Bronchoconstriction, after removal of a catecholamine-producing tumour, is physiologically foreseeable owing to the sudden deprivation of catecholamines, as well as deprivation of other tumour-secreted bronchodilator substances, such as adrenomedullin [4], vasoactive intestinal peptide or pituitary adenylate cyclase-activating peptide [5]. There are, however, few reports of respiratory problems in patients with pheochromocytoma and all, in contrast to ours, had a history of asthma and/or were being treated with β-blockers [6, 7]. Our patient has, since the acute post-operative period, been feeling perfectly well. She is back in the gym on a regular basis, her cardiac frequency is normal and she has not had any further respiratory problems.

It is therefore good to keep in mind that bronchospasm, and not only cardiovascular collapse, is a possible incident that can occur after removal of a catecholamine-producing tumour.

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STATEMENT OF INTEREST

None declared.

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Statistical analysis of COPD exacerbations

From the authors:

We would like to thank S. Suissa for his letter, which appeared in a recent issue of the *European Respiratory Journal* [1]. We share his interest in the methodology of chronic obstructive pulmonary disease (COPD) trials. The issues he raised are important and deserve a more comprehensive response than is possible here. We would, however, like to address the two major points regarding the design of the TRISTAN (Trial of Inhaled Steroids and Long-acting β_2-agonists) and ISOLDE (Inhaled Steroids in Obstructive Lund Disease) trials, which lead him to claim that the trials ''violate fundamental principles of randomised trial methodology'' [1].

First, S. Suissa contends that intent-to-treat analysis is impossible when there is incomplete follow-up of patients who withdraw from the study [1]; but this assertion is incorrect. Intent-to-treat analysis does require inclusion of all available subjects in the analysis but the principle allows for missing data. The CONSORT (Consolidated Standards of Reporting Trials) statement is the standard guideline for reporting randomised clinical trials adopted by major medical journals [2]. An accompanying article to the 2001 revision of CONSORT states: ''It is common for some patients not to complete a study – they may drop out or be withdrawn from active treatment – and thus are not assessed at the end. Although these patients cannot be included in the analysis, it is customary still to refer to analysis of all available participants as an intent-to-treat analysis'' [3]. In the analysis of TRISTAN and ISOLDE, all available patients were included and therefore the results presented are from a valid intent-to-treat analysis.

Secondly, S. Suissa states that the design of COPD trials needs to be stratified by prior use of inhaled corticosteroids (ICS) and suggests that this deficiency ''cannot simply be corrected by data analysis'' [1]. Stratifying a design by important predictors of outcome can be helpful in terms of ensuring balance, but it is not essential for data analysis. In large trials, randomisation will lead to similar proportions of patients in each treatment arm with prior use of ICS. Indeed, the standard textbook on clinical trials, *Clinical Trials: a Practical Approach*, states: ''if the trial is very large, say several hundred patients […] then stratification has little point'' [4].

Thus, the designs of ISOLDE and TRISTAN conform to conventional clinical trial methodology and therefore have no major flaws. It remains valid to draw conclusions regarding the effectiveness of inhaled corticosteroids based on their outcome.

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STATEMENT OF INTEREST

Statements of interest for all authors of this manuscript can be found at www.erj.ersjournals.com/misc/statements.shtml

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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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STATEMENT OF INTEREST

Statements of interest for D. Liu and S. Menjoge can be found at www.erj.ersjournals.com/misc/statements.shtml

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