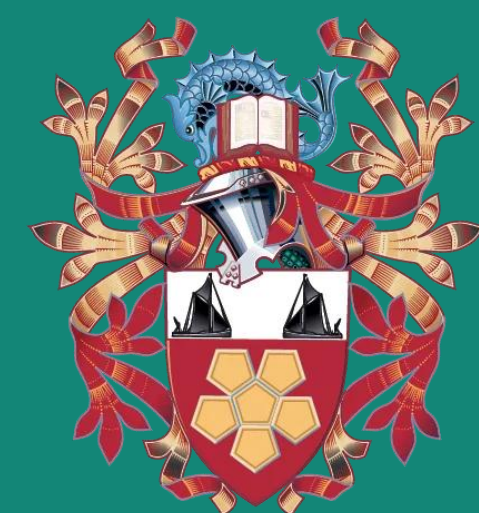




London
South Bank
University

PK/PD data analysis is a cornerstone of drug development and efficacy and safety studies. However, individual-level PK/PD data is difficult to obtain. Ideally, the availability of individual patient data (IPD) would allow methods such as model-based meta-analysis (MBMA), to provide a better characterization of the relationships between covariates and PK/PD parameters. Differently from previous research aiming to integrate AD and IPD in a combined meta-analysis (S.Weber [1], L.Yang [2]), we exploit generative-AI to regenerate IPD from AD, with the ultimate aim of enabling an IPD MBMA.

To test the methodology, we simulated a scenario where a generative model is trained using IPD from a single study and can then generate IPD data from the population statistics of a number of other simulated studies.

IPD of drug effect on the Forced Expiratory Volume in 1 second (FEV1) were simulated using eq.1, based on a similar model structure as described in C. Llanos-Paez [3].

$$\begin{aligned} & FEV1_{i,j,k}(t) \\ &= B_{i,j,k}(COV, \theta_{Bi}, \eta_{Bik}) + DP_{i,jk}(t, B_{i,j,k}, \theta_{DPi}, \eta_{DPik}) PBO_{ik}(t, \theta_{PBOi}, \eta_{PBOik}) \\ &+ E_{i,j,k,x}(t, x, B_{i,j,k}, \theta_{Eix}, \eta_{Eikx}) + \varepsilon_{i,j,k} \end{aligned}$$

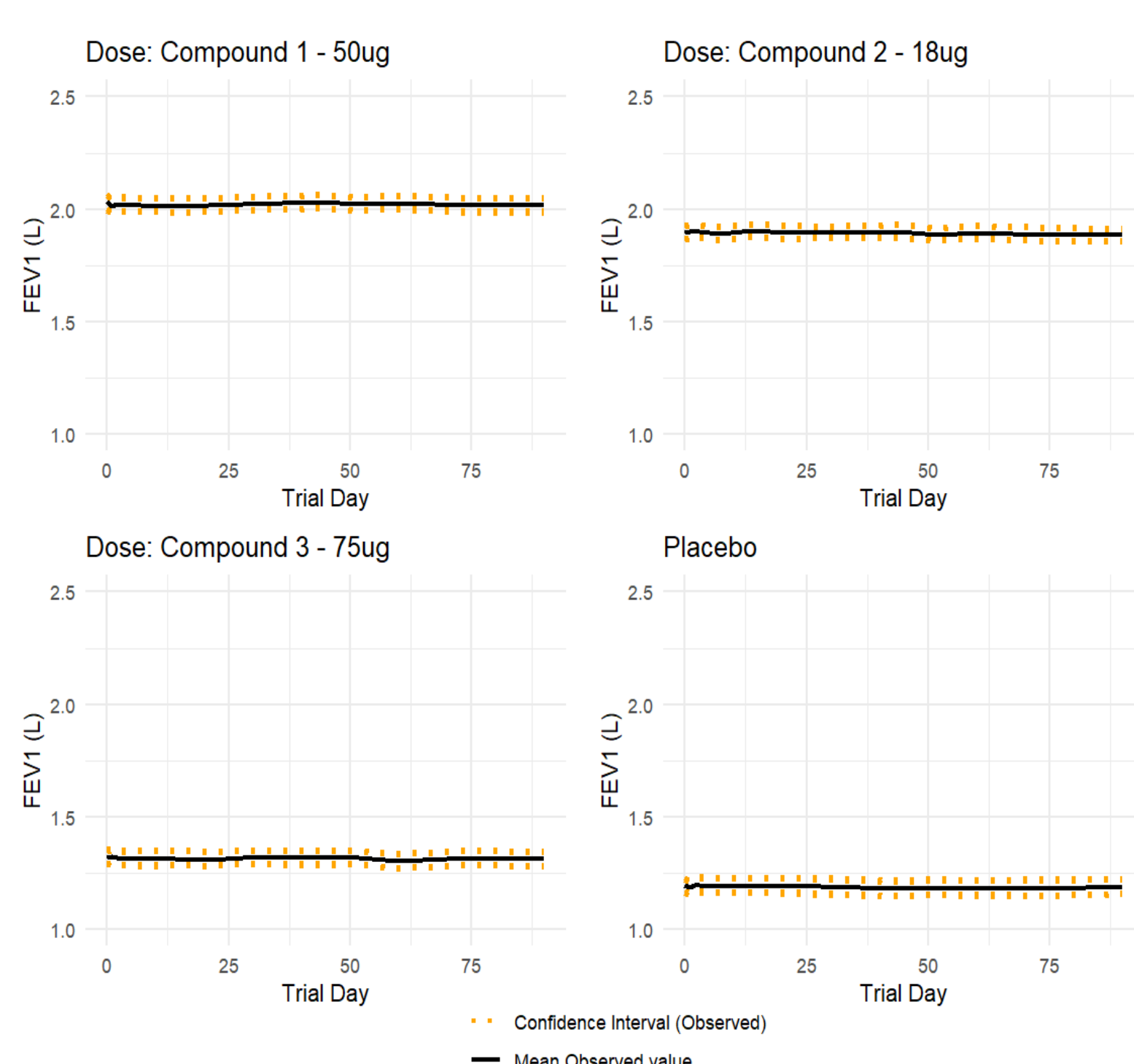
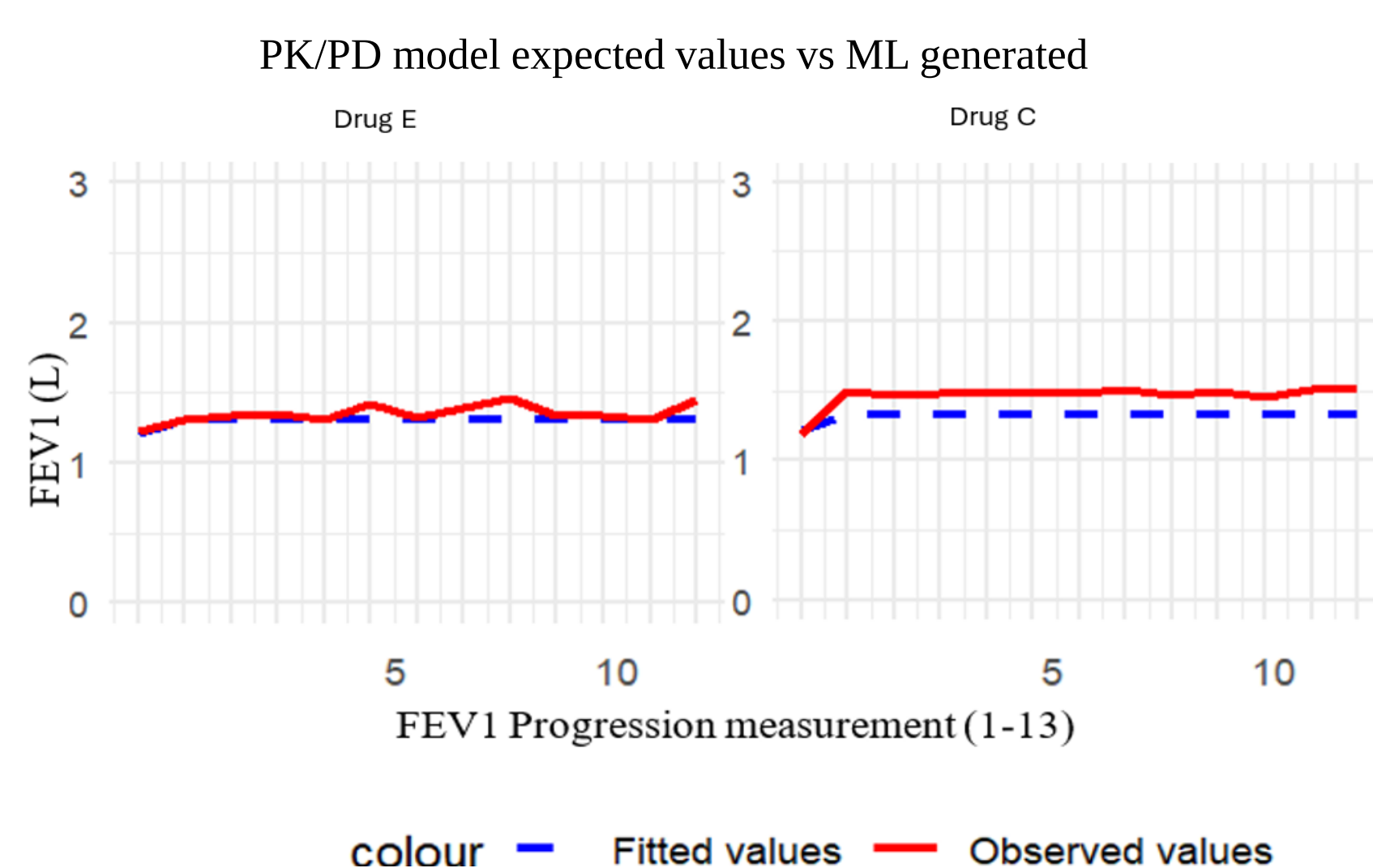
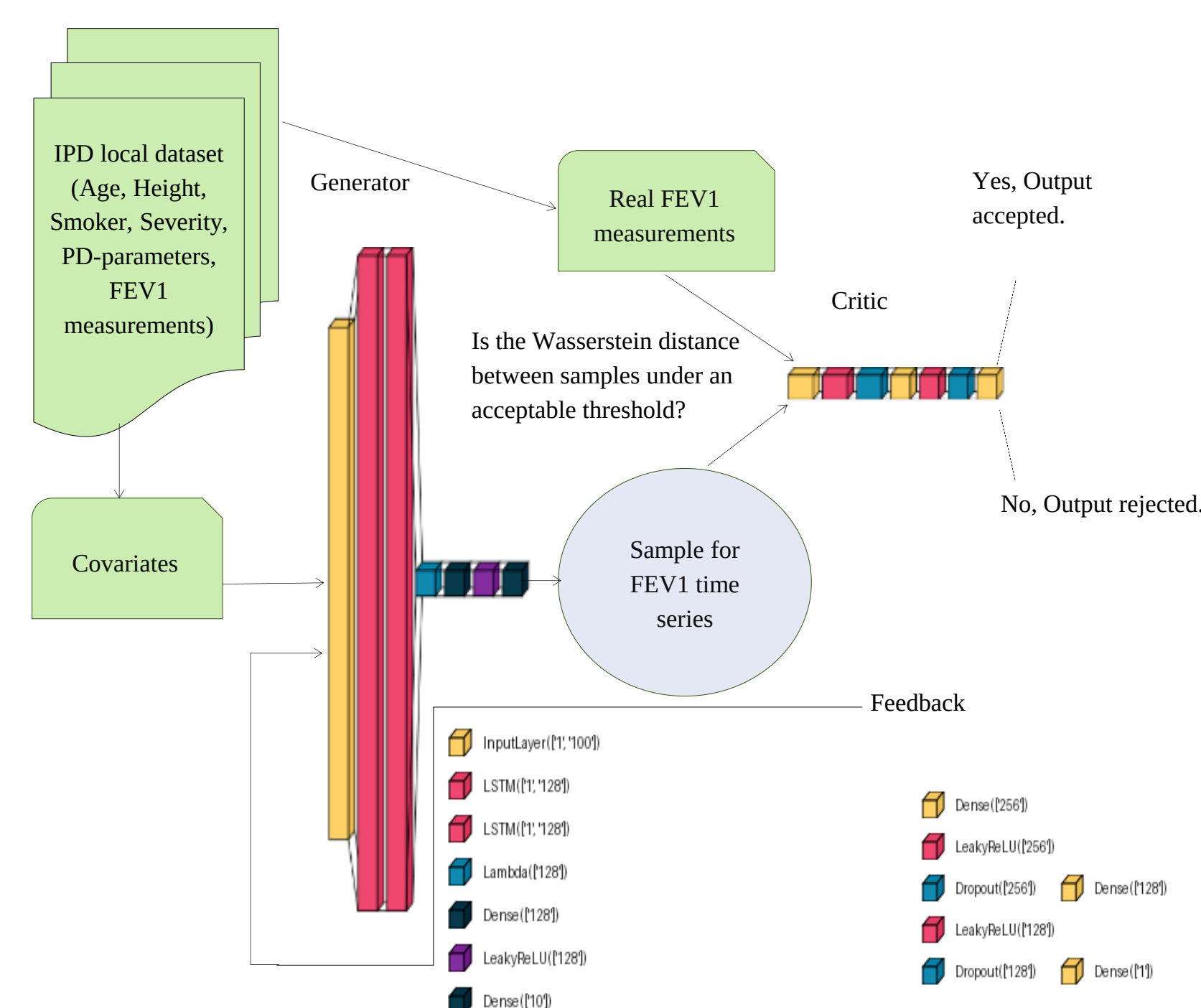


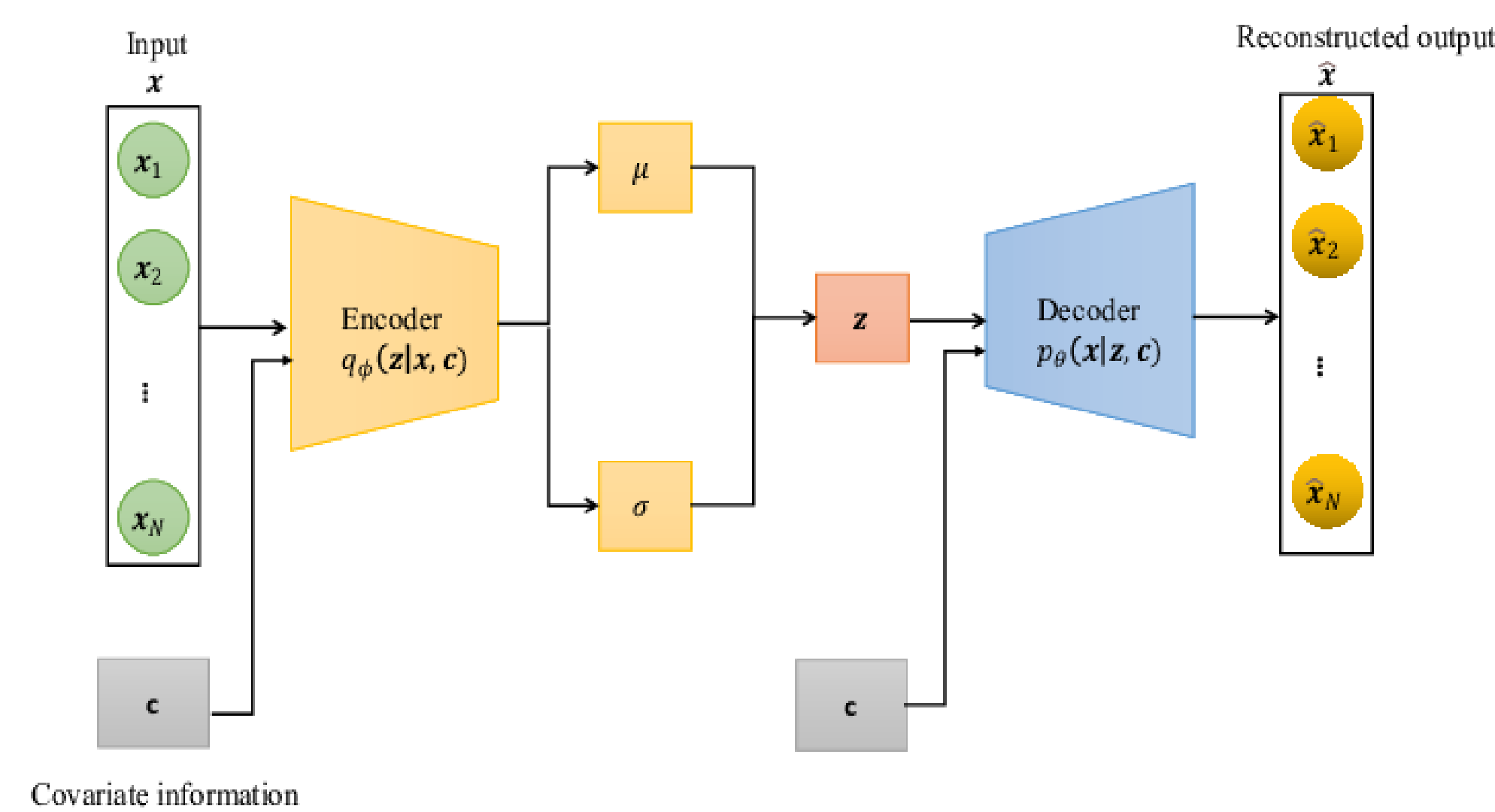
Figure 1 displays six histograms showing the posterior distributions for the parameters of the model. The parameters are: CovAge, CovSmoker, CovHT, CovSev, eta_pbo, and eta_dt_p. Each plot shows the frequency of the parameter value on the y-axis and the parameter value on the x-axis. A vertical red dashed line is present in each plot, indicating a specific value for each parameter.



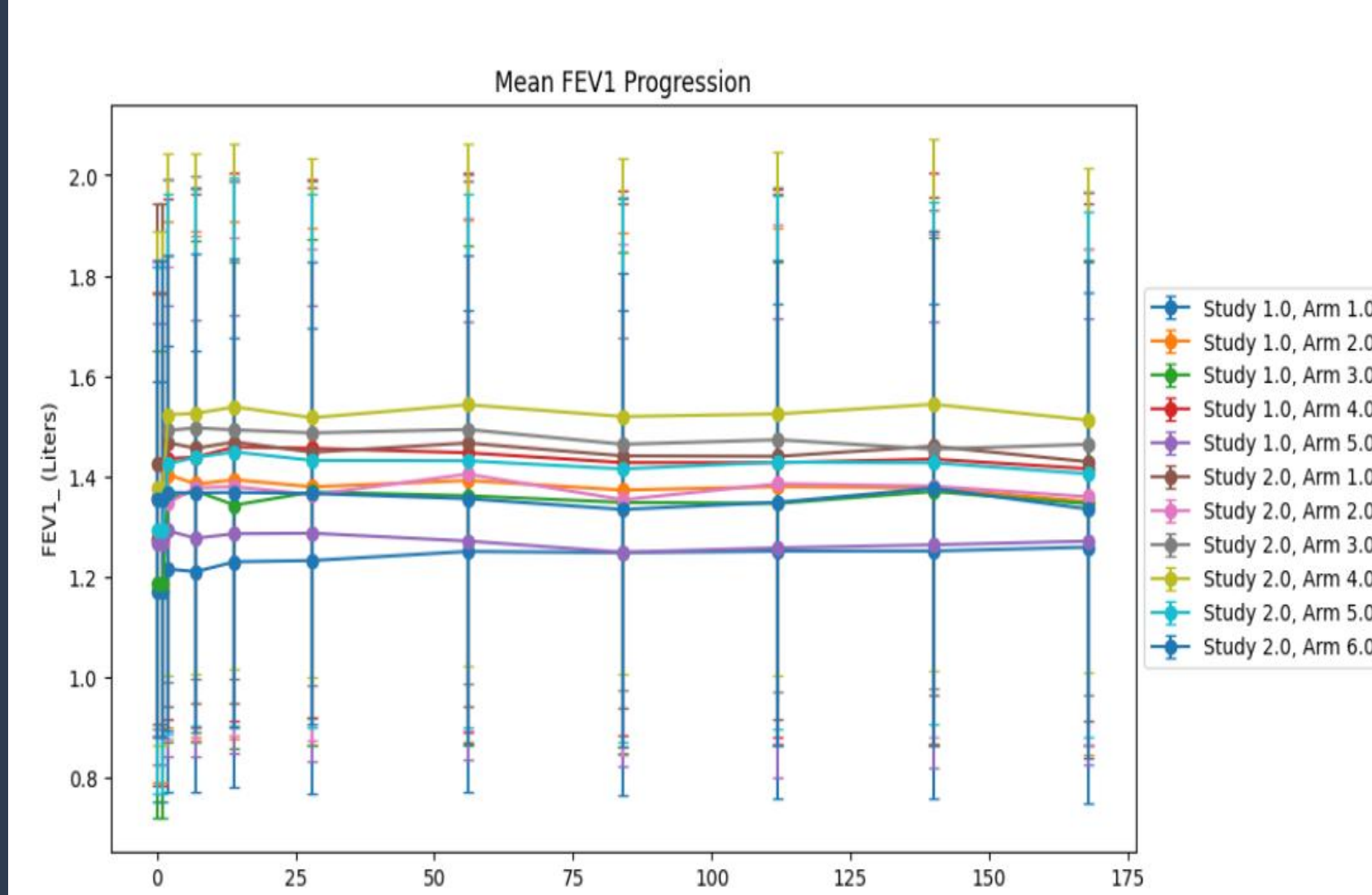
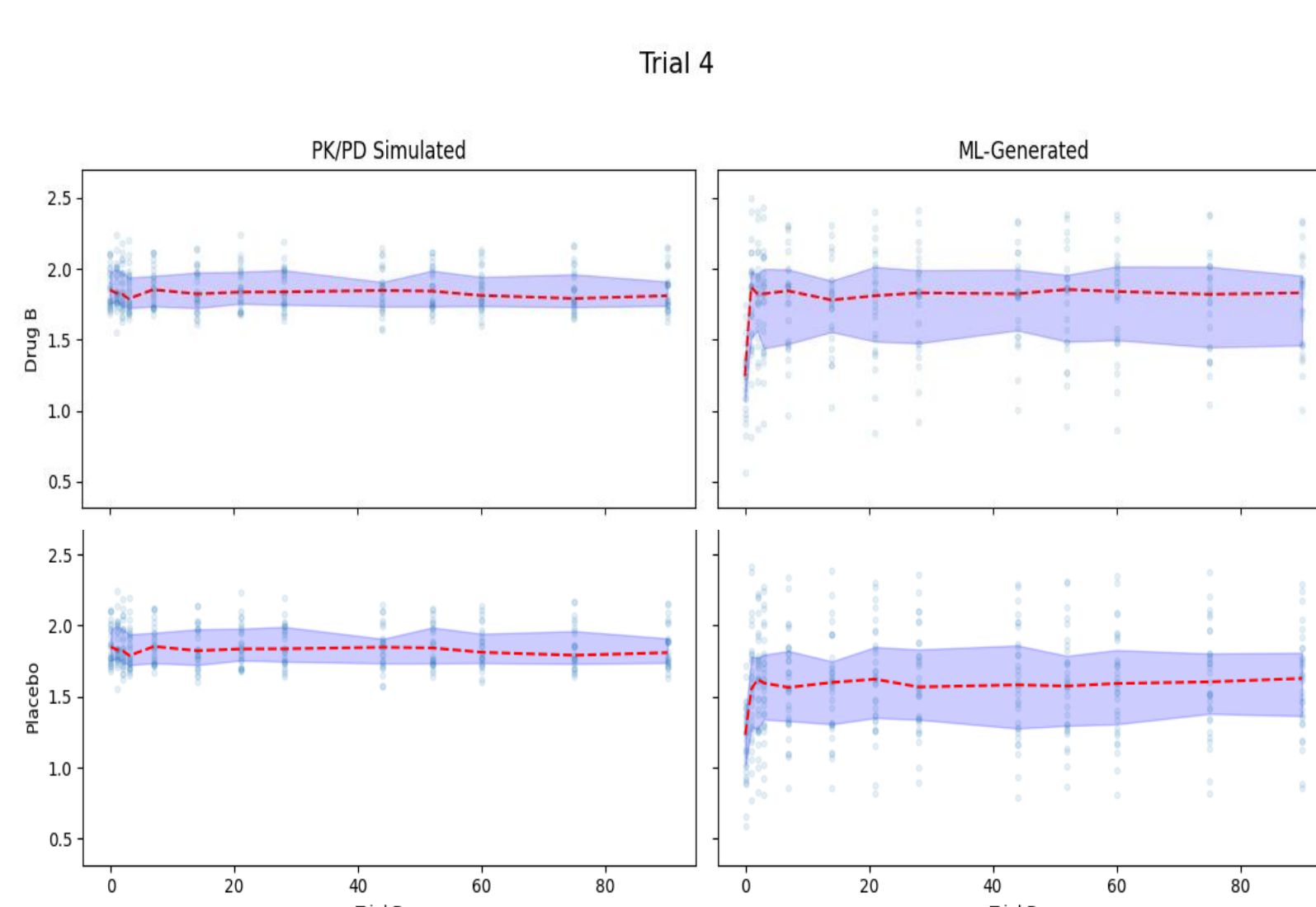
Initially, the core computational framework employed a WGAN architecture, with a Long Short-Term Memory (LSTM)-based generator and a dense critic network. The generator is trained to capture temporal dependencies in trial data, in particular between $FEV(t)$, COV , and $ED50$ and $E_{\max}$. During the training, the critic evaluates the generated data to optimize the Wasserstein distance, guiding the generator towards producing realistic outputs. During the test phase, a set of covariates are sampled from the AD of Trials 1-7 for each individual we want to simulate, and used as input to the model that will generate the corresponding $FEV1(t)$ profile. This results in the reconstructed external IPD dataset (the *external ML-generated* data). The mechanism of the network as well as the structure of the generator and critic can be seen in Figure 1



After further consideration, we decided to employ a Conditional Variational Auto-Encoder structure to provide a methodology independent of drug-specific parameters (ED50, Emax...) and solely based on the averaged evolution of FEV1 during the trials, traditionally reported in publications.



Results – CVAES regeneration

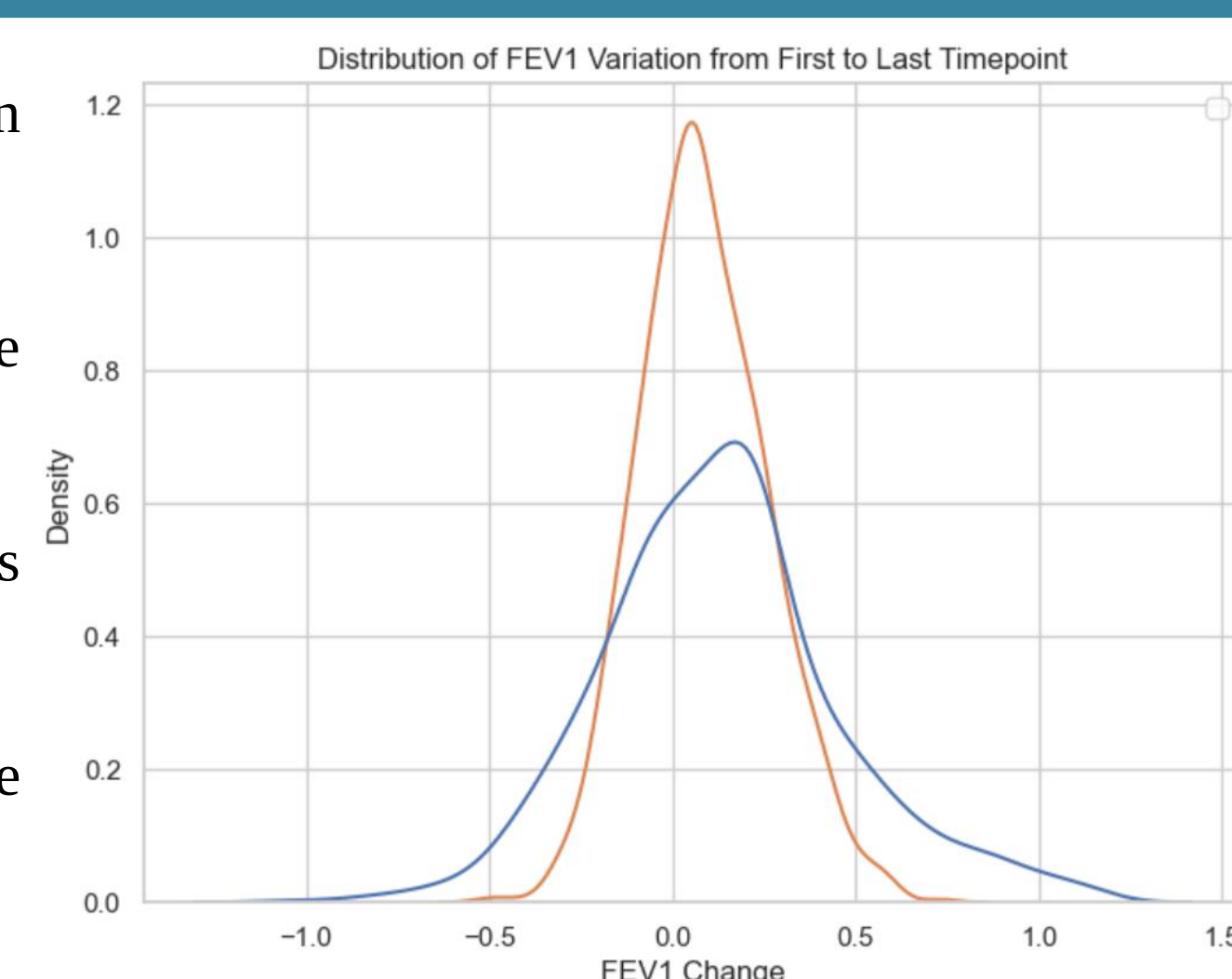


The ML-generated values greatly resemble the values obtained by the PK/PD model that we consider as ground-truth. The experiment produced a set of samples that scored an average sum of squared estimate errors of 0.3311 (0.2117 – 0.4799) against the expected PK-PD model response.

This methodology demonstrates a scalable approach for generating synthetic pharmacological individual trial data, providing a foundation for further analysis and predictive modelling while mitigating concerns associated with data privacy and scarcity.

A limitation of the performed analysis is that assumes a PK/PD model very similar across studies, which implies that comparative studies should be performed only for drugs with a similar mechanism of action to avoid bias in profile generation.

The main aim once the ML data reconstruction algorithm is fully optimized is to study model improvement by performing IPD MBMA. Early attempts at meta-analyzing the data generated can be seen in the figure to the right.



1. S. Weber, A. Gelman, D. Lee, M. Betancourt, A. Vehtari, and A. Racine-Poon, "Bayesian aggregation of average data: An application in drug development," *The Annals of Applied Statistics*, vol. 12, no. 3, Sep. 2018, doi: 10.1214/17-AOAS1122.
2. L. Yang, C. Llanos-Paez, S. Yang, C. Ambery, A. Berges, M. Kjellsson, M. O. Karlsson." A combined model meta-analysis of aggregated and individual FEV1 data from randomized COPD trials". PAGE 32 (2024) Abstr 10848.
3. C. Llanos-Paez, C. Ambery, S. Yang, M. Beerahee, E. L. Plan, and M. O. Karlsson, "Joint longitudinal model-based meta-analysis of FEV1 and exacerbation rate in randomized COPD trials," *Journal of Pharmacokinetics and Pharmacodynamics*, vol. 50, no. 4, pp. 297–314, Aug. 2023, doi: 10.1007/s10928-023-09853-z.