MODELING DOSE EFFECT AND CYCLE EFFECT IN DOSE FINDING STUDIES OF TARGETED AGENTS

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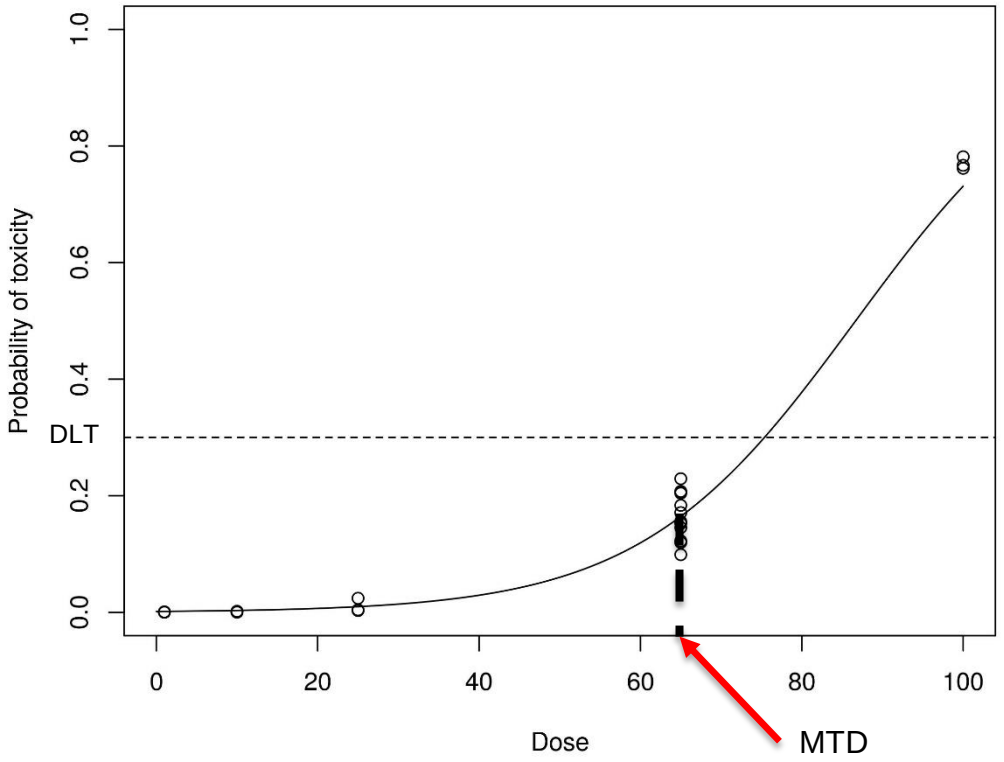
Motivation

Phase I trial objective:

Assessing drug safety finding the maximum tolerated dose (MTD) before Phase II & III efficacy trials

Standard adaptive designs for dose allocation:

- **3+3**
- **Continual reassessment method[1] (CRM)**



Evaluation criteria = % of dose limiting toxicity (DLT = Toxicity grade ≥ 3) at 1st cycle

Appropriate criteria for conventional cytotoxic therapy

But…

[1] O'Quigley J, Pepe M, Fisher L. 1990

Motivation

Temporal evolution, especially relevant for long term toxicity:

- Targeted therapy: **late** severe toxicities or **persistent low grade toxicities**

European Medical Agency recommendations:

"**Lower grade toxicity** **over longer periods** of time that affect tolerability and the possibility of maintaining the intended dose intensity may need to be addressed in the DLT and MTD definitions"

Need to consider a **finer scale of toxicity intensity** and **temporal evolution** of toxicities

Motivation

More informative model considering all toxicity grades (= ordinal variable):

- **Continuation ratio (CR) model based continuous reassessment method (CRM) design[2] (CR-CRM)**

More complex than the standard binary CRM but similar dose finding performance than classical binary CRM design

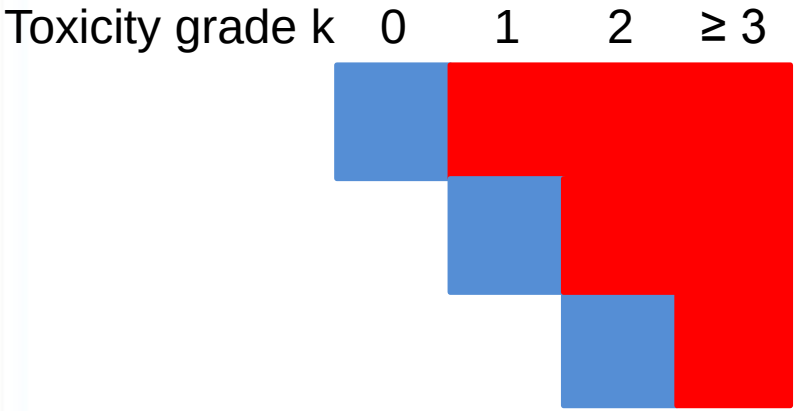
[2] Van Meter et al. 2012

Continuation ratio model

Given that a patient experiment a toxicity of grade *k*, which is the expected increase of his odds of more severe toxicity with dose?

$$P(Y_i > k | Y_i \geq k) = logit^{-1}(\beta_k + \gamma D_i)$$

With $\exp(\gamma) =$ **Odd Ratio**



$$P(Y_i > 0 | Y_i \geq 0) = logit^{-1}(\beta_0 + \gamma D_i)$$

$$P(Y_i > 1 | Y_i \geq 1) = logit^{-1}(\beta_1 + \gamma D_i)$$

$$P(Y_i > 2 | Y_i \geq 2) = logit^{-1}(\beta_2 + \gamma D_i)$$

Low number of patients → Proportional odds (PO) assumption required for stable results

Reasonable assumption?

Objectives

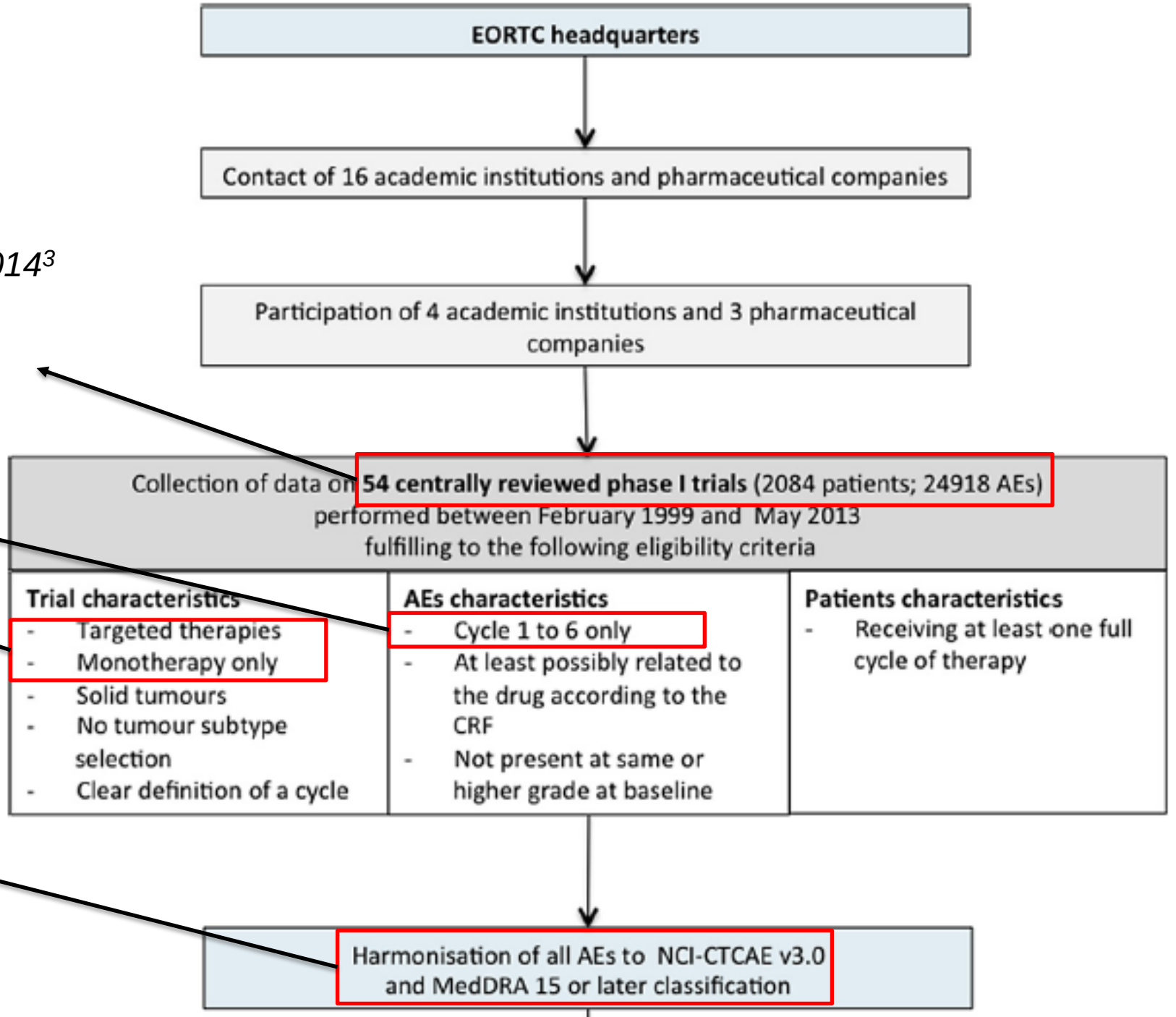
Essential to validate the PO assumption before further developments

Idea: Pooled analysis of 54 phase I clinical trials ↗ ↗ information to:

- **Verify plausibility of PO assumptions for dose**
- **Consider other untapped information:**
  - Cycle (log linear effect + verify plausibility of PO assumption)
  - Heterogeneous mechanisms between types of toxicity?

Material

Source: Postel-Vinay et al. 2014[3]



Standardization

Repeated measurement

Single agent (avoid confusion and synergic effect)

Toxicity grades defined according to NCI scales

Material

- **Most severe grade of type of toxicity *j* experienced by the patient *i* at the t^{th} cycle:**

$$Y_{i,j,t} = \begin{cases} 0 \\ 1 \\ 2 \\ 3 \end{cases}$$

No toxic response

Experience of grade 1 toxicity
Experience of grade 2 toxicity

Experience of DLT (grade ≥ 3 toxicity)

- **Different types of toxicity (total = 9,904 for 2,048 patients):**

Grade	Cutaneous	Digestive	General disorder	Hematologic	Other	Total
1	549	1,754	403	1,344	1,513	5,563
2	207	794	433	748	946	3,128
>=3	31	190	345	200	447	1,213
Total	787	2,738	1,181	2,292	2,906	9,904

Statistical model

Standardized dose:

$$D_i = \frac{Planned\ dose_i}{MTD_{study_i}}$$

Multivariate CR model (proportional odds):

Patient specific multivariate random effect (for each toxicity type)

$$\alpha_{ij} \sim \boldsymbol{MVN}(\mathbf{0}, \boldsymbol{\Sigma})$$

Toxicity type specific intercept

Cycle number of the t^{th} observation of the patient *i*

$$P\left(Y_{ijt} > k \middle| Y_{ijt} \geq k\right) = logit^{-1}\left(\alpha_{ij} + \beta_{jk} + \gamma_j D_i + \vartheta_j C_{ijt}\right)$$

$$\rightarrow \begin{cases} P\left(Y_{ijt} > 0 \middle| Y_{ijt} \geq 0\right) = logit^{-1}\left(\alpha_{ij} + \beta_{j\mathbf{0}} + \gamma_j D_{\boldsymbol{i}} + \vartheta_j C_{ijt}\right) \\ P\left(Y_{ijt} > 1 \middle| Y_{ijt} \geq 1\right) = logit^{-1}\left(\alpha_{ij} + \beta_{j\mathbf{1}} + \gamma_j D_{\boldsymbol{i}} + \vartheta_j C_{ijt}\right) \\ P\left(Y_{ijt} > 2 \middle| Y_{ijt} \geq 2\right) = logit^{-1}\left(\alpha_{ij} + \beta_{j\mathbf{2}} + \gamma_j D_{\boldsymbol{i}} + \vartheta_j C_{ijt}\right) \end{cases}$$

Proportional odd for dose

Proportional odd for cycle

Statistical model

Multivariate CR model (non-proportional odds):

$$P\left(Y_{ijt} > k \middle| Y_{ijt} \geq k\right) = logit^{-1}\left(\alpha_{ij} + \beta_{jk} + \left(\sum_{m=0}^{k-1} \gamma_{jm}\right) D_i + \left(\sum_{m=0}^{k-1} \vartheta_{jm}\right) C_{ijt}\right)$$

$$\rightarrow \begin{cases} P\left(Y_{ijt} > 1 \middle| Y_{ijt} \geq 0\right) = logit^{-1}\left(\alpha_{ij} + \beta_{j0} + \gamma_{j0} D_i + \vartheta_{j0} C_{ijt}\right) \\ P\left(Y_{ijt} > 1 \middle| Y_{ijt} \geq 1\right) = logit^{-1}\left(\alpha_{ij} + \beta_{j1} + \left(\gamma_{j0} + \gamma_{j1}\right) D_i + \left(\vartheta_{j0} + \vartheta_{j1}\right) C_{ijt}\right) \\ P\left(Y_{ijt} > 2 \middle| Y_{ijt} \geq 2\right) = logit^{-1}\left(\alpha_{ij} + \beta_{j2} + \left(\gamma_{j0} + \gamma_{j1} + \gamma_{j2}\right) D_i + \left(\vartheta_{j0} + \vartheta_{j1} + \vartheta_{j2}\right) C_{ijt}\right) \end{cases}$$

For *K* types of toxicity, PO if: **for dose:** $1_{\gamma_{j1} \neq 0} + 1_{\gamma_{j2} \neq 0} = 0$
for cycle: $1_{\vartheta_{j1} \neq 0} + 1_{\vartheta_{j2} \neq 0} = 0$

Statistical model: Bayesian inference

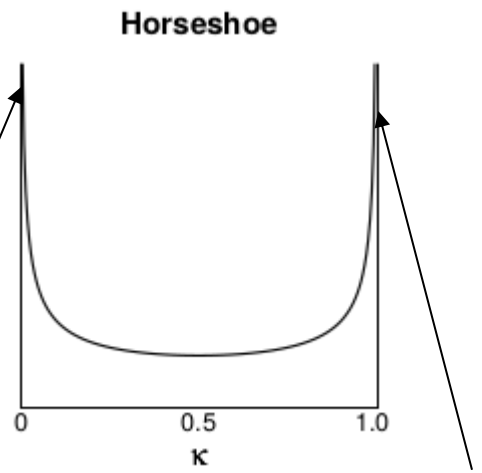
<u>Aim:</u> Statistical model able to generalize to future trial → predictive model

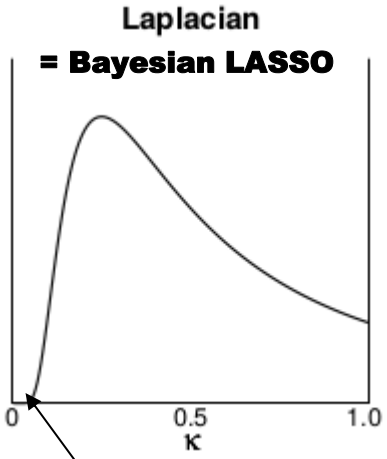
<u>Prior for fixed effects:</u>

Bayesian model averaging too computationally demanding → approximation using sparse model using the global-local mixture shrinkage horseshoe prior[4]

κ density

HS mimics BMA[4]





Shrinkage parameter formulation:

$$\bar{\theta} = (1 - \kappa)\hat{\theta}$$

Posterior mean of θ

Maximum likelihood solution of θ

Expected weak shrinkage of strong θs (small bias)

Expected strong shrinkage of weak θs

No low shrinkage → Bias for all estimators

[4] Carvalho, Polson and Scott 2010

Statistical model: Bayesian inference

Prior for random effects correlation matrix: **LKJ prior[5]**

Sampling: **Hamiltonian Monte Carlo[6] (using Stan[7], 4 chains, 5,000 iterations including 1,000 burning)**

Model comparison (PO vs non PO models): **Widely applicable information criterion[8] (WAIC)**

- **Averaging over the full posterior instead of rely on a single point estimation as for AIC or DIC**
- **Asymptotically equal to the leave-one-out cross-validation**

[5] Lewandowski, Kurowicka and Joe 2009
[6] Duane et al 1987
[7] Carpenter et al 2017
[8] Watanabe 2010

Results

Odds ratio [95% credible interval] for dose

	Cutaneous	Digestive	General disorders	Hematologic	Others
Dose ($exp(\gamma_{j0})$)	**3.11 [2.35; 3.87]**	**2.58 [2.19; 2.95]**	**2.55 [2.12; 3.00]**	**3.13 [2.31; 4.01]**	**2.77 [2.36; 3.17]**
Cycle ($exp(\vartheta_{j0})$)	**0.33 [0.23; 0.42]**	0.01 [-0.04; 0.06]	0.03 [-0.02; 0.09]	0.06 [-0.01; 0.15]	**0.12 [0.07; 0.17]**

- **Increase of the severity of toxicity with dose**
- **Slight increase with cycle only for cutaneous and other types of toxicity**

Comparison with non PO model:

$WAIC_{PO}$ = 31, 432.10 $WAIC_{nonPO}$ = 30, 911.58 Difference = 520,52 (+ 1,7% for PO)

- **Small decrease of patient toxicity risk prediction performance for PO model**
- **Deviance from PO assumption?**

Results

$$P(Y_{ijt} > 1 | Y_{ijt} \geq 0) = logit^{-1}(\alpha_{ij} + \beta_{j0} + \gamma_{j0} D_i + \vartheta_{j0} C_{ijt})$$
$$P(Y_{ijt} > 1 | Y_{ijt} \geq 1) = logit^{-1}(\alpha_{ij} + \beta_{j0} + (\gamma_{j0} + \gamma_{j1}) D_i + (\vartheta_{j0} + \vartheta_{j1}) C_{ijt})$$
$$P(Y_{ijt} > 2 | Y_{ijt} \geq 2) = logit^{-1}(\alpha_{ij} + \beta_{j0} + (\gamma_{j0} + \gamma_{j1} + \gamma_{j2}) D_i + (\vartheta_{j0} + \vartheta_{j1} + \vartheta_{j2}) C_{ijt})$$

Odds ratio [95% credible interval] for dose

	Cutaneous	Digestive	General disorders	Hematologic	Others
$exp(\gamma_{j0})$ Grade 0 → ≥ 1	**2.98 [2.27; 3.96]**	**2.35 [1.96; 2.72]**	**2.16 [1.77; 2.65]**	**2.87 [2.17; 3.75]**	**2.51 [2.12; 2.98]**
$exp(\gamma_{j1})$ Grade 1 → ≥ 2	0.06 [-0.41; 0.43]	0.22 [-0.06; 0.51]	**0.37 [0.10; 0.67]**	0.30 [-0.01; 0.72]	0.08 [-0.19; 0.38]
$exp(\gamma_{j2})$ Grade 2 → ≥ 3	0.33 [-0.56; 1.41]	**1.37 [0.84; 1.87]**	**0.67 [0.05; 1.23]**	0.03 [-0.37; 0.42]	0.26 [-0.03; 0.58]

→ **PO assumption reasonable, excepting for digestive and general disorder toxicities**

Results

$$P(Y_{ijt} > 1 | Y_{ijt} \geq 0) = logit^{-1}(\alpha_{ij} + \beta_{j0} + \gamma_{j0} D_i + \vartheta_{j0} C_{ijt})$$
$$P(Y_{ijt} > 1 | Y_{ijt} \geq 1) = logit^{-1}(\alpha_{ij} + \beta_{j0} + (\gamma_{j0} + \gamma_{j1}) D_i + (\vartheta_{j0} + \vartheta_{j1}) C_{ijt})$$
$$P(Y_{ijt} > 2 | Y_{ijt} \geq 2) = logit^{-1}(\alpha_{ij} + \beta_{j0} + (\gamma_{j0} + \gamma_{j1} + \gamma_{j2}) D_i + (\vartheta_{j0} + \vartheta_{j1} + \vartheta_{j2}) C_{ijt})$$

Odds ratio [95% credible interval] for cycle

	Cutaneous	Digestive	General disorders	Hematologic	Others
$exp(\vartheta_{j0})$ Grade 0 → ≥ 1	**0.37 [0.27; 0.48]**	0.04 [-0.01; 0.11]	**0.07 [0.01; 0.14]**	0.08 [-0.00; 0.17]	**0.18 [0.11; 0.24]**
$exp(\vartheta_{j1})$ Grade 1 → ≥ 2	**-0.16 [-0.33; -0.02]**	-0.08 [-0.17; 0.00]	**-0.08 [-0.17; -0.00]**	-0.02 [-0.12; 0.05]	**-0.09 [-0.17; -0.00]**
$exp(\vartheta_{j2})$ Grade 2 → ≥ 3	0.05 [-0.20; 0.37]	-0.01 [-0.13; 0.11]	-0.08 [-0.26; 0.06]	0.00 [-0.10; 0.12]	-0.09 [-0.20; 0.01]

Small cycle effect with attenuation for grade > 1

No cycle effect or attenuation?

Results

Random effect correlation matrix [95% credible intervals]

	Cutaneous	Digestive	General disorders	Hematologic	Others
Cutaneous	1	0.22 [0.15; 0.28]	0.05 [-0.01; 0.12]	-0.18 [-0.27; -0.07]	0.01 [-0.06; 0.08]
Digestive		1	0.45 [0.40; 0.51]	0.28 [0.23; 0.35]	0.42 [0.36; 0.46]
General disorders			1	0.26 [0.21; 0.33]	0.41 [0.36; 0.46]
Hematologic				1	0.37 [0.32; 0.43]
Others					1

Low correlation

Moderate correlation: vomiting and pain (digestive disorder) tires (General disorders) a lot

Low to moderate correlation between random effects

- **Provide different information**

Discussion

P1 data not fully exploited: More detailed toxicity intensity definition and temporal aspects could be considered

Low correlation and heterogeneous results between the different type of toxicity:

- **Complementary information → useful for patient management**

Slight loss of patient risk prediction performance using PO model:

- **PO assumption questionable for digestive and general disorder toxicities**
  - Discourage the CR-CRM design for study with large expected proportion of these types of toxicity
- **Cycle effect not clear:**
  - Distinction between time and cumulative dose?
  - More investigation on its functional form (other than log-linear) should be performed

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