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ARTICLE

A stochastic mixed effects model to assess treatment effects and fluctuations in home-measured peak expiratory flow and the association with exacerbation risk in asthma

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Abstract

Home-based measures of lung function, inflammation, symptoms, and medication use are frequently collected in respiratory clinical trials. However, new statistical approaches are needed to make better use of the information contained in these data-rich variables. In this work, we use data from two phase III asthma clinical trials demonstrating the benefit of benralizumab treatment to develop a novel longitudinal mixed effects model of peak expiratory flow (PEF), a lung function measure easily captured at home using a hand-held device. The model is based on an extension of the mixed effects modeling framework to incorporate stochastic differential equations and allows for quantification of several statistical properties of a patient's PEF data: the longitudinal trend, long-term fluctuations, and day-to-day variability. These properties are compared between treatment groups and related to a patient's exacerbation risk using a repeated time-to-event model. The mixed effects model adequately described the observed data from the two clinical trials, and model parameters were accurately estimated. Benralizumab treatment was shown to improve a patient's average PEF level and reduce long-term fluctuations. Both of these effects were shown to be associated with a lower exacerbation risk. The day-to-day variability was neither significantly affected by treatment nor associated with exacerbation risk. Our work shows the potential of a stochastic model-based analysis of home-based lung function measures to support better estimation and understanding of treatment effects and disease stability. The proposed analysis can serve as a complement to descriptive statistics of home-based measures in the reporting of respiratory clinical trials.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Home-based measurements of lung function are frequently collected in respiratory clinical trials. Novel statistical methods for analyzing these data-rich measurements are emerging, but more work is needed to better characterize the data and what it can tell us about treatment effects and disease stability.

WHAT QUESTION DID THIS STUDY ADDRESS?

Can a stochastic model-based analysis of home-based measurements of peak expiratory flow (PEF) be used to improve the understanding of lung function dynamics, treatment response, and exacerbation risk in asthma?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

A stochastic model of home-measured PEF was developed, providing a robust way of characterizing statistical properties of the data. Results show that both trends and fluctuations in PEF can be affected by treatment and are associated with exacerbation risk.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

A stochastic model-based analysis of PEF can support better estimation and understanding of treatment effects, disease stability, and exacerbation risk. Furthermore, it can serve as a complement to descriptive statistics of home-based PEF in the reporting of clinical trials.

INTRODUCTION

Respiratory clinical trials commonly include the collection of home-based measurements, allowing for the frequent monitoring of patients. Home-based measurements may include, for example, peak expiratory flow (PEF), forced expiratory volume in 1 s, fractional exhaled nitric oxide (FeNO), and patient reported outcomes, such as symptoms and reliever medication use. Currently, the use of these variables is often limited to the triggering of alerts, for example, that the patient should contact the treating physician, or as exploratory efficacy end points reported with descriptive statistics. However, in the search for new end points to characterize respiratory disease severity and treatment efficacy, new ways of analyzing these data-rich variables are emerging.

One concept currently being evaluated for use in respiratory clinical trials is disease fluctuations,[1] that is, seemingly random deviations in frequently measured disease variables. CompEx[2] is one example of a novel end point where changes in daily diary variables—specifically PEF, symptoms, and reliever use—are used to identify episodes of asthma deteriorations based on prespecified thresholds. Combined with severe exacerbations—a frequently used primary end point in late-phase asthma clinical trials defined as disease worsening requiring systemic corticosteroids or hospital admission—these deteriorations create a composite event end point with a higher event rate compared to exacerbations alone, thus providing an opportunity to detect treatment effects in shorter and/or smaller trials. Similar diary-based end points developed for chronic obstructive pulmonary disease (COPD) are COPDCompEx[3] and EXACT-PRO.[4]

In addition to these event end points—which essentially reduce the information in frequently sampled longitudinal data to one or a few timepoints—other approaches to analyze disease fluctuations have been suggested. One such approach is detrended fluctuation analysis (DFA), which assesses the self-similarity (long-range correlation) of time series data.[5,6] The self-similarity is quantified by a positive parameter α, where $\alpha = 0.5$ indicates a noncorrelated random time series and $\alpha > 0.5$ indicates the presence of long-range correlations. DFA has mainly been applied to daily sampled PEF data,[1,7–10] where a patient's α_{PEF} is shown to be significantly associated and predictive of exacerbation risk. α_{PEF} also appears to change with type of treatment,[7] and results from Donaldson et al.[10] indicate that fewer patients may be needed to detect a treatment difference in α_{PEF} compared with exacerbation frequency.

Another stochastic property of daily sampled PEF data often assessed together with α_{PEF} is the coefficient of variation (CV_{PEF}), giving an overall measure of a patient's lung function variability over a certain time period. High CV_{PEF} has been shown to be associated with loss of asthma control,[7,9] further highlighting the value of assessing lung function fluctuations in respiratory diseases.

Although α_{PEF} and CV_{PEF} seem to hold potential for use in disease management and as clinical trial end points, most analyses evaluating these variables have included a limited number of patients. In addition, the standard DFA comes with some limitations, including the assumed log-log linearity of the measured signal's power spectrum, its sensitivity to missing values, and the need for rather long time series to avoid biased estimates of α.[11] In large phase III clinical trials, diary compliance is not always perfect, and many patients can have periods of missing values. Patients may also end the trial early, with limited data available for estimating both α_{PEF} and CV_{PEF}.

In this work, we present an alternative way to model and analyze the statistical properties of PEF time series in a clinical trial setting. Specifically, we identified stochastic

differential equations mixed effects (SDEME) models as a suitable statistical framework to model PEF data.[12–16] The framework provides several advantages: (1) stochastic differential equations offer great flexibility when modeling stochastic processes and can be designed to have arbitrary complexity, (2) the use of mixed effects allows sharing information on parameter values across individuals, (3) treatment effects can be easily incorporated and estimated, and (4) missing values are typically not an issue.

We develop our SDEME model based on data from two pivotal phase III clinical trials demonstrating the effects of benralizumab (Fasenra®, AstraZeneca) on top of standard of care in patients with moderate to severe asthma.[17,18] The estimated model parameters—including a patient's long-term and short-term PEF variability as well as average PEF response—are compared with estimates of α_{PEF} and CV_{PEF} and related to asthma exacerbation risk using a repeated time-to-event (RTTE) model. We also investigate treatment differences in these model parameters.

METHODS

Clinical trial data

Patient-level data from two phase III, randomized, double-blind, parallel-group, placebo-controlled, multicenter clinical trials including patients with moderate to severe asthma served as the basis for model development and analysis (Table 1). Both trials investigated the efficacy of benralizumab on top of standard of care and were selected based on (1) a long study period and a large sample size; (2) the availability of daily, diary-based PEF measurements; and (3) the presence of a significant treatment effect on lung function and exacerbations. The details of the trials have been presented elsewhere,[17,18] but a summary follows.

Trial A (NCT01914757) enrolled patients aged 12–75 years with severe uncontrolled asthma and at least two exacerbations while on medium-to-high-dosage inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA) in the previous year. In total, 1306 patients were randomly assigned to either placebo, benralizumab 30 mg every 4 weeks, or benralizumab 30 mg every 8 weeks (first three doses every 4 weeks) as an add on to their standard treatment. The treatment period was 56 weeks.

Trial B (NCT01928771) enrolled patients aged 12–75 years with a diagnosis of asthma for at least 1 year and at least two exacerbations while on high-dosage ICS and LABA in the previous year. In total, 1205 were randomly assigned to either placebo, benralizumab 30 mg every 4 weeks, or benralizumab 30 mg every 8 weeks (first three doses every 4 weeks) as an add on to their standard treatment. The treatment period was 48 weeks.

Both trials were conducted in accordance with the Declaration of Helsinki, the International Conference on

TABLE 1 Summary of clinical trial data sets

	Data set A	Data set B
Description	CALIMA study[17] (NCT01914757)	SIROCCO study[18] (NCT01928771)
Treatment duration (weeks)	56	48
Treatment groups (1:1:1 randomization ratio)	Placebo Benralizumab 30 mg every 4 weeks Benralizumab 30 mg every 8 weeks (three first doses every 4 weeks)	Placebo Benralizumab 30 mg every 4 weeks Benralizumab 30 mg every 8 weeks (three first doses every 4 weeks)
Number of patients in original[a] data set	1306	1205
Number of patients in analysis[b] data set	1245	1107
Analysis[b] data set characteristics		
Age, mean (SD)	49.4 (14.2)	48.9 (14.4)
Number of males (%)	480 (39%)	375 (34%)
Baseline PEF, mean (SD)	248.1 (113.7)	236.1 (113.2)
Number of PEF observations	421 859	311 958
Average number of PEF observations/patients	338.8	281.8
Total number of moderate/severe exacerbations	989	1012
Number of patients with at least one exacerbation	516	474

Abbreviations: PEF, peak expiratory flow; SD, standard deviation.

[a]Before removal of patients not eligible for data reuse.

[b]After removal of patients not eligible for data reuse.

Harmonization Guidelines for Good Clinical Practice, and applicable regulatory requirements. Before the analysis, all informed consent forms were reviewed for data reuse in accordance with AstraZeneca data-sharing rules. Patients from countries where ethics committees do not approve data reuse as well as patients who had withdrawn consent were excluded. Consequently, the data used in this work are a subset of the original trial data and any direct comparison with the original trial results should be made with care (see Table 1 for a comparison of the number of patients included in the original trials and in this analysis). We refer to the trial data used in this analysis as data sets A and B.

PEF and exacerbations

Home-measured morning PEF (unit: L min^{-1}) measurements, collected daily in an electronic diary system, were considered for development of the SDEME model. Observations from 2 weeks before the first dose (baseline measurements) up to 4 weeks after the last dose were included based on study designs and the pharmacokinetic properties of benralizumab.[19]

Before model development, obvious outliers in the PEF time series were removed. This was done by calculating the interquartile range (IQR) for each patient and removing observations outside the interval (Q1 − 2 × IQR, Q3 + 2 × IQR), where Q1 and Q3 denote the first and third quartiles of the observations. In total, 7077 of 740,894 (0.96%) PEF observations were removed.

For the analysis of association between the properties of a patient's PEF response and asthma exacerbation risk, exacerbations taking place after the first dose and up to 4 weeks after the last dose were considered. Asthma exacerbations were defined as in the original study protocols, that is, as worsening of asthma that led to (1) use of systemic corticosteroids for 3 days or more or a temporary increase in a stable, background dosage of oral corticosteroids; (2) an emergency department or urgent care visit (<24 h) attributed to asthma that required systemic corticosteroids; and/or (3) an inpatient admission to hospital (≥24 h) attributed to asthma. Worsening of asthma was defined as any new or increased symptoms or signs that were concerning to the patient or related to an Asthma Daily Diary alert.

Statistical modeling and analysis

The statistical modeling and analysis of the PEF and exacerbation data consists of the following three parts: (1) development of an SDEME model of PEF, (2) the analysis of the association between a patient's SDEME model parameter estimates and asthma exacerbation risk, and (3) the comparison of the SDEME model results to a standard DFA and coefficient of variation (CV) analysis of PEF data.

A stochastic differential equation mixed effects model of PEF

SDEME models are extensions of the frequently used nonlinear mixed effects models with differential equations, where the underlying dynamical system includes stochasticity (e.g., biological and environmental stochastic effects). Thus, SDEME models provide a means to distinguish the following three sources of variability: interindividual variability (IIV), stochasticity in the dynamics (also known as system noise), and measurement noise.[16,20] As this is—to the authors' best knowledge—the first application of an SDEME model to analyze daily lung function measurements, the model structure was developed with the following criteria in mind: (1) the model should be conceptually simple with interpretable parameters, (2) it should be able to describe the most important stochastic characteristics and trends of the PEF data, and (3) it should be computationally feasible and robust enough to be applied to large sets of clinical trial data.

The PEF model is illustrated in Figure 1. The model has the following three components: one component that describes a deterministic response (i.e., the trend induced by treatment), one component that describes long-term fluctuations around the deterministic response, and one additional component to capture day-to-day variability. The three components are detailed in the next paragraphs.

The deterministic response was described using a turnover model given by the ordinary differential equation

$$\frac{dx(t)}{dt} = k_{tr}\left(PEF_{base}\,(1+eff) - x(t)\right),\; x(0) = PEF_{base}.$$

In this equation, PEF_{base} (unit: L min^{-1}) and eff (unitless) represent the baseline PEF and asymptotic treatment effect (set to zero before treatment initiation), respectively. The two arms with benralizumab treatment in each trial were pooled into a single active treatment group. The treatment effect was modeled as relative to baseline, which was supported by exploratory data analyses and model diagnostics. The parameter k_{tr} (unit: day^{-1}) is the rate constant of the turnover process describing the onset of treatment effect (different values estimated for active treatment and placebo, respectively). Exploratory analyses revealed a strong influence of age (centered around 50 years of age) and sex (female as the reference group) on the PEF baseline, and this together with a random effect,

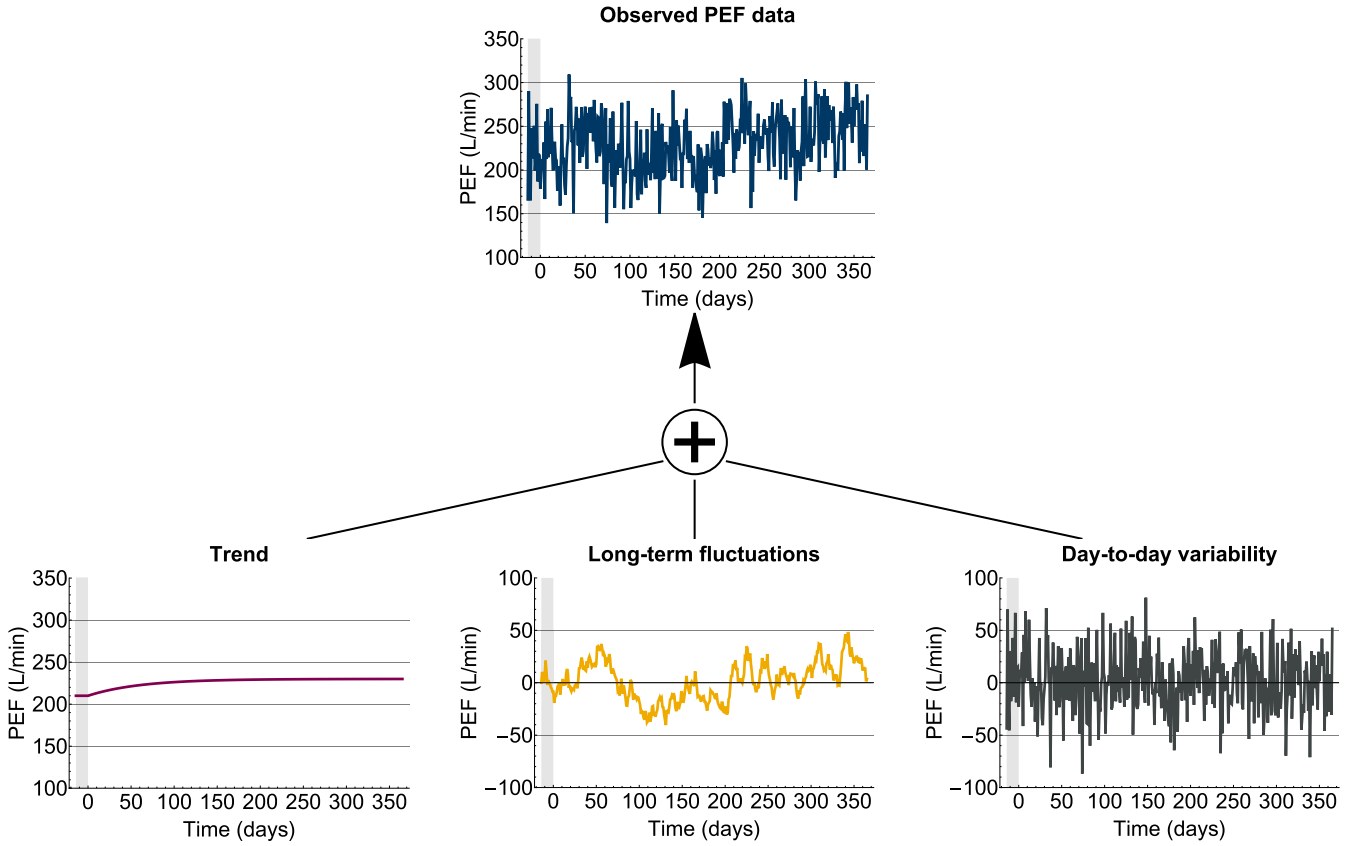

FIGURE 1 Illustration of the longitudinal PEF model. The observed PEF time series is modeled by the following three components: trend, long-term fluctuations, and day-to-day variability. PEF, peak expiratory flow

η_{base}, were incorporated to model the PEF baseline on an individual level:

$$PEF_{base} = \left(PEF_{base,\,female} + sex\,\Delta PEF_{base,\,male} + PEF_{base,\,age}(age - 50)\right)\,\exp\left(\eta_{base}\right),$$

where the covariate *sex* is 0 for female and 1 for male. In addition, *eff* was allowed to take different values depending on treatment group (active or placebo) and modelled using an additive random effect η_{eff}

$$eff = eff_k + \eta_{eff}, k \in \{plac,\ active\}$$

The stochastic dynamics (here referred to as long-term fluctuations) is modeled by an Ornstein-Uhlenbeck (OU) process. The OU process is a stationary stochastic process, which tends to drift toward its mean (set to zero in this case). The process is described by the following stochastic differential equation:

$$\mathrm{d}v(t) = -k_v\, v(t)\ \mathrm{d}t + g\,\mathrm{d}W(t),\ v(0) = 0,$$

where $W(t)$ is a standard Wiener process, k_v (unit: day^{-1}) is the so-called mean reversion speed, and g (unit: L min^{-1} day$^{-1/2}$) is a scaling factor for the stochastic component, referred to as the magnitude of the long-term fluctuations. Note that in the case $g = 0$, this corresponds to a standard turnover model with the constant solution $v(t) = 0$, whereas for $g > 0$, the process will fluctuate around 0. The larger the value of g, the more the fluctuations will deviate from the mean. The frequency distribution and correlation over time of the fluctuations is determined by k_v (increasing correlation over time with decreasing mean reversion speed). The quantity $1/k_v$ is sometimes referred to as the characteristic correlation time of the process.

The actual PEF observations are finally modeled by the sum of the deterministic response, the long-term fluctuations, and the day-to-day variability, denoted $\sigma\, e(t_k)$:

$$PEF(t_k) = x(t_k) + v(t_k) + \sigma e(t_k)$$

where $e(t_k) \sim \mathcal{N}(0,1)$, $k = 1, \cdots, n$ are independent standard normal random variables, and σ (unit: L min^{-1}) is the magnitude (standard deviation) of the day-to-day variability. The day-to-day variability is assumed to include, for example, uncorrelated physiological changes on short timescales and device measurement errors.

To account for IIV in the day-to-day variability, as well as the long-term fluctuations, random effects on σ and g are introduced according to the following relationships:

$$\sigma = \sigma_{plac}\left(p_{\sigma,\,active}\right)^{treatment}\exp(\eta_\sigma),$$

$$g = g_{plac}\left(p_{g,\,active}\right)^{treatment}\exp(\eta_g),$$

where *treatment* denotes the treatment covariate, which is set to 0 for placebo and 1 for active. The parameters σ_{plac} and g_{plac} denote the population-typical values for the magnitude of the day-to-day variability and the magnitude of the long-term fluctuations for the placebo group, respectively, and $p_{\sigma,\,active}$ and $p_{g,\,active}$ denote multiplicate (additive on log-scale) treatment covariate effects. Note that the inclusion of IIV on the day-to-day variability implies that the magnitude of the day-to-day variability varies between patients, but not within. The inclusion of IIV on the residual error has previously been adopted by others in the context of pharmacokinetic–pharmacodynamic modeling.[21]

In total, the model has four random effects, and the random-effects vector $\boldsymbol{\eta} = \left(\eta_{base}, \eta_{eff}, \eta_\sigma, \eta_g\right)$ is assumed to be multivariate normally distributed with a mean of zero and covariance matrix $\boldsymbol{\Omega}$.

Separate PEF models were estimated for data sets A and B.

Estimation of model parameters and model selection

The model parameters were estimated using the first-order conditional estimation with interaction method, as implemented in the open-source Wolfram Mathematica package NLMEModeling.[22,23] Because of the stochastic dynamics of the underlying system, the extended Kalman filter (EKF) was used to estimate the state of the system.[16,24] Similar to other implementations,[25] NLMEModeling automatically generates the necessary equations for the EKF.

Model selection was based on a combination of measures, including log-likelihood value, goodness-of-fit assessments, visual predictive checks, inspection of empirical Bayes estimates (EBEs), and parameter precision. Inclusion of off-diagonal elements in the random-effects covariance matrix $\boldsymbol{\Omega}$ was guided by empirical assessment of the EBEs. The shrinkage for EBEs was calculated on the standard deviation scale.

The standard errors of the parameter estimates were calculated from the variance–covariance matrix of the parameter estimates.

Association with asthma exacerbation risk

The association between a patient's PEF model parameters (using the EBEs) and the risk of asthma exacerbations was assessed in an RTTE analysis based on pooled data from data sets A and B. The RTTE analysis was done based on a Cox proportional hazards model with a γ-distributed frailty parameter, resulting in an RTTE model often referred to as a shared frailty model.[26,27] The frailty describes the (unexplained) between–patient variability in exacerbation risk and acts proportionally on the baseline hazard. Hence, the exacerbation risk for individual i is modeled according to the relationship

$$h_i(t) = h_0(t)\, u_i \exp\left(\boldsymbol{X}_i^T \boldsymbol{\beta},\right)$$

where $h_0(t)$ denotes the baseline hazard, u_i is the γ-distributed frailty, $\boldsymbol{X}_i$ denotes the individual covariates, and $\boldsymbol{\beta}$ are the corresponding regression coefficients. Covariates considered in the RTTE analysis were the factors study, treatment group, age, and sex as well as the individual model parameters PEF_{base}, eff, and g.

The R package frailtyEM was used to perform the RTTE analysis using the Anderson–Gill method for counting processes to handle repeated events.[28,29]

Detrended fluctuation analysis

DFA is a method for studying long-range correlations in a signal. The output of the analysis is a positive scaling exponent α, where $\alpha = 0.5$ indicates the signal is uncorrelated and increasing values of α indicate increasingly stronger long-range correlations.[5,6] Several published articles have used DFA to quantify long-range correlations in frequently measured PEF data and assessed its association with exacerbation risk.[7,8,10]

The DFA implementation in the Python package fathon was used to calculate α in this analysis.[30] Because of the sensitivity of the method to missing data and short time series, a DFA was only performed on patients with more than 6 consecutive months of PEF observations including less than 3% missing values.[7] Linear interpolation was used to get a regularly sampled time series in case of missing values. The steady-state CV (CV_{ss}), based on data 100+ days after treatment initiation, was also calculated for each of these patients, and between–group (active vs. placebo) comparisons of α and CV_{ss} were performed on pooled data (data sets A and B) using a two-sample t-test. The α values were also correlated with the EBEs of g and σ for each patient using the Spearman rank correlation.

RESULTS

Clinical data characteristics

The clinical trial data used in the analysis are summarized in Table 1. In total, 421,859 and 311,958 observations of

morning PEF were available for analysis in data sets A and B, with an average number of 339 and 282 observations per patient, respectively. The total number of moderate to severe exacerbations in the two analysis data sets were 989 in data set A and 1012 in data set B, with 516 and 474 patients having at least one exacerbation, respectively. The observed PEF_{base} was slightly higher in data set A compared with data set B (mean 248 L/min and 236 L/min, respectively), whereas the age distribution in both trials were similar (median 49 years), and the majority of patients were female (61% and 66%, respectively).

Mixed effects PEF model

Parameter estimates for the two PEF models are listed in Table 2 and visual predictive checks are shown in Figure 2. Additional model diagnostics are provided in

TABLE 2 Estimated PEF model parameters for data sets A and B

			Data set A			Data set B		
Parameter	**Description**	**Unit**	**Estimate**	**RSE (%)**	**Shrinkage (%)[c]**	**Estimate**	**RSE (%)**	**Shrinkage (%)[c]**
$PEF_{base,\ female}$	Baseline PEF, female	$L\ min^{-1}$	212	1.04		202	1.18	
$\Delta PEF_{base,\ male}$	Baseline PEF, male effect	$L\ min^{-1}$	59.4	6.61		45.4	9.41	
$PEF_{base,\ age}$	Baseline PEF, age effect	$year^{-1}$	−0.514	26.3		−0.504	28.1	
$k_{tr,\ placebo}$	Rate constant, treatment, placebo	day^{-1}	0.0104	8.90[d]		0.0103	10.2[d]	
$k_{tr,\ active}$	Rate constant, treatment, active	day^{-1}	0.0166	5.28[d]		0.0297	6.06[d]	
k_v	Mean reversion speed, long-term fluctuations	day^{-1}	0.0314	2.18[d]		0.0309	2.53[d]	
eff_{plac}	Treatment effect, placebo	–	0.0313	24.6		0.0396	22.4	
eff_{active}	Treatment effect, active	–	0.0912	6.01		0.0956	6.31	
σ_{plac}	Magnitude of day-to-day variability, placebo	$L\ min^{-1}$	27.9	1.36[d]		28.7	1.53[d]	
$p_{\sigma,\ active}$	Magnitude of day-to-day variability, active effect	–	0.996	1.61[d]		0.975	1.79[d]	
g_{plac}	Magnitude of long-term fluctuations, placebo	$L\ min^{-1}\ day^{-1/2}$	5.75	1.96[d]		6.29	2.16[d]	
$p_{g,\ active}$	Magnitude of long-term fluctuations, active effect	–	0.953	2.27[d]		0.884	2.49[d]	
Ω, IIV[a]								
PEF_{base}			0.404	1.57	1.90	0.455	1.65	1.95
σ			0.418	1.45	1.27	0.449	1.52	0.853
g			0.535	1.68	4.44	0.568	1.76	3.51
eff			0.180	2.42	14.1	0.182	2.86	16.0
Ω (off-diagnal elements)[b]								
$PEF_{base} - \sigma$			0.447	4.12		0.492	3.70	
$PEF_{base} - g$			0.411	4.72		0.487	3.92	
$\sigma - g$			0.673	1.98		0.679	2.05	
$\sigma - eff$			0.128	17.1		0.170	13.7	
$g - eff$			0.268	8.76		0.293	8.60	

Abbreviations: CV%, percent coefficient of variation; IIV, interindividual variability; PEF, peak expiratory flow; RSE, relative standard error.

[a]Reported on the standard deviation scale.

[b]Reported as pairwise correlations.

[c]Calculated on the standard deviation scale.

[d]Estimated on log-scale, reported as CV%.

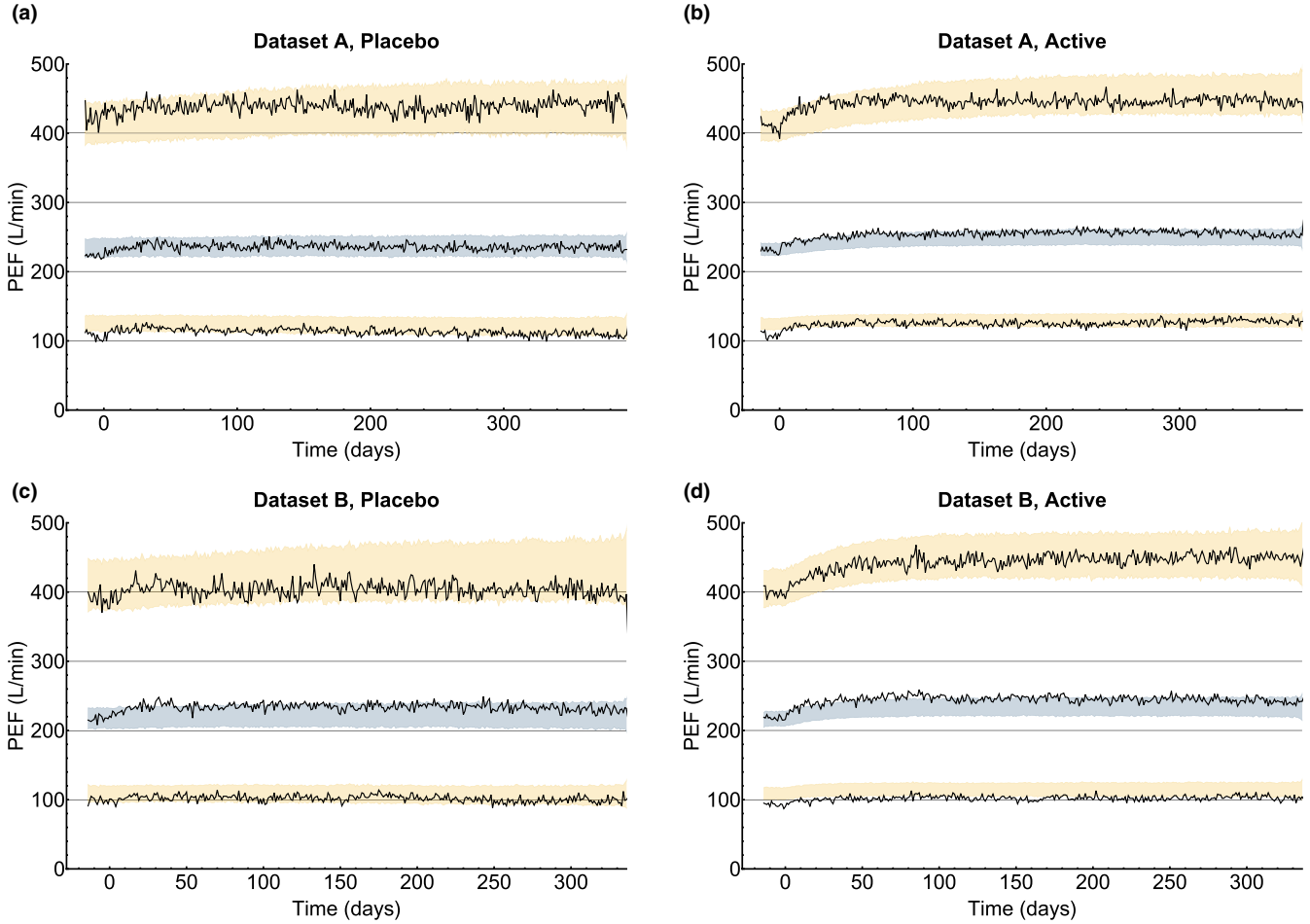

FIGURE 2 Visual predictive checks for the two analysis data sets. The black lines show the 10th, 50th, and 90th percentiles of the observations. The shaded areas are the 95% confidence intervals of the median (light blue) and the 10th and 90th (light gold) percentiles predicted by the model. PEF, peak expiratory flow

Figures S1–S4. Parameter estimates were estimated with adequate precision (relative standard error percentage, <30 for all parameters). The PEF_{base} were estimated slightly higher in data set A, and there was a significant effect of both sex and age in both trials. The estimated asymptotic treatment effects eff_{active} were similar (9.1% and 9.6%, respectively), whereas the placebo effect eff_{plac} was slightly higher in data set B (3.1% and 4.0%, respectively).

During model development, correlations between the EBEs were apparent, and a full random-effects covariance matrix was assessed. However, the correlation between the baseline and treatment random effect was small and hence fixed to zero to improve numerical stability. The shrinkage of the random-effect parameters was small (largest 16.0% for the random effect on treatment effect in data set B).

The rate constant k_{tr} for the treatment response were estimated higher in the active than in the placebo group, with the time to reach 90% of steady state being 80–140 days for the active groups and 220 days for placebo.

The magnitude of the long-term fluctuations g was significantly lower in the active group compared with placebo: −4.7% (95% confidence interval [CI], −8.8% to −0.36%) in data set A and −11.6% (95% CI, −15% to −7.2%) in data set B. No significant difference was seen in the magnitude of the day-to-day variability σ, but there was a trend toward lower values in the active group: −0.4% (95% CI, −3.5% to +2.9%) in data set A and −2.5% (95% CI, −5.9% to +0.98%) in data set B. Similar parameter estimates were obtained using data up to the first exacerbation only, as listed in Table S1.

In Figure 3, the observed PEF time series (black dots) for six randomly selected patients are depicted together with the model prediction for PEF (yellow) and the deterministic treatment response (black, solid line).

Association with exacerbation risk

The results of the RTTE analysis are presented in Table 3. Both sex and age were found to be nonsignificant (p values of 0.63 and 0.41, respectively) and were not

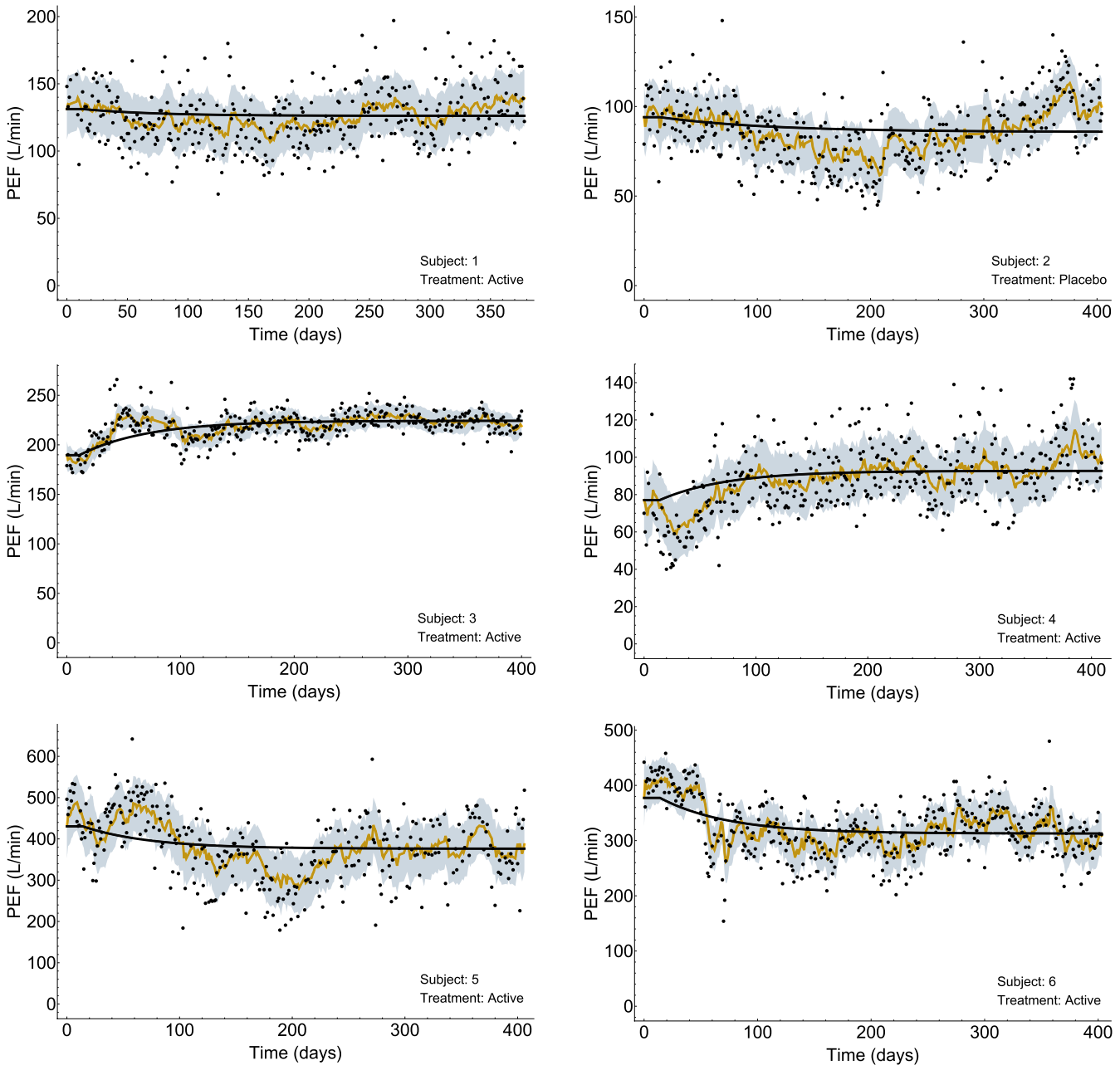

FIGURE 3 Observed and model-predicted PEF response for six randomly selected patients from data set B. The black solid lines show the deterministic treatment response, whereas the yellow fluctuating curves show the long-term fluctuations around the deterministic response. The light-blue shaded areas reflect the uncertainty in the prediction (± standard deviation). PEF, peak expiratory flow

included in the final time-to-event model. Study, treatment group, PEF_{base}, *eff*, and *g* were found to be significantly associated with exacerbation risk. Overall, the risk of exacerbation was slightly higher in data set B, with a hazard ratio (HR) of 1.20 (95% CI, 1.05–1.36) compared with data set A. The estimated HR for active treatment versus placebo was 0.70 (95% CI, 0.61–0.79), with an additional benefit of active treatment being described via some of the PEF parameters. Specifically, both a larger PEF treatment effect asymptote and a reduced magnitude of long-term fluctuations were associated with a lower exacerbation risk (HR < 1). Finally, a high PEF_{base} was also associated with lower risk, whereas σ had no significant association with exacerbation risk ($p = 0.57$). The RTTE results for the sensitivity analysis, listed in Table S2, identified the same significant covariates.

DFA analysis

About one third of all patients (data set A, $n = 464$; data set B, $n = 355$) fulfilled the data quality criteria (≥6 months of data, <3% missing values) to be included in the DFA

TABLE 3 Hazard ratios with corresponding standard errors and *p* values for the estimated repeated time-to-event model[a]

Covariate	Description	Hazard ratio[b]	RSE (%)	*p* value
Study	Study effect, data set B	1.20	6.61	$p < 0.01$
Treatment	Treatment group, active	0.697	6.80	$p < 0.001$
PEF_{base}	Baseline PEF (L min^{-1})	0.996	0.0373	$p < 0.001$
eff	Asymptotic treatment effect (%)	0.981	0.231	$p < 0.001$
σ	Magnitude of day-to-day variability (L min^{-1})	0.998	0.329	0.573
g	Magnitude of long-term fluctuations (L min^{-1} day$^{-1/2}$)	1.10	1.22	$p < 0.001$

Note: Estimated variance of the frailty: 1.13 (95% confidence interval, 0.950–1.29).

Abbreviations: PEF, peak expiratory flow; RSE, relative standard error.

[a]Placebo as a reference treatment group, and data set A as reference study group.

[b]Hazard ratio for one unit increase in continuous variables.

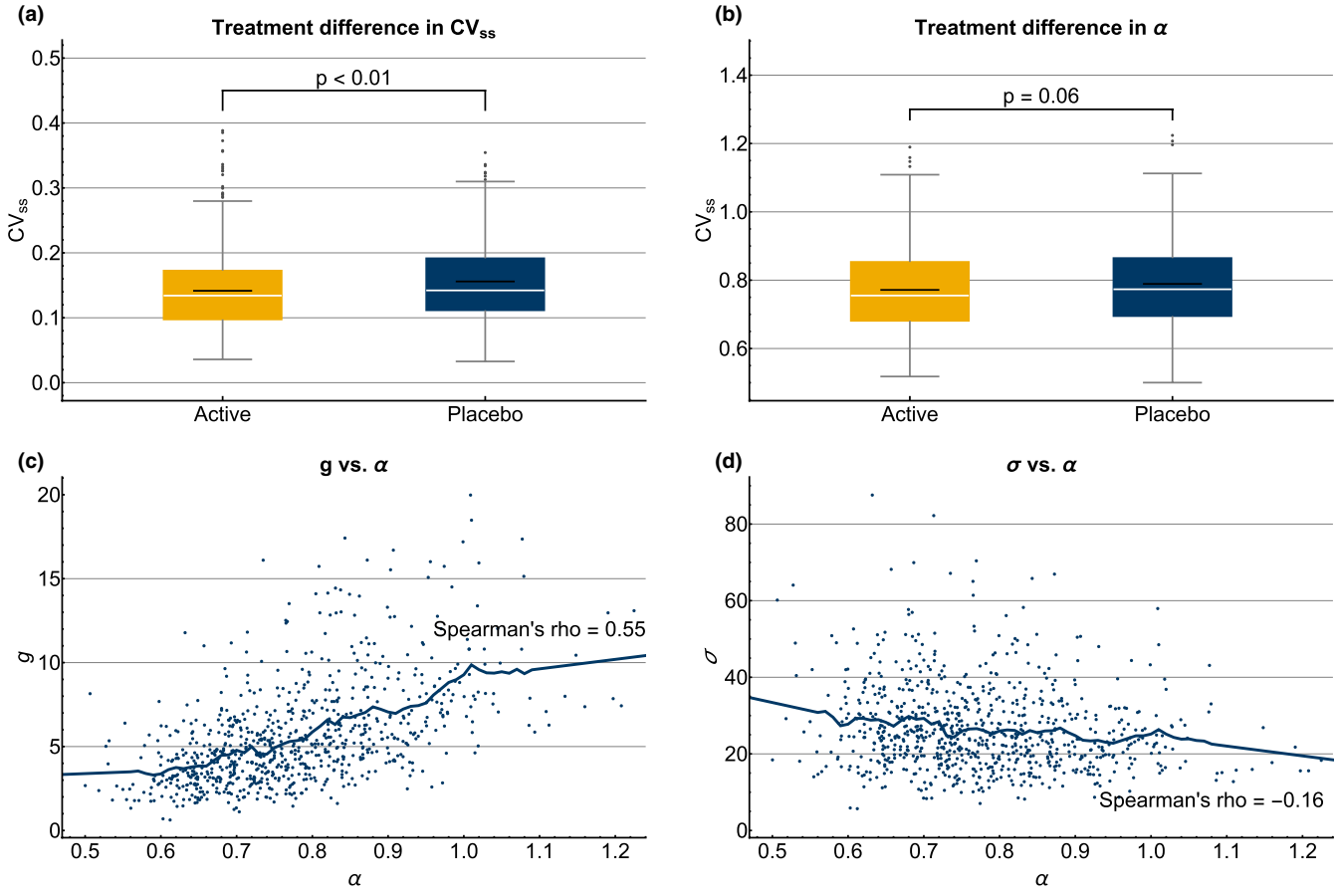

FIGURE 4 Detrended fluctuation analysis results and comparison to individual stochastic differential equations mixed effects model-derived parameters (pooled data). Box plots for (a) CV_{ss} and (b) α for the two treatment groups. Correlation between α and (c) the magnitude of the long-term fluctuations *g* and (d) the magnitude of the day-to-day variability σ; solid lines show a local regression weighted smoother. CV_{ss}, steady-state coefficient of variation

analysis. The distribution of α and CV_{ss} values in placebo and active patients (pooled from the two data sets) are shown in Figure 4a,b. On average, both α and CV_{ss} were lower in patients on active treatment, but only the difference in CV_{ss} was statistically significant ($p < 0.05$).

Figure 4c,d illustrate the correlations between α and *g* and α and σ. The scaling exponent α exhibited a positive correlation with *g* (Spearman $\rho = 0.55$; $p < 0.001$) and a negative correlation with σ (Spearman $\rho = -0.16$; $p < 0.001$).

DISCUSSION

As the use of home-based assessments in respiratory trials increases, the amount of clinical data available to characterize patients and treatment effects is rapidly growing. To make the most out of the data, new statistical approaches are required.

By developing an SDEME model, we have been able to characterize trends and fluctuations in frequently sampled, home-measured PEF data from a large number of patients with asthma enrolled in two phase III clinical trials. With the model, we show that benralizumab, an established effective treatment of asthma, both improves a patient's average PEF level and reduces the magnitude of long-term fluctuations around that level. Furthermore, we show that these effects can be associated with a reduced asthma exacerbation risk.

Our developed PEF model adequately described the observed data in both trial data sets, with consistent estimates of the model parameters overall. The population-typical *eff* of benralizumab (defined as percent change from baseline) was estimated to approximately 9.5% compared with 3.5% for placebo, whereas g was 5%–12% smaller in the benralizumab group. The RTTE analysis indicates that these population-typical improvements in the average PEF level and long-term fluctuations are associated with an exacerbation risk reduction of 11% ($p < 0.001$) and 3%–7% ($p < 0.001$), respectively. It should be noted that these effects constituted only a part of the overall risk reduction, as benralizumab also showed an additional 30% risk reduction ($p < 0.001$) not explained by changes in PEF parameters. Interestingly, the magnitude of the day-to-day variability σ was neither affected by treatment nor associated with exacerbation risk ($p = 0.573$), suggesting that it is particularly longer term PEF fluctuations that are important.

As a drop in PEF is often seen during an asthma exacerbation, it may be no surprise that PEF fluctuations are associated with exacerbation risk. However, in our sensitivity analysis—where we only use data up to before the first exacerbation—we still saw a significant association between a patient's estimated g and exacerbation risk.

Comparing the results the SDEME model to the DFA method, an expected positive correlation between α and g and negative correlation between g and σ were observed—noting that a direct comparison between the approaches is not straightforward.[31] In the subset of patients selected for DFA, there was a nonsignificant trend of lower α values in patients treated with benralizumab as well as a significant difference in CV values (lower in the active group). This is consistent with the significant treatment difference seen in g because a smaller g corresponds to both a smaller α and CV.

An important strength of the SDEME analysis, in contrast to the DFA method, is that information on g is shared between patients and that the weighting of patients with different amounts of data (including missing data) is automatically taken care of in the estimation process. Similar to the DFA, however, our approach also involves making assumptions about the underlying data-generating process. Importantly, we describe the trends in the PEF data using a turnover model, the long-term fluctuations using the OU process, and the day-to-day variability using a white noise process. The sampled version of the OU process is in fact known to be equivalent to an autoregressive process of order 1. Hence, the PEF model includes a correlation between adjacent timepoints, similar to the approach described in Karlsson et al.,[32] but is generalized to also allow for an independent and uncorrelated (between timepoints) part of the residual error.

Our work is limited by the fact that we did not explore alternative stochastic processes to describe the PEF data. Thus, we cannot conclude how well the OU process compares with other possible stochastic models. The SDEME framework, however, makes it convenient to extend our model to possibly capture more complex stochastic characteristics of the data. The OU process is a linear dynamical system, meaning that the Kalman filter provides an optimal estimator.[33] To handle more complex and possibly nonlinear models, one could consider nonlinear estimators, for example, particle filters.[34] There are most likely also other types of variables and information that could be added to our model to explain some of the fluctuations in PEF. Examples of such variables could be known external stimuli, for example, seasonality, rescue medication use, and change in treatment. Another natural extension of the current model would be to incorporate PEF measured in the evening. However, there is evidence on a difference in the PEF level between morning and evening,[35] which an extended model would have to account for.

For future perspectives, one could potentially develop stochastic models that simultaneously integrate multiple types of home-based measurements, for example, FeNO, rescue medication use, and patient-reported symptoms. Such models would have the potential advantage to provide a more robust estimate of disease fluctuations compared with studying each variable in isolation.

In conclusion, we have developed a novel, extendable, model-based approach for analyzing home-based measurements of PEF collected in respiratory clinical trials. Our model enables characterization of multiple statistical properties of PEF time series data to support better estimation and understanding of treatment effects, disease stability, and exacerbation risk. We recommend including this type of model-based analysis as a complement to

descriptive statistics of home-measured PEF data in the reporting of respiratory clinical trials.

CONFLICTS OF INTEREST

J.L. and U.G.E. are employees of AstraZeneca and may own stock or stock options. R.P. was an employee of AstraZeneca at the time when the work was conducted. M.J. declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.L., M.J., U.G.E., and R.P. wrote the manuscript. J.L., M.J., U.G.E., and R.P. designed the research. J.L. and R.P. performed the research. J.L. and R.P. analyzed the data.

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SUPPORTING INFORMATION

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