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## STATEMENT OF INTEREST

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*To the Editors:*

For statistical analysis of chronic obstructive pulmonary disease (COPD) exacerbations, one of the key arguments against the Poisson model with overdispersion correction in the study by KEENE *et al.* [1] is that only the negative binomial model takes into account variability across the patients. However, the Poisson model with overdispersion can also be viewed as equivalent to each individual having their own rate of exacerbations and the rate varying across the population following a gamma distribution [2, 3]. Another key argument by KEENE *et al.* [1] against the Poisson model with overdispersion is that it assumes a common mean for the entire population and weighs each unit of time equally. The negative binomial model also assumes a common mean for the entire population but weighs each unit of time differently. The variance for the Poisson model with overdispersion is a linear function of the mean while the variance for the negative binomial model is a quadratic function of the mean. Therefore, large and small counts are weighted differently in the two models but one set of weights is not necessarily better than the other [4]. Because of the comparable complexity of these two models, one should compare model fitting to select a better model. It is possible that for the specific trials the authors described [1] the negative binomial model fitted better; however, in other trials the Poisson model with overdispersion would fit better. In a trial of short duration, very few patients are expected to have exacerbations and the zero-inflated Poisson model [5] is likely to fit the data better than either of the two models previously described.

One of the problems with the analysis of multiple exacerbations is that the exacerbations are not of similar duration or severity. Some are resolved within a few days while others may continue for several months. In a trial of fixed duration, the number of exacerbations may depend on the length of exacerbations. If a patient has an exacerbation of long duration in the early stages of the trial there is less time remaining for the patient to have additional exacerbations. This could be erroneously considered as an advantage over a patient who has two exacerbations of short duration towards the end of the trial. Another issue with analysing multiple exacerbations using the Poisson or negative binomial model is that both models implicitly assume a constant rate of exacerbation over time, which is highly questionable as the reoccurrence of exacerbations depends on how a patient recovers from previous events. KEENE *et al.* [1] question the assumption of proportional hazard in the analysis of time-to-first exacerbation but in fact the underlying assumption of the Poisson or negative binomial model is a Poisson process, *i.e.* for a patient the occurrences of exacerbations are independent and the time interval between two adjacent exacerbations follows an exponential distribution. Such assumption further implies not only proportional hazard but also a constant baseline hazard. Overall, the assumptions behind the Poisson or negative binomial model are much stronger than the assumption of proportional hazard. Therefore, in terms of relying on less stringent assumptions, time-to-first event is superior to analysis of number or rate of COPD exacerbations to compare clinical interventions. A clinical intervention that reduces the risk of the first moderate-to-severe COPD exacerbation should be of great clinical value. Subsequent exacerbations may depend on how the first exacerbation is treated and, therefore, the effect of the study drug would be confounded with the medical treatment of the first exacerbation.

In summary, the key difference between the Poisson model with overdispersion and the negative binomial model is the form of mean-variance function. The two models have different weighting schemes, but one is not always superior to the other. The time-to-first event analysis methods assume constant hazard ratio between treatments over time but that is a much weaker assumption than the assumptions for the Poisson and negative binomial models. Time-to-first exacerbation is a much cleaner end-point than number of exacerbations, and should be considered as the most appropriate way to analyse chronic obstructive pulmonary disease exacerbations.

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*From the authors:*

We would like to thank D. Liu and S. Menjoge. Their letter has raised some statistical issues regarding the Poisson model with overdispersion correction and analysis of time-to-first event.

For the Poisson model with overdispersion correction, they state that this model ''can also be viewed as equivalent to each individual having their own rate of exacerbations and the rate varying across the population following a gamma distribution'' and provide two references for this statement. Unfortunately neither reference actually supports this view. In the first, McCullagh and Nelder [1] specifically state that a mixture of a Poisson rate for each individual with a gamma distribution across the population ''leads to the negative binomial distribution''. In the second, Liu and Dey [2] briefly mention using a Poisson model with overdispersion correction as a simple approach but again do not place the quoted interpretation on this model. In fact, most of the paper is devoted to the negative binomial model and states ''we confirm that negative binomial regression usually accounts for microlevel heterogeneity (overdispersion) satisfactorily'' [2].

D. Liu and S. Menjoge further state that in order to decide between the Poisson model with overdispersion correction and the negative binomial model ''one should compare model fitting to select a better model''. This advice is contrary to the need in clinical trials to pre-specify the statistical analysis ahead of unblinding the data. In another cited paper, ver Hoef and Boveng [3] discuss difficulties in determining the best model based on the model fit and advise that ''a good understanding of the theoretical differences between them can form the basis for an *a priori* decision based on scientific purposes''.

For the time-to-first event analysis, D. Liu and S. Menjoge state that this assumes a ''constant hazard ratio between treatments over time but that is a much weaker assumption than the assumptions for Poisson and negative binomial models''. Our study [4] clearly states that the time-to-first event approach is a simpler analysis than that involving the negative binomial model and we acknowledge the extra assumptions needed by the more sophisticated model. However, use of time-to-first event analysis requires that data collected on exacerbations beyond the first exacerbation be explored. The analysis of time-to-first exacerbation leads to a hazard ratio for the risk of experiencing an exacerbation in any given time interval. This is not as easy to interpret clinically as the reduction in exacerbation rates from the negative binomial model.

Therefore, we maintain our view that, currently, negative binomial regression is the method of choice for analysing exacerbation rates. In contrast to the overdispersed Poisson model, this model does not assume one single rate and then introduce an arbitrary correction for overdispersion. As we have stated, it can be useful to supplement the primary analysis with secondary sensitivity analysis using time-to-first event methods.

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# Is air travel safe for those with lung disease?

*To the Editors:*

We are grateful to Marchand [1] for his interest in our report, ''Is air travel safe for those with lung disease?'' [2], and we would like to make the following response to the interesting questions he posed [1].

A total of 464 patients had resting sea-level arterial oxygen saturation measured by pulse oximetry ($S_{p,O_2}$) of 92–95%. Out of these, 132 (28%) underwent hypoxic challenge testing (HCT). Current British Thoracic Society (BTS) guidelines on air travel and lung disease [3] do not recommend HCT in all of these patients, but only in those with an additional risk factor,