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ISCB

Birmingham

Speaker:

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InSPiRe WP1

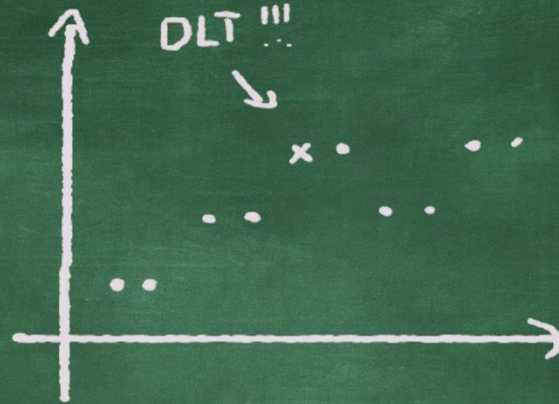
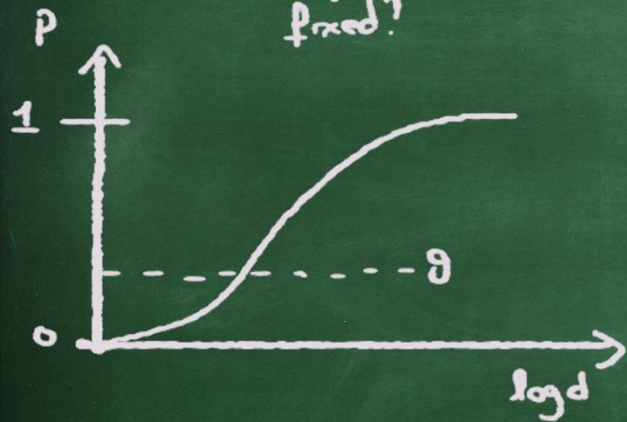
A Bayesian weighted quasi-likelihood design for Phase I/II clinical trial with repeated dose administration in preterm newborns

time $\sim f(t, \underline{\beta})$ $\underline{\beta} = (\beta_1, \beta_2)$

$$w_{r,i} = n_i / N_{\text{Tot}}$$

$$\text{logit}(p_T) = \alpha_0 + \alpha_1 \log(d)$$

\uparrow
fixed?



$\theta = 0,1$

$$d_{j+1} = \underset{d \in D}{\text{argmin}} |p_T - \theta|$$

$\alpha_0 = 3?$

$$\mathcal{L}(\underline{\alpha} | \underline{y}) = \prod [p_T^{y_i} (1-p_T)^{1-y_i}]$$

$$\pi(\underline{\alpha} | \underline{y}) \propto \mathcal{L}(\underline{\alpha} | \underline{y}) \pi(\underline{\alpha})$$

Innovative methodology for small populations research

WP1 AIM

To develop novel methodology for improving **dose-finding** in early phase clinical trials.

Levneonat Clinical trial NCT02229123: a phase I/II trial aiming at finding the recommended dose of Levetiracetam for treating neonate's seizures was planned with a maximum sample size of 50.

Collaboration with:

- Dr Ying Yuan (MD Anderson Cancer Center, Houston, USA)
- Dr Geraldine Fevrais (Neonatal and pediatric intensive care unit, CHRU de Tours, Tours, France)



Members :

- Sarah Zohar
- Emmanuelle Comets
- Corinne Alberti
- Frederike Lentz
- Nigel Stallard
- Tim Friede
- Moreno Ursino

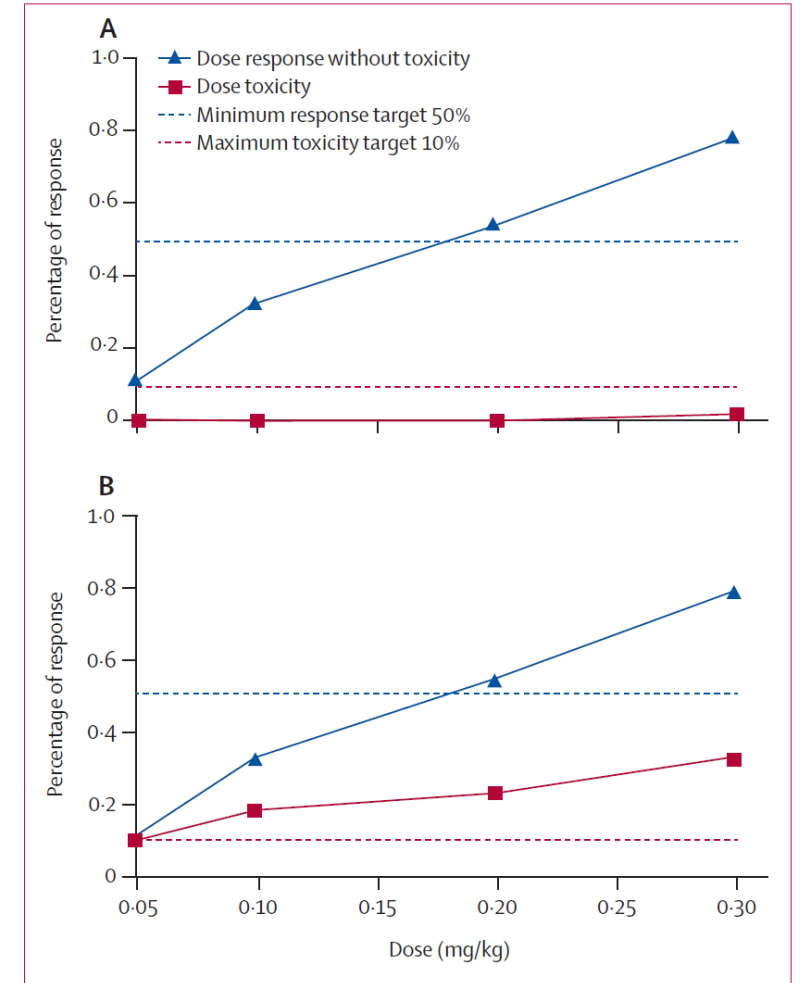
NEMO: NEonatal Seizure Using Medication Off-patent (NCT01434225)

Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy (NEMO): an open-label, dose finding, and feasibility phase 1/2 trial

Ronit M Pressler*, Geraldine B Boylan*, Neil Marlow, Mats Blennow, Catherine Chiron, J Helen Cross, Linda S de Vries, Boubou Hallberg, Lena Hellström-Westas, Vincent Jullien, Vicki Livingstone, Barry Mangum, Brendan Murphy, Deirdre Murray, Gerard Pons, Janet Rennie, Renate Swarte, Mona C Toet, Sampsa Vanhatalo, Sarah Zohar, for the NEonatal seizure treatment with Medication Off-patent (NEMO) consortium†

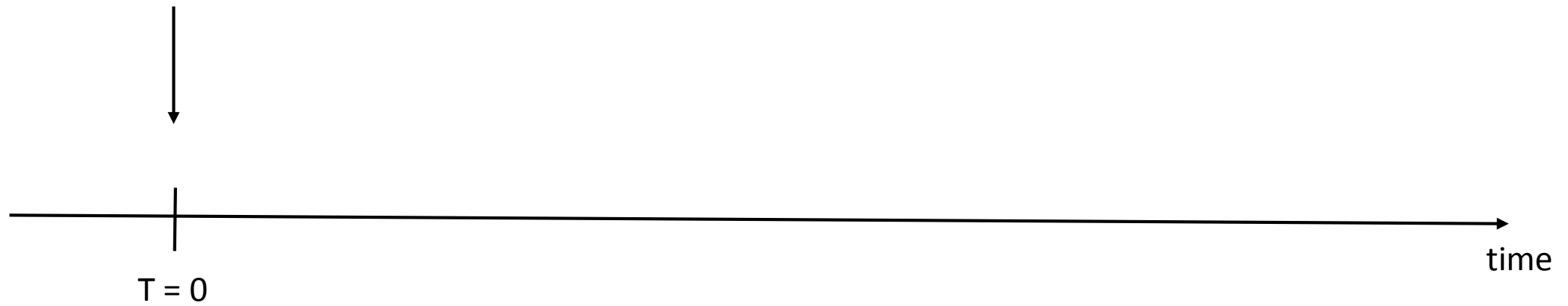
A phase I/II dose-finding design with dual binary efficacy and safety endpoints.

During the trial no major adverse event were observed according to the safety composite endpoint defined in the protocol. However, after the inclusion of 14 patients unexpected safety event was measured, that is, hearing loss observed in three neonates at different doses.



LEVNEONAT NCT02229123

**Levetiracetam
loading dose (LD)**

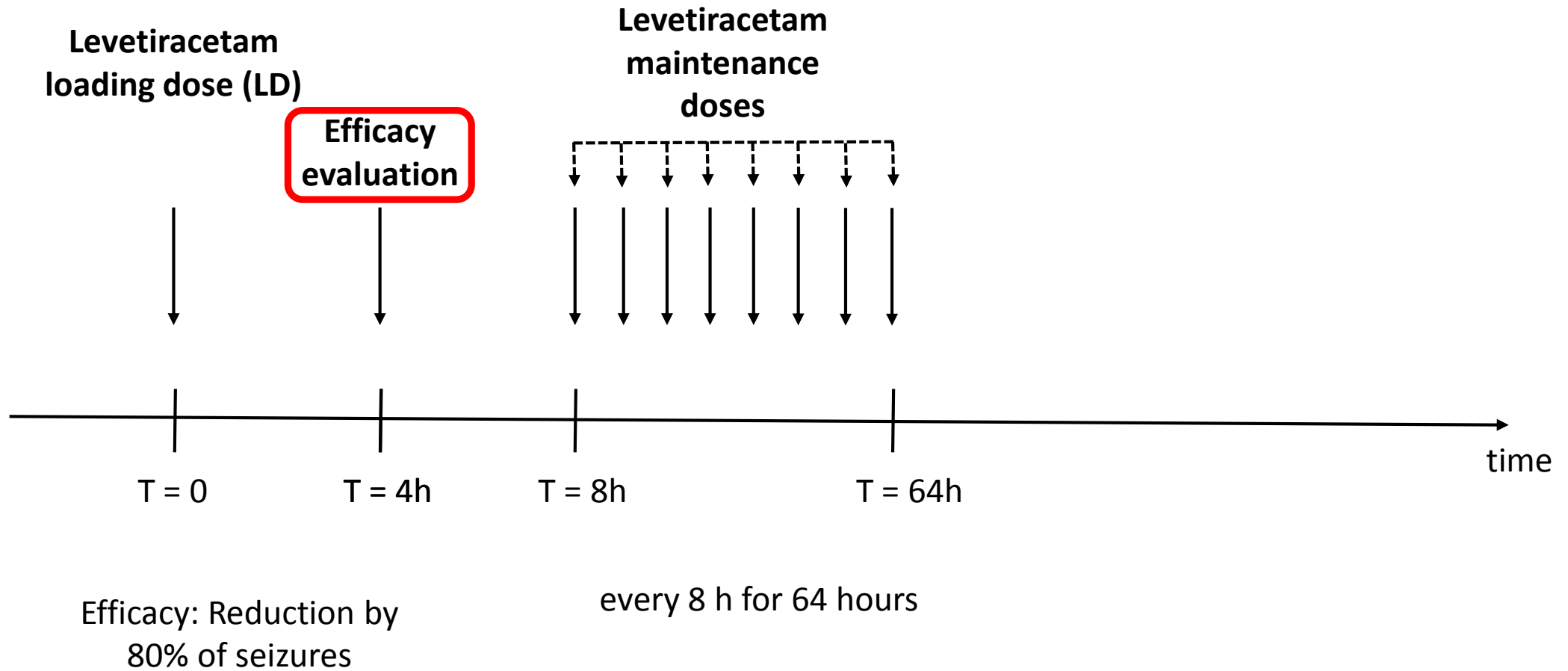


LEVNEONAT NCT02229123

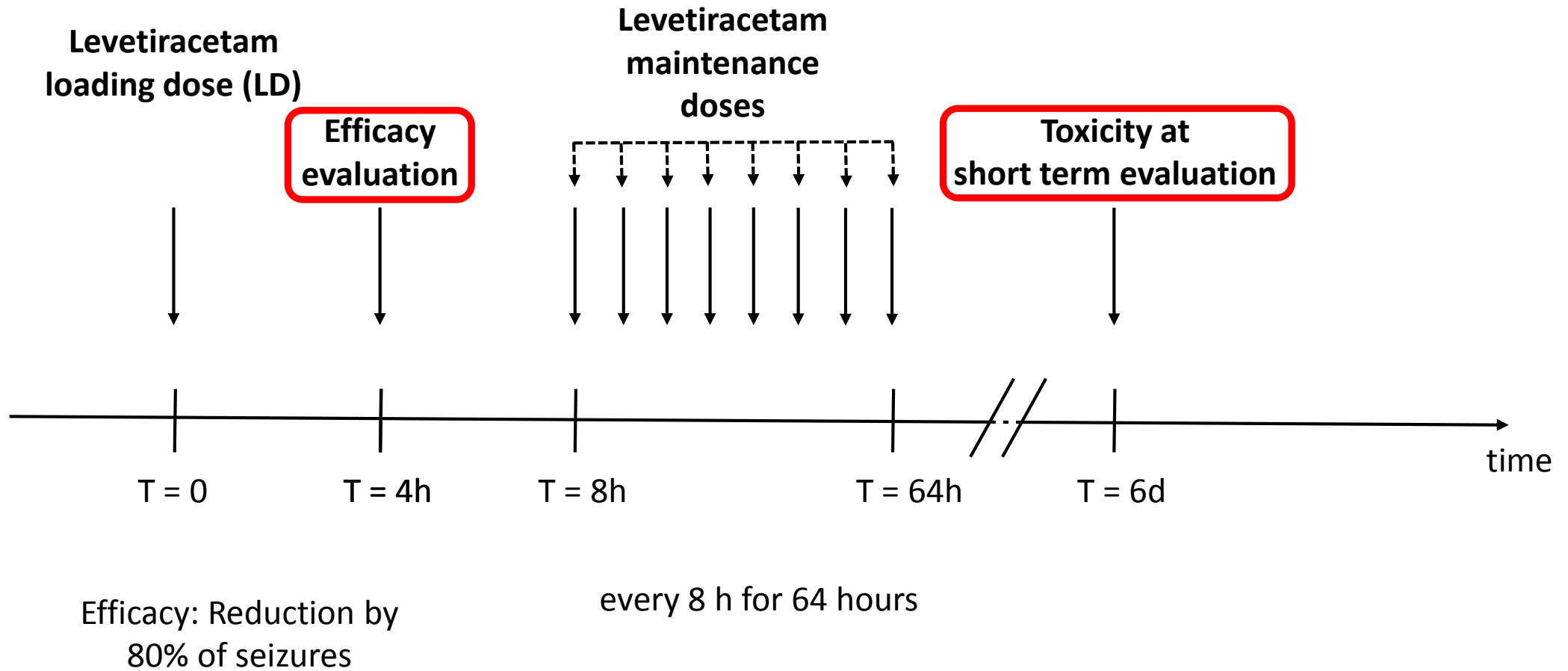


Efficacy: Reduction by
80% of seizures

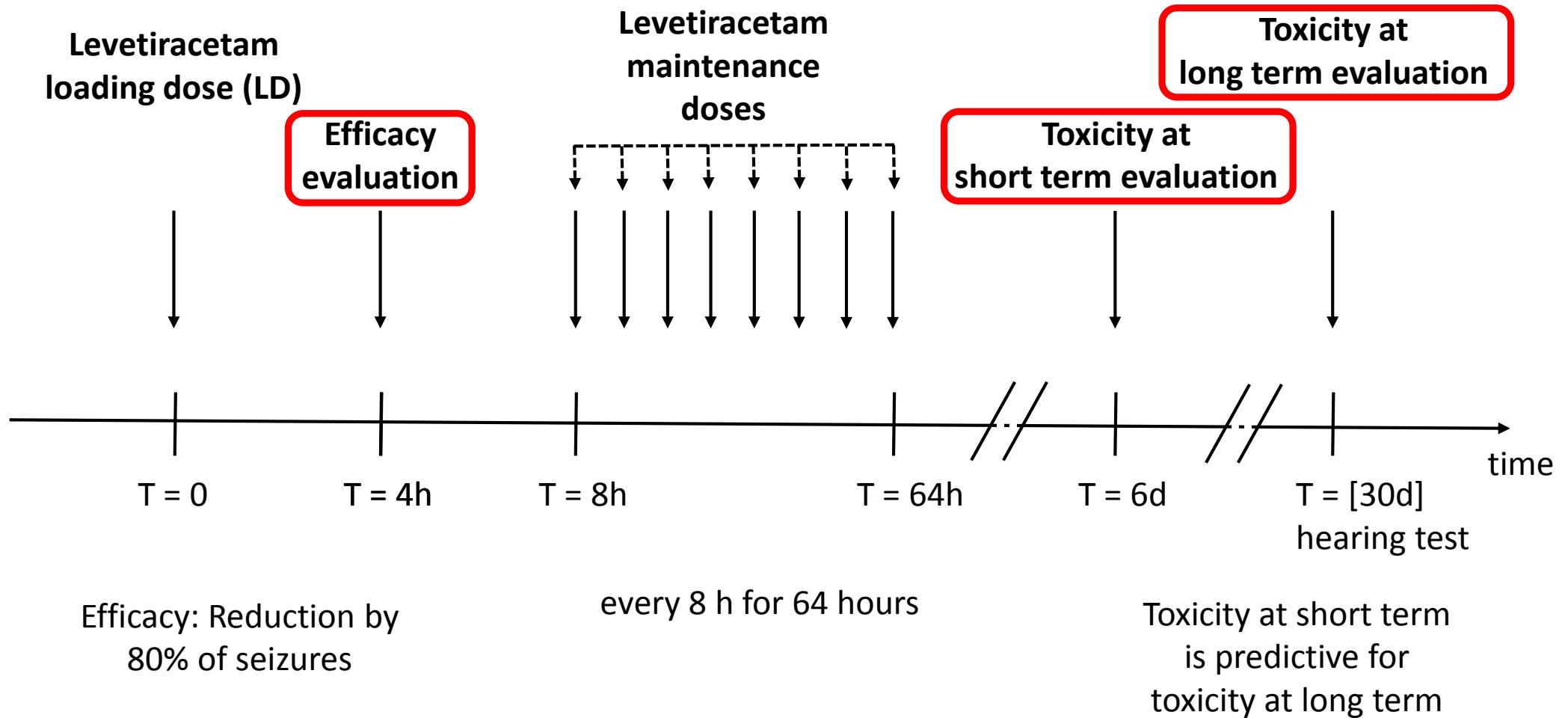
LEVNEONAT NCT02229123



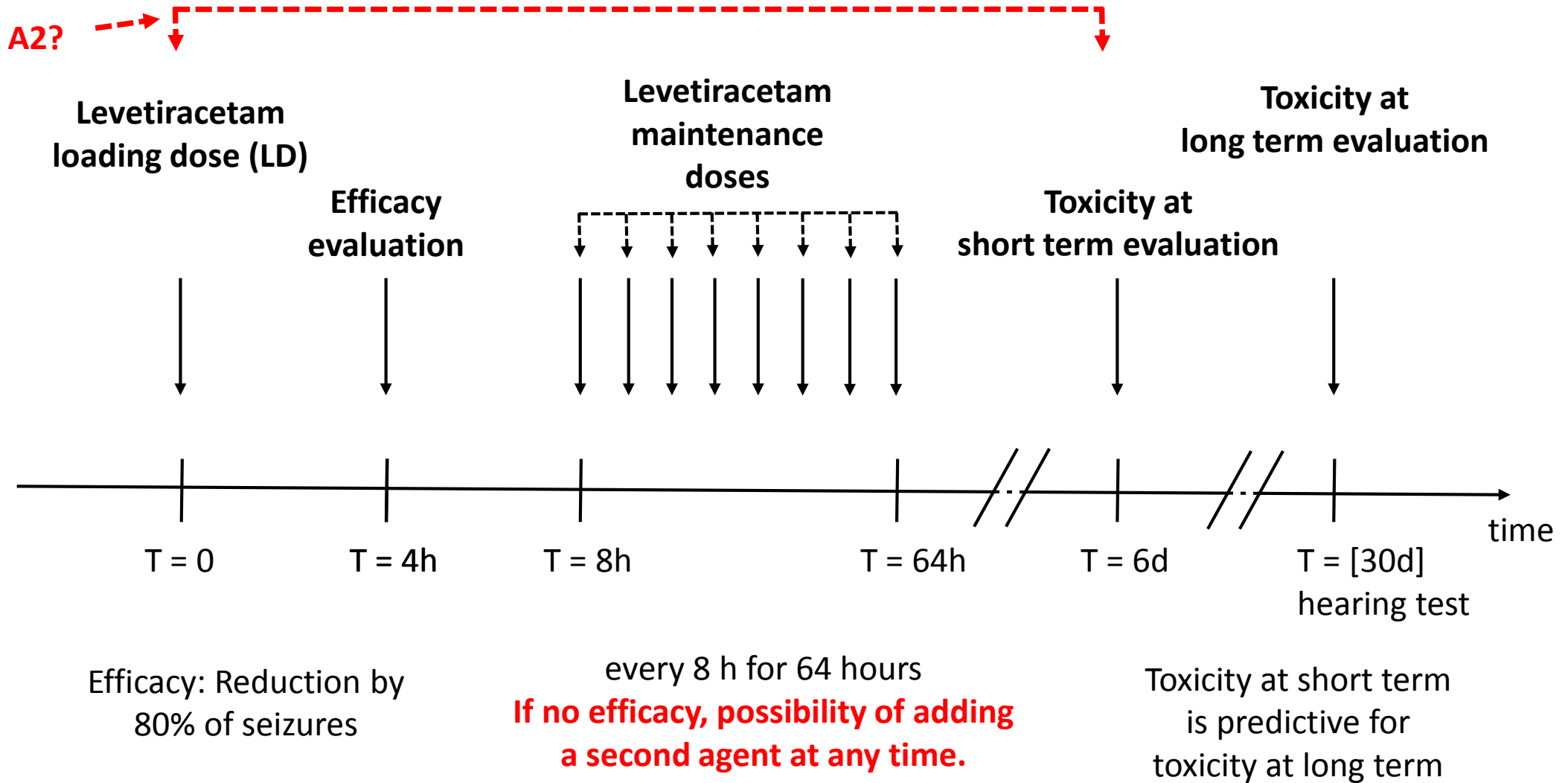
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LEVNEONAT NCT02229123



LEVNEONAT NCT02229123



Efficacy model

Bayesian logistic model (dose monotonicity)

$$\text{logit}(P_E) = \alpha_1 + e^{\beta_1} x$$

$$x \in \{\tilde{d}_1, \dots, \tilde{d}_K\}$$

α_1 fixed

$$\beta_1 \sim \mathcal{N}(0, 1.34)$$

$$\mathcal{L}_E(\beta_1 | \underline{y}_E) = \prod_{i=1}^{N_E} p_{E,i}^{y_i} (1 - p_{E,i})^{1 - y_i}$$

Toxicity at short term (1)

$$WQ\alpha_1(\gamma_1 | \underline{y}_1, \alpha_1, \xi) =$$

$$\prod_{i=1}^{N_1} \left(\left[1 - \left(1 - \frac{\mu_i}{T_{\max}} \right)^{\xi} \right]^{p_{T_1}} \right)^{w r_i \gamma_i^*}$$

$$\cdot \left(1 - \left[1 - \left(1 - \frac{\mu_i}{T_{\max}} \right)^{\xi} \right]^{p_{T_1}} \right)^{w r_i (1 - \gamma_i^*)}$$

Toxicity at short term (2)

$$\text{WQ} \alpha_1(\gamma_1 | \underline{y}_1, \alpha_1, \xi) =$$
$$\prod_{i=1}^{N_1} \left(\left[1 - \left(1 - \frac{\mu_i}{T_{\max}} \right)^\xi \right] p_{T_1} \right)^{w_i \gamma_i^*}$$
$$\cdot \left(1 - \left[1 - \left(1 - \frac{\mu_i}{T_{\max}} \right)^\xi \right] p_{T_1} \right)^{w_i (1 - \gamma_i^*)}$$

Probability of toxicity at short term

$$\text{logit}(p_{T_1}) = \alpha_2 + e^{\delta_1} x$$

$$x \in \{\bar{d}_1, \dots, \bar{d}_k\}$$

α_2 fixed

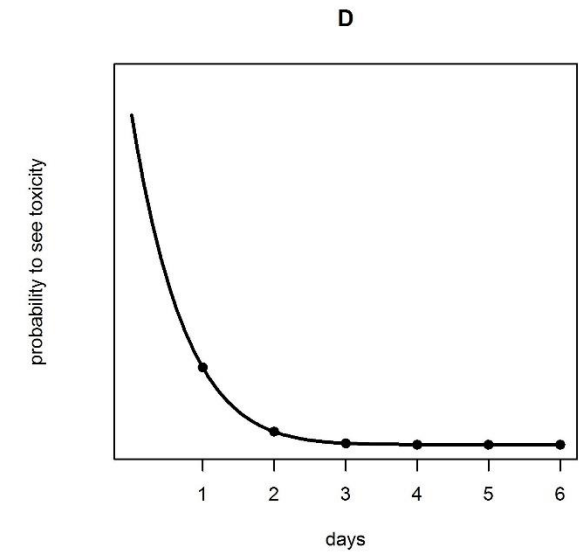
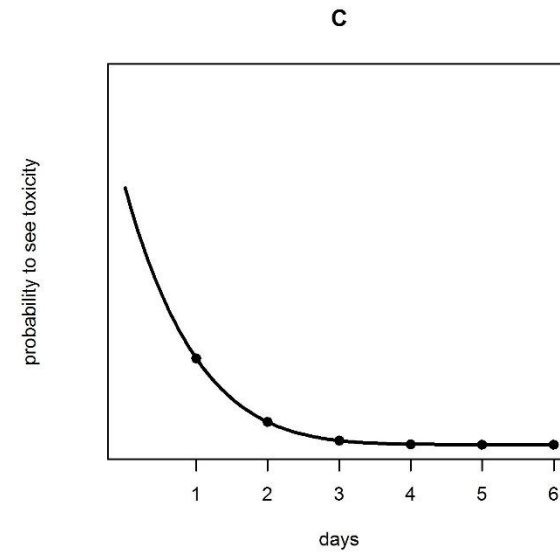
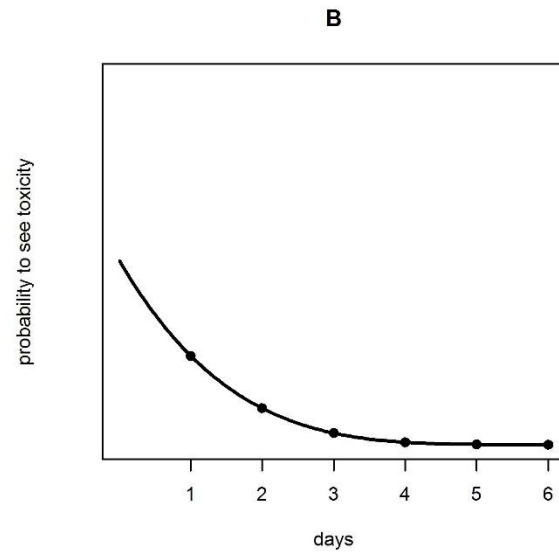
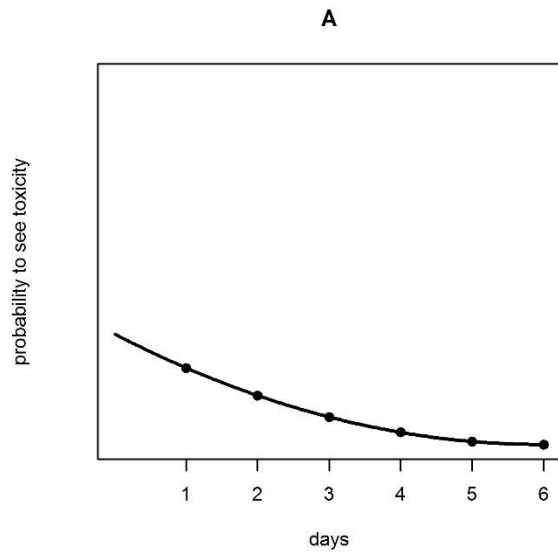
$$\delta_1 \sim \mathcal{N}(0, 1.34)$$

Toxicity at short term (3)

$$WQ\mathcal{L}_1(\gamma_1 | \gamma_1, \alpha_1, \xi) = \prod_{i=1}^{N_1} \left[1 - \left(1 - \frac{\mu_i}{T_{max}} \right)^\xi \right]^{p_{T_1} w_i \gamma_i^*} \cdot \left[1 - \left[1 - \left(1 - \frac{\mu_i}{T_{max}} \right)^\xi \right]^{p_{T_1}} \right]^{w_i (1 - \gamma_i^*)}$$

“Time-to-event”

$$\mu \sim \text{Beta}(1, \xi)$$



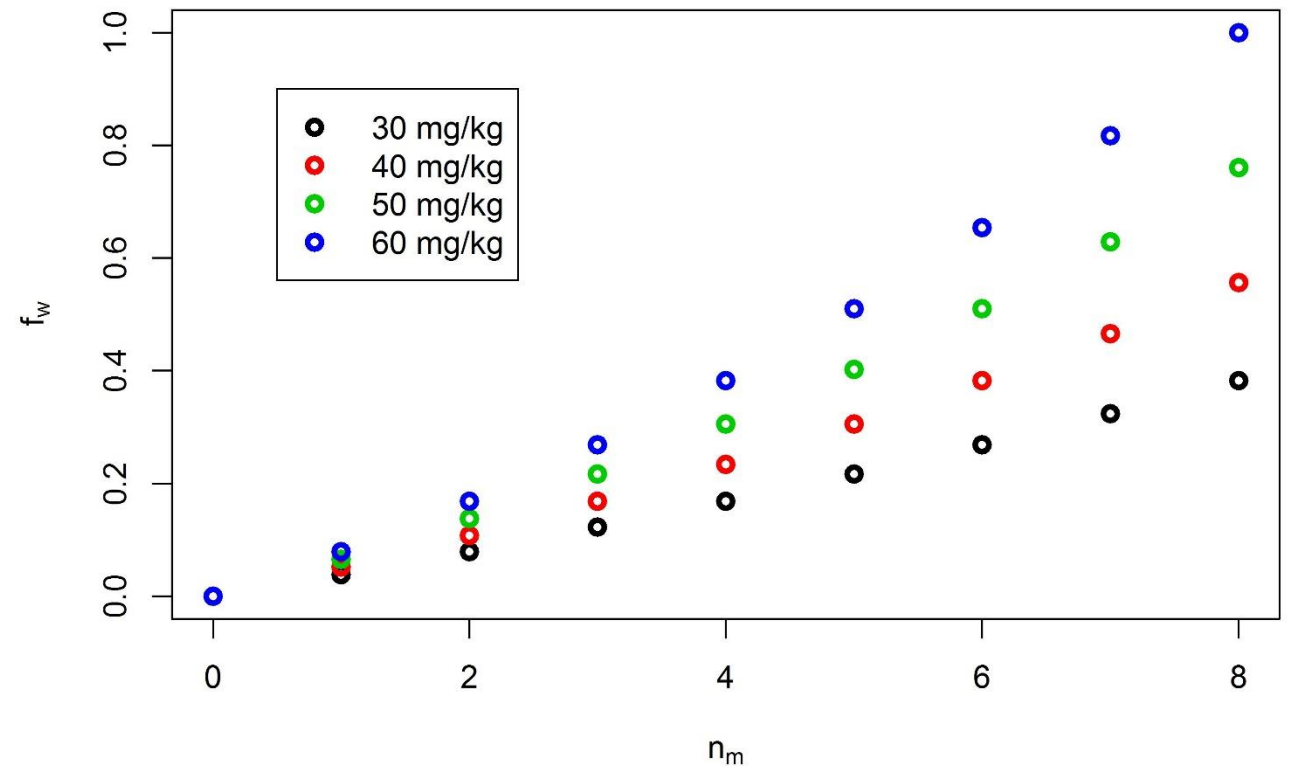
Toxicity at short term (4)

$$WQ\mathcal{L}_1(\gamma_1 | y_1, d_1, \xi) = \prod_{i=1}^{N_1} \left(\left[1 - \left(1 - \frac{\mu_i}{T_{max}} \right)^\xi \right]^{p_{T_1}} \right)^{w_i \gamma_i^*} \cdot \left(1 - \left[1 - \left(1 - \frac{\mu_i}{T_{max}} \right)^\xi \right]^{p_{T_1}} \right)^{w_i (1 - \gamma_i^*)}$$

$$y_i^* = w y_i$$

$$w = \begin{cases} 1 & \text{if } A_2 = 0 \\ \frac{e^{\delta n_m x} - 1}{e^{\delta N_m x} - 1} \tau & \text{if } A_2 = 1 \end{cases}$$

with $\gamma = 0.002$

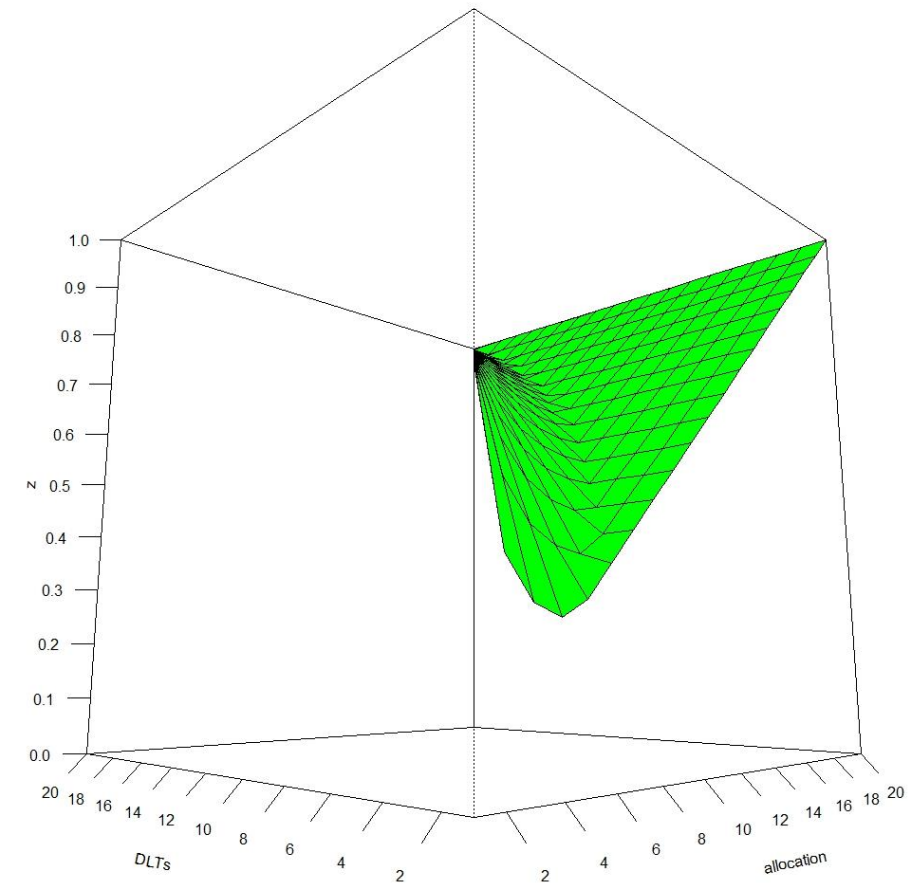


Toxicity at short term (5)

$$WQL_1(y_1 | y_1, d_1, \xi) =$$

$$\prod_{i=1}^{N_1} \left(\left[1 - \left(1 - \frac{w_i}{T_{max}} \right)^\xi \right]^{p_{T_1}} \cdot w_i \gamma_i^* \right) \cdot \left(1 - \left[1 - \left(1 - \frac{w_i}{T_{max}} \right)^\xi \right]^{p_{T_1}} \cdot w_i (1 - \gamma_i^*) \right)$$

$$w_i = \begin{cases} 1 & \text{if } y_i = 0 \\ \min \left[\max \left(\pi \frac{n_{alloc, d_i}}{n_{max}} + (1 - \pi) \frac{n_{DLT, d_i}}{n_{alloc, d_i}}, \frac{n_{alloc, d_i}}{n_{max}} \right), 1 \right] & \text{if } y_i = 1 \end{cases}$$



Toxicity at long term

Conditional probability

$$\text{logit}(P_{T_2} | Y_{T_1}) = \alpha_3 + e^{\delta_1} x + e^{\delta_2} y_1^*$$

$$x \in \{d_1, \dots, d_k\}$$

α_3 fixed

$$\delta_1 \sim \mathcal{N}(0, 1.34)$$

$$\delta_2 \sim \mathcal{N}(0, 1.34)$$

Trial settings

Cohort: 2 neonates

Stopping rules:

$$P(p_{T1} > 0.1 | d_1) > 0.9$$

$$P(p_{T2} > 0.1 | d_1) > 0.9$$

$$P(p_E < 0.6 | d_K) > 0.9$$

Dose allocation rules:

$$P(p_E < \tau_e - \epsilon_e) < g(N_e)^{1_{N_e > 11}}$$

$$P(p_{T1} > \tau_{p1} + \epsilon_1) < g(N_1)$$

$$P(p_{T2} > \tau_{p2} + \epsilon_2) < g(N_2)^{1_{N_2 > 1}}$$



$$g(N) = \max \left(0.5, 0.9 \frac{1}{1 + 0.04 * N} \right)$$

Dose selected: the one which has the highest efficacy among them selected through the previous constraints

Dose selection rules:

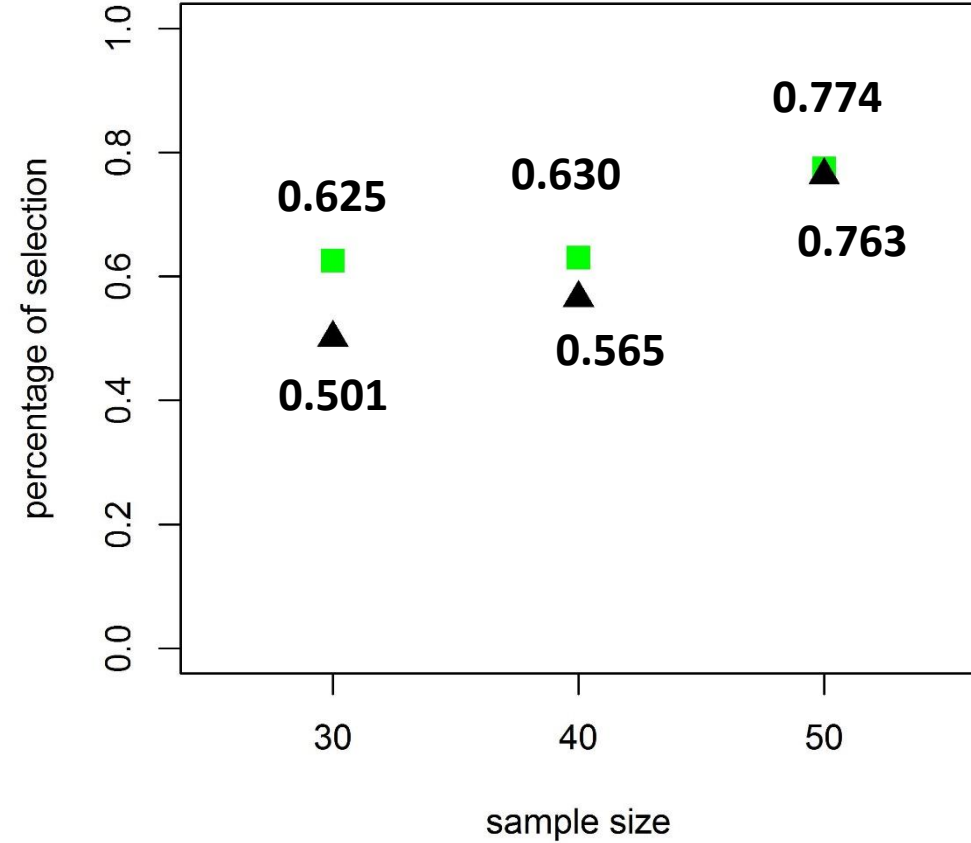
$$d_{e,\min} = \arg \min_{d \in D} |d - \tau_e|$$

$$d_{t,\max} = \min \left(\arg \min_{d \in D} |d - \tau_{p1}|, \right.$$

$$\left. \arg \min_{d \in D} |d - \tau_{p2}| \right)$$

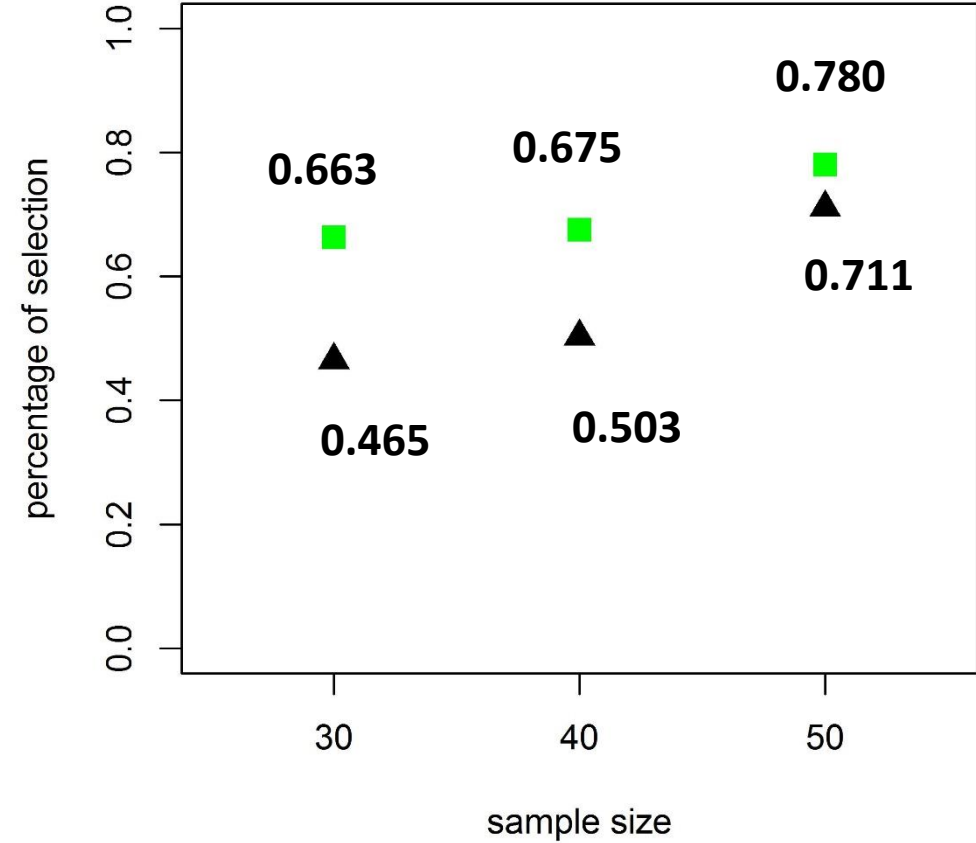
Simulations and Results (1)

	d_1	d_2	d_3	d_4
p_E	0.001	0.01	0.1	0.2
p_{T1}	0.001	0.01	0.1	0.2
p_{T2}	0.6	0.7	0.8	0.9
P add A2	0			
$p_{T1 A2}$				
$p_{T2 A2}$				



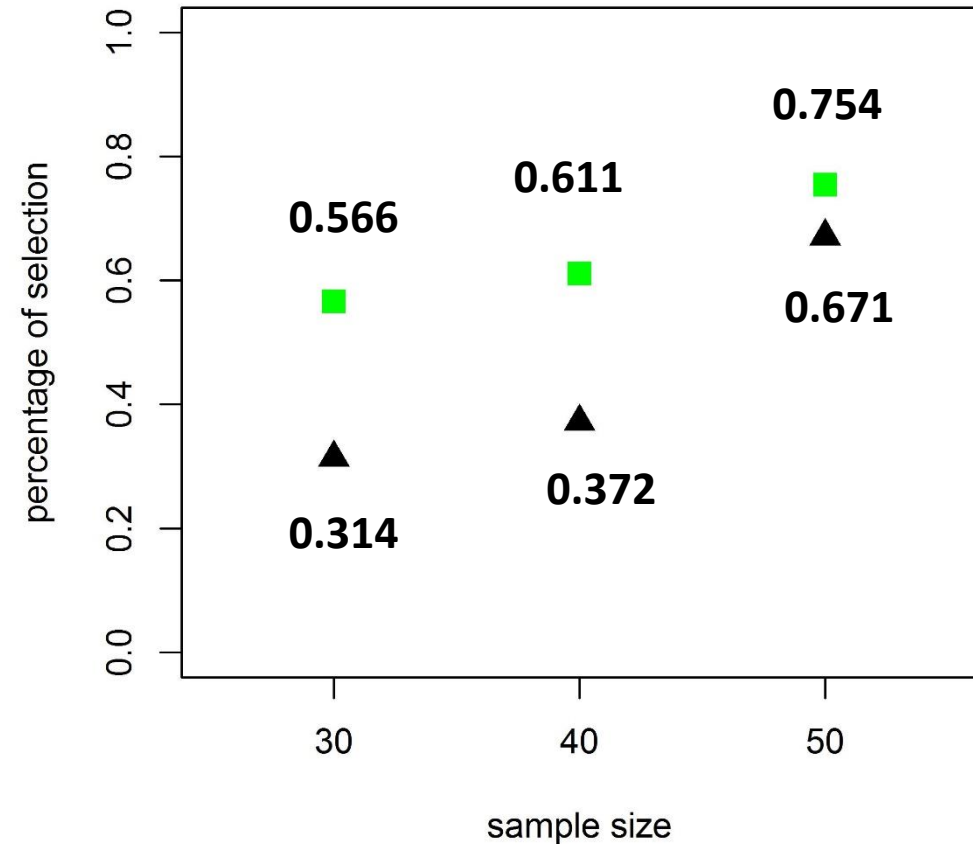
Simulations and Results (2)

	d_1	d_2	d_3	d_4
p_E	0.001	0.01	0.1	0.2
p_{T1}	0.001	0.01	0.1	0.2
p_{T2}	0.6	0.7	0.8	0.9
P add A2	0.5			
$p_{T1 A2}$	0.005	0.05	0.15	0.25
$p_{T2 A2}$	0.005	0.05	0.15	0.25



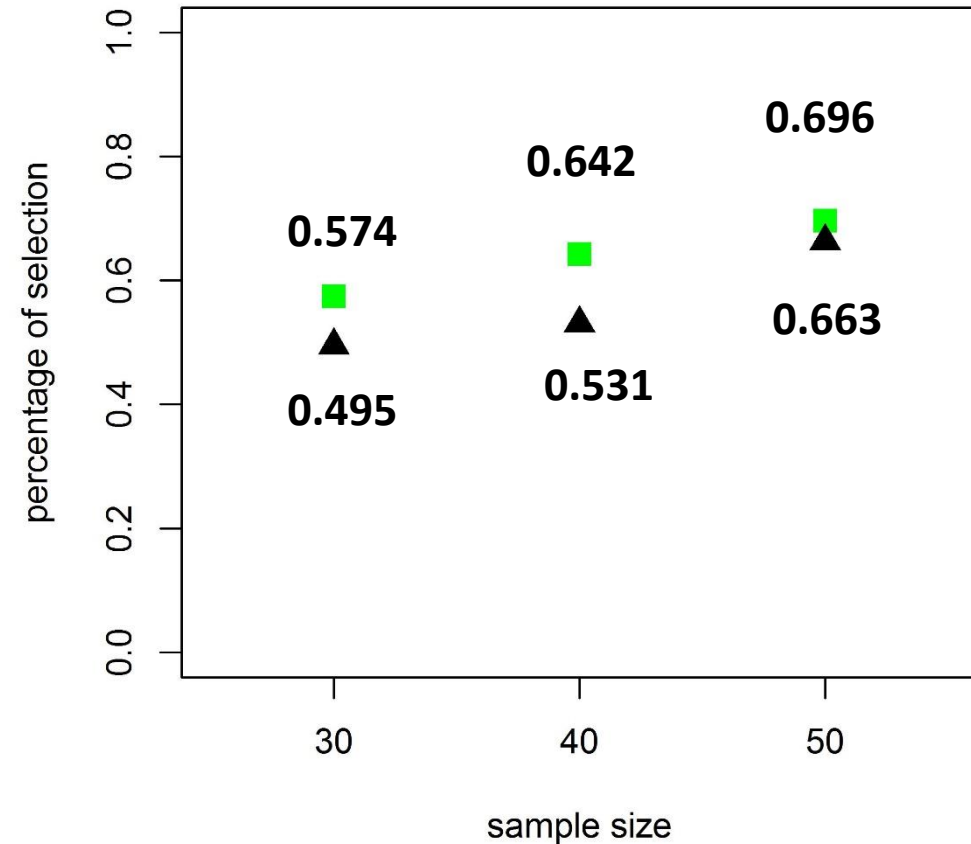
Simulations and Results (3)

	d_1	d_2	d_3	d_4
p_E	0.01	0.1	0.25	0.35
p_{T1}	0.009	0.1	0.18	0.26
p_{T2}	0.6	0.7	0.8	0.9
P add A2	0.5			
$p_{T1 A2}$	0.01	0.01	0.25	0.35
$p_{T2 A2}$	0.01	0.01	0.25	0.35



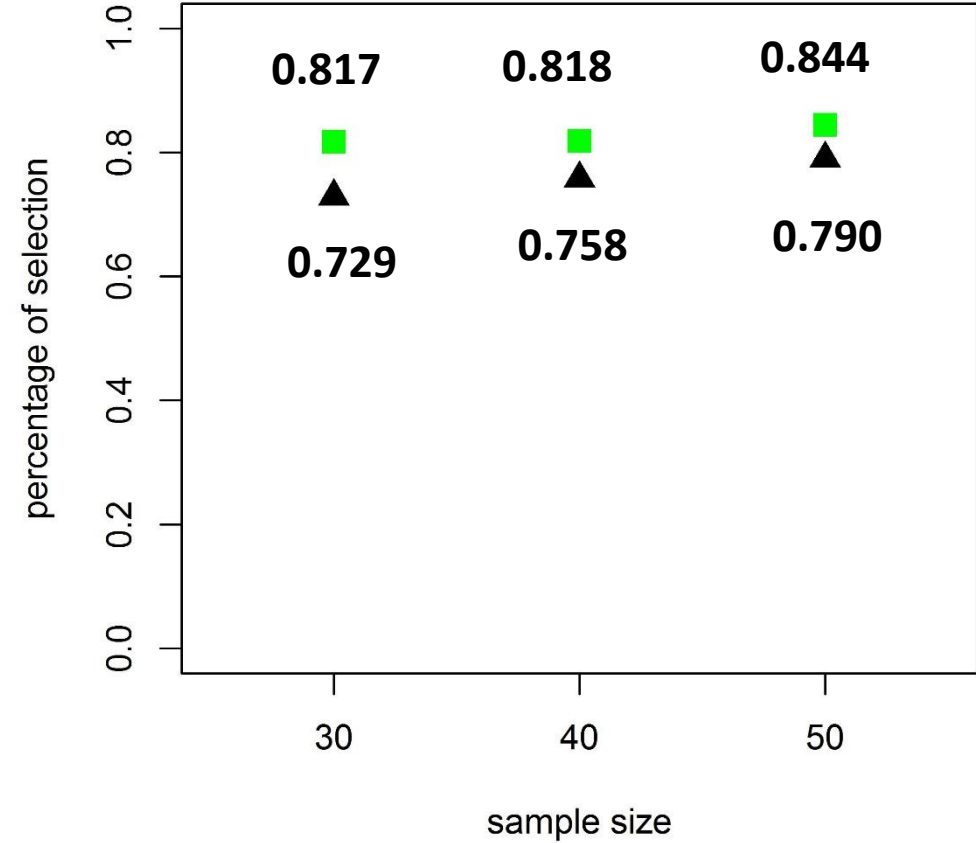
Simulations and Results (4)

	d_1	d_2	d_3	d_4
p_E	0.001	0.01	0.1	0.2
p_{T1}	0.01	0.1	0.2	0.3
p_{T2}	0.6	0.7	0.8	0.9
P add A2	0.5			
$p_{T1 A2}$	0.005	0.05	0.15	0.25
$p_{T2 A2}$	0.005	0.05	0.15	0.25



Simulations and Results (5)

	d_1	d_2	d_3	d_4
p_E	0.001	0.005	0.01	0.05
p_{T1}	0.001	0.007	0.015	0.05
p_{T2}	0.3	0.4	0.5	0.6
P add A2	0.5			
$p_{T1 A2}$	0.005	0.009	0.012	0.06
$p_{T2 A2}$	0.005	0.009	0.012	0.06



Conclusion

This model could be a good trade-off for this clinical trial in which we need to deal with small sample size, tail probability estimation and, of course, safety of neonates.

Relevance weight can help at the beginning of the dose allocation to avoid to be stuck.

We improve the percentage of right dose selection without increasing a lot the dose limiting toxicities.

Improvements:

- Continuous analysis for efficacy at the end of the trial:
 - Bayesian beta regression
- Pharmacokinetics analysis including covariables in order to try to adjust the dose selected for each neonate subgroups

Aknowledgement



Sarah Zohar

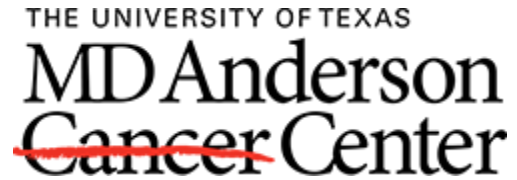
Emmanuelle Comets

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Tim Friede



Dr Ying Yuan



Dr Geraldine Fevrais (Neonatal and pediatric intensive care unit, CHRU de Tours)
and all the statisticians and physicians of the group.