manuscript. We think that to our best understanding of the reviewers’ comments, we improved in many of these in the reviewed manuscript.

VERSION 2 – REVIEW

REVIEWER	Toyib OLANIYAN University of Cape Town, South Africa
REVIEW RETURNED	19-Oct-2017

GENERAL COMMENTS	Thank you for incorporating the changes to the revised version with regard to highlighting the limitation of the scoping review methodology.