Model-based characterization of neutrophil dynamics in children receiving busulfan or treosulfan for haematopoietic stem cell transplant conditioning

Belén P. Solans, Robert Chiesa, Zinnia P Parra-Guillén, Paul Veys,
Iñaki F. Trocóniz, Joseph F. Standing

Pharmacometrics and Systems Pharmacology
Department of Pharmaceutical Technology and Chemistry
School of Pharmacy and Nutrition
www.unav.edu/psp

UCL

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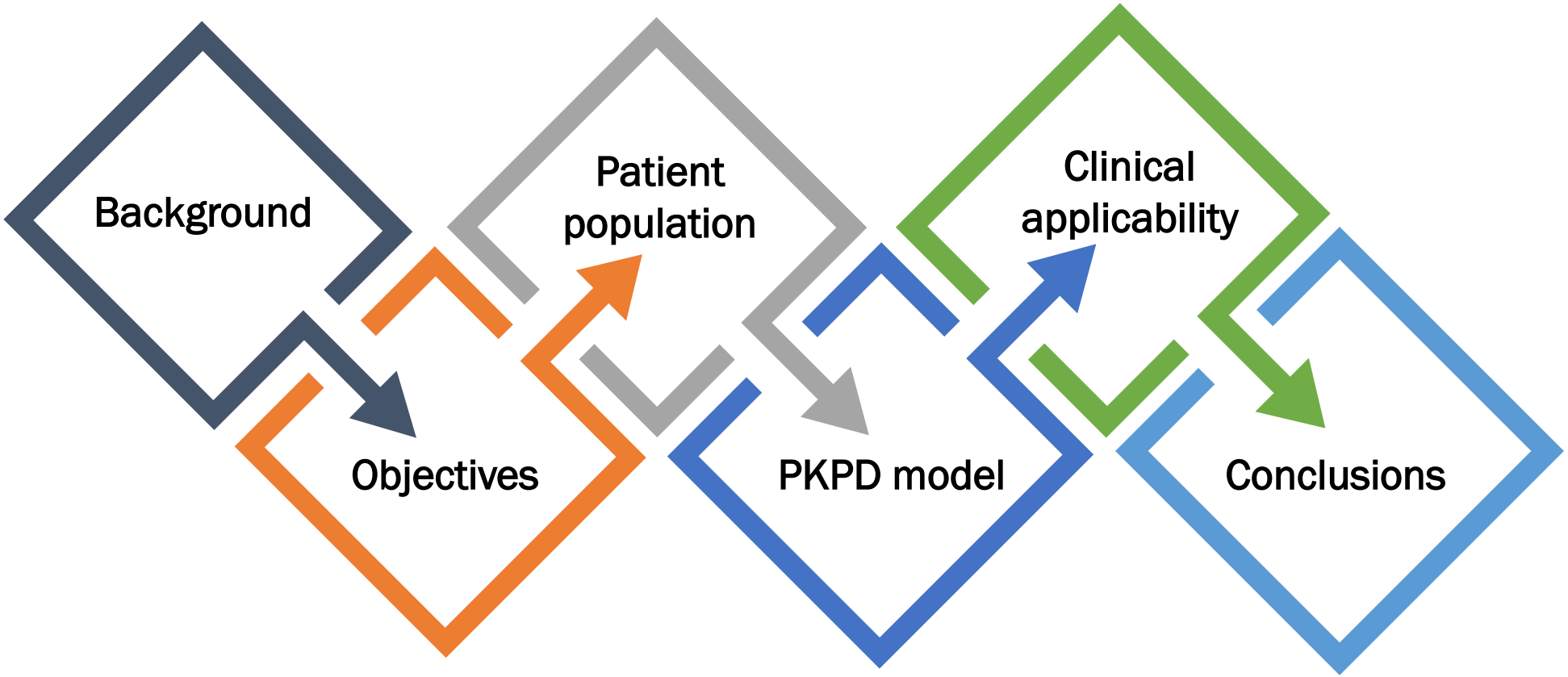
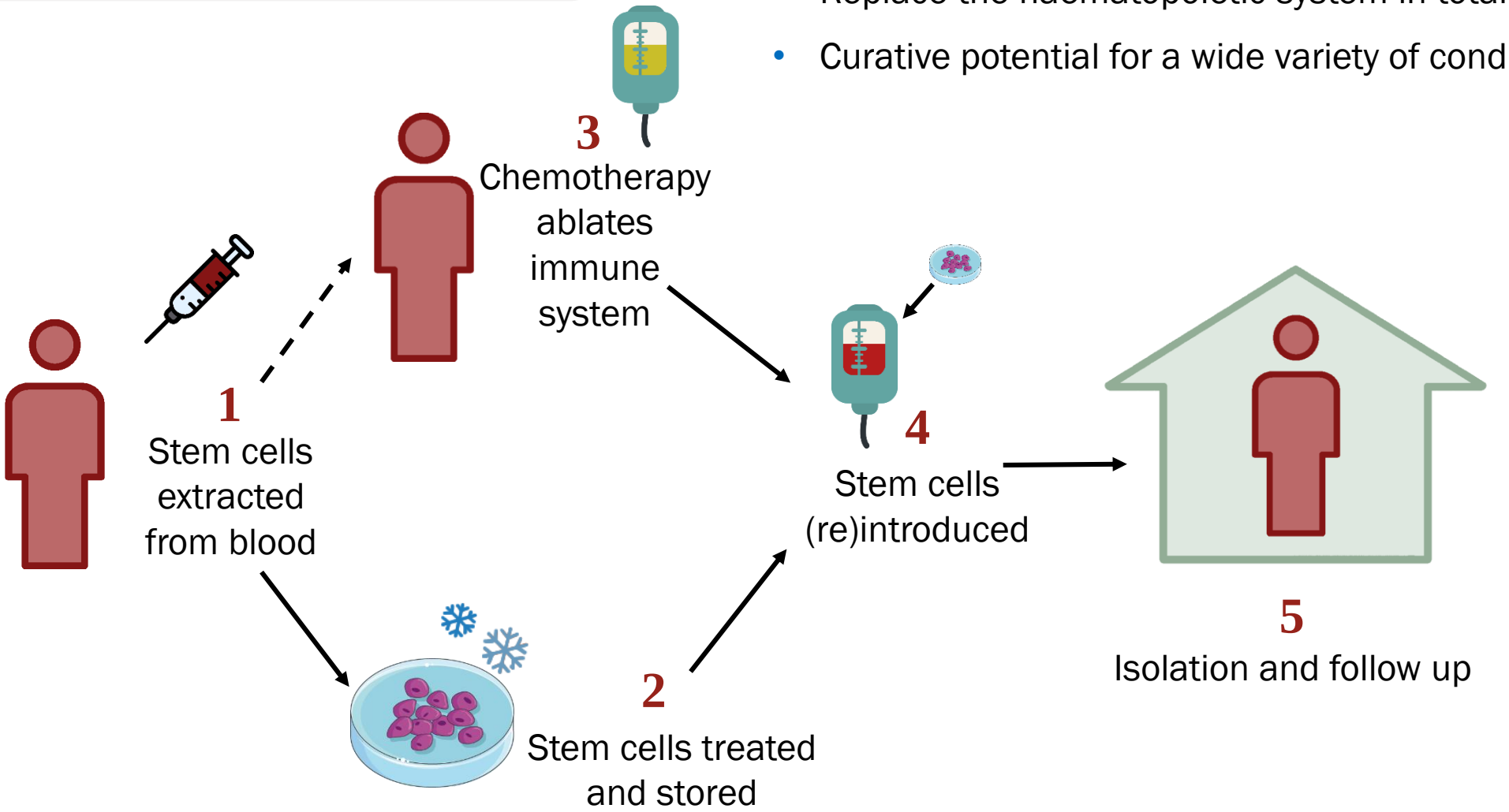
Outline

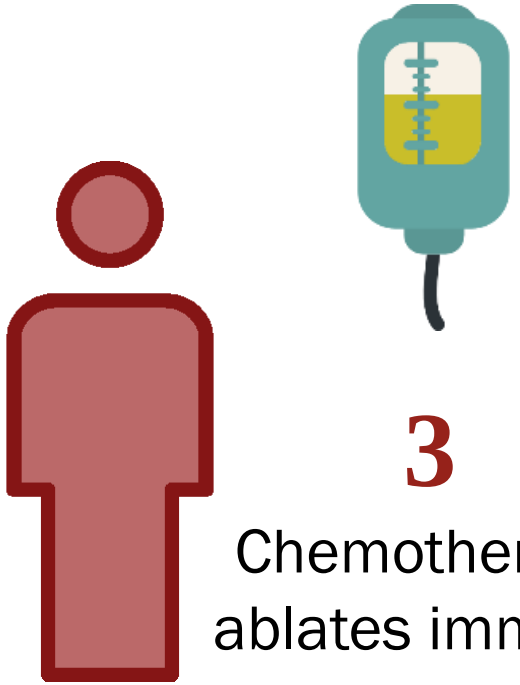


Haematopoietic stem cell transplantation - HSCT

- Replace the haematopoietic system in total or in part
- Curative potential for a wide variety of conditions



Background



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Chemotherapy ablates immune system

- Severely immunocompromised and liable to infections

  ↓

  Main cause of transplant-related death

- Different depending on diagnosis, age, clinical conditions, donor type and source of cells

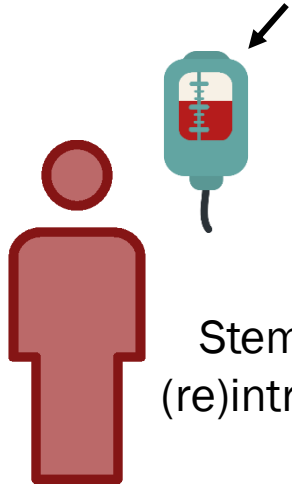
Debate surrounding the relative methods of **Busulfan (Bu)** and **Treosulfan (Treo)**

Background

3

Chemotherapy ablates immune system

TIME??



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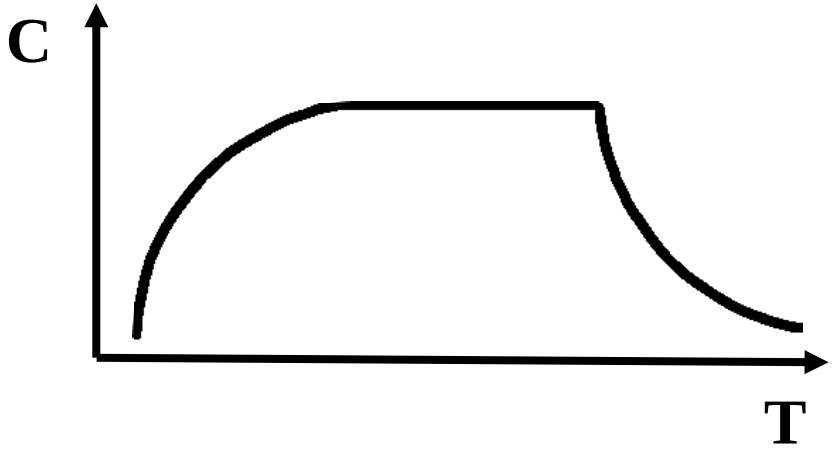
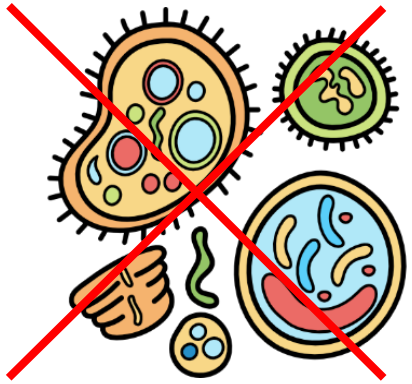
Stem cells (re)introduced





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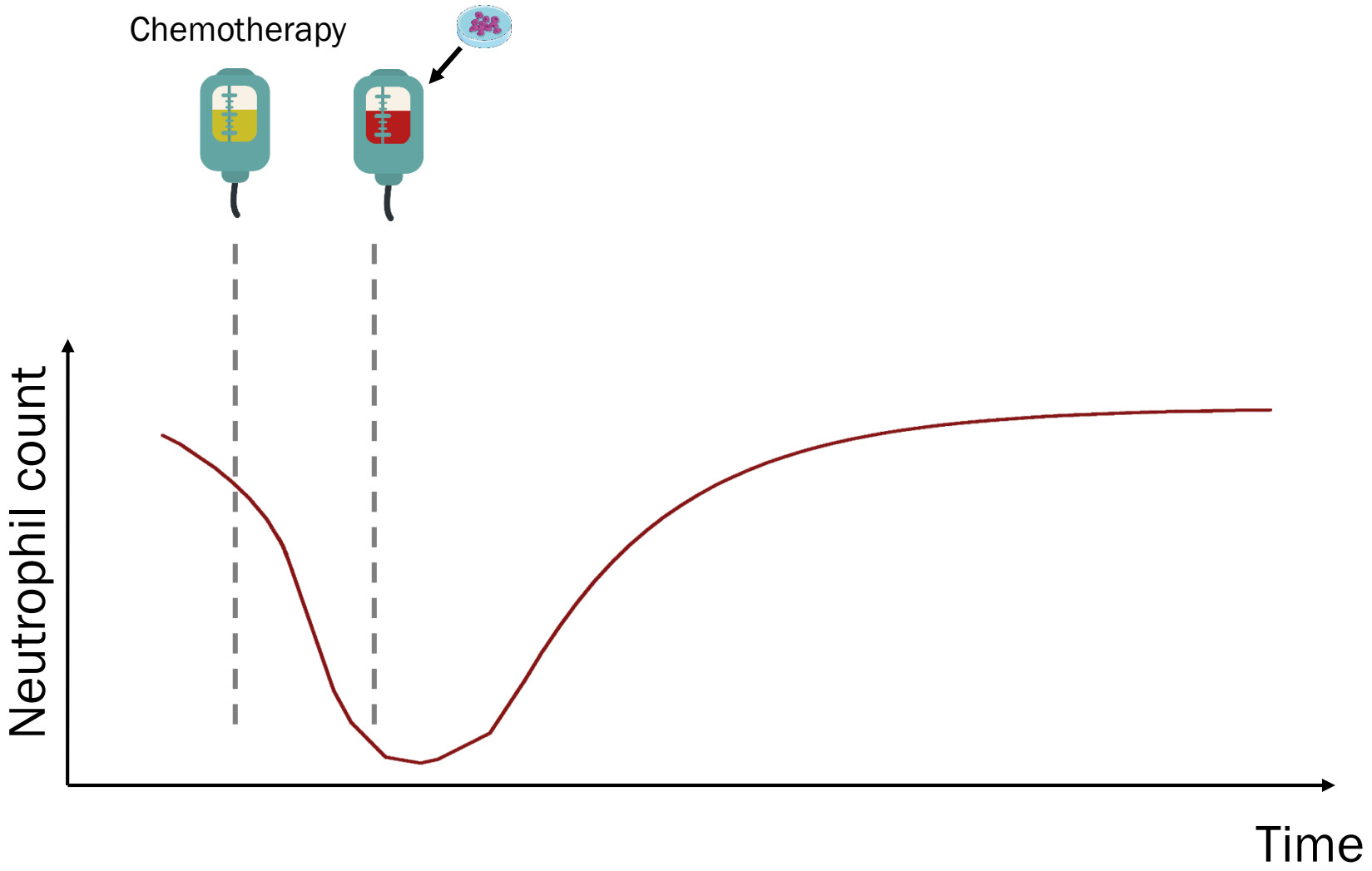
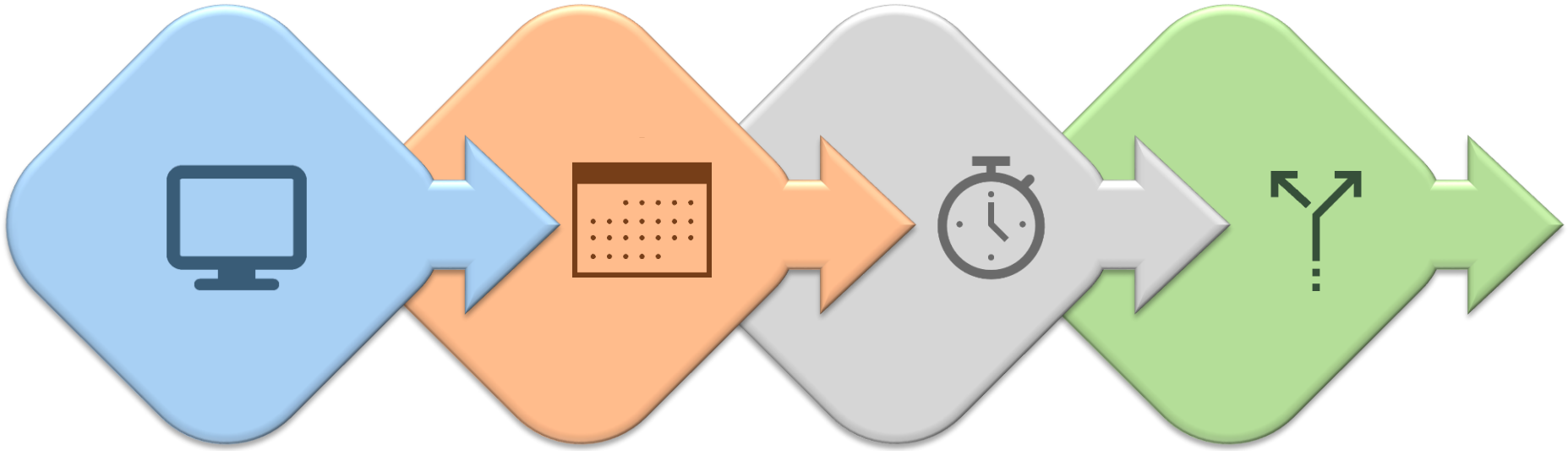


Objectives

Establish a PKPD model for the treatment and engraftment effects on neutrophil counts comparing busulfan and treosulfan

Optimise PK sampling schedules for therapeutic drug monitoring of busulfan



Evaluate the dosing schedules of busulfan and treosulfan with respect to time to HSCT

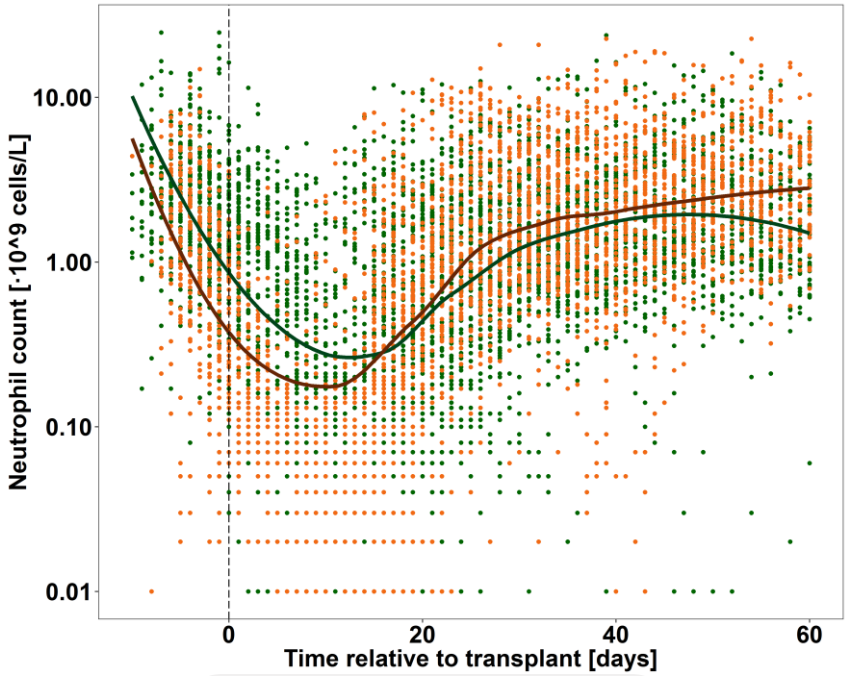
Establish the relationship between neutropenia and overall survival

Patient Population

	Busulfan	Treosulfan
	72 children	54 children
	5.1 – 47.0 Kg 7 months – 18 years	3.8 – 35.8 Kg 4 months – 17 years
DIAGNOSIS		
Non-Solid tumours	30	18
Non-malignancies	42	36
TRANSPLANT TYPE		
Autologous	12	1
Allogeneic	60	53
CONDITIONING GROUPS		
Different combinations	8	4

Response data

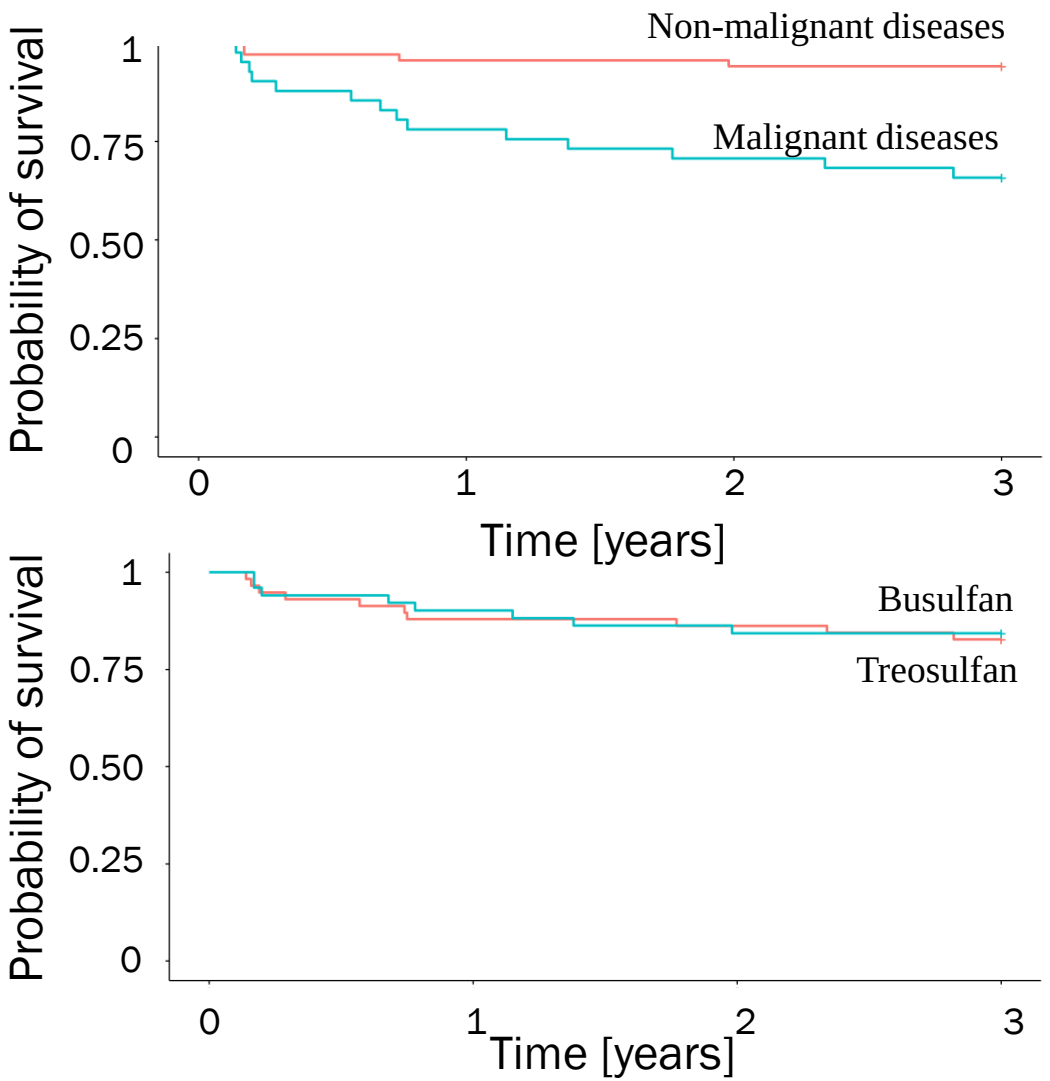
Neutrophil counts



Baseline values

	Busulfan	Treosulfan
Mean	5.10	2.95
Median	3.42	2.49

Overall Survival



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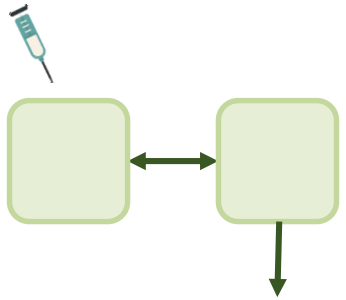
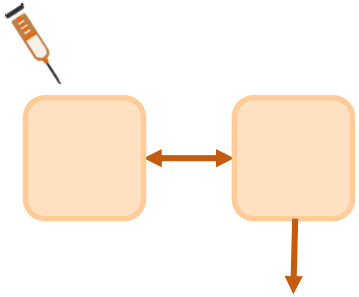
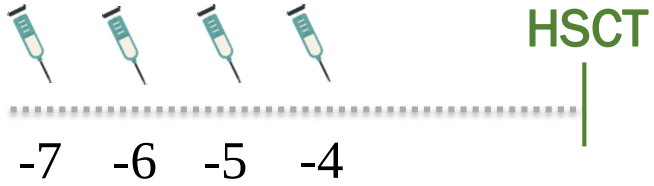
Busulfan

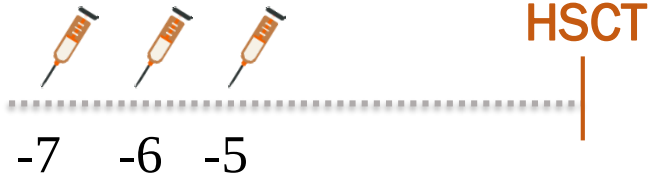


Treosulfan

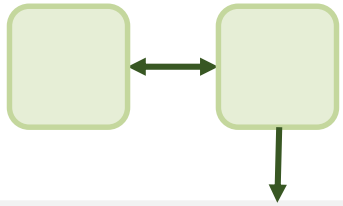


Allometric scaling
Maturation function affecting elimination
IOV on CL





Busulfan

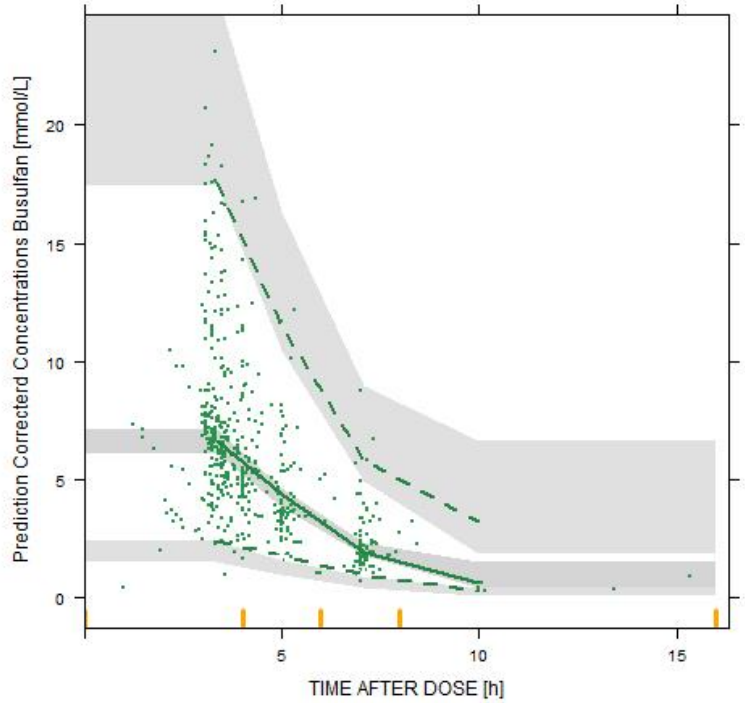


Allometric scaling
Maturation function affecting elimination*
IOV on CL and V1

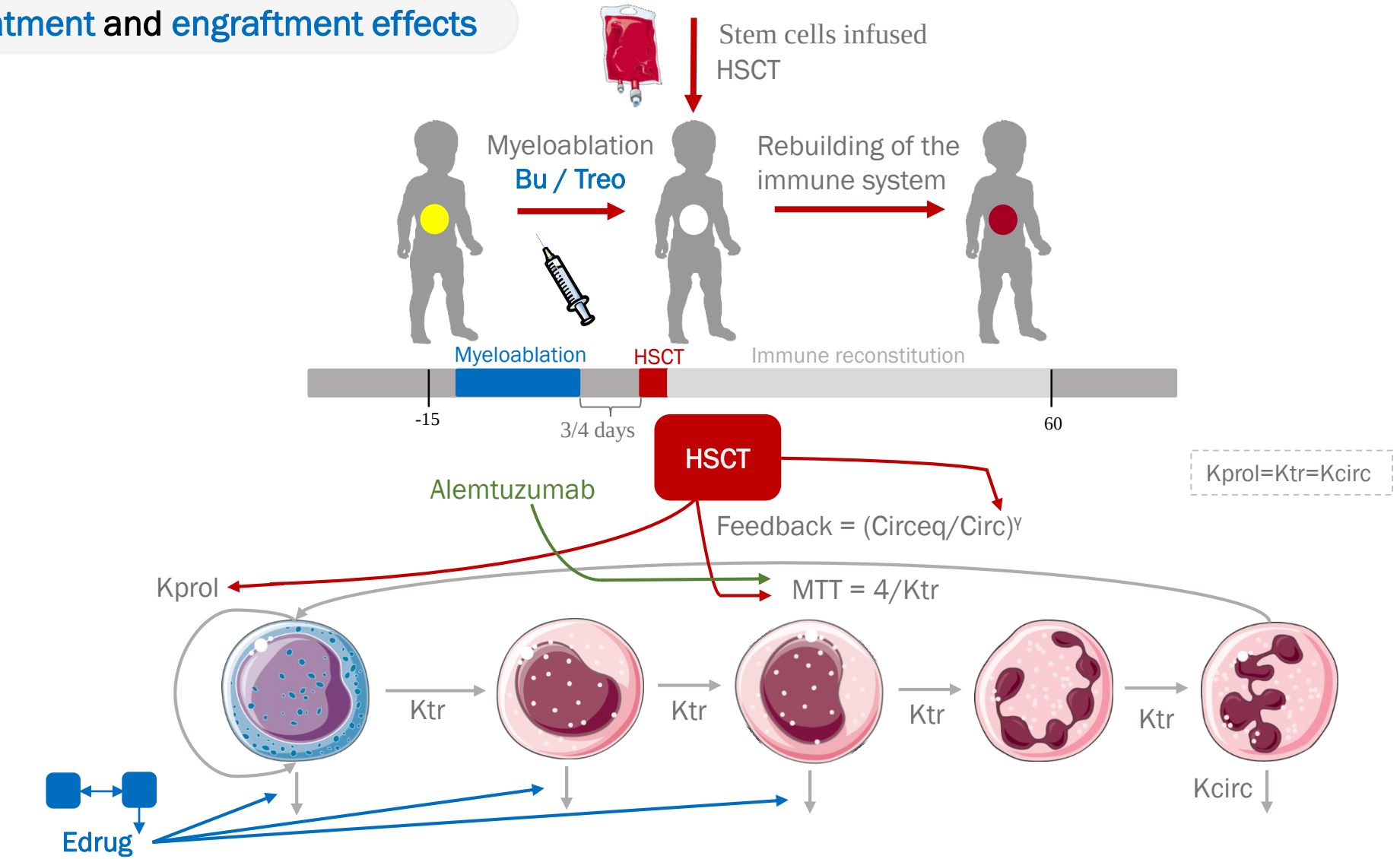
* In this case fixed from Clin Cancer Res 2014;20:754-6

$$AGEF = \frac{1}{\left(1 + \left(\frac{PM50}{PMAW}\right)^{HILL}\right)}$$

PMAW – Post-menstrual age in weeks



PKPD - treatment and engraftment effects



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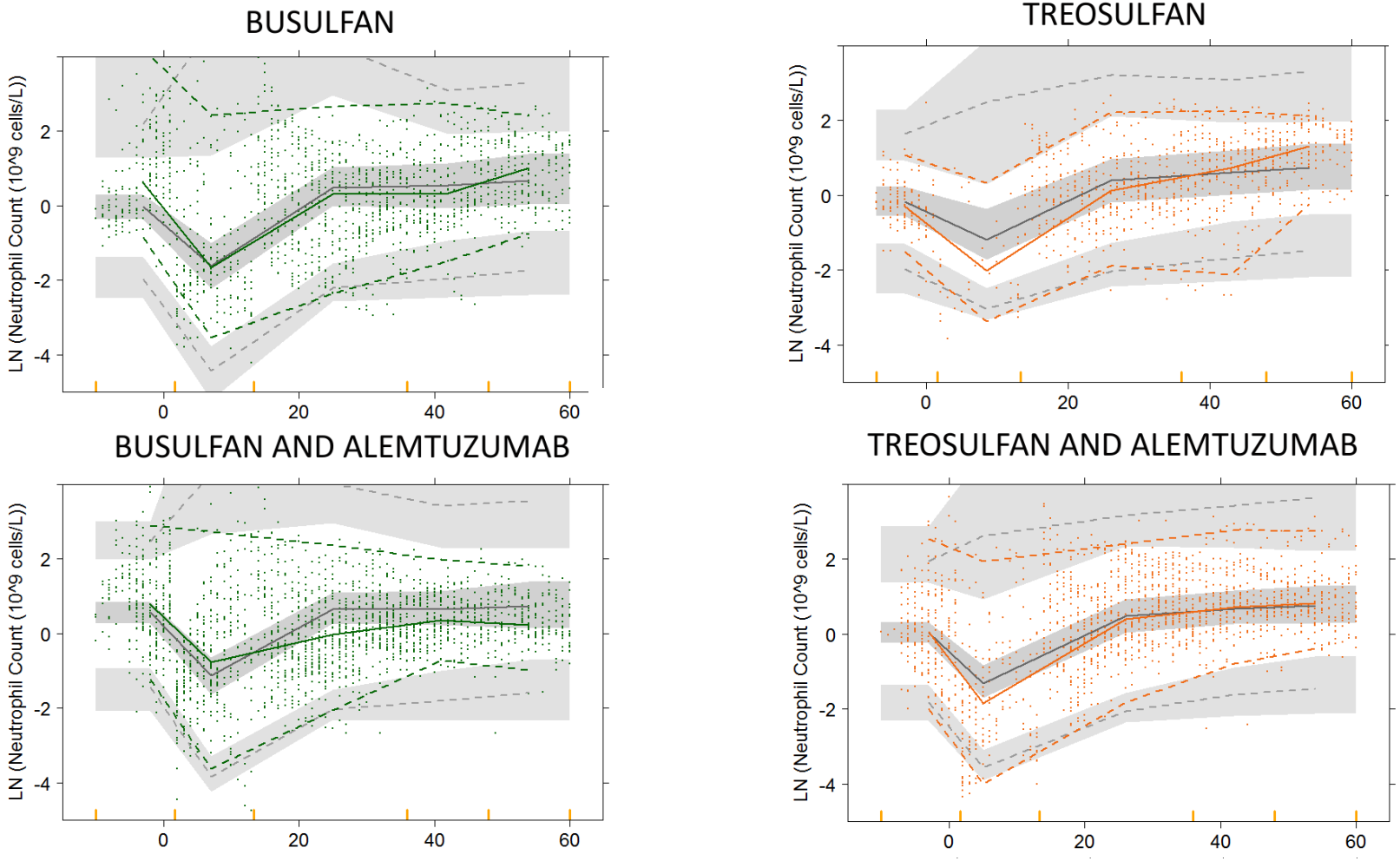
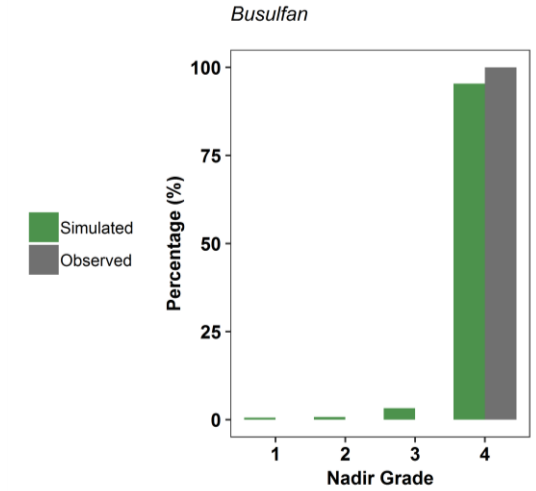
OVERALL MODEL PERFORMANCE

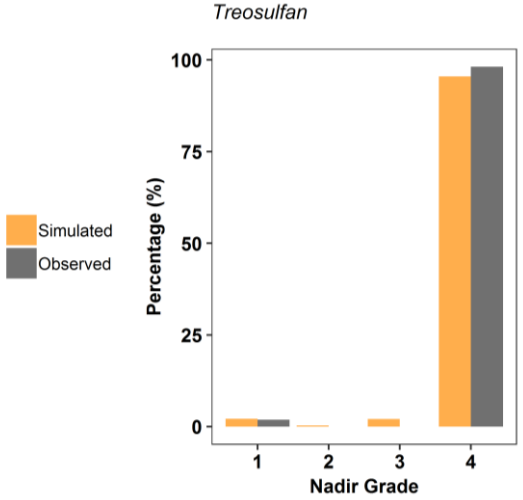


Model Evaluation

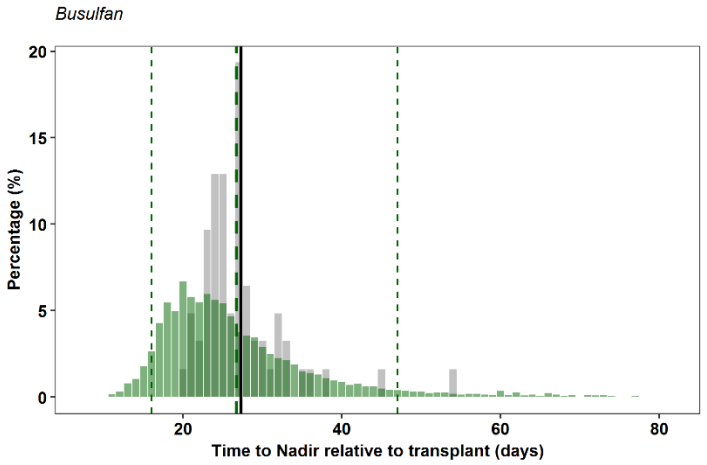
CLINICALLY RELEVANT METRICS

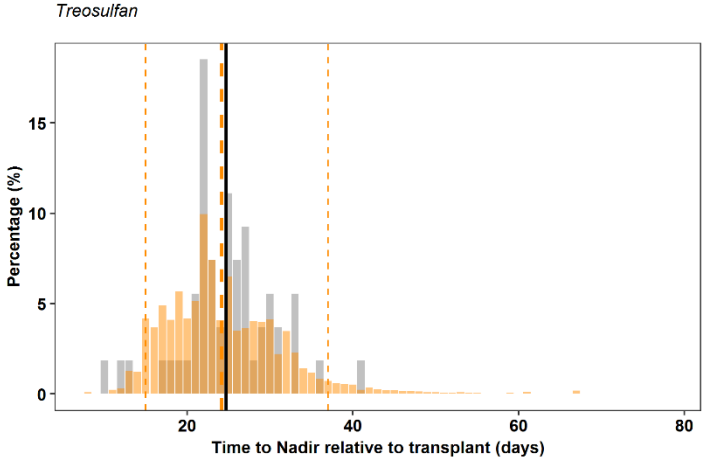
Nadir Grade



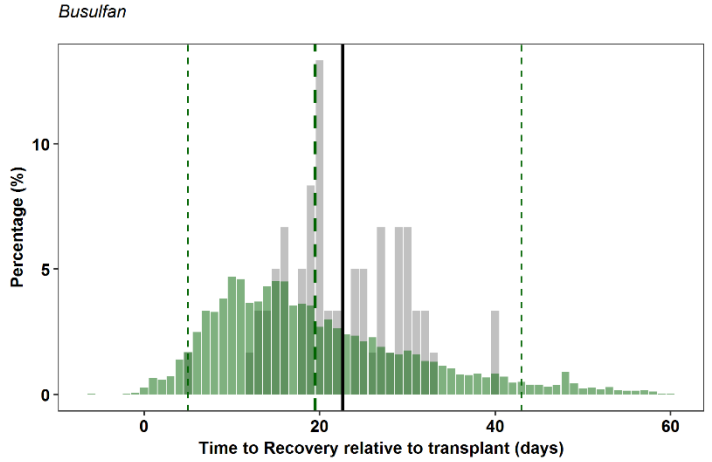


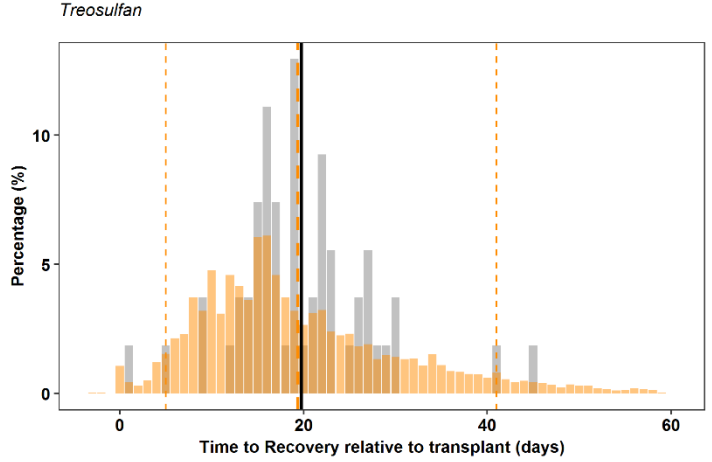
Time to Nadir





Time to Recovery





Model Evaluation

SYSTEM PARAMETERS

Parameter	Estimate (RSE%)	IIV [CV%]
Circ0	0.79 (18.91)	75.90
MTT [h]*	94.8 (12.04)	35.41
γ*	0.11 (13.93)	77.10

*** After transplant effect**

- High IIV
- Multiple factors
  - Not initially at steady state

PKPD Model of Neutropenia in Patients with Myeloma receiving high-dose melphalan for Autologous Stem Cell Transplant

	Structural model			Final model			Bootstrap	
	Estimate	RSE, %	IIV, CV% (% shrinkage)	Estimate	RSE, %	IIV, CV% (% shrinkage)	Estimate median (95% CI)	IIV, CV% median (95% CI)
BASE (K/μL)	5.69	4.5	35.1 (11.5)	5.61	4.7	34.4 (59.6)	5.62 (5.17–6.01)	33.9 (29.4–39.2)
SLOPE (mL/μg)	11.3	4.4	33.3 (12.1)	7.46	7.4	25.1 (18.3)	7.48 (6.67–8.99)	24.2 (19.0–29.4)
MTT (hours)	106	2.4	10.7 (11.5)	97	2.5	6.6 (22.7)	96.7 (92.56–101.00)	6.3 (4.3–7.7)
γ	0.221	2.3	–	0.218	2.3	–	0.218 (0.206–0.230)	–

Cho YK *et al.* CPT Pharmacometrics Syst Pharmacol. 2018 Nov;7(11):748-758

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SYSTEM PARAMETERS

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*** After transplant effect**

TABLE 1

Population pharmacodynamic parameter estimates corresponding to the reference model for neutropenia (Friberg et al., 2002)

Parameters	Estimate	Shrinkage (%)	Bootstrap (n = 500)	
			Median	2.5–97.5th Percentiles
$Circ_0$ (× 10^9/l)	4.70		4.65	3.9–5.4
MTT (d)	4.81		4.75	3.9–6.0
θ_{Slope} (ml/ng)	1.49		1.51	0.6–3.2
E_{max}	4.03		3.96	2.1–11.2
γ	0.14		0.14	0.08–0.2

Mangas-Sanjuan *et al.* J Pharmacol Exp Ther. 2015 Jul;354(1):55-64

Table 1 Pharmacokinetic and pharmacodynamic parameters for BI 2536

Parameter	Estimate	IPV	η-shrinkage
Pharmacokinetics			
CL (L/h)	69.9 (4.7)	49 (27.9)	3.8
V_1 (L)	69.1 (9.8)	79 (25.3)	12.5
Q_2 (L/h)	48.5 (7.3)	Ne	Na
V_2 (L)	1,350 (9.7)	45 (27.7)	31.6
Q_3 (L/h)	108 (10.5)	Ne	Na
V_3 (L)	190 (15.5)	134 (21.8)	6.2
Additive error (ng/mL)	0.410 (36.6)	Na	Na
Proportional error (%)	39.2 (8.7)	Na	Na
Pharmacodynamics			
$Circ_0$ (cells × 10^9/L)	4.96 (4.0)	421 (15.3)	3.3
MTT (h)	107 (3.8)	22 (46.4)	20.9
Slope (mL/ng)	0.0147 (8.6)	65 (24.3)	19.1
γ	0.161 (5.9)	Ne	Na
Additive error (cells × 10^9/L)	0.278 (47.8)	Na	Na
Proportional error (%)	21.1 (9.0)	Na	Na

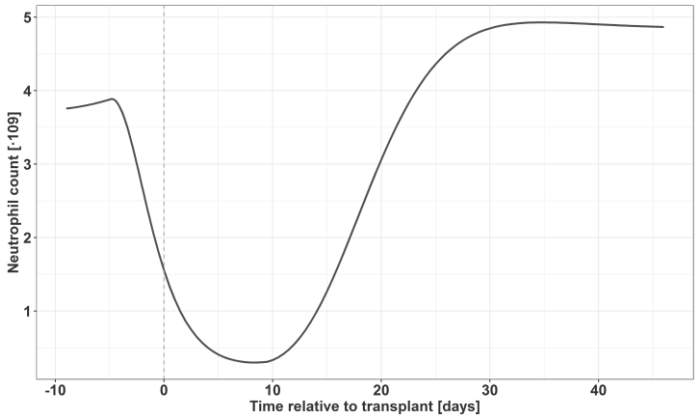
Parameters are listed together with the coefficient of variation [CV(%)] in parenthesis. *CL*, total plasma clearance; V_1, volume of distribution in the central compartment; V_2 and V_3, volume of distribution in the peripheral compartments; Q_2 and Q_3, Intercompartmental clearances; $Circ_0$, basal ANC; *MTT*, maturation mean transit time; γ, feedback parameter; *IPV*, inter-patient variability expressed as CV (%); *Ne*, not estimated; *Na*, not applicable

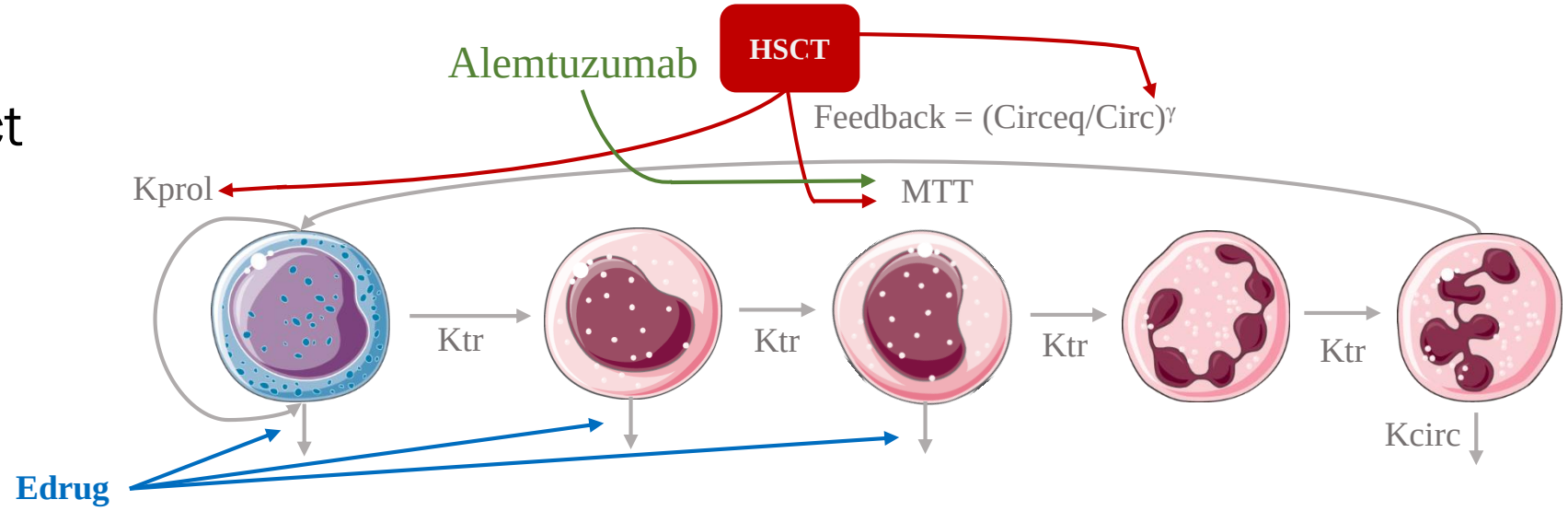
Soto E *et al.* Cancer Chemother Pharmacol. 2010 Sep;66(4):785-95

Summary PKPD Model

First time, to our knowledge, that the HSCT effect is introduced in a neutropenia model in children

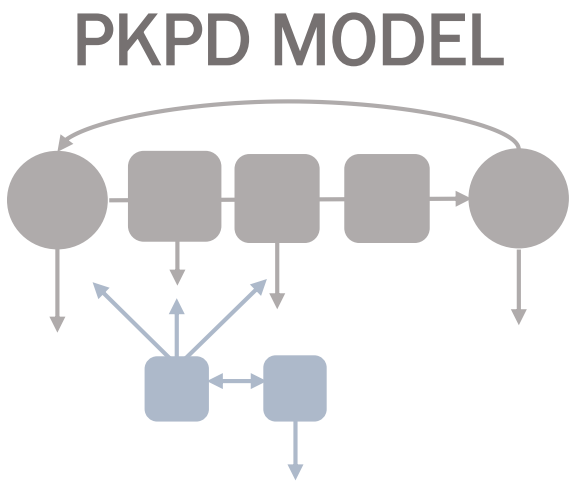
- Different value at baseline and at steady state
- Transplant effect
  - Enhancing Proliferation
  - Enhancing Feedback
  - Decreasing MTT
- Alemtuzumab effect
  - Decreasing MTT
- Drug effect
  - Eliminating cells





Same transplant effect regardless type of transplant

Model Applicability



Clinical Applications

Model Applicability

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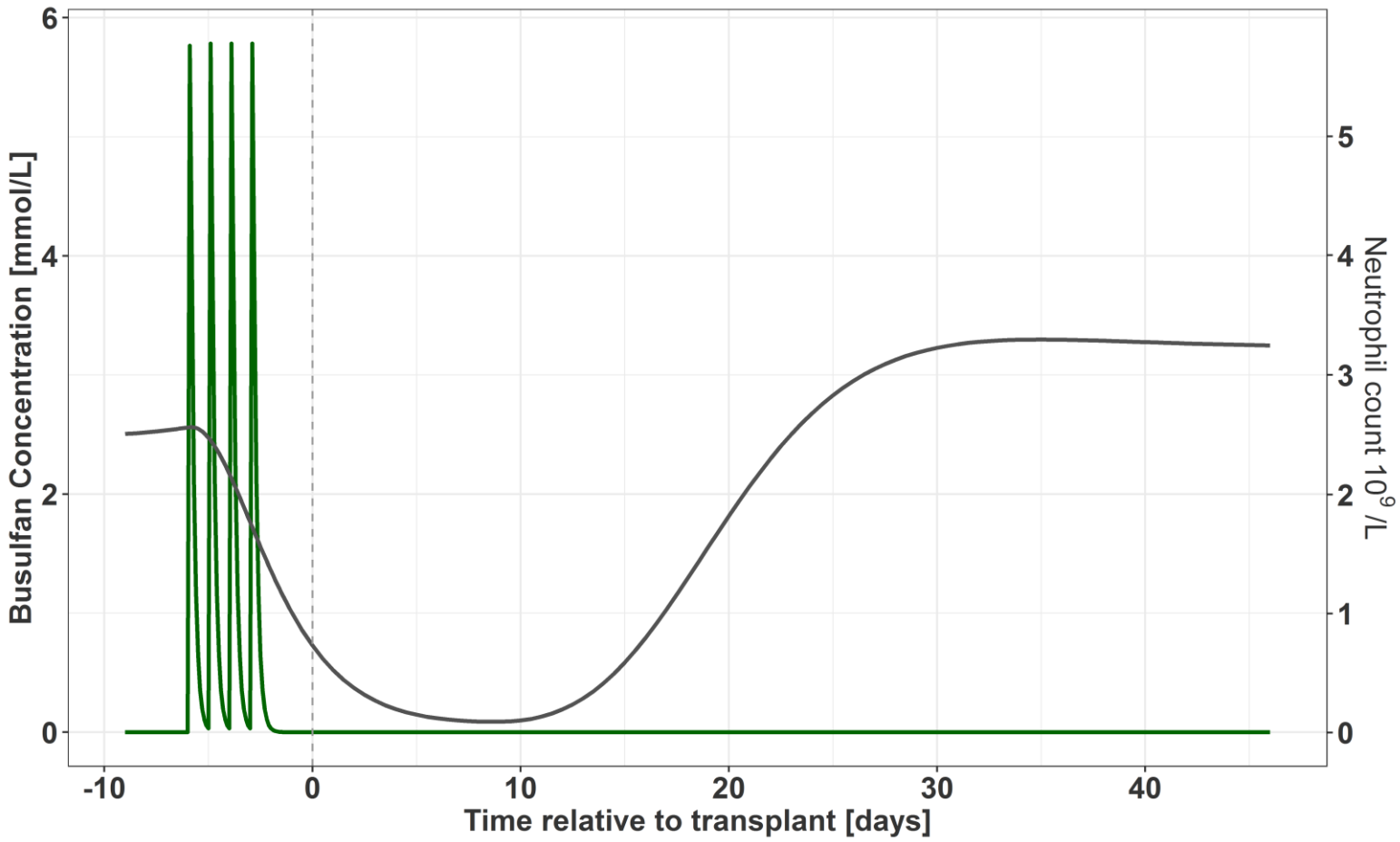
Evaluation of the dosing schedules



Model Applicability

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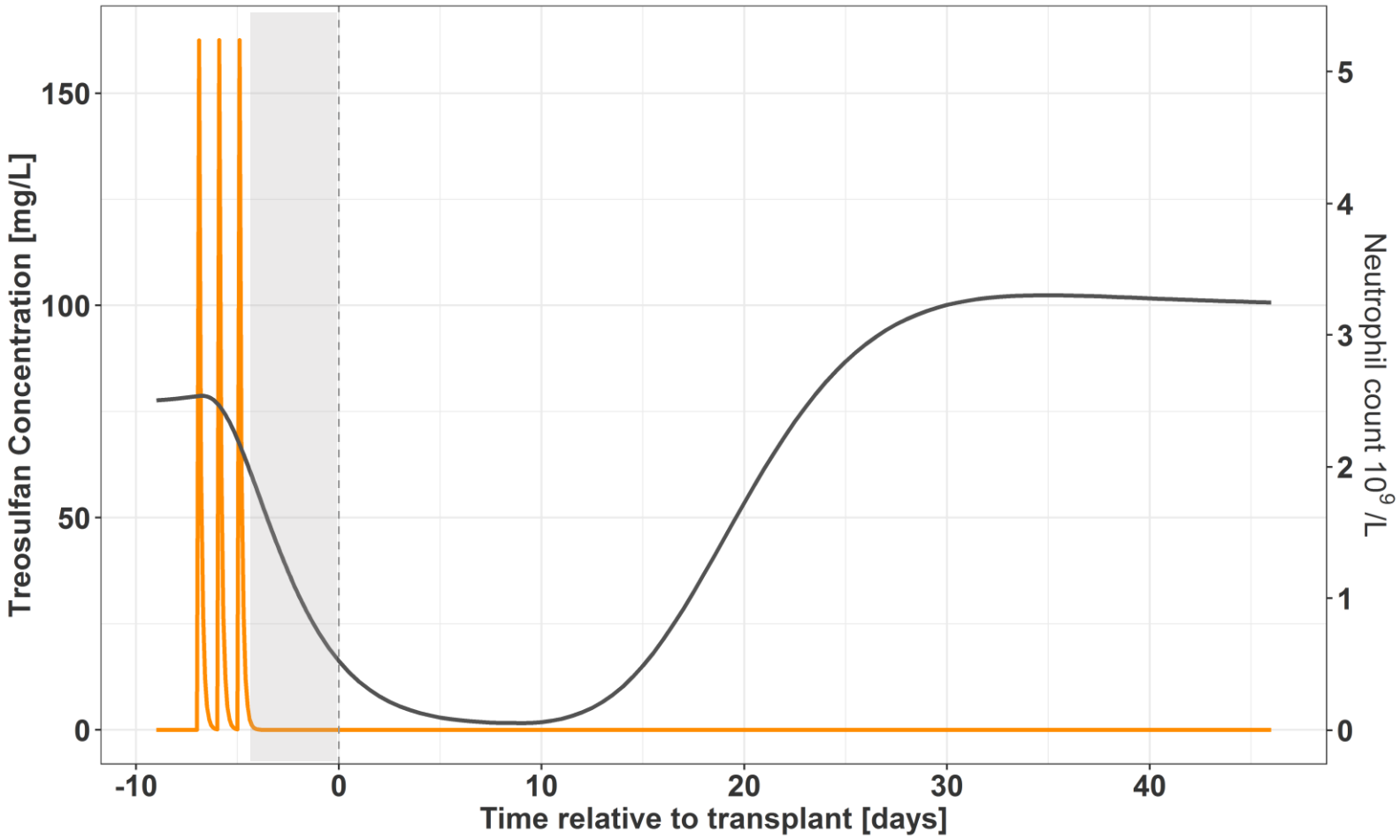

Model Applicability

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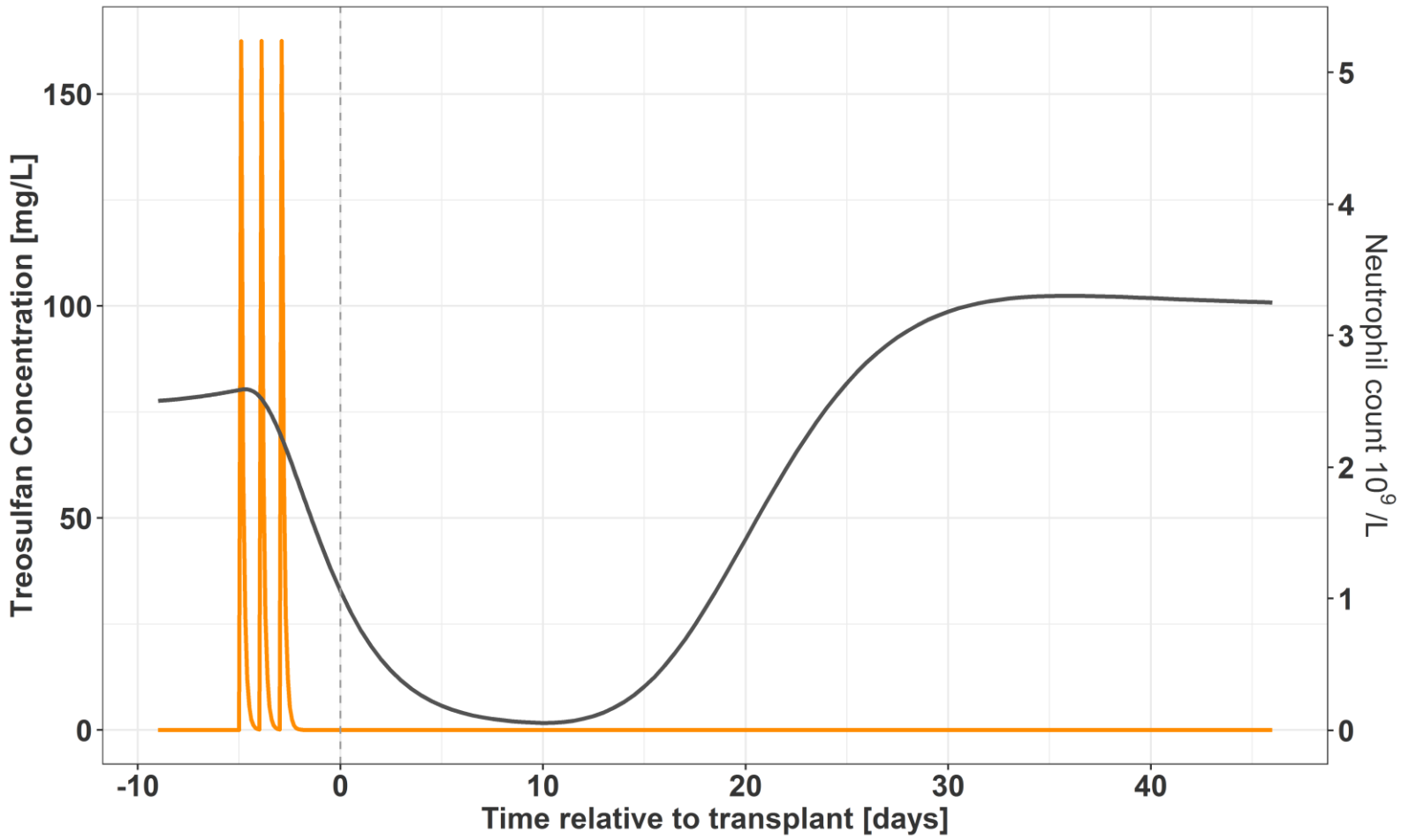
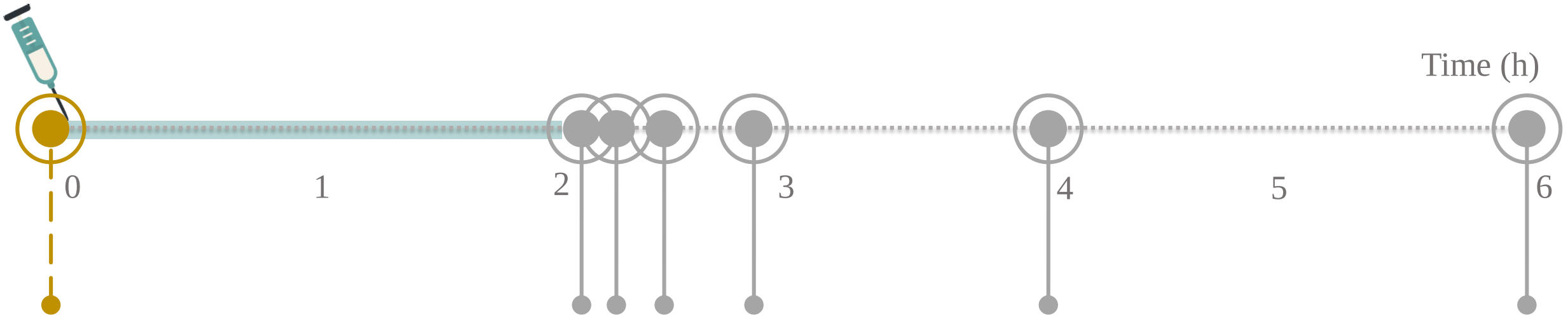
Evaluation of the dosing schedules



Model Applicability

Optimization of the PK sampling schedules

Protocol sample times



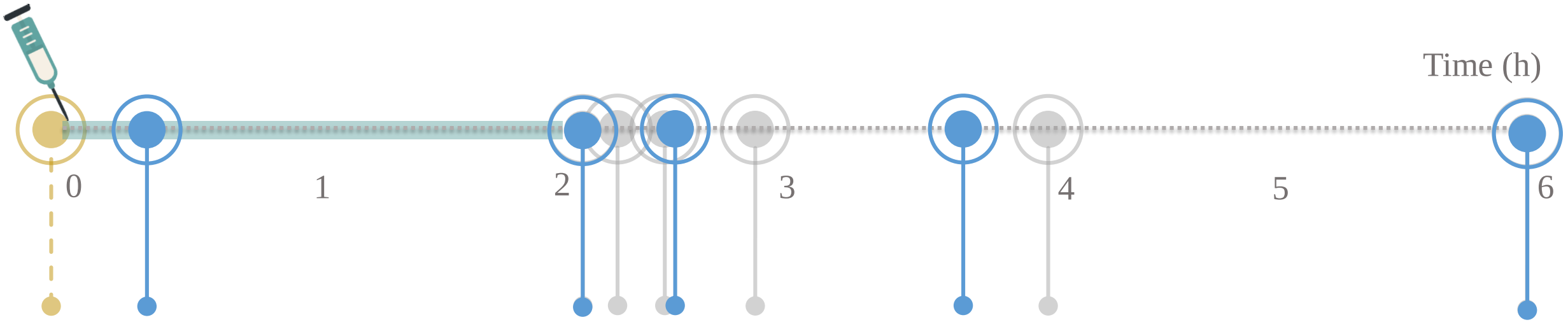
Software used: PopED

*Foraccia, Hooker, Vicini and Ruggeri 2004

Model Applicability

Optimization of the PK sampling schedules

Protocol sample times



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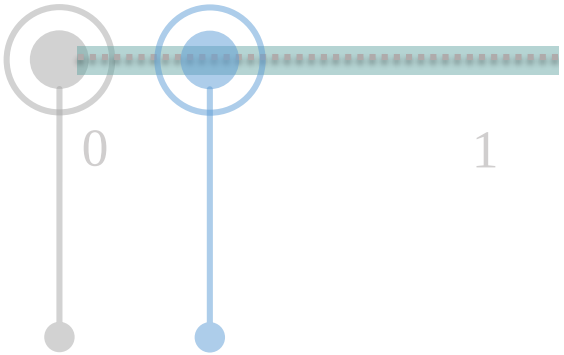
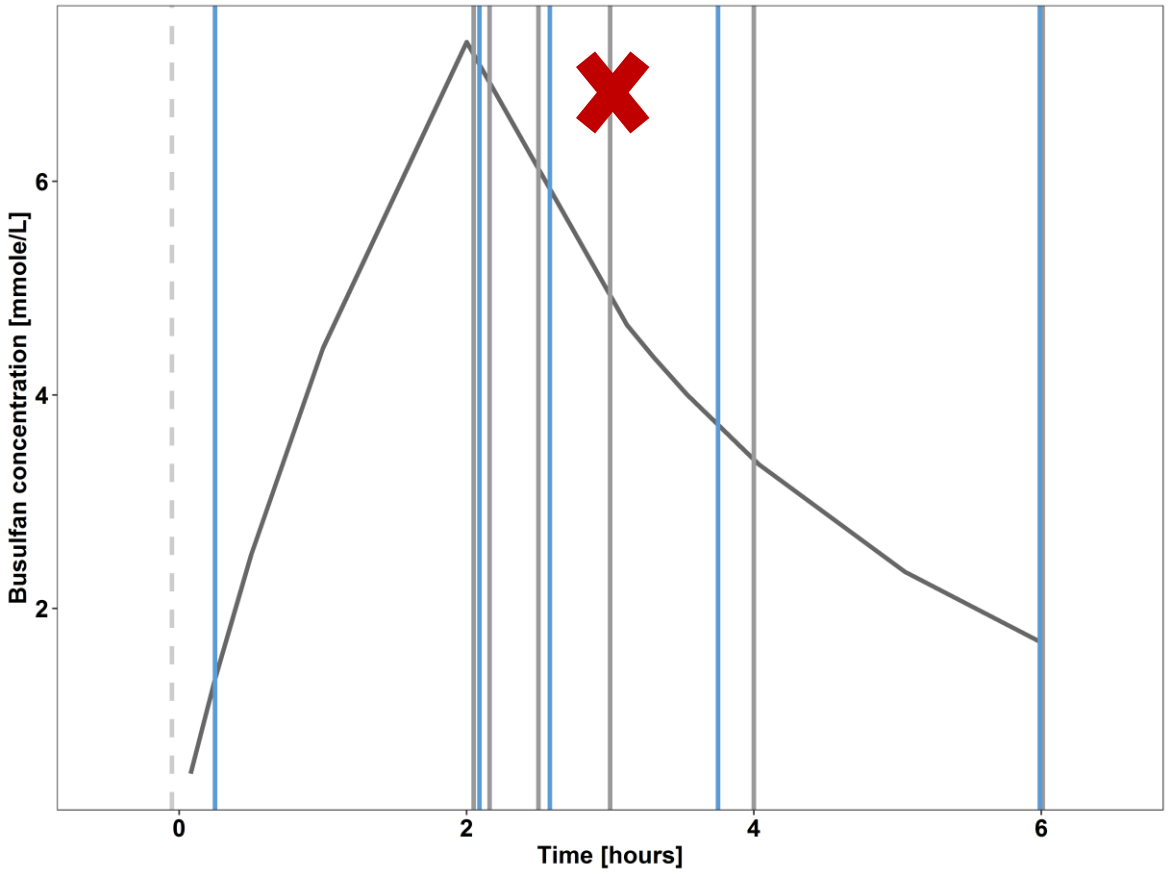
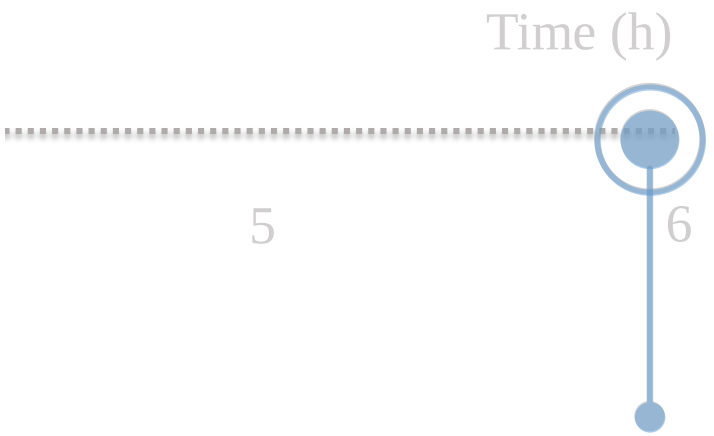
Model Applicability

Optimization of the PK sampling schedules







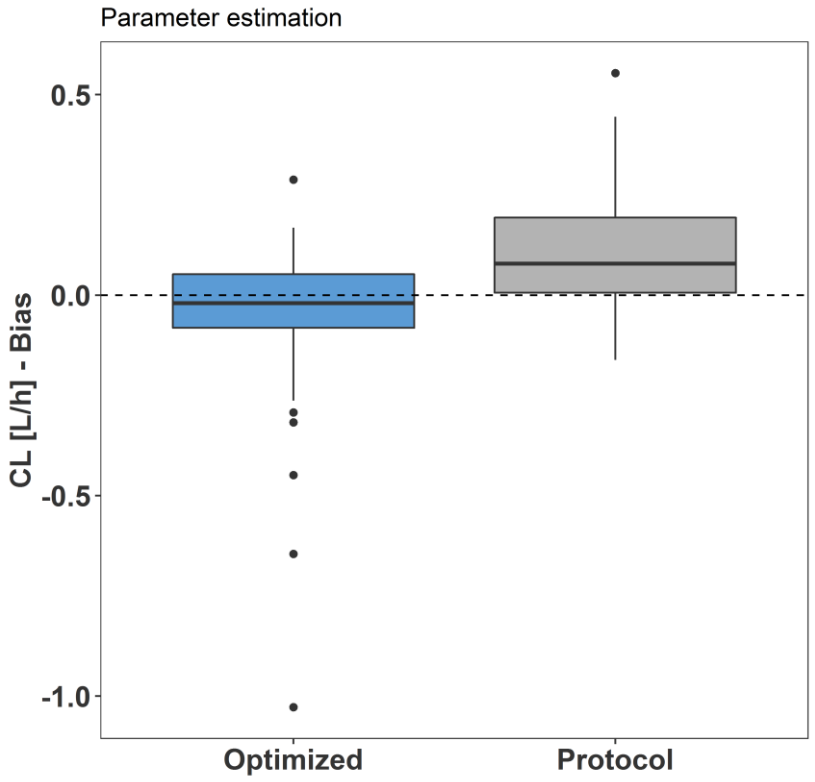
Software used: PopED

*Foraccia, Hooker, Vicini and Ruggeri 2004

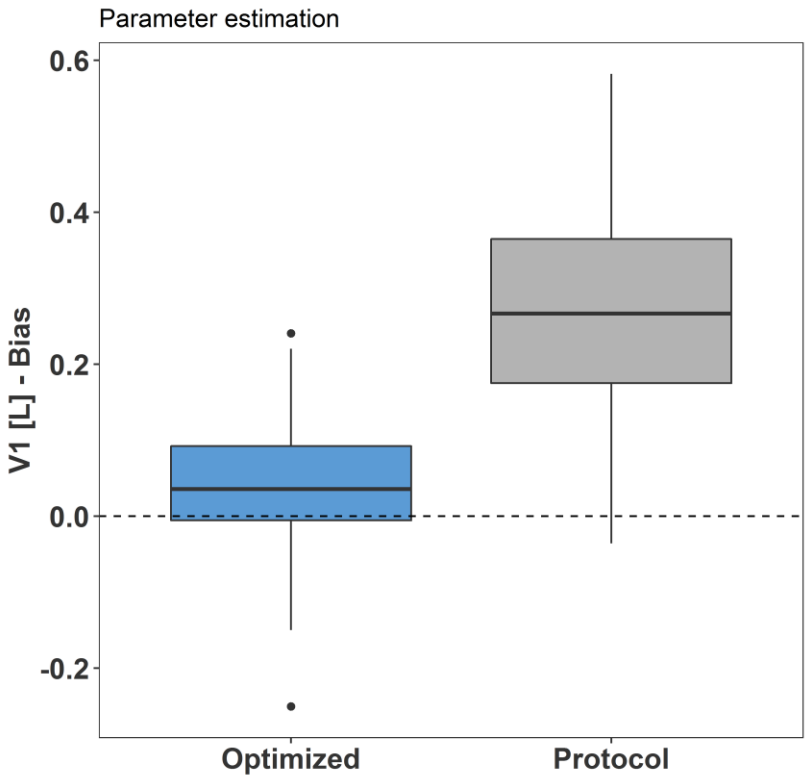
Model Applicability

$$\text{Bias} = \frac{\theta_{Real} - \theta_{Est}}{\theta_{Real}}$$

CL (L/h)



V (L)



Model Applicability

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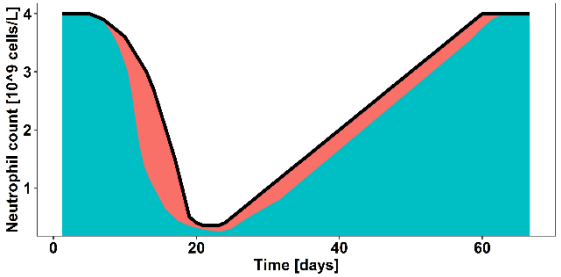
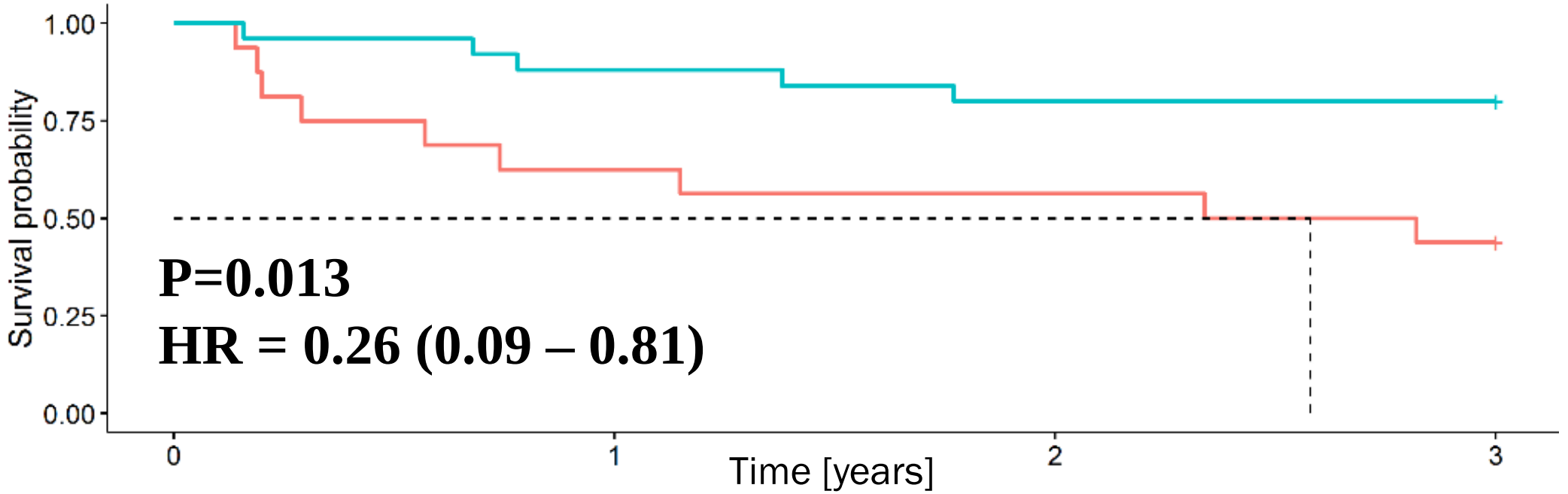
Neutropenia and overall survival



AUC stratification > 141 [10^9cells·days/L] ≤141 [10^9cells·days/L]

Malignancies



Model Applicability

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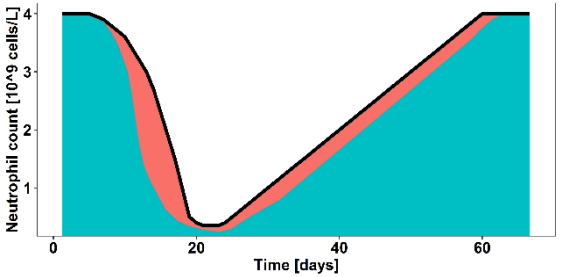
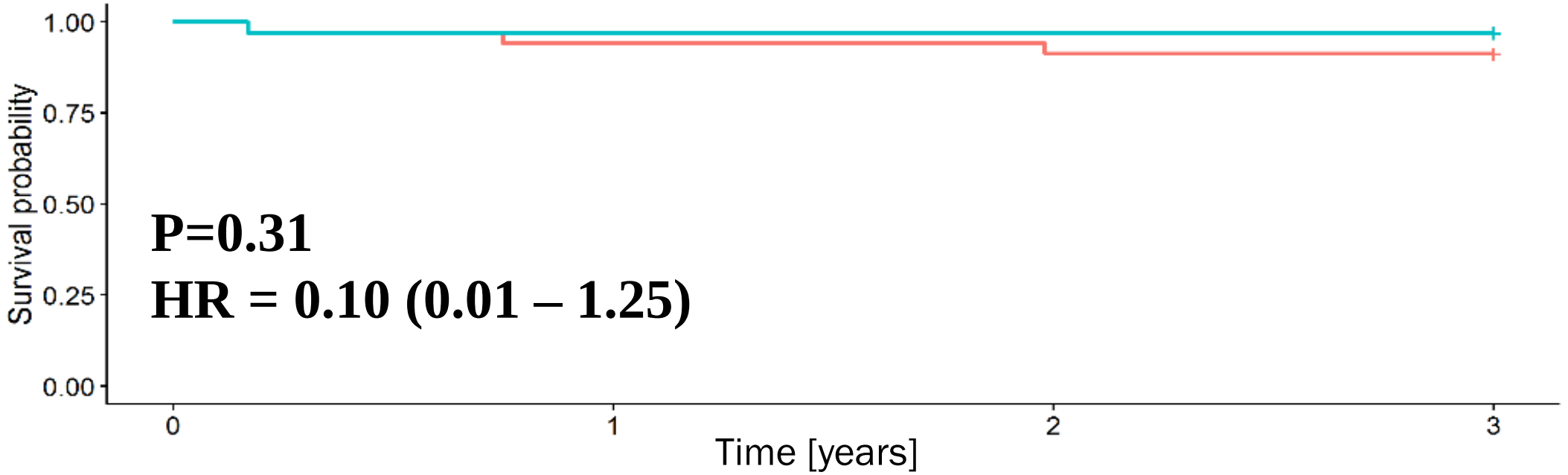
Neutropenia and overall survival

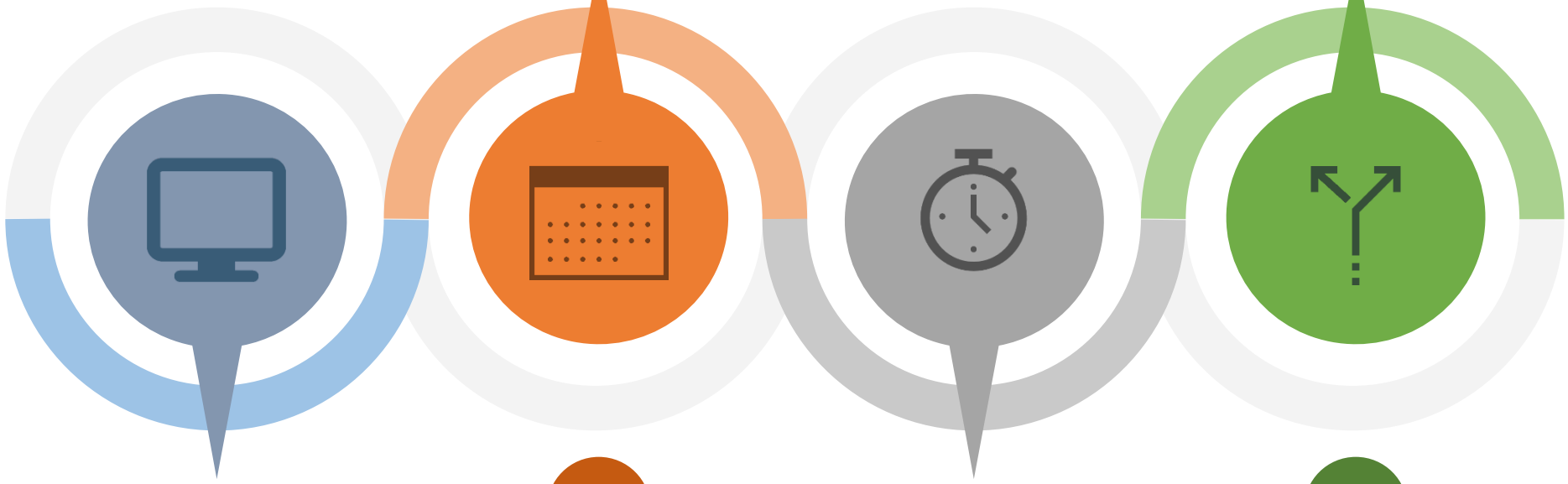


AUC stratification > 141 [10^9cells·days/L] ≤141 [10^9cells·days/L]

Non-Malignancies



Conclusions



1. PKPD model developed predicts neutrophil reconstitution trajectories after HSCT
2. New dosing schedules are proposed
3. Different sampling schedules are found to be more informative
4. Differences between patients with malignant and non-malignant diseases are found

Conclusions

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1 New dosing schedules are proposed

3 Differences between patients with malignant and non-malignant diseases are found

Useful tool to improve the clinical management of children receiving HSCT

PKPD model developed predicts neutrophil reconstitution trajectories after HSCT

2

Different sampling schedules are found to be more informative

4


MOCHCHAKKERAN
DANKE
MANANA
SPAS
TACK
DAKUJEM
TENKI
AKUN
ASANTE
MERCI
THANK YOU
KIITOS
GRAZIE
TAU
GRACIAS
OBRIGADO
DIOLCH
PALDIES
TAKK
VINAKA
DANKON
MËSI
ESKERRIK ASKO
DANKJE
MISAOTRA
WELALIN
GRAZZI