Effect of Uncertainty About Population Parameters on Pharmacodynamics-Based Prediction of Clinical Trial Power

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Background

In clinical trial simulation (CTS), uncertainty about input parameters, e.g., population PKPD parameters, will influence the precision and accuracy of the simulation output, e.g., trial power.

However, the impact of uncertainty about single input parameters on the quality of the prediction provided by CTS may vary considerably. In this sense, 'important' parameters, required to be fed into simulations with a high degree of precision to allow reliable CTS outcomes can be distinguished from 'unimportant' parameters, uncertainty about which has no serious consequences for the accuracy and precision of the predicted variable.

If such discrimination is done prior to trial simulations, research resources expended to inform CTS can be focused on the 'important' model parameters.

Suggested Method

Given a non-linear model, the importance of input parameters for the precision of a CTS outcome variable can be evaluated with a 3-step procedure:

1. Establish a full Bayesian predictive model of the CTS outcome
2. Simulate the model at varying input parameter settings using principles of effective experimental design
3. Perform variance-based sensitivity analysis to explore the consequences for CTS outcome precision of uncertainty about individual input parameters

Simulated Example

The approach is exemplified by application to the design of a completely randomized, placebo-controlled parallel-groups efficacy trial, in which the effect of the study drug is measured as a continuous outcome variable during steady-state conditions. It is assumed that previous learning trials have provided information about the population distribution of clearance and of parameters of a sigmoidal Emax model linking steady state concentration with treatment outcome. To focus on principles, we also assume that the study is performed in a specific stratum of the target population, where no known predictors of PKPD characteristics exist, and that adherence to the trial protocol is perfect. The submodels used for simulations are briefly described below.

Placebo Outcome Model

$R_P = P + e$

R_p - change of the outcome variable from baseline

P - placebo response

e - error term

$P \sim N(\mu_P, \sigma_P^2)$ and $e \sim N(0, \sigma_e^2)$,

The distribution of P in the population is assumed to be normal with mean μ_P and variance σ_P^2. The normal error term e and its variance σ_e^2 represent the deviation of the measured response from the subject-specific placebo response P due to intraindividual variation, measurement error and model misspecification. The summands are assumed to be independent of each other. Expectation and variance of the total measured response to placebo given μ_P, σ_P^2 and σ_e^2 are thus $\mu_{RP} = E(R_P \mid \mu_P) = \mu_P$, and $\sigma_{RP}^2 = Var(R_P \mid \sigma_P^2, \sigma_e^2) = \sigma_P^2 + \sigma_e^2$.

Verum Outcome Model

$R_A = P + S + e$

R_A - change of the outcome variable from baseline

S - Specific drug effect

The distributions of P and S including their parameters μ_P, σ_P^2 and σ_e^2 are assumed to be the same as those assumed for the placebo group, as characterized above.

$S = Emax / [1 + (EC50 \times Cl / D)^G]$

Emax - Maximum attainable effect

EC50 - Concentration producing 50% of Emax

G - Hill factor

Cl - Clearance

D - Dose rate (Bioavailability is assumed to be 1.)

Population PKPD Model

Emax, EC50, G and Cl are assumed to be independent, positive variables with log-normal population distributions:

$$\theta_{PD} \sim N(\mu_{PD,} \text{diag}(\sigma_{PD}^2))$$

$$\theta_{PD} = [\log(Emax), \log(EC50), \log(G), \log(Cl)]^T$$
$$\mu_{PD} = (\mu_{logEmax}, \mu_{logEC50}, \mu_{logG}, \mu_{logCl})^T$$
$$\sigma_{PD}^2 = (\sigma_{logEmax}^2, \sigma_{logEC50}^2, \sigma_{logG}^2, \sigma_{logCl}^2)^T$$

Population mean and variance of S are thus given by
$\mu_S = E(S|\mu_{PD}, \sigma_{PD}^2) = \int\{Emax/[1+(EC50\times Cl/D)^G]\} \times N(\theta_{PD}| \mu_{PD}, \text{diag}(\sigma_{PD}^2))\, d\theta_{PD}$ and
$\sigma_S^2 = V(S|\mu PD, \sigma_{PD}^2) = \int\{Emax/[1+(EC50\times Cl/D)^G]-\mu_S\}^2 \times N(\theta_{PD}|\mu_{PD}, \text{diag}(\sigma_{PD}^2))\, d\theta_{PD}$.

Given μ_S and σ_S^2, expectation and variance of RA, i.e., μ_{RA} and σ_{RA}^2, are now
$\mu_{RA} = E(RA \mid \mu_P, \mu_S) = \mu_P + \mu_S$ and $\sigma_{RA}^2 = Var(RA \mid \sigma_P^2, \sigma_S^2, \sigma_e^2) = \sigma_P^2 + \sigma_S^2 + \sigma_e^2$,
since independence of P, S and e is assumed.

Approximation of Trial Power

Power $= 1 - \Phi\,(Z_{1-\alpha/2} + (CWD - \mu_\Delta)/\sigma_\Delta))$

Φ - Cumulative standard normal distribution function

$Z_{1-\alpha/2}$ - $(1-\alpha/2)$-percentile (α set to 0.01 ⇨ $Z_{1-\alpha/2} = 2.5758$)

CWD - Clinically worthwhile difference

$\mu_\Delta = \mu_{RA} - \mu_{RP} = \mu_S$

$\sigma_\Delta^2 = \sigma_{RP}^2/150 + \sigma_{RA}^2/150 = (2\sigma_P^2 + \sigma_S^2 + 2\sigma_e^2) / 150$
(for a sample size of 150 in both treatment groups)

Uncertainty Model

In the present model, independent normal and inverse Gamma distributions are used for modeling uncertainty about population means and variances μ_{PD}, σ_{PD}^2, σ_P^2, and σ_e^2. Indexing the components of σ_{PD}^2 and μ_{PD} with j (j = log(Emax), log(EC50), log(G), or log(Cl)), this may be expressed as:

$$\sigma_j^2 \sim \text{Inv-Gamma}\,(n_{j,s}/2,\ n_{j,s} \times s_j^2/2) \text{ for all j}$$
$$\sigma_P^2 \sim \text{Inv-Gamma}\,(n_P/2,\ n_P \times s_P^2/2)$$
$$\sigma_e^2 \sim \text{Inv-Gamma}\,(n_e/2,\ n_e \times s_e^2/2)$$
$$\mu_j|\sigma_j^2 \sim N\,(m_j,\ \sigma_j^2/n_{j,m}) \text{ for all j}$$

Interpretation: The locations of the uncertainty distributions for the components of μ_{PD} are described by the hyperparameters m_j, while their scales are tied to the corresponding σ_j^2. Given σ_j^2, the uncertainty about the μ_j is also determined by the hyperparameters $n_{j,m}$, which may be envisaged as the number of subjects previously observed to estimate μ_j. If the information about μ_j is actually derived on a previous sample of $n_{j,m}$ observations of j, m_j would typically be chosen to equal the maximum-likelihood estimate of μ_j. In analogy, the hyperparameters s_j, s_P and s_e may be previous estimates of the corresponding population variances derived from $n_{j,s}$, n_P and n_e observations, respectively.

Thus, the hyperparameters $n_{j,m}$, $n_{j,s}$, n_P and n_e, generically referred to as $n_\bullet$ in the following, quantify the amount of existing information about the respective population parameters.

Uncertainty about Power

As a consequence of power predictions being based on uncertain means and standard deviations of individual PKPD parameters in the population, power itself is uncertain and may be represented by a probability distribution. The spread of this uncertainty function is an indicator of uncertainty about, or precision of, predicted power. It is determined by all input constants $m_{\bullet}$, $s_{\bullet}$ and $n_{\bullet}$, and can be approximated by simulation.

Spread is operationalized by the standard deviation, SD_{Power}, and 5% quantile. The 5% quantile, $Q5_{Power}$, provides the power estimate above which true trial power falls with a probability of 95%.

Mean predicted power, M_{power}, is used as a point predictor of power in the presence of parameter uncertainty.

Simulation of Predictive Distributions

In the present study, four scenarios, referred to as 10&10, 10&40, 40&10 and 40&40, were simulated with hyperparameters (input variables) set to the following values:

Scenario	s_P, s_e	$m_{logEmax}$, $m_{logEC50}$	m_{logG}, m_{logCl}	$s_{logEmax}$, $s_{logEC50}$, s_{logG}, s_{logCl}	$n_\bullet$
10&10	10	4.60020	0.911316	0.099751	2 or 100
10&40	10	4.53096	0.842081	0.385253	2 or 100
40&10	40	4.60020	0.911316	0.099751	2 or 100
40&40	40	4.53096	0.842081	0.385253	2 or 100

The first number in the labels of the scenarios provides the values chosen for both s_P and s_e. The values selected for $m_{logEmax}$, $m_{logEC50}$, m_{logG}, m_{logCl}, $s_{logEmax}$, $s_{logEC50}$, s_{logG}, s_{logCl} are expected first and second moments for log(Emax), log(EC50), log(G) and log(Cl), if the true means of Emax, EC50, G and Cl were 100, 100, 2.5 and 2.5, respectively, and if the true coefficients of variation of these four parameters were 10% (scenarios 10&10 and 40&10) and 40% (scenarios 10&40 and 40&40). Values for $n_\bullet$ were set according to the sensitivity analysis procedure described below.

For each scenario and settings of the $n_\bullet$ (2 or 100), 5000 samples of $\mu_{logEmax}$, $\sigma_{logEmax}^2$, $\mu_{logEC50}$, $\sigma_{logEC50}^2$, μ_{logG}, σ_{logG}^2, μ_{logCl}, σ_{logCl}^2, σ_P^2, and σ_e^2 were drawn from their probability distribution, corresponding power approximations were obtained, and SD_{Power}, $Q5_{Power}$ and M_{Power} were computed.

Sensitivity Analysis

To evaluate the differential effects of the 10 hyperparameters $n_{j,m}$, $n_{j,s}$, n_P and n_e (n_*) on the precision and expectation of predicted power, we used a 2^{10} factorial design with the different $n_\bullet$ set at either 2 ("little existing information") or 100 ("much existing information"). For each factor combination, 2 repetitions were simulated. Moreover, the whole experiment was performed for three different dose rates, i.e., D = 144, D = 250 and D = 435. In a typical subject with Emax = EC50 = 100 and G = Cl = 2.5 (that is, a subject whose PKPD parameters correspond to θ_{PD} = m and P = e = 0), these dose rates would generate responses of 20%, 50% and 80% of Emax. Values for CWD were selected to provide similar ranges of expected power in the order of 99% (based on a model with certainty about parameters) for all doses and scenarios.

The impact of the 10 input variables $n_\bullet$ on the precision of predicted power (expressed by SD_{Power} and $Q5_{Power}$) was studied separately for the 3 dose rates and 4 scenarios. Conventional analysis of variance was used to model the variance components of main effects and interactions. Thus, in ANOVA terminology, SD_{Power} or $Q5_{Power}$ were univariate response variables, and the 10 different $n_\bullet$ served as factors used to explain the variation of SD_{Power} or $Q5_{Power}$. For each main and interaction effect, the corresponding sum of squares was expressed as a percentage of the total sum of squares (eta-squared). Moreover, a total sensitivity index quantifying the importance for SD_{Power} or $Q5_{Power}$ of each of the 10 input variables $n_\bullet$ was obtained by adding all eta-squared statistics for main and interaction effects involving that variable.

Results (1)

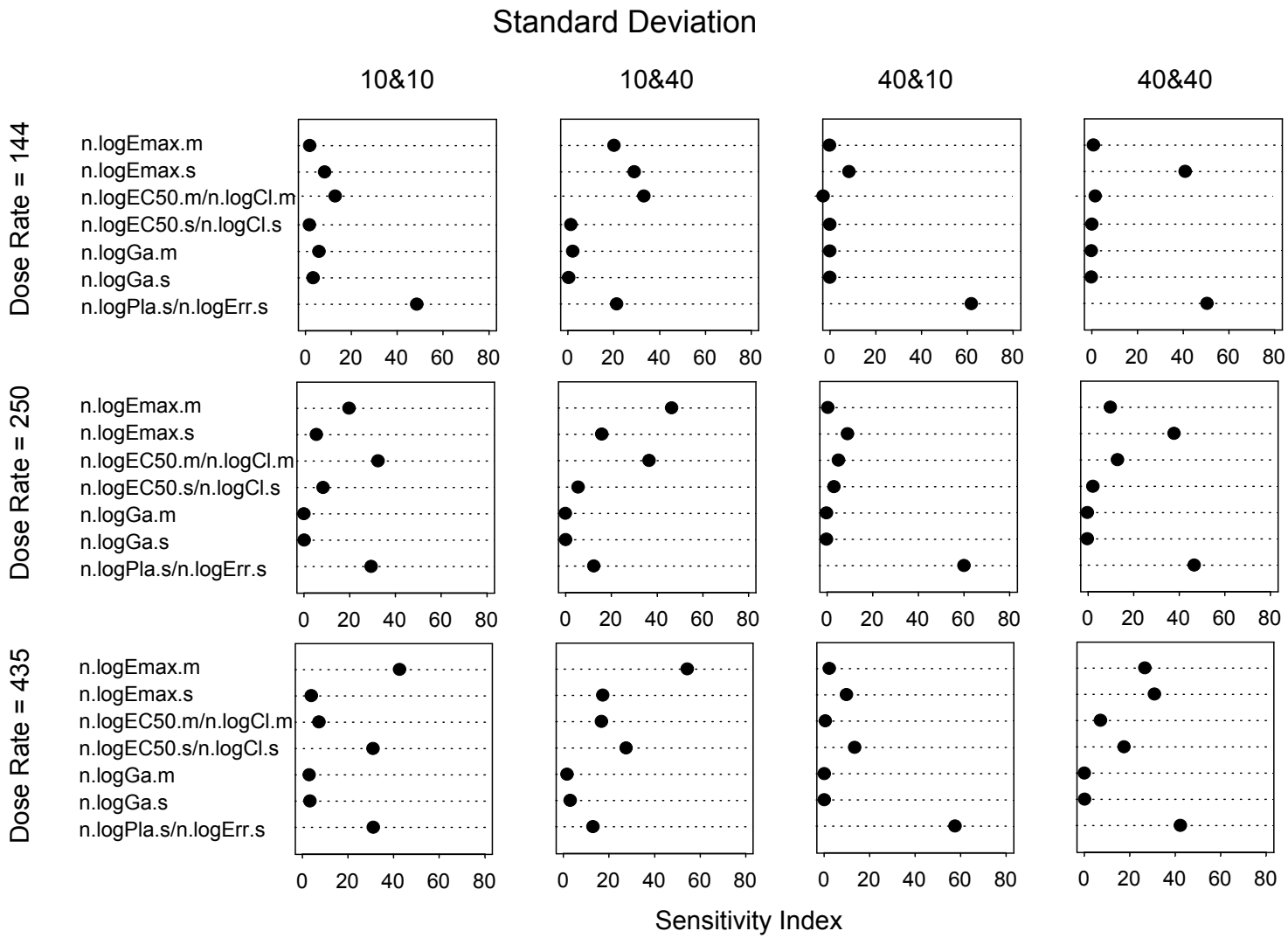
Descriptive measures of uncertainty about predicted power were first obtained with all $n_{\bullet}$ set at either 2 or 100 (Table below). This confirmed that high overall uncertainty associated with PKPD population parameters (all $n_{\bullet}$ set to 2), resulted in large values for SD_{Power} (between 38.8% and 43.5%) and small values for $Q5_{Power}$ (between 0.00% and 0.92%) for all scenarios and dose rates. In contrast, with low uncertainty about these parameters (all $n_{\bullet}$ set to 100), maximal SD_{Power} was 8.53% and minimal $Q5_{Power}$ was 77.2%. Except for scenario 10&40, low levels of uncertainty were associated with values of SD_{Power} below 5% and of $Q5_{Power}$ above 85%.

Results (2)

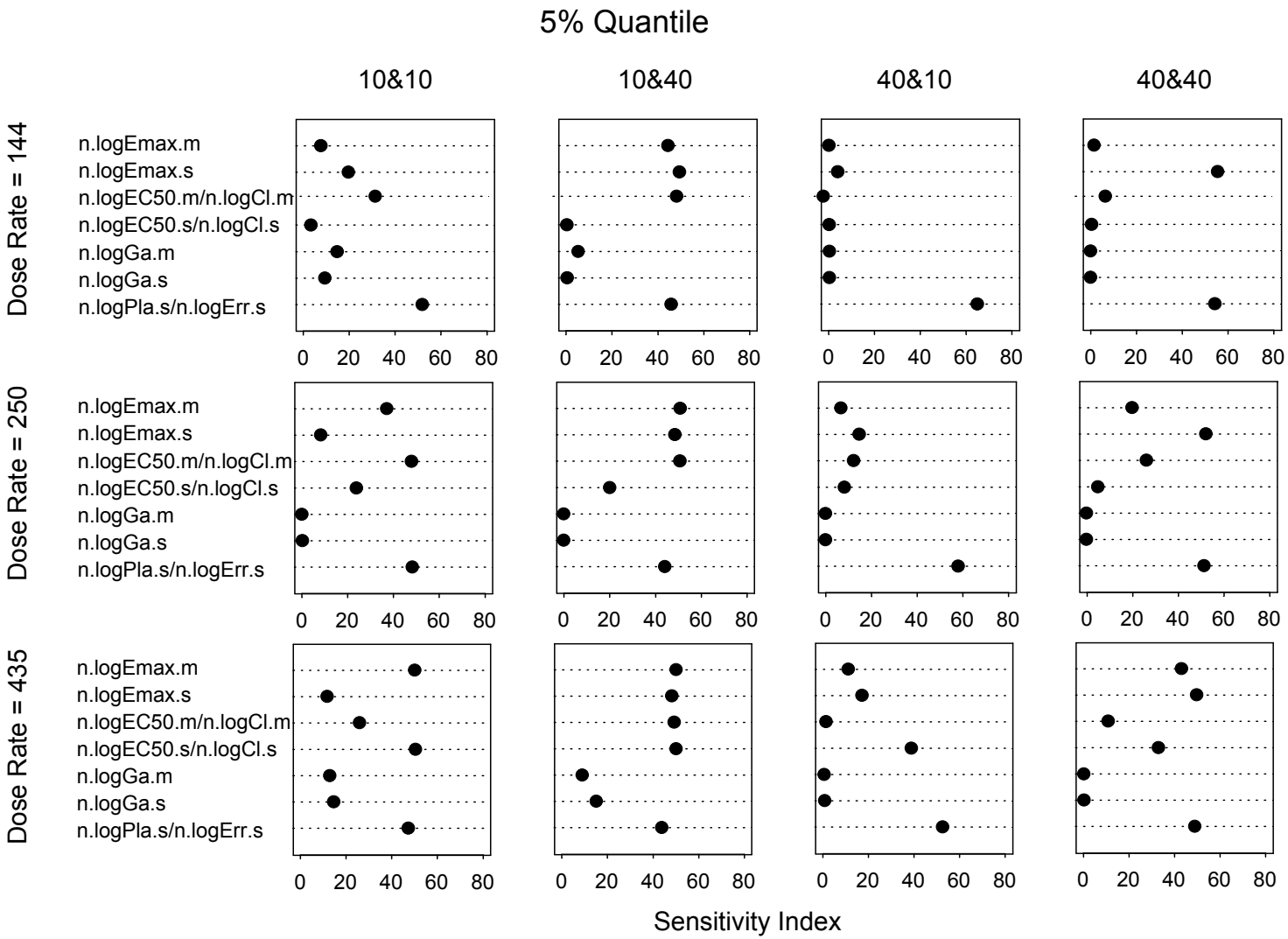
With the $n_\bullet$ set to infinity, that is, when assuming certainty about input parameters, power predictions with the current model would have exceeded 95% for all scenarios and dose rates. As a consequence, and because power is restricted to values between 0 and 1, wider prediction intervals associated with high levels of uncertainty about parameters ($n_\bullet = 2$) shifted the expected value for predicted power, M_{Power}, towards values closer to zero (between 32.1% and 50.1%). The median of predicted power (not shown) ranged between 3.9% and 47.2% for the different scenarios and dose rates.

Simulation Results

Scenario	Dose Rate	CWD	n[a]	SD_{Power} (%)	$Q5_{Power}$ (%)	M_{Power} (%)
10&10	144	13	2	42.9	0.13	48.6
			100	2.41	92.8	97.7
	250	42	2	42.8	0.00	39.5
			100	4.40	87.7	96.6
	435	71	2	41.0	0.00	32.1
			100	4.18	88.6	96.9
10&40	144	20	2	43.5	0.01	47.0
			100	8.53	77.2	94.5
	250	40	2	42.8	0.00	39.2
			100	7.37	82.6	96.4
	435	60	2	41.2	0.00	32.2
			100	7.61	82.8	96.4
40&10	144	-10	2	40.1	0.92	50.1
			100	1.20	95.8	98.1
	250	20	2	39.9	0.64	42.5
			100	1.61	94.4	97.6
	435	48	2	39.6	0.18	38.1
			100	1.22	95.9	98.3
40&40	144	0	2	40.4	0.82	43.6
			100	2.11	93.7	97.8
	250	20	2	39.9	0.51	37.7
			100	1.53	95.9	98.8
	435	40	2	38.8	0.05	32.4
			100	1.47	96.2	99.0



Sensitivity of standard deviation of trial power (SD_{Power}) to uncertainty about input parameters (quantified by $n_{\bullet}$). Large values of sensitivity indices indicate an important influence on SD_{Power} and corresponding parameters need to be input with high precision into CTS to allow reliable power predictions.



Sensitivity of standard deviation of the 5% quantile of predicted power to uncertainty about input parameters (quantified by $n_{\bullet}$). Large values of sensitivity indices indicate an important influence, and corresponding parameters need to be input with high precision into CTS to allow reliable power predictions.

Conclusions

Due to non-linearity and non-normality of CTS models, use of point estimates of PKPD parameters may result in biased CTS predictions.

Full Bayesian modeling makes uncertainties about PKPD parameters explicit and incorporates uncertainty in CTS models, thus allowing more realistic outcome predictions.

Variance-based sensitivity analysis may be used to identify PKPD population parameters that, for reliable CTS-based predictions, need to be fed into simulations with a high degree of precision.