

First-order longitudinal population model of FEV1 data: single-trial modeling and meta-analysis

E. Marostica¹, S. Yang², A. Russu^{1*}, G. De Nicolao¹, S. Zamuner², M. Beerahee²

¹Department of Industrial and Information Engineering, University of Pavia, Pavia, Italy

²Clinical Pharmacology Modeling & Simulation, GlaxoSmithKline, Stockley Park, UK

*Current address: Model Based Drug Development, Janssen Research & Development, Beersse, Belgium



University of Pavia



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Introduction

- Asthma is a complex and multi-factorial disease and the underlying physio-pathological mechanism is not completely known.
- Therefore, empirical models are usually adopted to describe the evolution of the patient's health state.
- The clinical response is measured by the Forced Expiratory Volume in the first second (FEV1).

Objectives

- Develop a parsimonious population model, based on a single-trial analysis, in order to describe the time course of placebo response.
- Perform a model-based meta-analysis, in order to assess differences among studies and estimate the inter-trial variability.

Methods

- Placebo FEV1 longitudinal data from 11 clinical trials in subjects with mild-to-moderate asthma were available.
- All studies lasted 12 weeks.

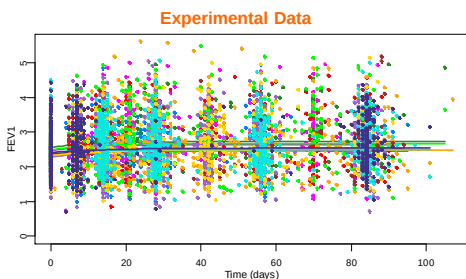


Figure1: Experimental data of the 11 trials and typical curves of each trial obtained with meta-analysis (see Results for details). Different colours are used for the different trials.

Single-trial Analysis

- A first-order exponential model was developed and identified on each dataset.

$$FEV1(t) = A + G \left(1 - e^{-\frac{t}{T}}\right)$$

- Based on a single-trial analysis, the proposed model was compared to four parametric models:

Linear	Polynomial
$FEV1(t) = A + Bt$	$FEV1(t) = A + Bt + Ct^2$
Inverse Bateman	Weibull + Linear
$FEV1(t) = A + B(e^{-k_{out}t} - e^{-k_{rec}t})$	$FEV1(t) = Ae^{(\frac{t}{t_2})^b} + h_{rec}t$

- All the models were implemented in WinBUGS 1.4.3[1] and compared through the Deviance Information Criterion (DIC).

Meta-Analysis

- The best model (exponential) was then used to perform a meta-analysis of all the 11 datasets together.
- In the meta-analysis model, each individual parameter was defined as the sum of a subject- and study-related term.

Individual Parameters

Definition	Priors
$\log A = \log A_{ind} + \log A_{study}$	$\log A \sim N(\mu_A, \rho_A + \tau_A)$
$\log G = \log G_{ind} + \log G_{study}$	$\log G \sim N(\mu_G, \rho_G + \tau_G)$
$\log T = \log T_{ind} + \log T_{study}$	$\log T \sim N(\mu_T, \rho_T + \tau_T)$

Subject effect - priors

$\log A_{ind} \sim N(0, \tau_A)$	$\tau_A \sim \Gamma(1, r_A)$
$\log G_{ind} \sim N(0, \tau_G)$	$\tau_G \sim \Gamma(1, r_G)$
$\log T_{ind} \sim N(0, \tau_T)$	$\tau_T \sim \Gamma(1, r_T)$

Study effect - priors

$\log A_{study} \sim N(\mu_A, \rho_A)$	$\mu_A \sim N(m_A, t_A)$	$\rho_A \sim \Gamma(1, r_A)$
$\log G_{study} \sim N(\mu_G, \rho_G)$	$\mu_G \sim N(m_G, t_G)$	$\rho_G \sim \Gamma(1, r_G)$
$\log T_{study} \sim N(\mu_T, \rho_T)$	$\mu_T \sim N(m_T, t_T)$	$\rho_T \sim \Gamma(1, r_T)$

- For both the single-trial analysis and the meta-analysis, log-normal distribution was assumed for all parameters.
- Graphical outputs were obtained through R 2.13.1 [2].

Results

- In the single-trial analysis, the exponential model yielded the best performance in terms of DIC in all but one trial.

Trial	# Subjects	# Data	Linear	Polynomial	Inverse Bateman	Weibull + Linear	Exponential
FAP30008	100	554	39.573	36.516	18.093	-23.253	-172.057
FLD302	84	669	365.186	357.206	360.156	302.501	234.723
FLD304	40	301	152.981	156.467	152.576	101.757	37.811
FLI202	73	417	104.790	34.400	157.370	83.535	32.170
FLI302	87	495	455.460	385.193	419.873	319.735	304.227
FLTA2003	73	523	322.899	273.474	377.676	256.253	183.622
FLTA3020	43	457	199.467	227.276	186.490	164.620	152.962
FLTA4030	115	748	586.144	643.365	618.021	549.040	394.371
FLTA4031	114	731	341.573	372.242	364.830	279.347	197.536
FPD40009	210	965	233.841	247.942	131.643	138.807	60.782
SAS30022	212	600	418.767	143.605	-	-	210.653

Table 1: For each trial, the number of subjects and data and the DIC obtained with the Linear, Polynomial, Inverse Bateman, Weibull + Linear models and the proposed exponential model are reported.

- Good individual fittings (Figure 2a) and Visual Predictive Checks (VPCs, Figure 3b) were obtained for all the 11 trials with the exponential model.
- The proposed model yielded good performances both in terms of individual fittings (Figure 2b) and VPCs (Figure 3a) also when applied in a meta-analysis context.
- Typical curves of the 11 trials obtained through the meta-analysis are shown in Figure 1.
- VPCs of one trial obtained through the meta-analysis are shown in Figure 3c.
- It was found that the inter-individual variability (Table 2: red) is higher than the inter-trial one (Table 2: blue).

Parameter	Mean	SD	2.5 %	Median	97.5 %
TV of A	2.386	0.0502	2.291	2.385	2.487
TV of G	0.159	0.0178	0.127	0.158	0.199
TV of T	11.756	3.919	5.674	11.359	19.826
IIIV% of A_{ind}	23.977	0.591	22.867	23.965	25.177
IIIV% of A_{study}	6.0585	1.533	3.946	5.786	9.693
IIIV% of G_{ind}	148.0518	13.0558	119.913	148.092	173.0585
IIIV% of G_{study}	27.728	9.0203	14.942	26.150	49.372
IIIV% of T_{ind}	906.0525	892.403	36.0676	691.647	2883.057
IIIV% of T_{study}	70.867	190.238	17.0505	39.216	308.843

Table 2: Mean, Standard Deviation (SD), Median, 2.5th and 97.5th percentiles are reported for the posterior distributions of the typical values (TV) of A, G and T and for the inter-individual variability percentage of subject- and study-related effect of each parameter.

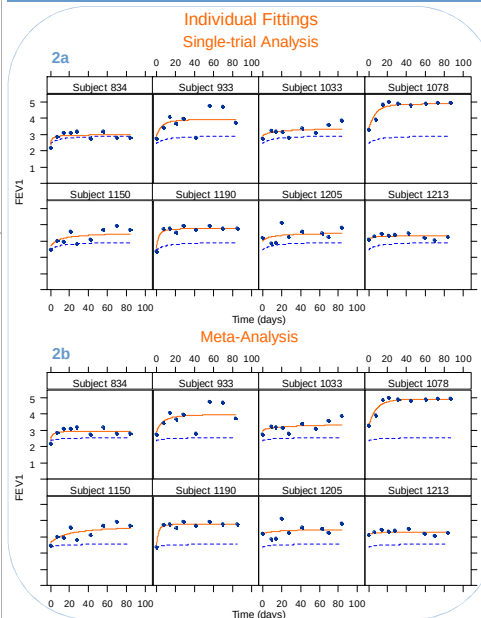


Figure 2: Example of individual fittings obtained with the single-trial analysis (2a) and meta-analysis (2b). Solid line: individual curve, dashed line: typical curve.

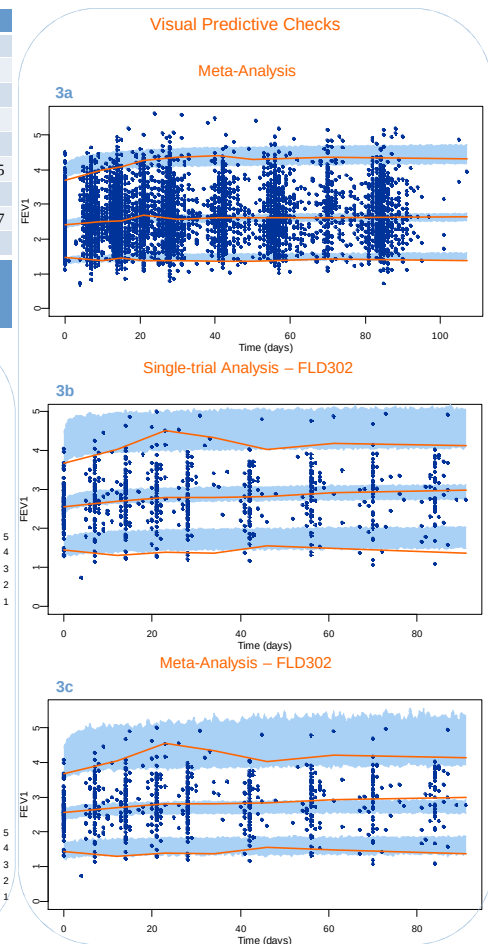


Figure 3: VPCs of all the trials obtained through the meta-analysis (3a) and of a trial obtained through the single-trial analysis (3b) and meta-analysis (3c). Solid lines: 95% observed intervals. Light blue: 95% simulated intervals.

Conclusions

- A parsimonious parametric model was developed to describe placebo FEV1 data from different studies in mild-to-moderate asthma. The model was able to well describe the individual responses and the inter-individual variability.
- The proposed model performs well both in the single-trial analysis and meta-analysis context.
- Moreover, the model can be extended by including clinically relevant covariates which may affect the patient's health state (e.g. age, height, smoking status, etc).
- A further development will be to assess the model capabilities in predicting long-term outcomes from short-term trials in placebo group.

References

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