PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Blood eosinophils, fractional exhaled nitric oxide, and the risk of asthma attacks in randomised controlled trials: protocol for a systemic review and control arm patient-level meta-analysis for clinical prediction modelling
AUTHORS	Couillard, Simon; Steyerberg, Ewout; Beasley, Richard; Pavord, Ian

VERSION 1 – REVIEW

REVIEWER	Sadatsafavi, Mohsen recommended University of British Columbia, Division of Respiratory Medicine, Faculty of Medicine I am a member of the Scientific Committee of the NOVELTY study which also includes two of the authors (RB and IDP). I did not perceive this to be a source of conflict. I am co-investigator on a grant currently under review (along with one of the authors) on creating a risk prediction model in severe asthma. That activity can partially overlap with this planned study. Independently of the fate of this protocol paper, I will encourage the principal investigator of the other grant to reach out to the authors of the present protocol (once the protocol is published or the authors communicated their plan in an alternative way) for potential collaboration and avoidance of duplicate efforts. I performed this review completely agnostic of the potential parallel activity.
REVIEW RETURNED	28-Nov-2021

GENERAL COMMENTS	Couillard and colleagues propose to perform an individual-patient data (IPD) meta-analysis of severe exacerbations in the placebo arm of major randomized clinical trials (RCTs) to develop a risk prediction model for severe exacerbations in asthma. This will be a fascinating study, with much potential to impact patient care and outcomes. The protocol is formulated by a great team including experts in asthma, clinical trials, and predictive analytics. This is an encouraging development for asthma research and care, and ultimately for patients. The focus on control arms is a god first move (the 'political' aspect of this is quite understandable). The internal-external validation approach considering the inevitably small number of events in some subgroups (eg mild asthma) and between-sample heterogeneity is highly relevant in this context. I have two major comments; while they do not preclude eventual acceptance of this protocol for publication, I think they do require specific updates to the protocol, as well as some minor comments or discretionary suggestions: Major comment: 1. Abstract – methods: why only placebo / no ICS / low dose ICS arms? Does this not exclude the bulk of asthma trials on biologics that have patients on high does ICS/LABA as the control arm (and correspondingly render the model irrelevant for considering a

	biologic for a person on maximal inhaled therapy)? Can the 'current treatment' be used as a predictor in the final scoring tool to bring these arms into the study (alternatively, the treatment indicator can be ignored noting that it is often not a strong predictor compared with innate covariates)? This also makes treatment step (Table 2) variable partially irrelevant. I think the authors need to carefully decide the target population in practice to whom this model is applicable, and select the samples (and analytical strategy) accordingly, and clearly communicate this in the protocol. 2. Absent from the protocol is the critical details on how exacerbation history will be modeled. Exacerbation history is, as mentioned, a major component of status quo treatment algorithms and will likely emerge as the single most powerful predictor of future events. This is a reality for recurrent events in asthma sand many diseases, given that despite all our efforts 'other' salient clinical features can explain a fraction of variation in the outcome, thus the previous history always remains an important predictor. The issue of concern is that RCTs with exacerbation as their primary endpoint have likely 'enriched' their samples by including only patients with a positive exacerbation history (examples include TRIGGER, TRIMARAN, DREAM, CIROCCO, MENSA). - Are the investigators planning to create a risk scoring tool only for individuals with a positive 12-month exacerbation history? If so, this should be very clearly mentioned in the protocol and attempts should be made to prevent potential mis-use of this tool in individuals with negative history. - Regardless of the target population (with regard to exacerbation history), the exact number of previous exacerbations is likely to carry much prognostic information about future risk. See for example see Peters MC, et al Am J Respir Crit Care Med. 2020;202:973–82 and Lee TY, et al Ann Am Thorac Soc. 2021 Nov 19, both clearly demonstrating this). Unfortunately, some (or even many) trials might only assert the positive history and not provide the exact number of events. In this case, exacerbation history will be a partially missing predictor. This also needs to be investigated and a preemptive plan be communicated in the protocol. Given enriched samples, the validity of predictions in patients with negative exacerbation history should be investigated in isolation. In a previous modeling work for COPD exacerbations (Adibi et al, Lancet Respir Med. 2020 Oct;8(10):1013-1021), conditional recruitment on exacerbation history and partial exacerbation history data were major challenges. I have provided (at the end of my comments) the overalls of a solution we formulated which the investigators might find useful. Minor comments: 3. Abstract, line 22: 'severe asthma exacerbations' might be a bit vague for non-asthma-expert readers as they might attribute severe to asthma (rather than to exacerbation). Also, might be prudent to define severe in the abstract too. 4. Page 10 (author-generated page number), line 40: So if a trial reports either of FeNo or BEC, but not both, will it be included? Given the central role of these two variables, a more specific modeling approach for such data would strengthen the protocol. 5. Page 14, line 27 : binomial negative regression -> negative binomial regression 6. The potential predictors in the "STATISTICAL ANALYSIS PLAN" is different from those in the main text. 7. Page 1 – line 43: as stated earlier the 'politics' of going for placebo arms is clear to this reviewer, but the use of political

	reasons' for a scientific protocol for a medical research project is a bit colloquial. Suggest either rewording or more objectively outlining the concerns (eg lack of vendor participation due to the potential new information about treatment effect of their marketed or under-development product). Suggestion for dealing with partial exacerbation history data: One solution is indeed to treat exacerbation counts in the previous year as (partially) missing data and apply imputation methods (albeit the systematic missingness in this case creates challenges). The generic section on missing predictor values does not do justice to this important predictor. Another, promising solution (based on encountering a similar situation in the afore-mentioned modeling work, please refer to the supplementary material of the original paper), is a Bayesian approach for explicitly incorporating event history, based on the assumption that the underlying exacerbation rate for an asthma patient remains (almost) constant in two consecutive years. This approach entails creating a model without exacerbation as predictor (or only a binary predictor as whether exacerbation history was a criterion). Using the Bayesian interpretation of the negative binomial regression (https://stats.stackexchange.com/questions/263063/relationship-between-negative-binomial-distribution-and-bayesian-poisson-with-ga) one can then generate predictions conditional on any number of previous exacerbations. This approach 1) enables using all RCT data regardless of exacerbation history information; 2) by not using exacerbation counts before randomization, this approach is relatively robust against the 'placebo' effect that the investigators mention (reduction in exacerbation rate after enrollment). The assumption of the exchangeability of previous year and next year events can be tested in the subset of data with fully history, or better in 'real world' data like NOVELTY that is available to the investigators.

REVIEWER	Dinh-Xuan, Anh-Tuan Université de Paris Ad hoc fees for pharmaceutical-sponsored lectures on type-2 inflammation biomarkers and asthma from AstraZeneca, Circassia, GSK and Sanofi-Genzyme.
REVIEW RETURNED	03-Dec-2021

GENERAL COMMENTS	This is a protocol for a systematic review and control arm patient-level meta-analysis for clinical prediction modelling. In essence, the authors proposed to do a systematic MEDLINE search from January 1993 to April 2021 looking for all randomised controlled trials (RCTs) that have investigated the effect of fixed treatment(s) regimen(s) on severe asthma exacerbation rates over at least a 6-months period, with documented values of blood eosinophils and FeNO at baseline. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and the methodological appraisal of the studies will be assessed by the Cochrane Risk-of-Bias Tool for RCTs. The predicted outcome is the absolute number of severe asthma attacks occurring in the following 12 months if anti-inflammatory therapy is not changed. The strenghts and weaknesses of this approach are thoroughly discussed by the authors highlighting the added-value of this clinical prediction model centered on two type-2 inflammatory biomarkers, namely blood eosinophils and exhaled nitric oxide, to improve treatable trait-based management of patients with asthma.

	The authors are seasoned experts in the field with respectable records of publications on this topic. The protocol is relevant and the information it will provide will help to advance the field of type-2 inflammatory biomarkers and asthma management.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Prof Sadatsafavi

Comments to the Author

Couillard and colleagues propose to perform an individual-patient data (IPD) meta-analysis of severe exacerbations in the placebo arm of major randomized clinical trials (RCTs) to develop a risk prediction model for severe exacerbations in asthma.

This will be a fascinating study, with much potential to impact patient care and outcomes. The protocol is formulated by a great team including experts in asthma, clinical trials, and predictive analytics. This is an encouraging development for asthma research and care, and ultimately for patients.

The focus on control arms is a god first move (the 'political' aspect of this is quite understandable). The internal-external validation approach considering the inevitably small number of events in some subgroups (eg mild asthma) and between-sample heterogeneity is highly relevant in this context.

Response: Thank you.

I have two major comments; while they do not preclude eventual acceptance of this protocol for publication, I think they do require specific updates to the protocol, as well as some minor comments or discretionary suggestions:

Major

1. Abstract – methods: why only placebo / no ICS / low dose ICS arms? Does this not exclude the bulk of asthma trials on biologics that have patients on high does ICS/LABA as the control arm (and correspondingly render the model irrelevant for considering a biologic for a person on maximal inhaled therapy)? Can the 'current treatment' be used as a predictor in the final scoring tool to bring these arms into the study (alternatively, the treatment indicator can be ignored noting that it is often not a strong predictor compared with innate covariates)? This also makes treatment step (Table 2) variable partially irrelevant. I think the authors need to carefully decide the target population in practice to whom this model is applicable, and select the samples (and analytical strategy) accordingly, and clearly communicate this in the protocol.

Response: This was a misunderstanding, and we have clarified the abstract. To be clear, by 'control arm' we mean 'no change to ICS dose compared to baseline'. Table 2 describes how the patients are classified in that context.

2. Absent from the protocol is the critical details on how exacerbation history will be modeled. Exacerbation history is, as mentioned, a major component of status quo treatment algorithms and will likely emerge as the single most powerful predictor of future events. This is a reality for recurrent events in asthma sand many diseases, given that despite all our efforts 'other' salient clinical features can explain a fraction of variation in the outcome, thus the previous history always remains an important predictor. The issue of concern is that RCTs with exacerbation as their primary endpoint have likely 'enriched' their samples by including only patients with a positive exacerbation history (examples include TRIGGER, TRIMARAN, DREAM, CIROCCO, MENSA).

   Are the investigators planning to create a risk scoring tool only for individuals with a positive 12-month exacerbation history? If so, this should be very clearly mentioned in the protocol and attempts should be made to prevent potential mis-use of this tool in individuals with negative history.

   Regardless of the target population (with regard to exacerbation history), the exact number of previous exacerbations is likely to carry much prognostic information about future risk. See for example see Peters MC, et al Am J Respir Crit Care Med. 2020;202:973–82 and Lee

TY, et al Ann Am Thorac Soc. 2021 Nov 19, both clearly demonstrating this). Unfortunately, some (or even many) trials might only assert the positive history and not provide the exact number of events. In this case, exacerbation history will be a partially missing predictor. This also needs to be investigated and a preemptive plan be communicated in the protocol. Given enriched samples, the validity of predictions in patients with negative exacerbation history should be investigated in isolation.

In a previous modeling work for COPD exacerbations (Adibi et al, Lancet Respir Med. 2020 Oct;8(10):1013-1021), conditional recruitment on exacerbation history and partial exacerbation history data were major challenges. I have provided (at the end of my comments) the overalls of a solution we formulated which the investigators might find useful.

Suggestion for dealing with partial exacerbation history data:

One solution is indeed to treat exacerbation counts in the previous year as (partially) missing data and apply imputation methods (albeit the systematic missingness in this case creates challenges). The generic section on missing predictor values does not do justice to this important predictor.

Another, promising solution (based on encountering a similar situation in the afore-mentioned modeling work, please refer to the supplementary material of the original paper), is a Bayesian approach for explicitly incorporating event history, based on the assumption that the underlying exacerbation rate for an asthma patient remains (almost) constant in two consecutive years. This approach entails creating a model without exacerbation as predictor (or only a binary predictor as whether exacerbation history was a criterion). Using the Bayesian interpretation of the negative binomial regression (https://can01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fstats.stackexchange.com%2Fquestions%2F263063%2Frelationship-between-negative-binomial-distribution-and-bayesian-poisson-with-

ga&data=04%7C01%7Cs.couillard%40usherbrooke.ca%7Ca2ec39c963934cb12bb208d9

dcfc7432%7C3a5a8744593545f99423b32c3a5de082%7C0%7C0%7C637783799107988192%

7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwi

LCJXVCI6Mn0%3D%7C3000&sdata=KdBdPNYYQ%2FuiXAZbVi83Zlyaz4cZ%2FYDLkagBGS

lebQc%3D&reserved=0) one can then generate predictions conditional on any number of previous exacerbations.

This approach 1) enables using all RCT data regardless of exacerbation history information;

2) by not using exacerbation counts before randomization, this approach is relatively robust against the ‘placebo’ effect that the investigators mention (reduction in exacerbation rate after

enrollment). The assumption of the exchangeability of previous year and next year events can be tested in the subset of data with fully history, or better in ‘real world’ data like

NOVELTY that is available to the investigators.

Response: As stated in the protocol, we requested the integer number of severe asthma attacks in the preceding 12 months. Furthermore, many requested studies have patients with / without asthma attack history (see below). Hence, we plan to assess the adjusted rate ratio in these specific trials, generalising afterwards to the entire sample. We will also have the NOVELTY adjusted rate ratio for reference (n=1000 in a real-world dataset. In summary, we definitely we plan to chart out the risk of asthma attacks for patients with and without asthma attacks, and thank the reviewer for his suggestion of a workaround if ever we encounter problems.

- **Novel START**, n=219: albuterol only arm, 9% with attack in past 12m
- **PRACTICAL**, n=449: fixed ICS + SABA prn arm, 12% with attack in past 12m
- **PACT**, n=95: montelukast arm, 23% with attack in past 12m
- **AZISAST**, n= 55: placebo arm, 87% with attack in past 12m

- **Lebri NEJM paper**, n=112: placebo arm, unknown% with attack in past 12m
- **LUTE-VERSE**, n=112: placebo arm, 49% with attack in past 12m
- **LAVOTA 1-2**, n=716: placebo arm, 63% with attack in past 12m

Minor

3. Abstract, line 22: 'severe asthma exacerbations' might be a bit vague for non-asthma-expert readers as they might attribute severe to asthma (rather than to exacerbation). Also, might be prudent to define severe in the abstract too.

Response: Abstract now defines a severe asthma attack.

4. Page 10 (author-generated page number), line 40: So if a trial reports either of FeNo or BEC, but not both, will it be included? Given the central role of these two variables, a more specific modeling approach for such data would strengthen the protocol.

Response: Although we include trials that report on FeNO and BEC, we do include the patients of those trials that have only one of these missing in their dataset.

5. Page 14, line 27 : binomial negative regression -> negative binomial regression

Response: Corrected.

6. The potential predictors in the "STATISTICAL ANALYSIS PLAN" is different from those in the main text.

Response: Correct; we now specify that the exhaustive list of potential predictors is shown in the statistical analysis plan.

7. Page 1 – line 43: as stated earlier the 'politics' of going for placebo arms is clear to this reviewer, but the use of political reasons' for a scientific protocol for a medical research project is a bit colloquial. Suggest either rewording or more objectively outlining the concerns (eg lack of vendor participation due to the potential new information about treatment effect of their marketed or under-development product).

Response: Thank you. Sentence now reads: 'We will not pursue the active arms' data to promote collaboration between competing sponsors but envision a de-centralised computation of individual treatment benefit and aggregate performance measures, such as the c-for-benefit statistic, at a later stage.'

Reviewer 2: Prof Dinh-Xuan

Comments to author

This is a protocol for a systematic review and control arm patient-level meta-analysis for clinical prediction modelling. In essence, the authors proposed to do a systematic MEDLINE search from January 1993 to April 2021 looking for all randomised controlled trials (RCTs) that have investigated the effect of fixed treatment(s) regimen(s) on severe asthma exacerbation rates over at least a 6-months period, with documented values of blood eosinophils and FeNO at baseline. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and the methodological appraisal of the studies will be assessed by the Cochrane Risk-of-Bias Tool for RCTs.

The predicted outcome is the absolute number of severe asthma attacks occurring in the following 12 months if anti-inflammatory therapy is not changed. The strenghts and weaknesses of this approach are thoroughly discussed by the authors highlighting the added-value of this clinical prediction model centered on two type-2 inflammatory biomarkers, namely blood eosinophils and exhaled nitric oxide, to improve treatable trait-based management of patients with asthma.

The authors are seasoned experts in the field with respectable records of publications on this topic.

The protocol is relevant and the information it will provide will help to advance the field of type-2 inflammatory biomarkers and asthma management.

Response: Thank you.

VERSION 2 – REVIEW

REVIEWER	Sadatsafavi, Mohsen recommended University of British Columbia, Division of Respiratory Medicine, Faculty of Medicine
REVIEW RETURNED	02-Feb-2022

GENERAL COMMENTS	I am happy with the response and changes made to the manuscript.