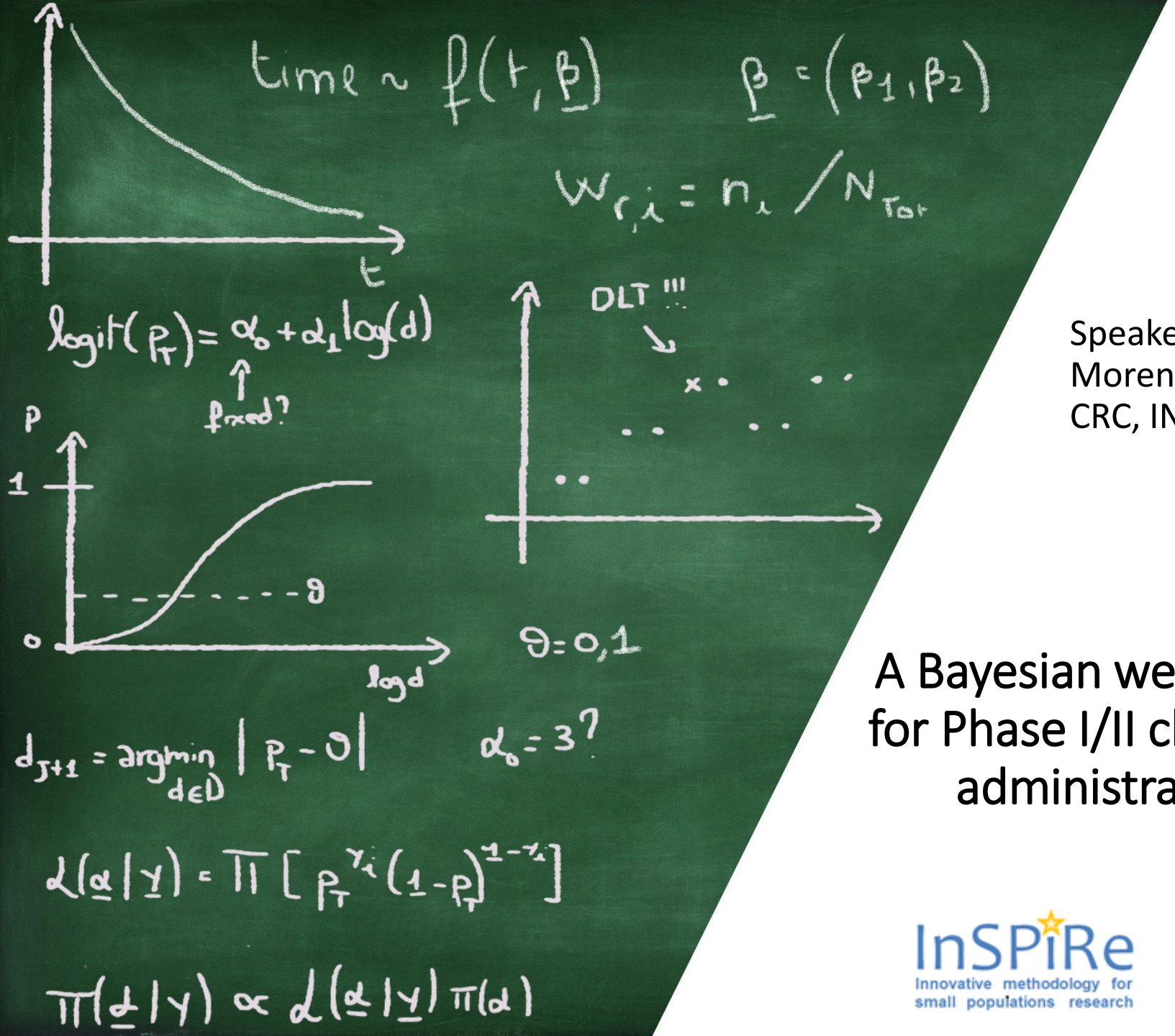



24/08/2016

ISCB

Birmingham

Speaker:
Moreno Ursino, PhD
CRC, INSERM UMR 1138

Co-Authors:
InSPiRe WP1

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

InSPiRe
Innovative methodology for small populations research

CRC
CENTRE DE RECHERCHE
DES CORDELIERS

Inserm
Institut national
de la santé et de la recherche médicale

# WP1 - InSPiRe

## Innovative methodology for small populations research

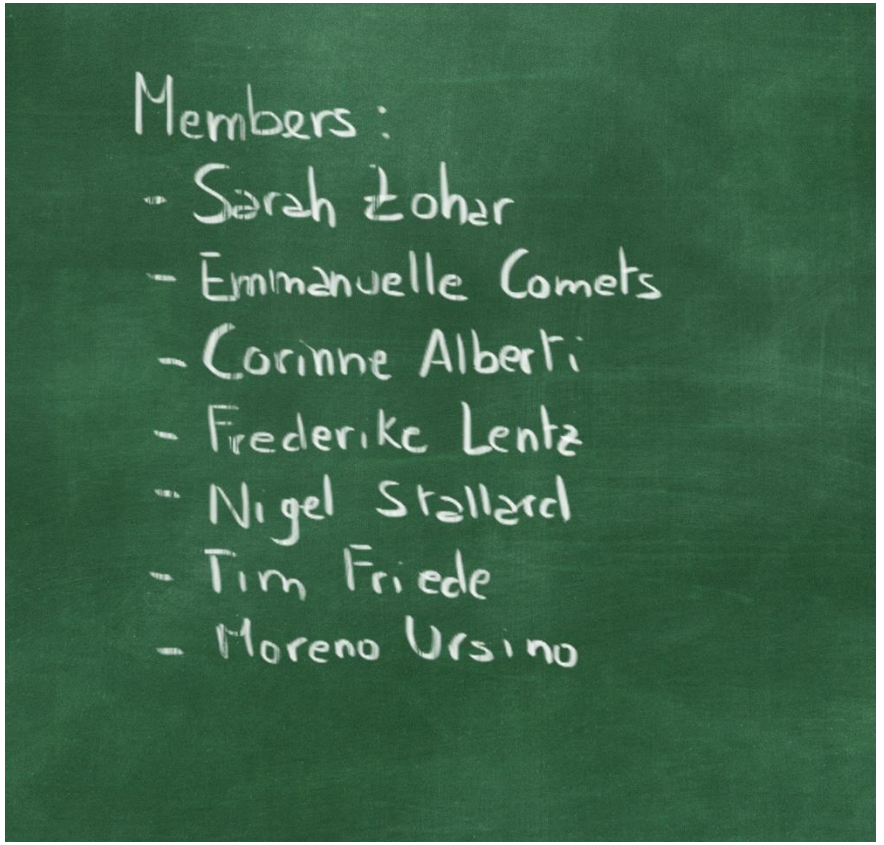
**WP1 AIM**

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)



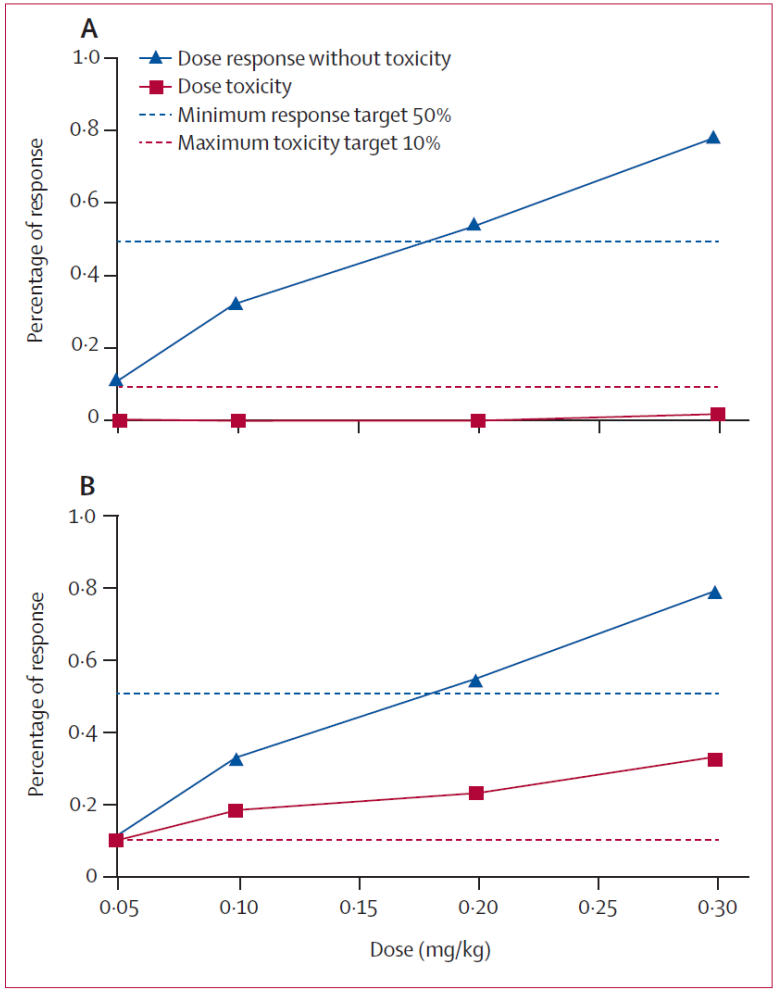
# NEMO: NEonatal Seizure Using Medication Off-patent (NCT01434225)

## 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.



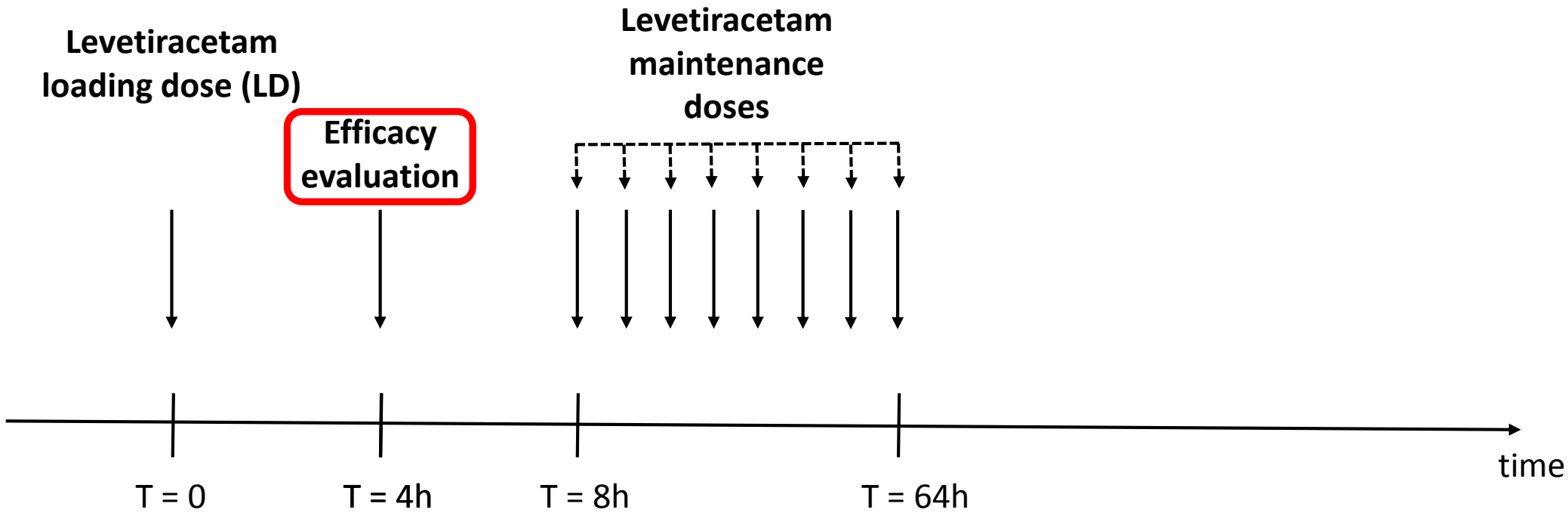

Pressler, Ronit M., et al. "Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy (NEMO): an open-label, dose finding, and feasibility phase 1/2 trial." The Lancet Neurology 14.5 (2015): 469-477.

# LEVNEONAT NCT02229123

# LEVNEONAT NCT02229123


Efficacy: Reduction by
80% of seizures

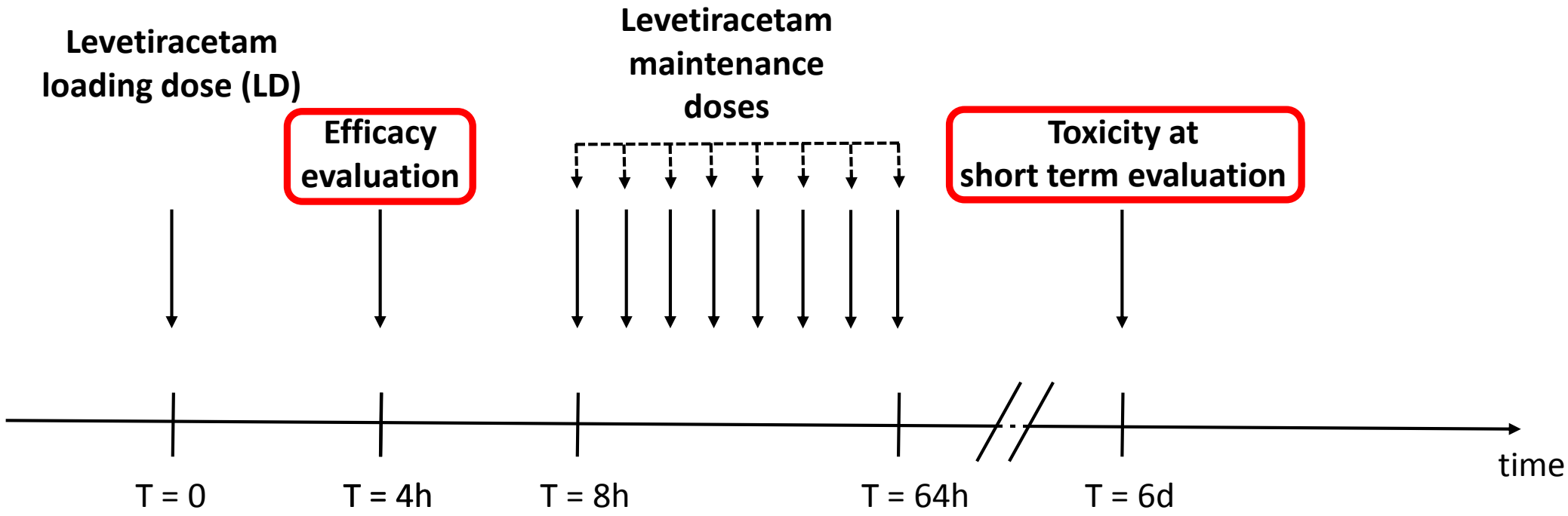
# LEVNEONAT NCT02229123




Efficacy: Reduction by 80% of seizures

every 8 h for 64 hours

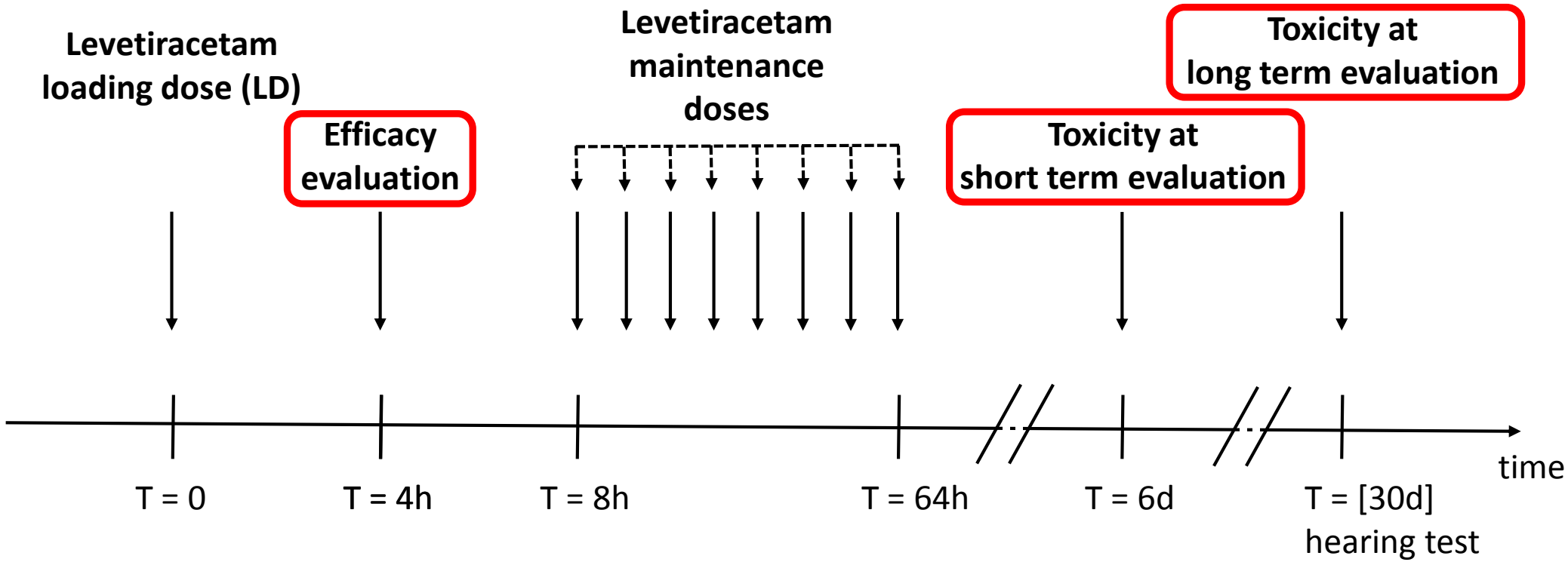
# LEVNEONAT NCT02229123




Efficacy: Reduction by 80% of seizures

every 8 h for 64 hours

# LEVNEONAT NCT02229123

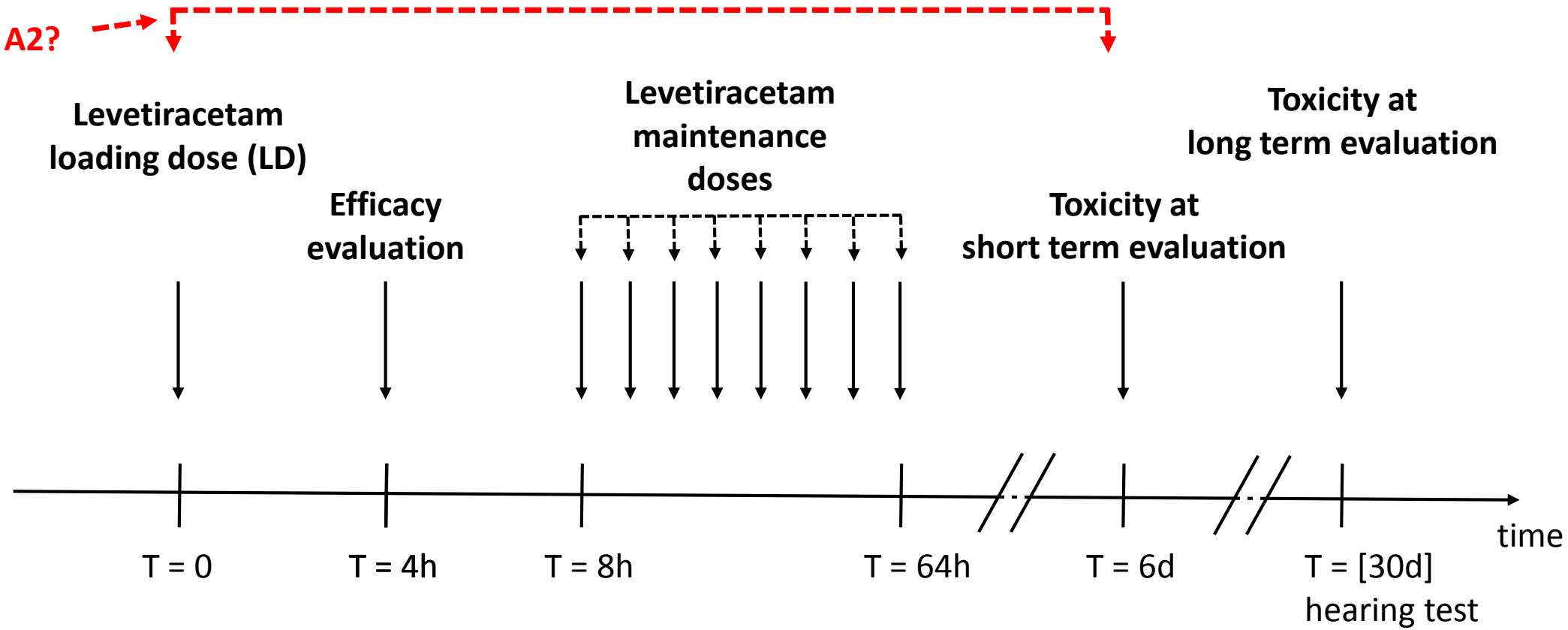



Efficacy: Reduction by 80% of seizures

every 8 h for 64 hours

Toxicity at short term is predictive for toxicity at long term

# LEVNEONAT NCT02229123




Efficacy: Reduction by 80% of seizures

every 8 h for 64 hours

**If no efficacy, possibility of adding a second agent at any time.**

Toxicity at short term is predictive for toxicity at long term

# Efficacy model

Bayesian logistic model (dose monotonicity)

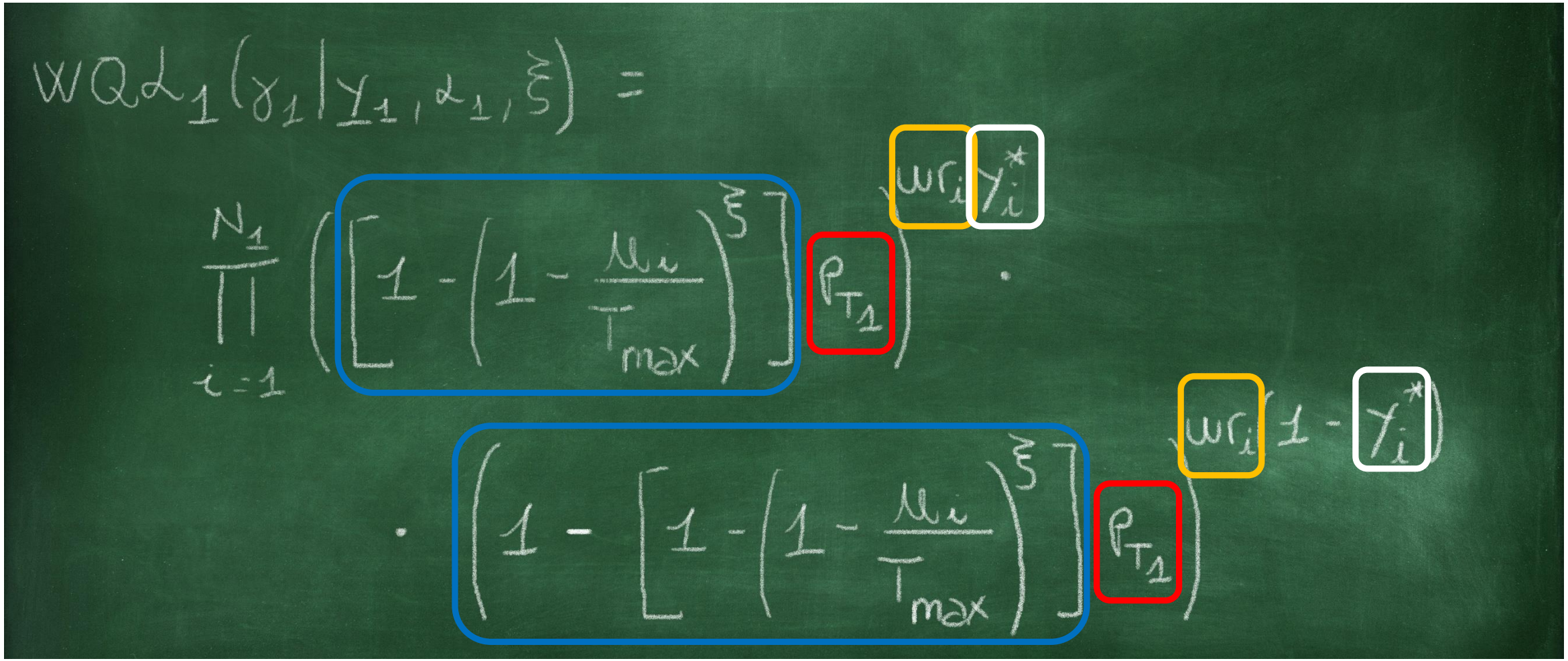
$$\text{logit}(p_E) = \alpha_1 + e^{\beta_1} x \qquad x \in \{\tilde{d}_1, \ldots, \tilde{d}_K\}$$

$$\alpha_1 \text{ fixed}$$

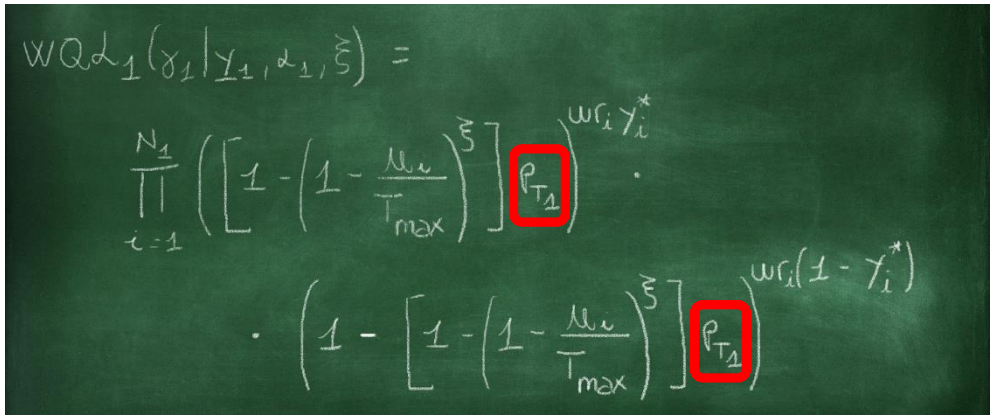
$$\beta_1 \sim \mathcal{N}(0, 1.34)$$

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

# Toxicity at short term (1)



# Toxicity at short term (2)



**Probability of toxicity at short term**

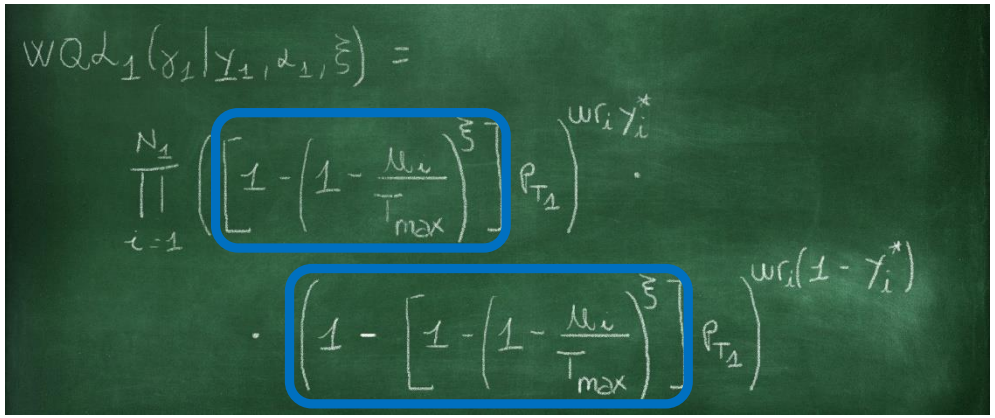
$$\text{logit}(p_{T_1}) = \alpha_2 + e^{\gamma_1} x$$

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

$\alpha_2$ fixed

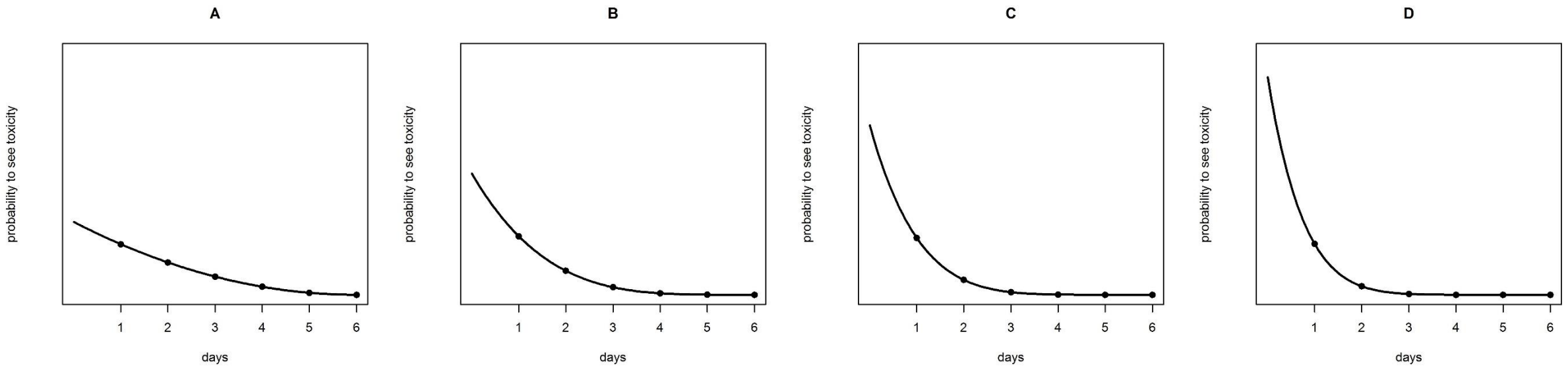
$\gamma_1 \sim \mathcal{N}(0, 1.34)$

# Toxicity at short term (3)



**“Time-to-event”**

$$u \sim Beta(1, \xi)$$



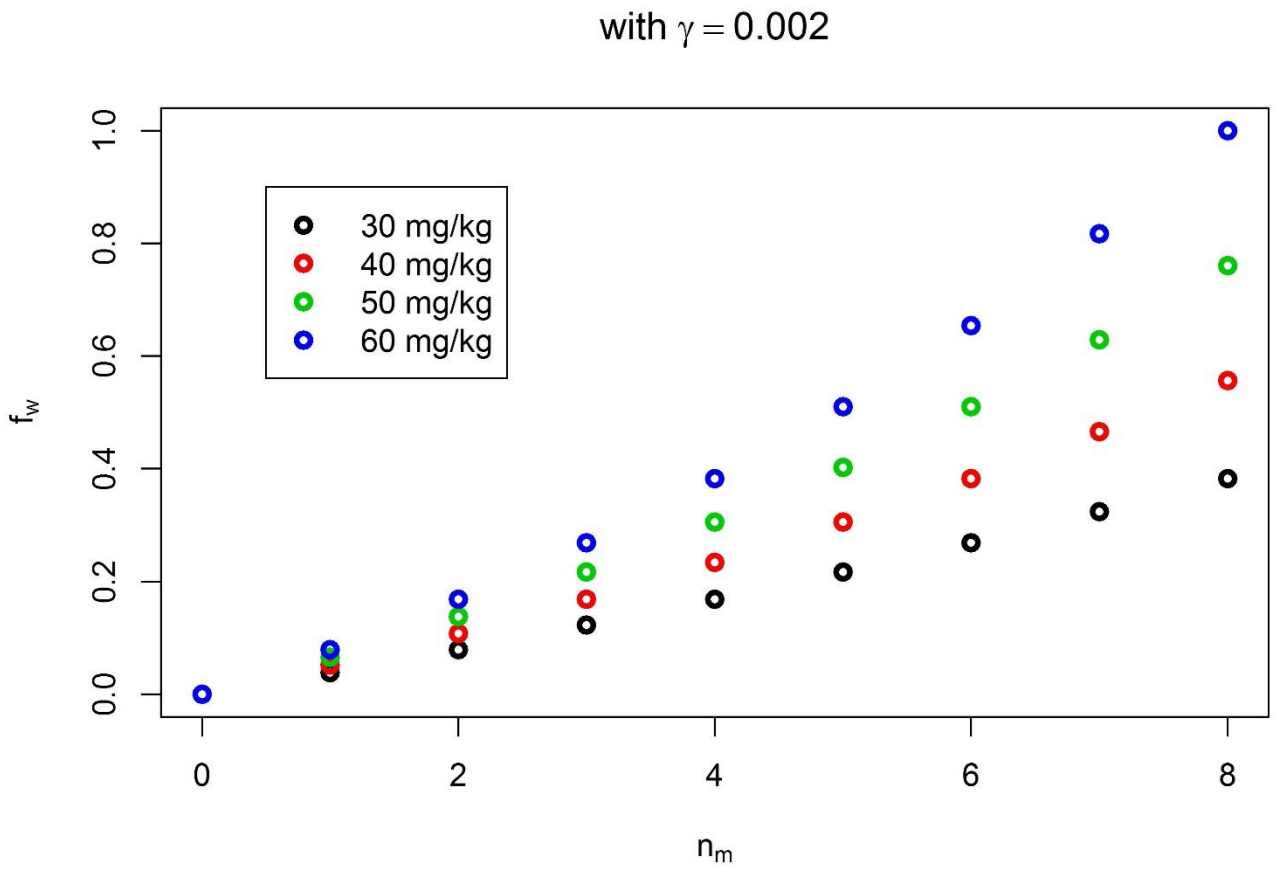

Braun, Thomas M. "Generalizing the TITE-CRM to adapt for early-and late-onset toxicities." Statistics in medicine 25.12 (2006): 2071-2083.

# Toxicity at short term (4)

$$wQL_1(\gamma_1 | \underline{Y}_1, \alpha_1, \xi) = \prod_{i=1}^{N_1} \left( \left[ 1 - \left( 1 - \frac{u_i}{T_{max}} \right)^{\xi} \right] p_{T_1} \right)^{w r_i \gamma_i^*} \cdot \left( 1 - \left[ 1 - \left( 1 - \frac{u_i}{T_{max}} \right)^{\xi} \right] p_{T_1} \right)^{w r_i (1 - \gamma_i^*)}$$

$$y_i^* = w y_i$$

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

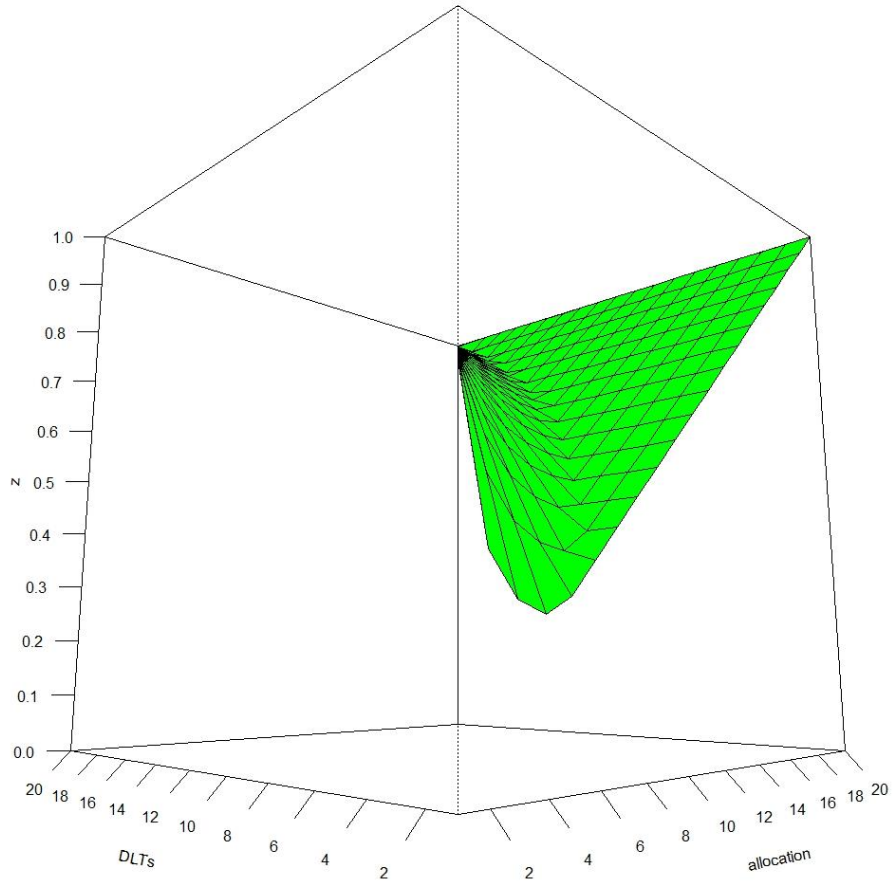



Yuan, Z., R. Chappell, and H. Bailey. "The Continual Reassessment Method for Multiple Toxicity Grades: A Bayesian Quasi-Likelihood Approach." Biometrics 63.1 (2007): 173-179.

# Toxicity at short term (5)

$$WQ\alpha_1(\gamma_1 \mid \underline{y}_1, \alpha_1, \tilde{\xi}) = \prod_{i=1}^{N_1} \left( \left[ 1 - \left( 1 - \frac{u_i}{T_{max}} \right)^{\tilde{\xi}} \right] p_{T_1} \right)^{wr_i y_i^*} \cdot \left( 1 - \left[ 1 - \left( 1 - \frac{u_i}{T_{max}} \right)^{\tilde{\xi}} \right] p_{T_1} \right)^{wr_i (1 - y_i^*)}$$

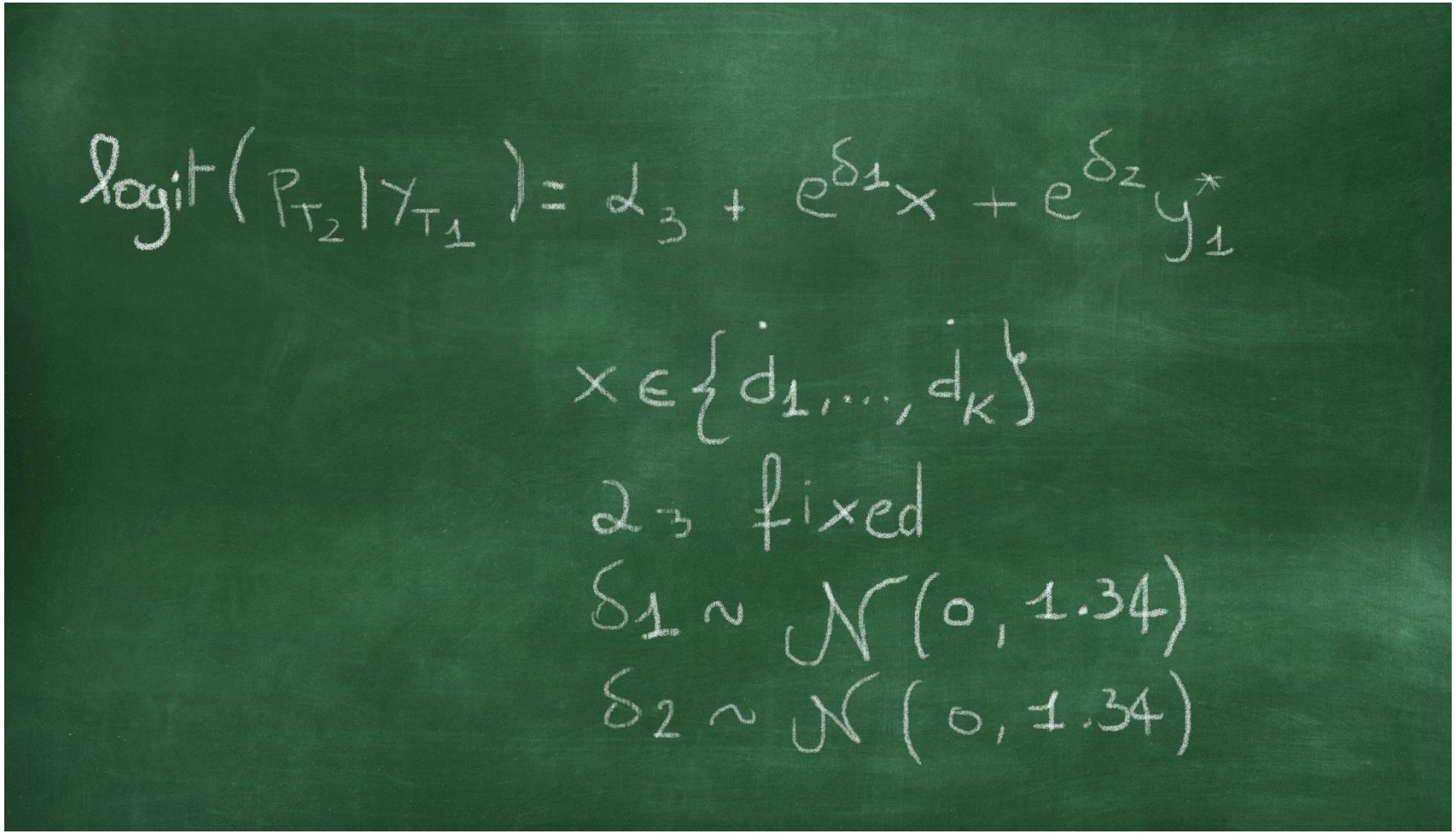
$$wr_i = \begin{cases} 1 & \text{if } y_i = 0 \\ \min\left[ \max\left( \pi \frac{n_{alloc,d_i}}{n_{max}} + (1-\pi) \frac{n_{DLT,d_i}}{n_{alloc,d_i}}, \frac{n_{alloc,d_i}}{n_{max}} \right), 1 \right] & \text{if } y_i = 1 \end{cases}$$




Resche-Rigon, Matthieu, Sarah Zohar, and Sylvie Chevret. "Maximum-relevance weighted likelihood estimator: Application to the continual reassessment method." Statistics and its Interface 3.2 (2010): 177-184.

# Toxicity at long term

## Conditional probability



# 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:**

$$P(p_E < \tau_e - \epsilon_e) < g(N_e)^{1_{N_e>11}}$$
$$P(p_{T1} > \tau_{p1} + \epsilon_1) < g(N_1)$$
$$P(p_{T2} > \tau_{p2} + \epsilon_2) < g(N_2)^{1_{N_2>1}}$$

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

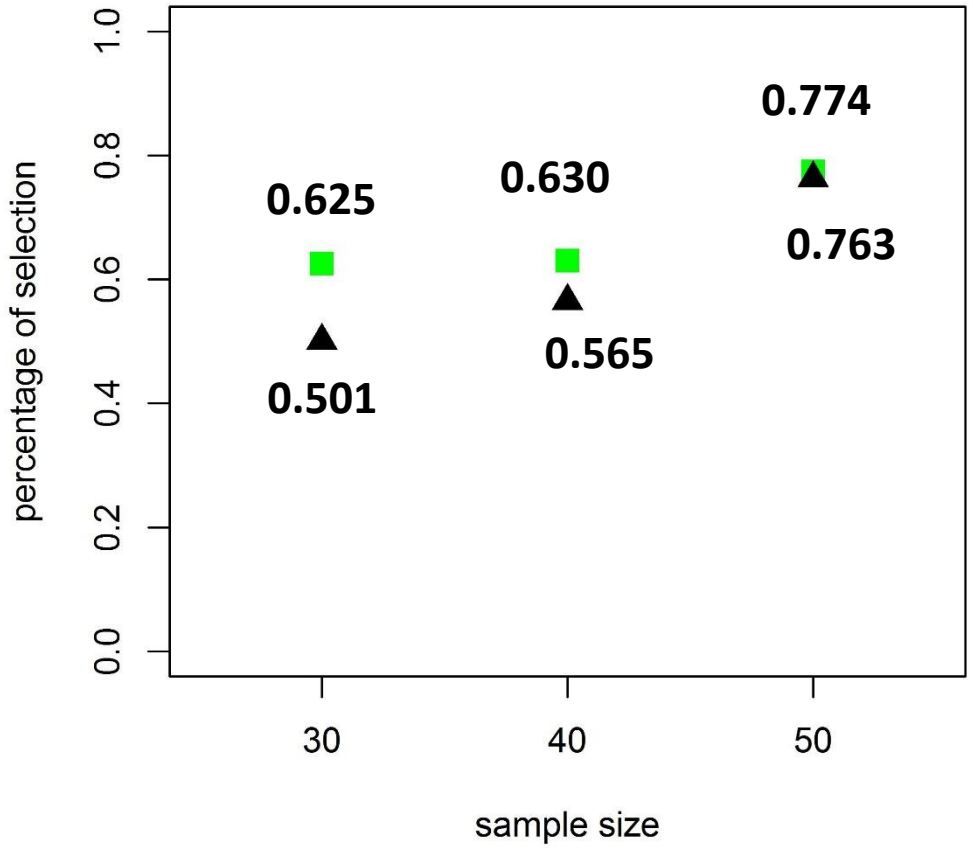
Dose selected: the one which has the highest efficacy among them selected through the previous constraints

**Dose selection rules:**

$$d_{e,\min} = \arg\min_{d \in D} |d - \tau_e|$$
$$d_{t,\max} = \min(\arg\min_{d \in D} |d - \tau_{p1}|, \arg\min_{d \in D} |d - \tau_{p2}|)$$

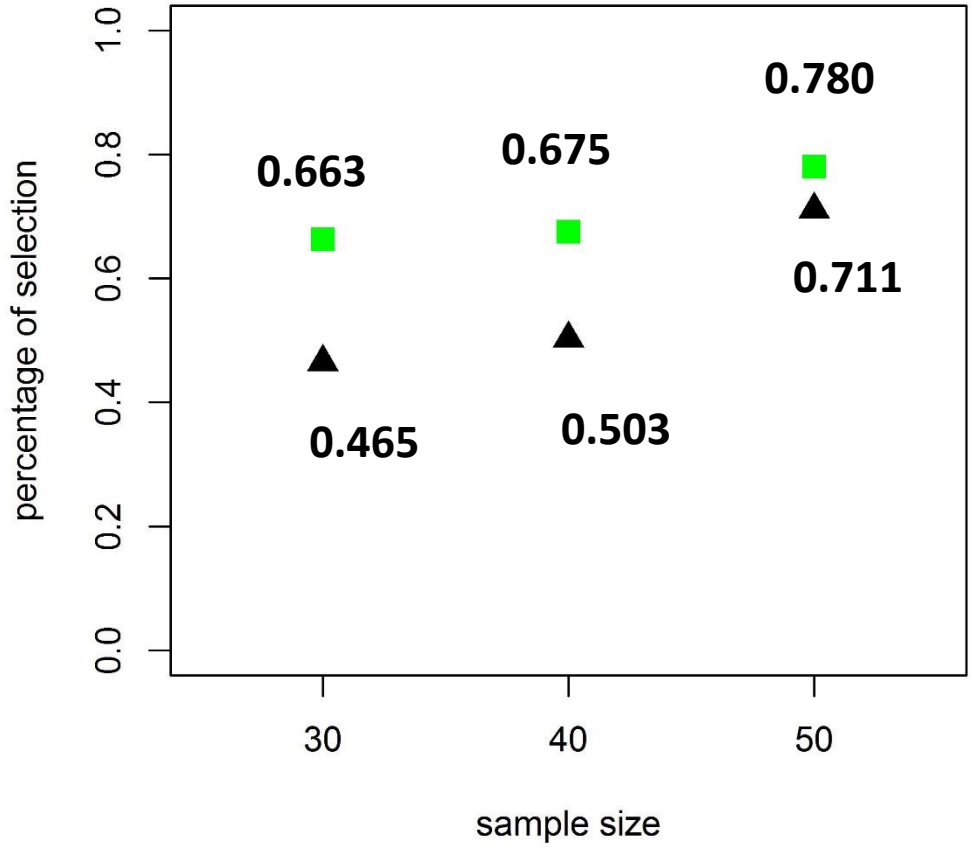
# Simulations and Results (1)

| | $d_1$ | $d_2$ | $d_3$ | $d_4$ |
|---|---|---|---|---|
| $p_E$ | 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 | |
| $p_{T1 \mid A2}$ | | | | |
| $p_{T2 \mid A2}$ | | | | |



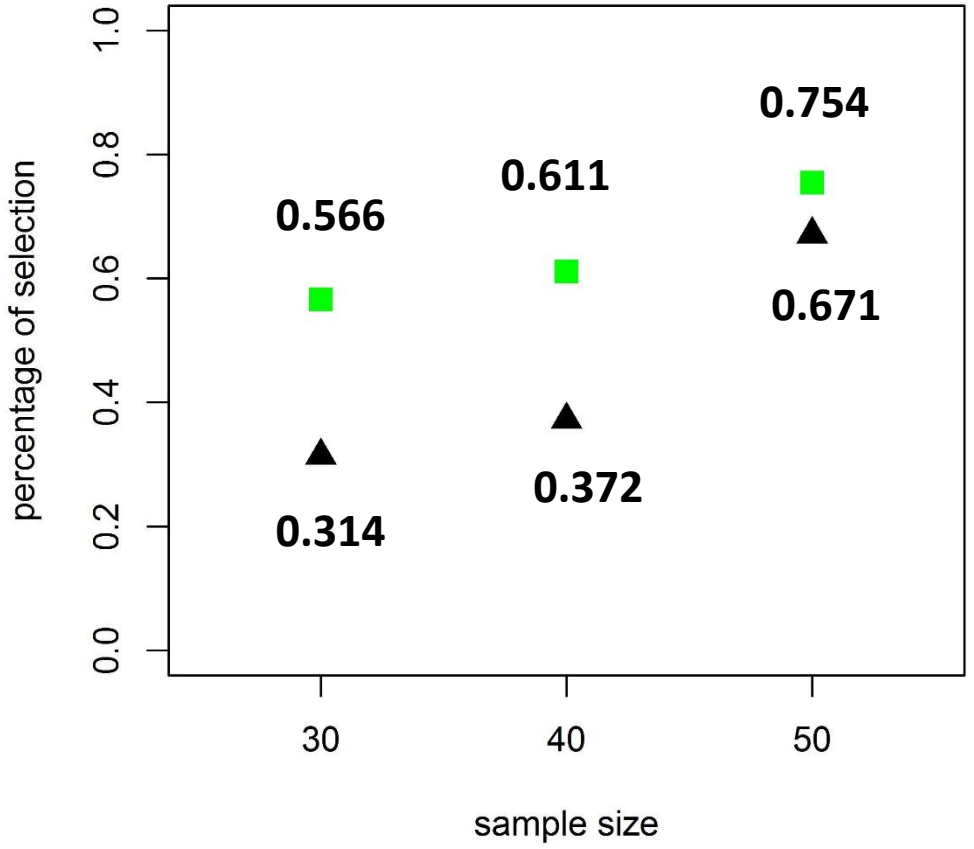
# Simulations and Results (2)

| | $d_1$ | $d_2$ | $d_3$ | $d_4$ |
|---|---|---|---|---|
| $p_E$ | 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 | | | |
| $p_{T1 \mid A2}$ | 0.005 | 0.05 | 0.15 | 0.25 |
| $p_{T2 \mid A2}$ | 0.005 | 0.05 | 0.15 | 0.25 |



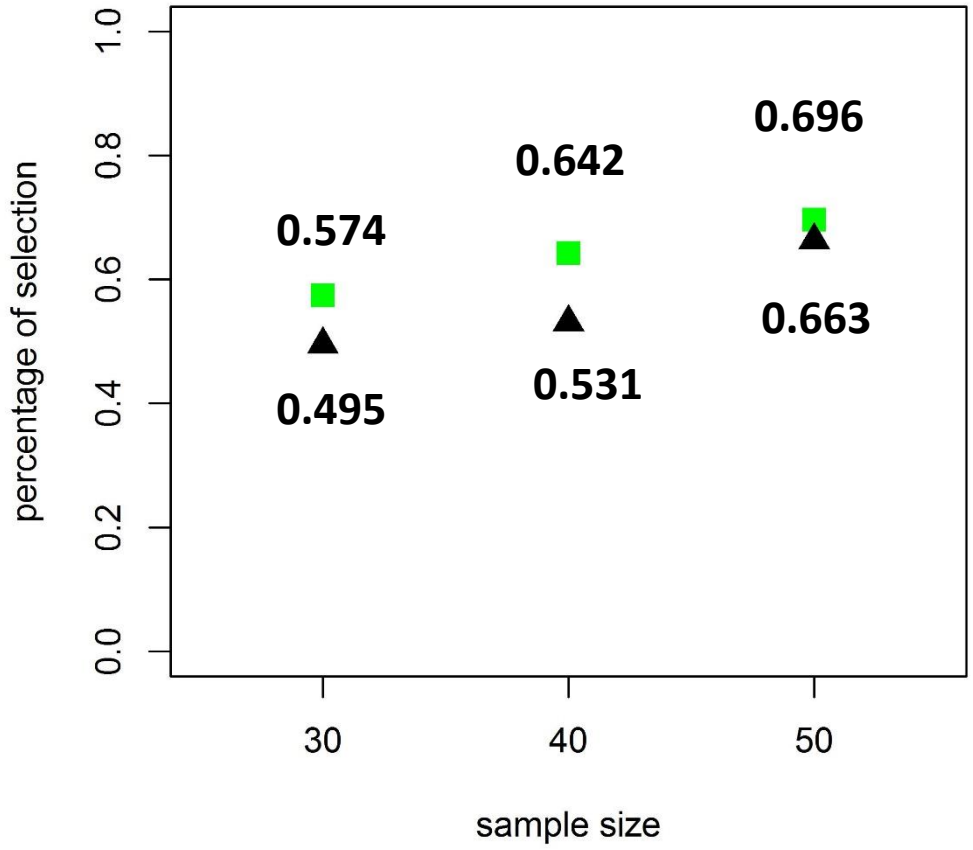
# Simulations and Results (3)

| | $d_1$ | $d_2$ | $d_3$ | $d_4$ |
|---|---|---|---|---|
| $p_E$ | 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 | | | |
| $p_{T1 \mid A2}$ | 0.01 | 0.01 | 0.25 | 0.35 |
| $p_{T2 \mid A2}$ | 0.01 | 0.01 | 0.25 | 0.35 |



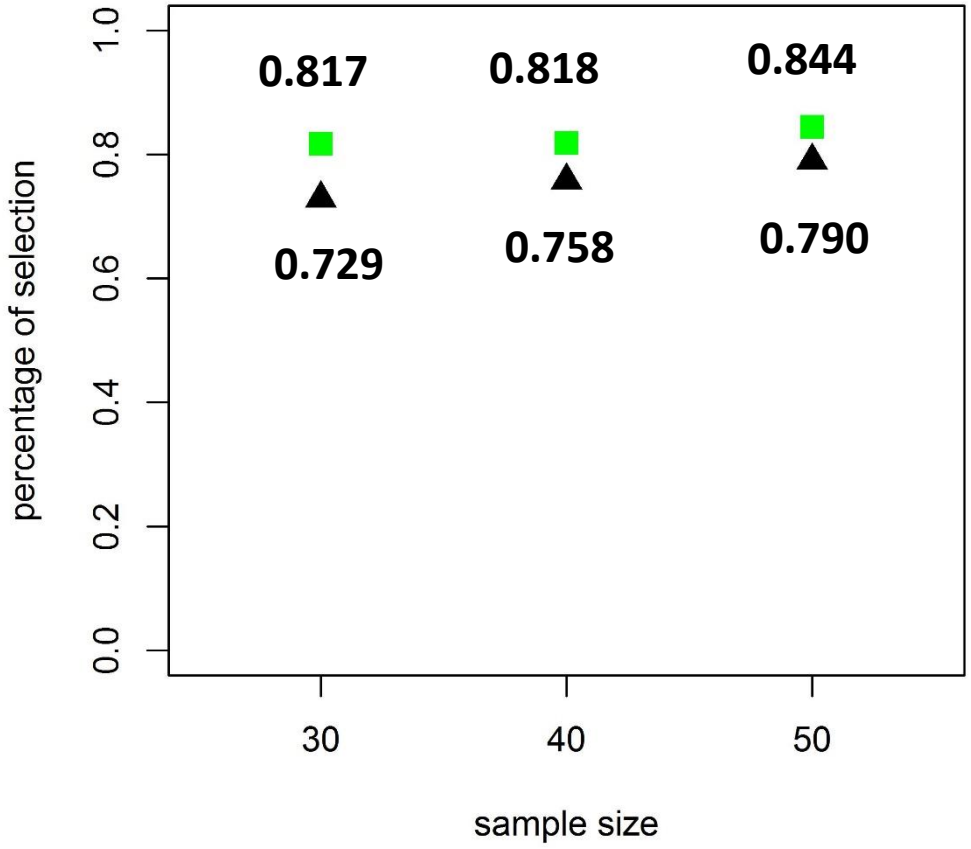
# Simulations and Results (4)

| | $d_1$ | $d_2$ | $d_3$ | $d_4$ |
|---|---|---|---|---|
| $p_E$ | 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 | | | |
| $p_{T1 \mid A2}$ | 0.005 | 0.05 | 0.15 | 0.25 |
| $p_{T2 \mid A2}$ | 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 | | | |
| $p_{T1 \mid A2}$ | 0.005 | 0.009 | 0.012 | 0.06 |
| $p_{T2 \mid A2}$ | 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


InSPiRe
Innovative methodology for small populations research

Sarah Zohar

Emmanuelle Comets

Frederike Lents

Corinne Alberti

Nigel Stallard

Tim Friede

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Dr Ying Yuan

CHRU HÔPITAUX DE TOURS

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