

BACKGROUND. Alternative designs can potentially facilitate the realization of paediatric trials, especially when compared to the standard practice. The objective of this analysis was to compare the performance of the classical parallel design (PaD) with that of a sequential design (based on the Triangular Test (TT) [1]) and of a Bayesian design (BD), exploiting priors from adult data [2], by using PK-PD based clinical trial simulation (CTS).

MATERIALS AND METHODS. A published paediatric PK-PD model of topiramate [3] was used as a paradigm for CTS in epileptic children. The model, $Y = \beta_0 + \beta_1 \cdot C_{min} + \varepsilon$, relates TPM steady-state trough plasma concentration (C_{min}) to the log-transformed percent reduction in seizure frequency from baseline $Y = \log(\frac{S-B}{B} \cdot 100 + 110)$, with S being the average seizure frequency per 28 days during the treatment phase and B the corresponding average during the baseline phase.

Clinical trial simulation framework



- 2000 virtual patients were generated based on weight-for-age tables from WHO
- 500 PK profiles were created for each virtual child by using NONMEM version 7.2.0
- The PD measurement was simulated once for each patient
- The study design-specific statistical analysis was applied to the simulated data

Steps 3 and 4 were reiterated 1000 times. R software (version 3.0.1) was used for the generation of virtual patients population, drug effect simulations and statistical analyses.

Study designs description



α	β	$(\bar{\mu}_{Y_{PCB}} - \bar{\mu}_{Y_{TPM}})$	σ (Y)	H0 (one sided)
0.05	0.20	0.241	0.752	$\delta < 0$

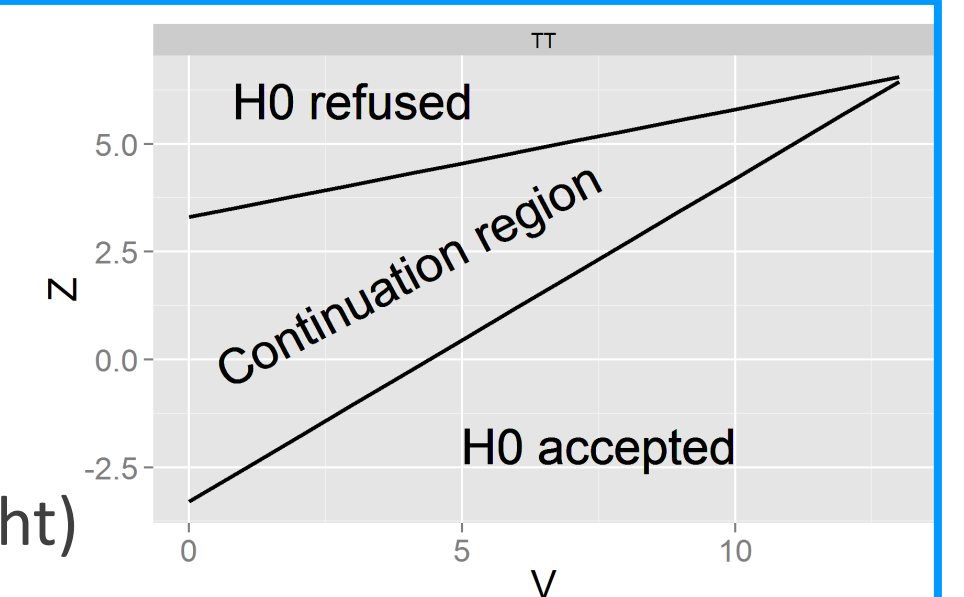
Parallel design

Sample size per group (SS) was obtained as follows:

$$n = 2 \left[\frac{(z_{1-\alpha} + z_{1-\beta}) \cdot \sigma}{\delta_P} \right]^2 \quad (1)$$

Sequential design: Triangular Test

- Statistical analyses are sequentially performed (sample size is not fixed a priori)
- A sample statistics Z (which can be thought of as the accumulated evidence of δ) is plotted against a second sample statistics V (which can be thought of as the amount of information about δ contained in Z)
- If Z exits the continuation region H0 is either accepted or refused (see figure on the right)



Bayesian design

- δ_A, δ_P : true improvement of TPM over placebo in adults and paediatrics
- Priors:** $\delta_A, \delta_P \sim N(\mu, \nu^2)$ (μ has non-informative prior and ν reflects the difference in improvement of TPM over placebo between children and adults)
- $\hat{\delta}_A$: MLE of δ based on an adult trial with m_A subjects
- $\hat{\delta}_P$: estimated δ in the paediatric trial with m_P subjects
- $s_A = 2\sigma_A$ and $s_P = 2\sigma_P$, where σ_A and σ_P are the standard deviations of Y in adults and paediatrics

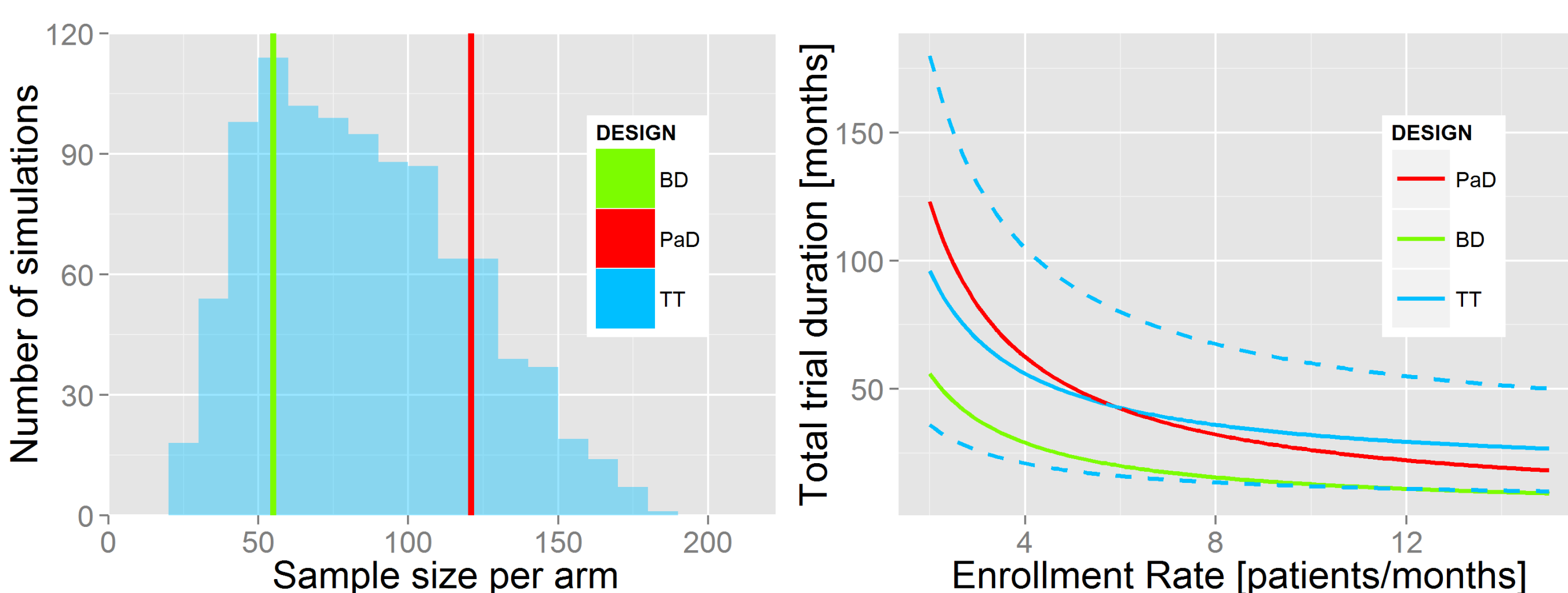
- Posterior** $\delta_P | \hat{\delta}_P, \hat{\delta}_A \sim N(\mu_{\delta_P}, \sigma_{\delta_P}^2)$, with:

$$\mu_{\delta_P} = \frac{\frac{m_P}{s_P^2} \hat{\delta}_P + \frac{\omega}{s_A^2} \hat{\delta}_A}{\frac{m_P}{s_P^2} + \frac{\omega}{s_A^2}}, \sigma_{\delta_P}^2 = \frac{s_P^2 s_A^2}{m_P s_A^2 + \omega s_P^2} \text{ and } \omega = \frac{m_A s_A^2}{s_A^2 + 2\nu m_A}$$

- Bayesian power (as a function of $\bar{\delta}_P$, Φ represents the normal cumulative distribution function):

$$\Phi \left(\frac{\sqrt{m_P}}{s_P} \left[\bar{\delta}_P - \frac{s_P^2}{m_P} \left(z_{1-\alpha} \sqrt{\frac{m_P}{s_P^2} + \frac{\omega}{s_A^2}} - \frac{\omega}{s_A^2} \hat{\delta}_A \right) \right] \right) \quad (2)$$

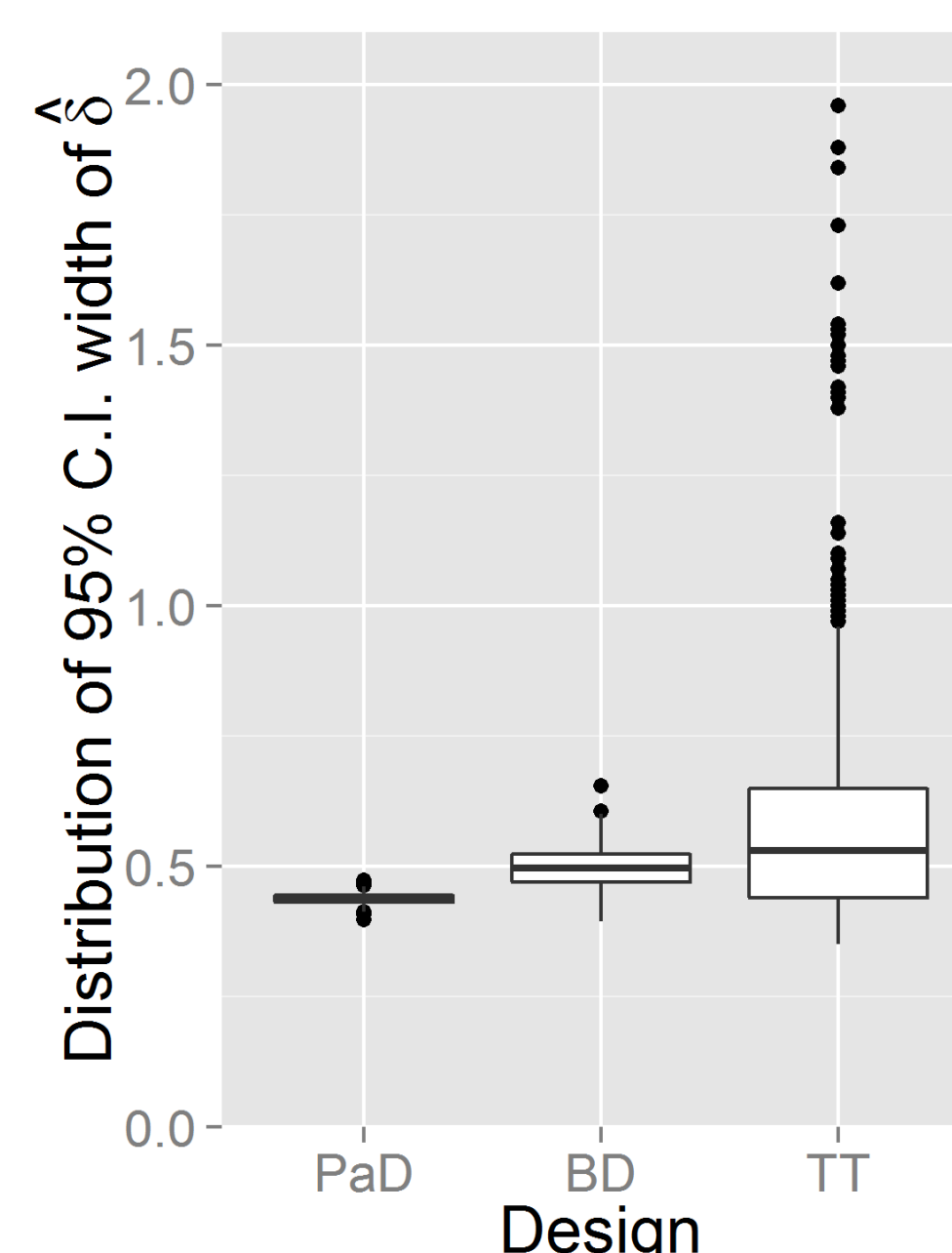
RESULTS. Type I and II errors are close to their predetermined levels of 5% and 20% for all designs except for the BD, whose type I error lies between 18.3% and 23.3%. SS for the PaD and BD was computed using equations (1) and (2) and resulted in 121 and 54 patients, respectively; TT's SS is not fixed a priori and its empirical distribution is shown in the left-hand figure below. Median TT's SS is lower than PaD's one, with a 28.4% probability of being lower than the BD's one.



Total trial duration reflects the required sample size for the PaD and the BD, whereas for the TT design this can span widely depending on the final SS.

The PaD guarantees the best precision of $\hat{\delta}$ as shown by the lowest median of the 95% confidence interval width (CIW). BD and median TT precision are only slightly lower than PaD's one, even though the value of the 97.5th percentile of CIW distribution in the TT suggests this design could lead to very imprecise estimates.

	DESIGN		
	PaD	TT	BD
Type I error (%)	5.4	6.3	20.8
(95% confidence interval)	(4.0-6.8)	(4.8-7.8)	(18.3-23.3)
Type II error (%)	20.8	20.2	19.9
(95% confidence interval)	(18.3-23.3)	(17.7-22.7)	(17.4-22.4)
Sample size per arm	50 th percentile	121	80
	75 th percentile	121	100
	95 th percentile	121	140
Median total trial duration (months)	4 pts/months	62.5	56
	10 pts/months	26.2	32
		29	12.8



CONCLUSIONS. This model-based analysis suggests that:

- if it is reasonable to assume that treatment effect in children is similar to that in adults, a BD allows to streamline paediatric trials
- if adult data cannot be leveraged, a TT design appears to outperform a classical PaD, especially if a large effect size is expected

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