UMC Utrecht

Optimizing fludarabine exposure:
accelerate immune recovery and enhance event free survival after allogeneic cell transplantation

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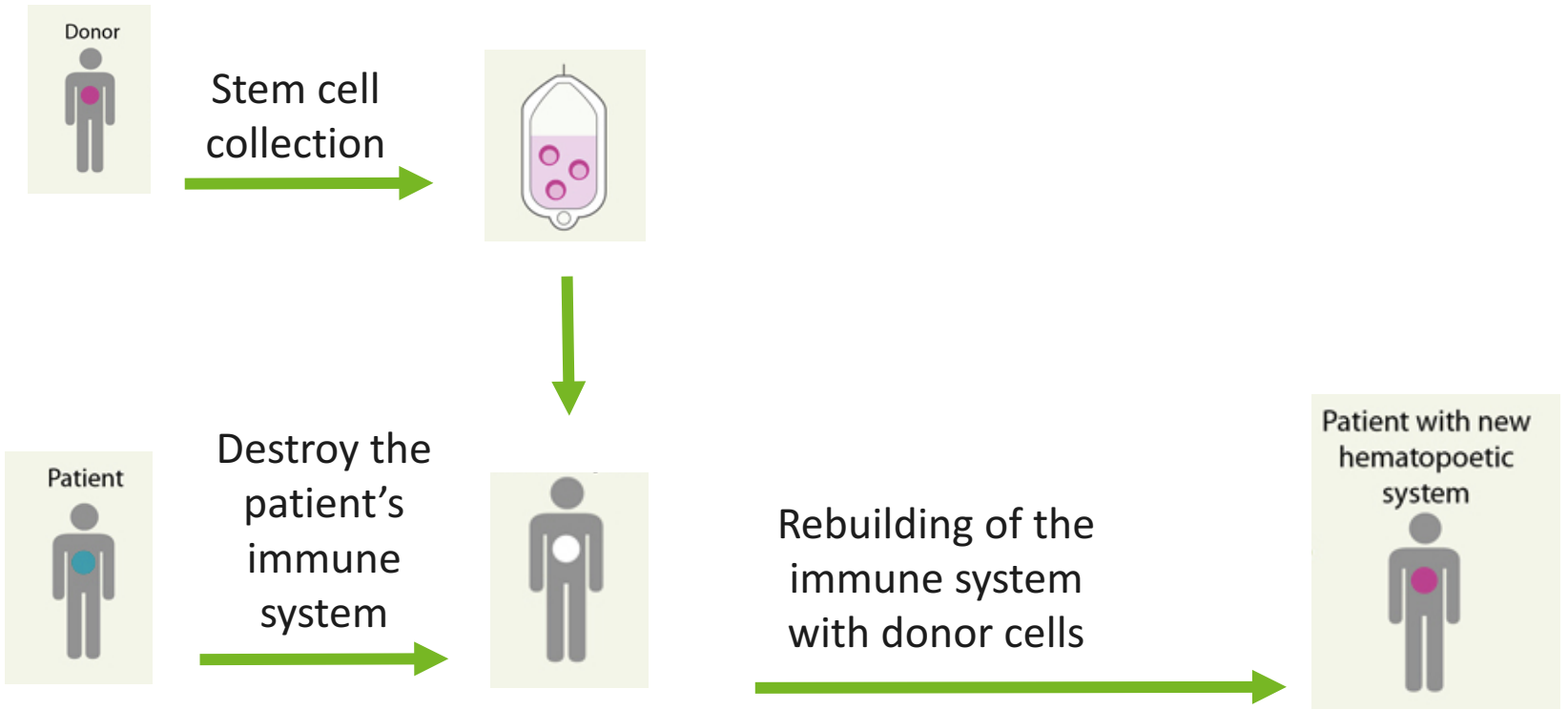
June 7th 2017

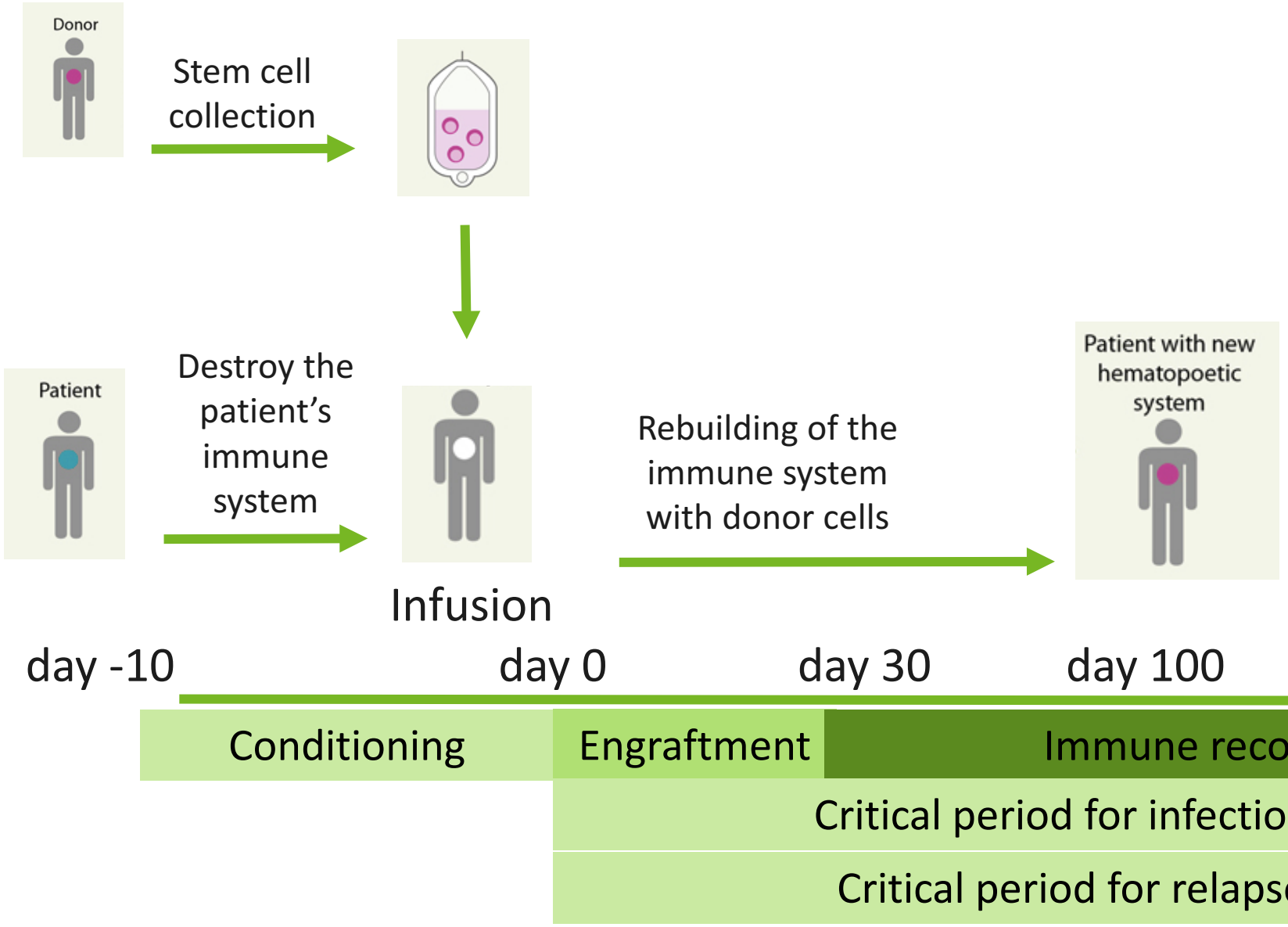
Allogeneic hematopoietic cell transplantation (HCT)



Indications:

Malignancies
Immune deficiencies
Metabolic/inborn errors
Autoimmune disease
Bonemarrow failure

Allogeneic hematopoietic cell transplantation (HCT)



Allogeneic hematopoietic cell transplantation (HCT)

ATG-FluBu as Standard Conditioning

Lympho-depletion

Bone marrow depletion

HCT

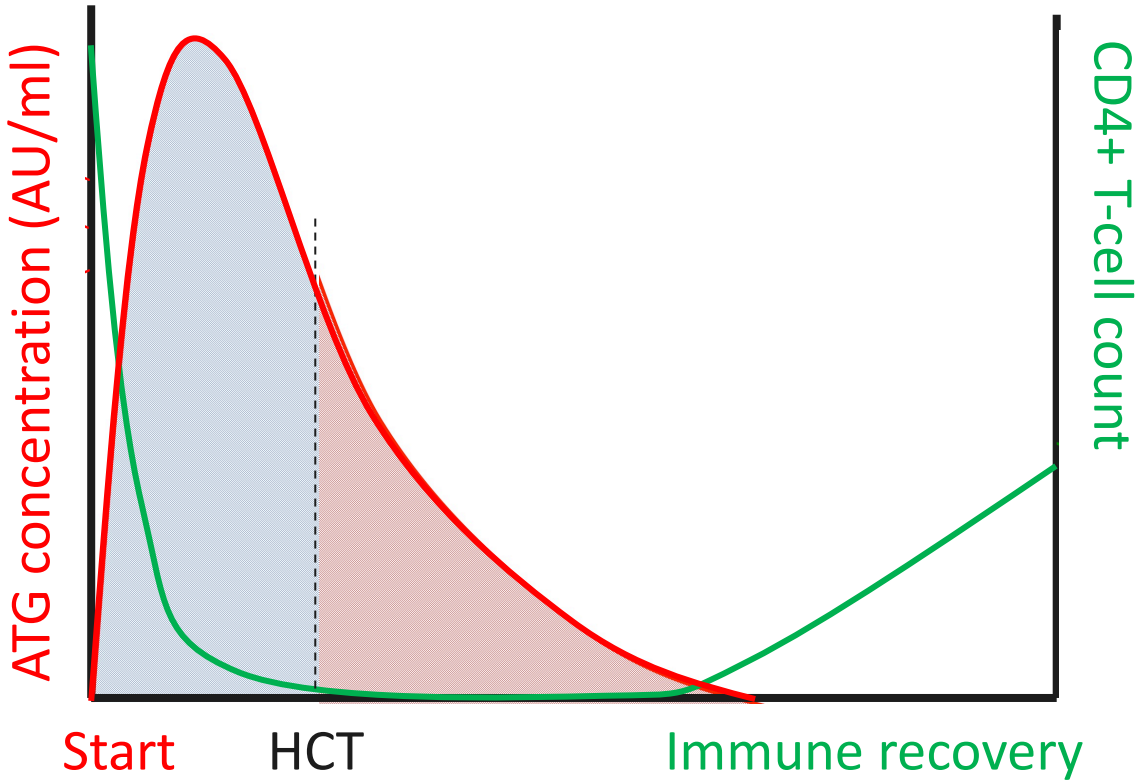
Anti Thymocyte Globulin (ATG)

Busulfan (Bu)

Fludarabine (Flu)

Day: -9 -8 -7 -6 -5 -4 -3 -2 -1 0

Previous results: ATG & Busulfan (Peds + Adults)



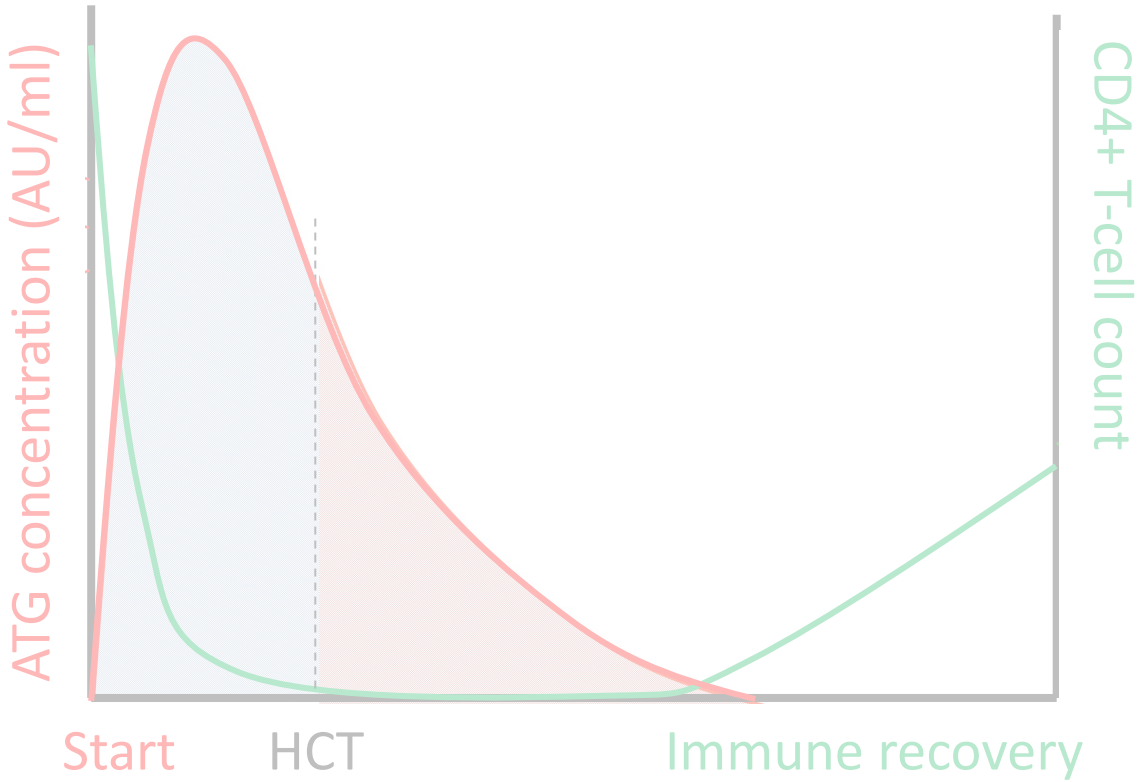
Children & adults:
before and after HCT exposure of **ATG** relates to outcomes

✓ High ATG exposure **before** HCT reduces complications

✗ High ATG exposure **after** HCT hampers immune recovery

Admiraal et al:
Lancet Hematology 2015, 2017 resp.

Previous results: ATG & Busulfan (Peds + Adults)



Children & adults:
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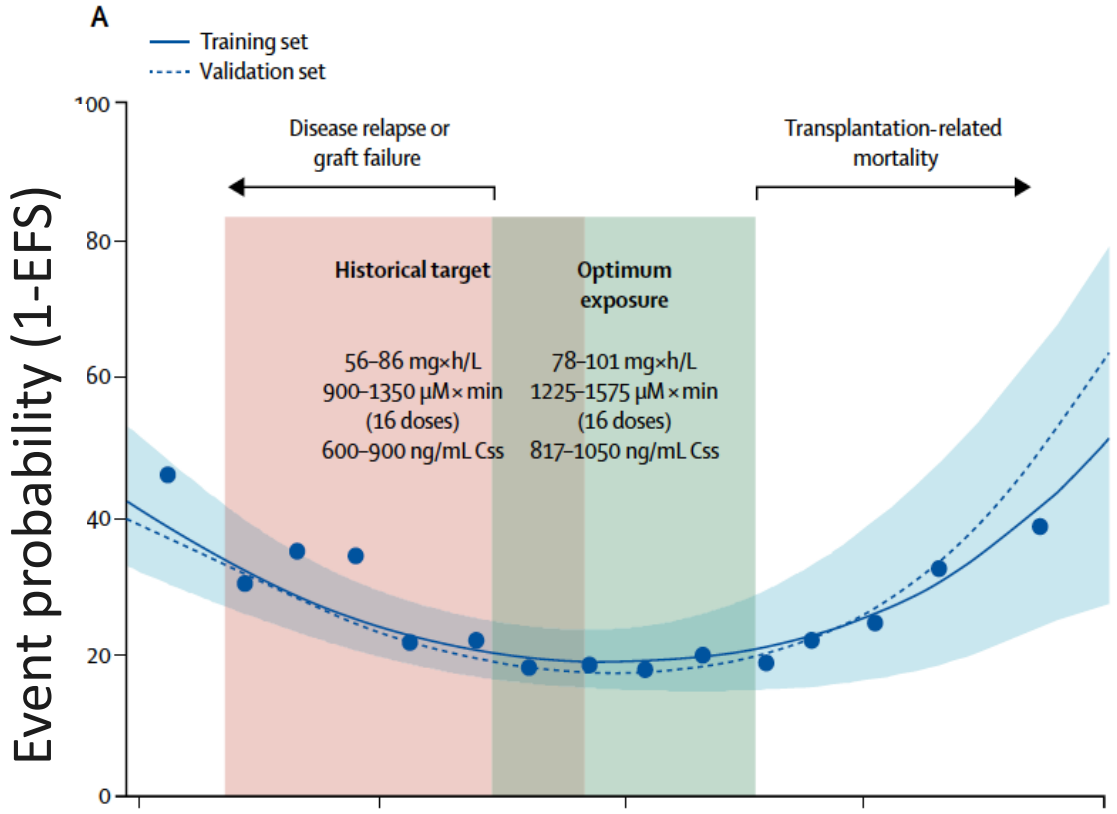


Busulfan exposure (AUC: mg*h/L)

Children & young adults:
Busulfan cumulative exposure related to outcome

Bartelink et al: **Lancet Hematology 2016**

ATG-FluBu as Standard Conditioning

Lympho-depletion

Bone marrow depletion

HCT

✓ **ATG:** targeted

✓ **Busulfan:** targeted

× **Fludarabine?**

Day: -9 -8 -7 -6 -5 -4 -3 -2 -1 0

Aim and Methods

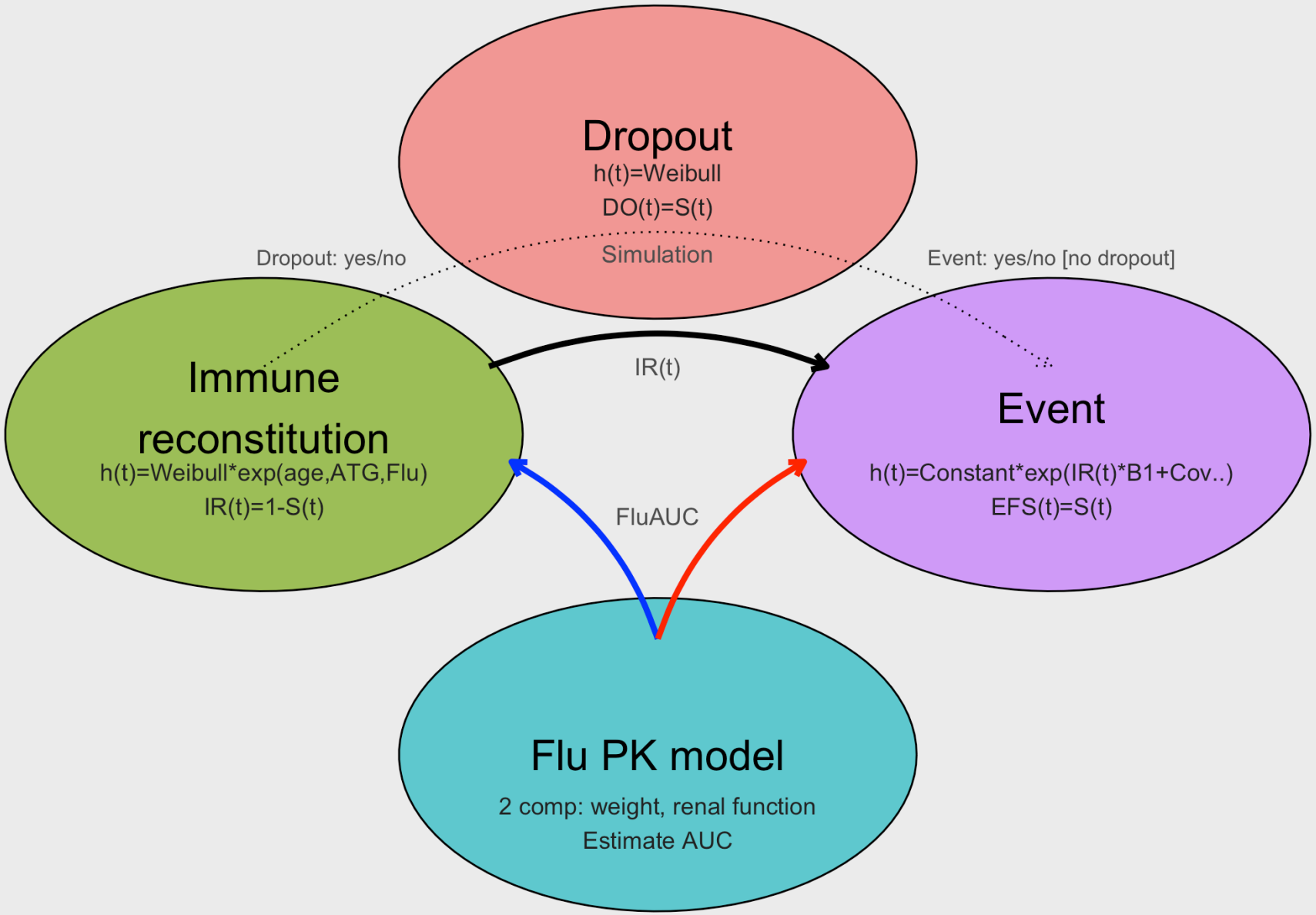
Aim: Optimizing Flu exposures to enhance **immune recovery (IR)** and Event free survival (**EFS**):

- **IR:** Two consecutive CD4+ T-cell counts >50
- **EFS:**
  1. Relapse
  2. Treatment related mortality (TRM)
  3. Graft failure

Methods

- Build Fludarabine PK model and calculate exposure
- Calculate effects of Flu exposure on IR and EFS: Kaplan-Meier estimation, Cox-PH models, Parametric TTE models
- Impute IR probability as covariate into EFS TTE model
- Simulating alternative dosing regimens to evaluate PK target attainment

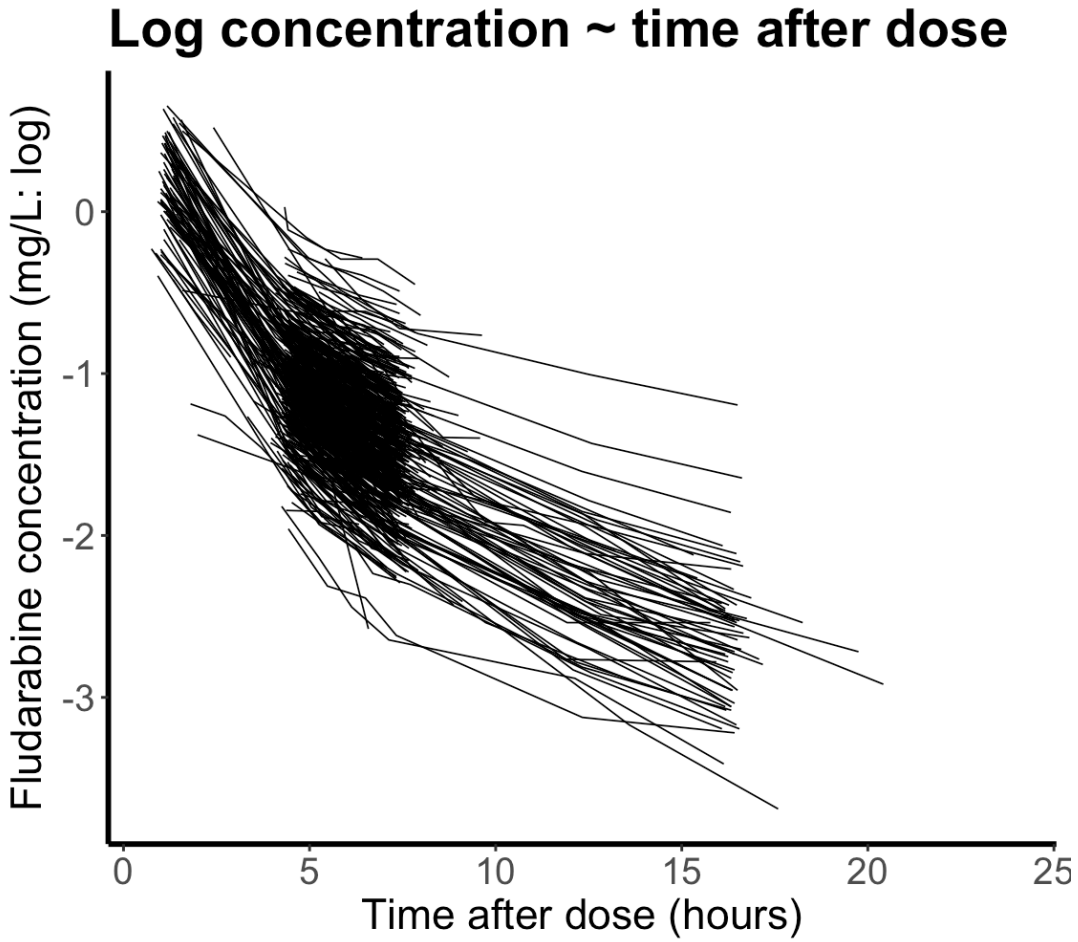
Exposure outcome model

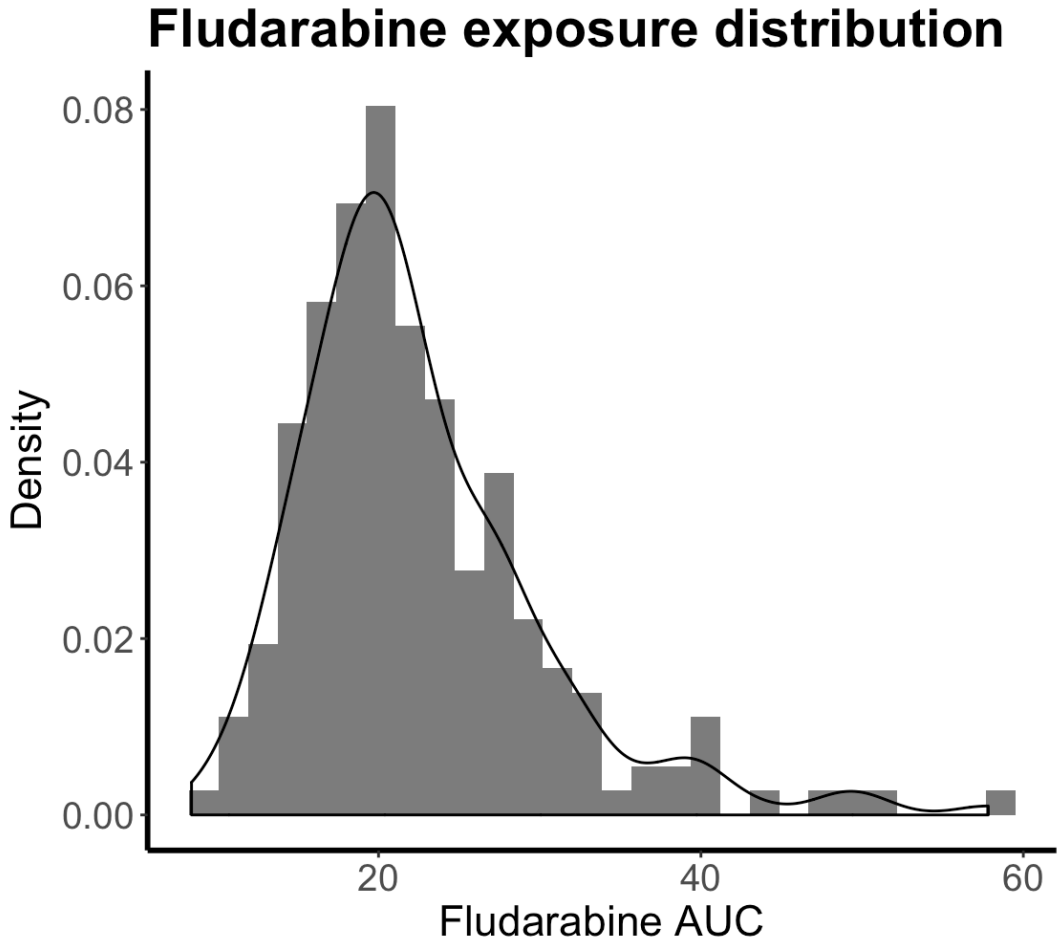


Patient cohort

Number of patients (IR available, PK model)	197 (181, 258)
Years of transplant	2010-2016
Adults (%)	65
Male sex (%)	60
Age in years (range)	37.7 (0.23 – 73.5)
Weight in kg (range)	65 (4.3 – 125)
Malignancies (%)	65
Median Busulfan exposure (IQR)	99 (92-107)
Cell source	
Cord Blood	65
Peripheral blood	116
Bone marrow	16

Flu-exposure variability

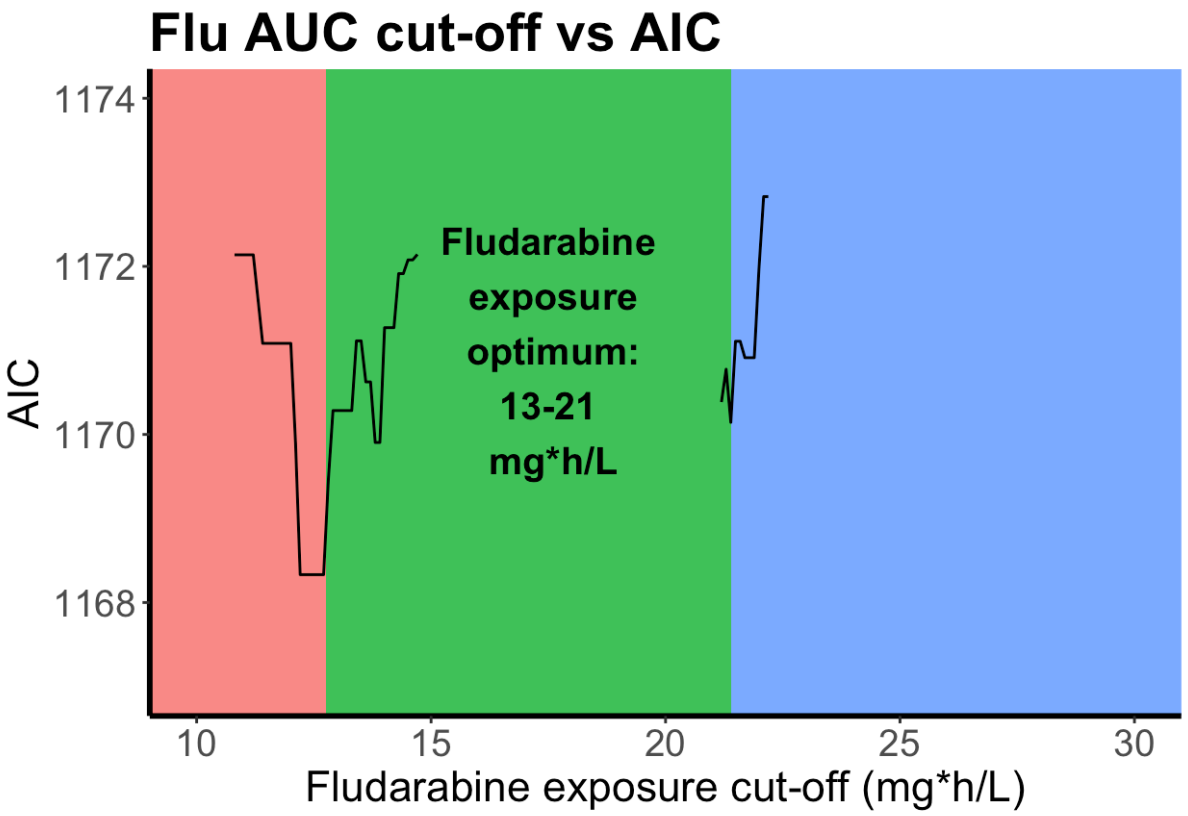


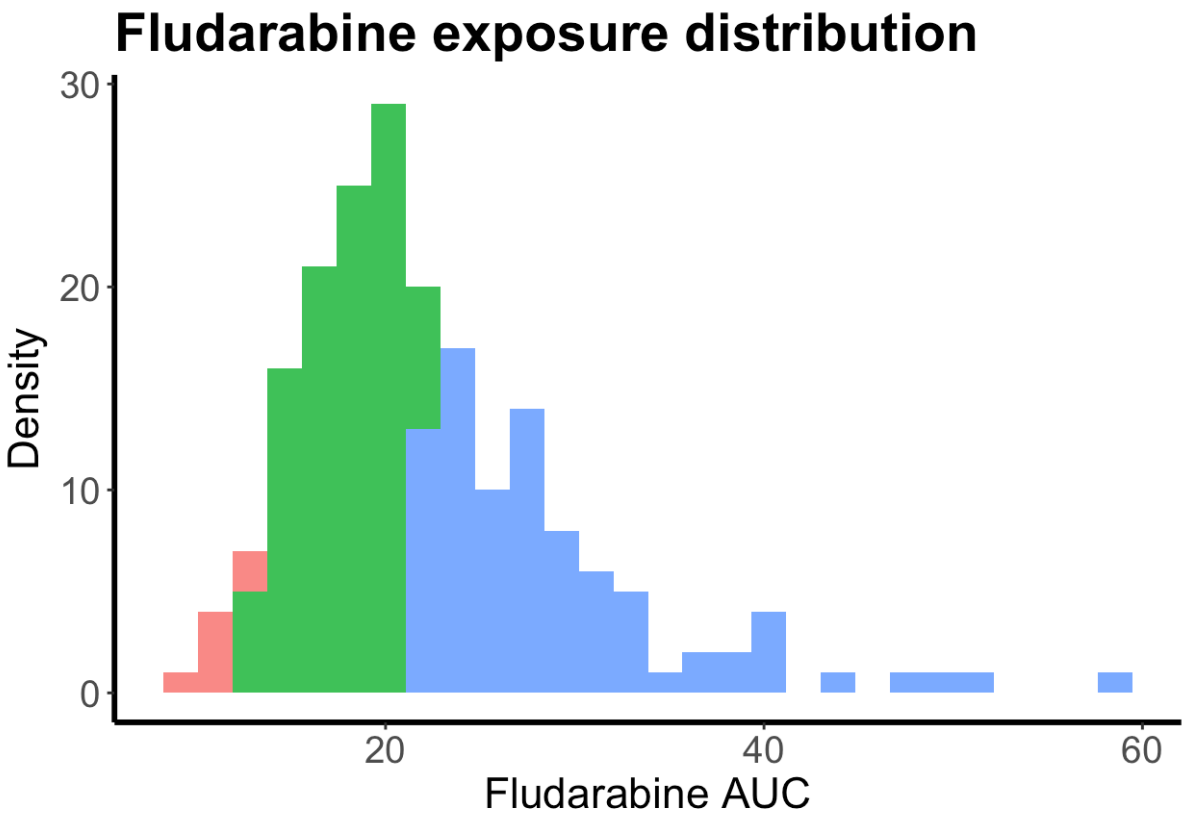


Fludarabine exposure range

Median (range) = 21 mg*h/l (9 – 57)

Dividing into groups according to exposure





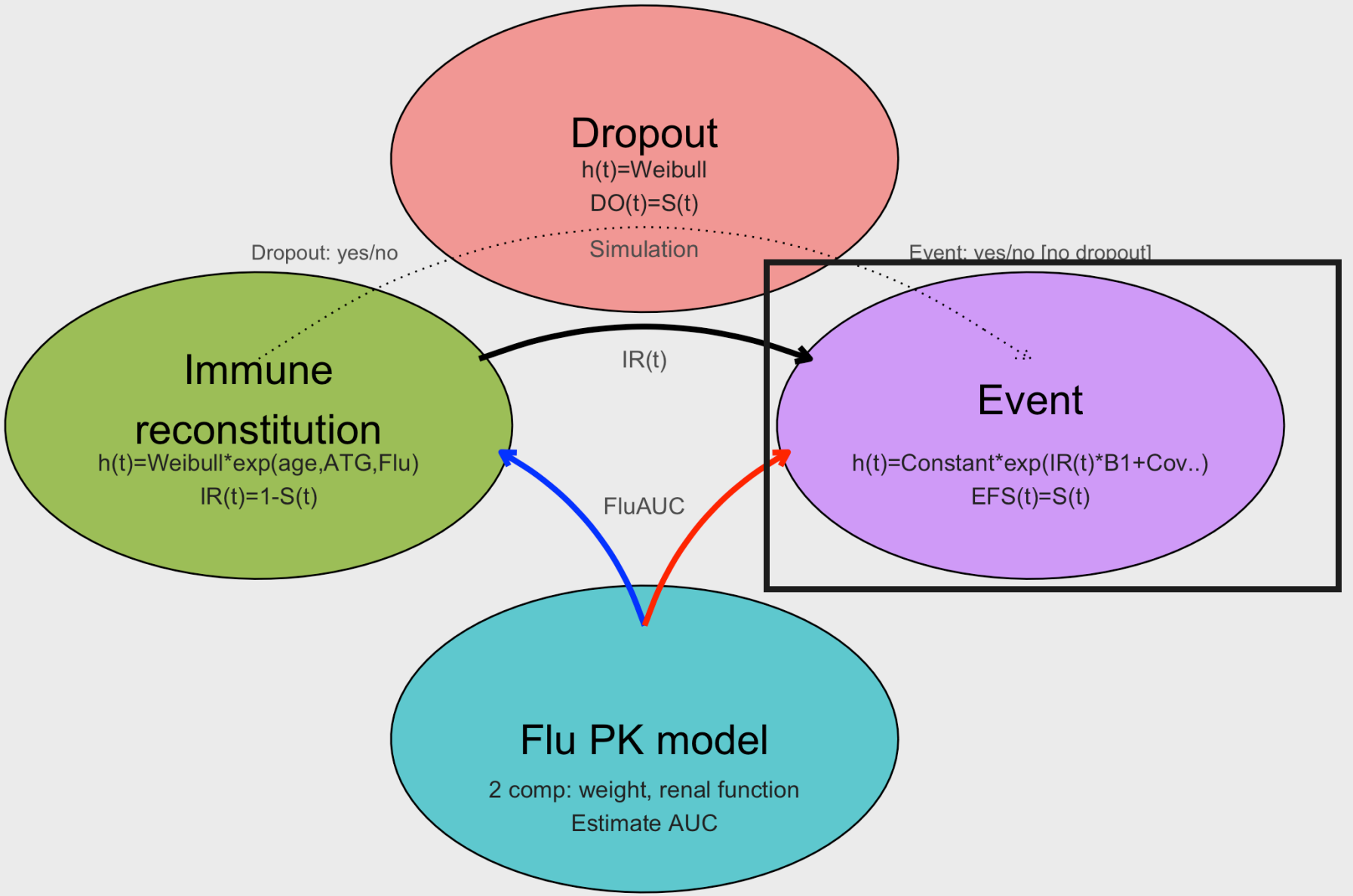
Below Optimum Optimum Above optimum

Outcome analysis: correcting for baseline risk

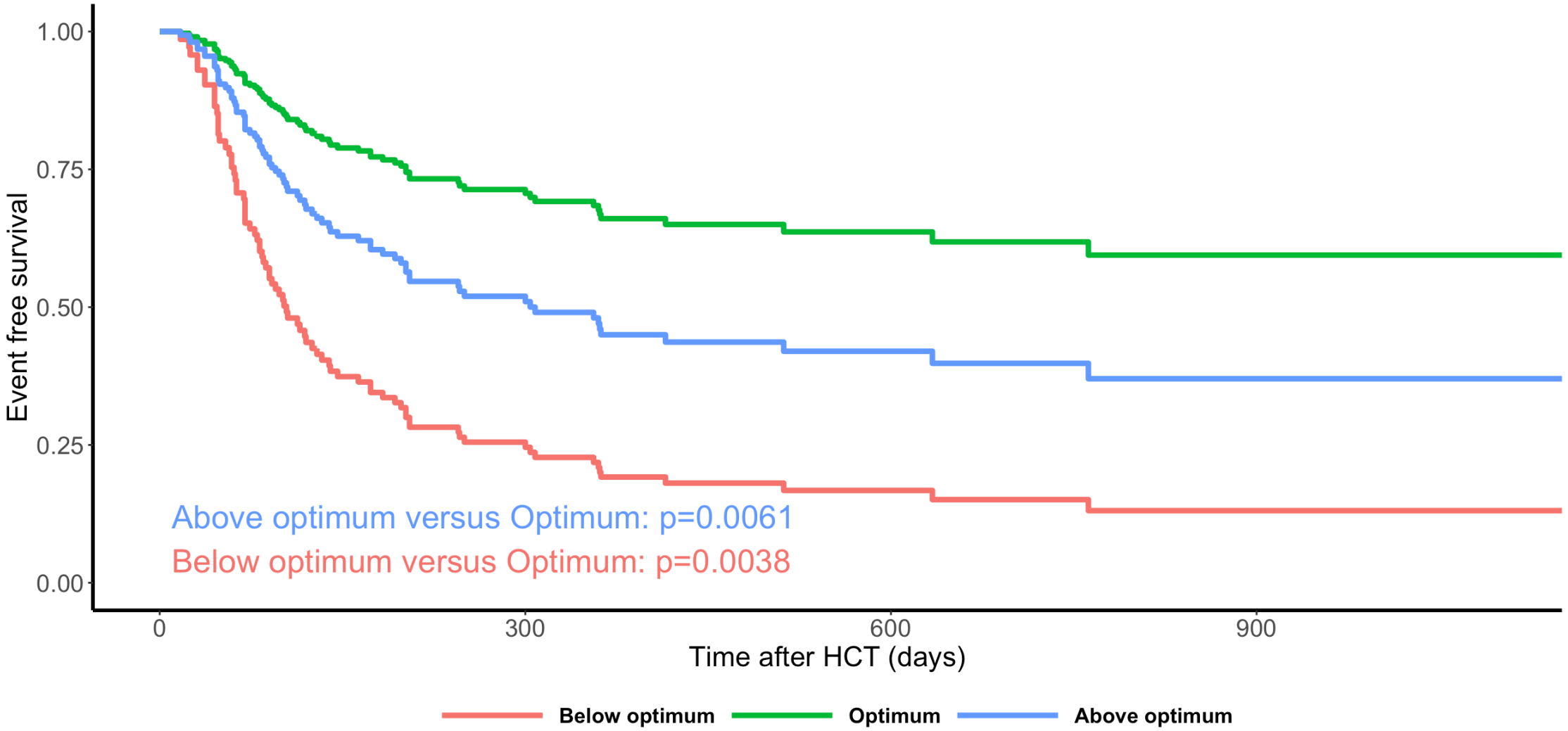
- **Event free survival**
  - Indication
    - Benign disorders: no relapse risk
    - Multiple Myeloma: high baseline risk
    - Myelodysplastic syndrome: high baseline risk
    - Leukemia/lymphoma: similar baseline risk
  - Older age was not associated with increased risk in this setting

- **Immune reconstitution**
  - Age: Children reconstitute faster than adults
  - ATG post transplantation exposure

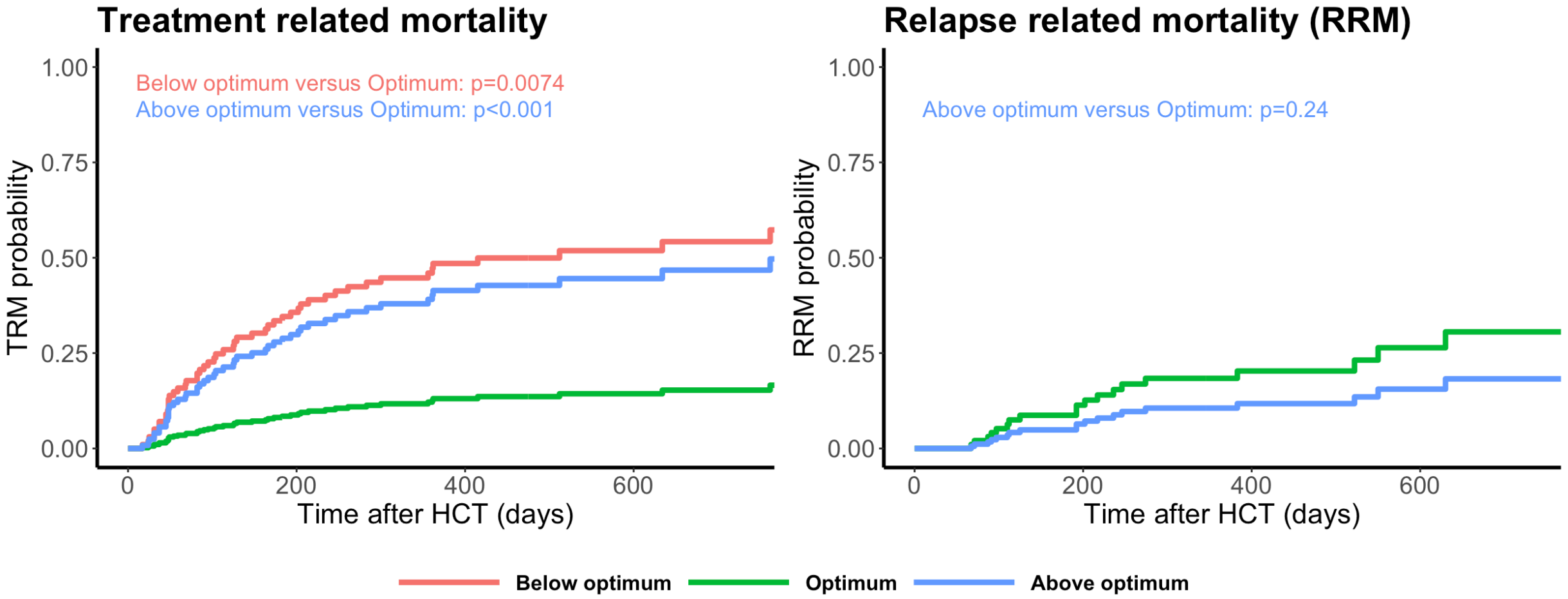
Exposure outcome model I



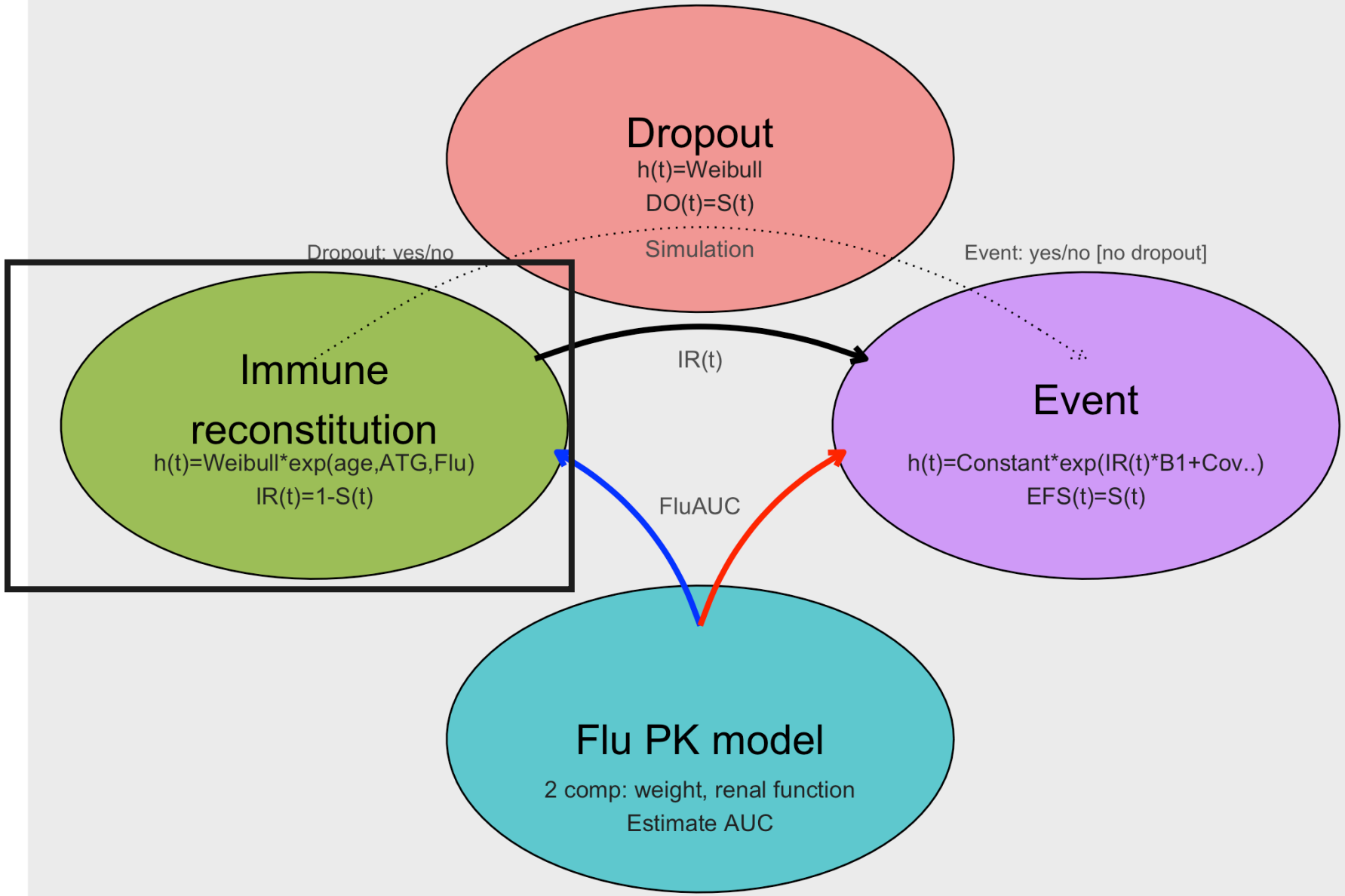
Events free survival according to cut-offs: adjusted



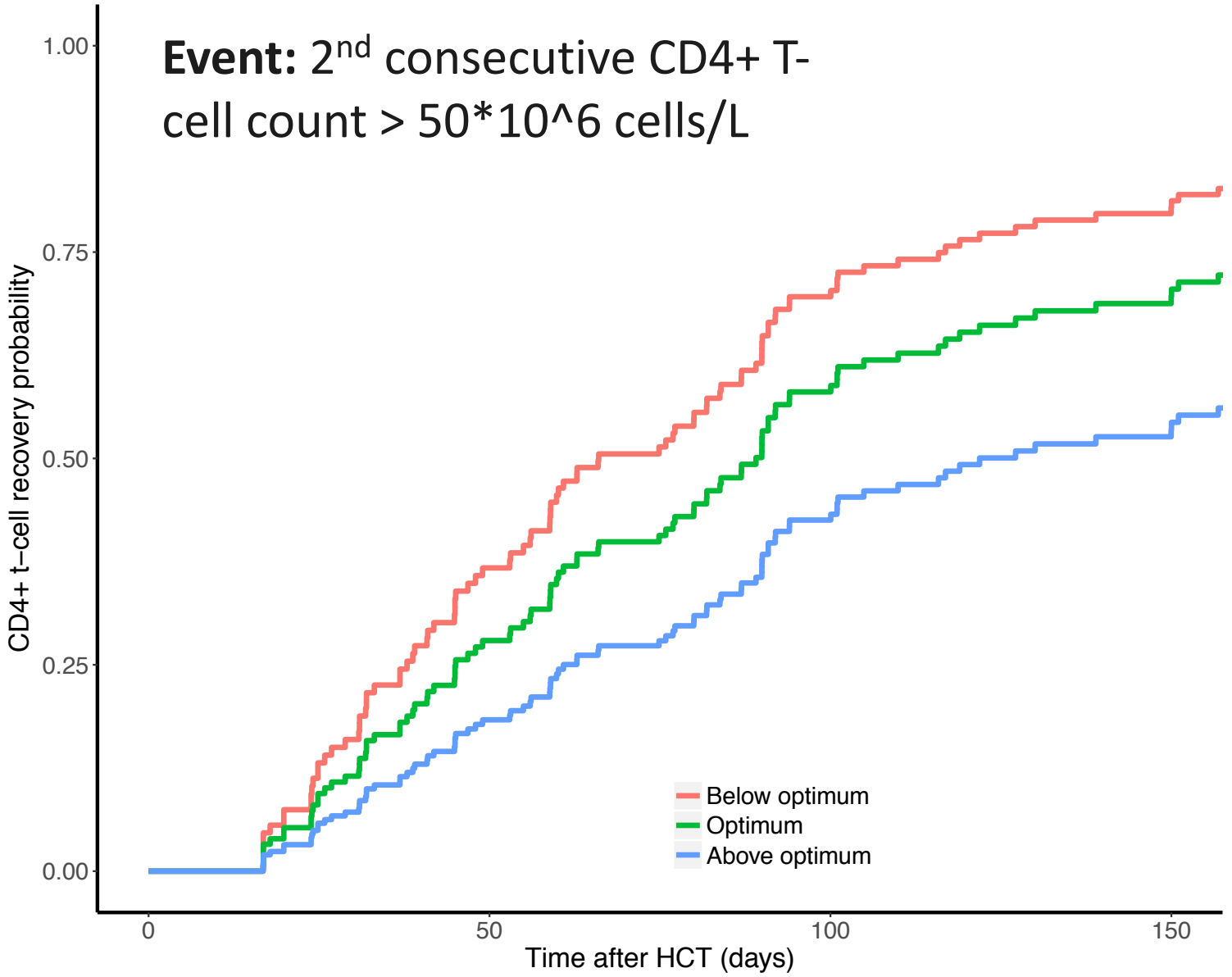
Events according to cut-offs: adjusted



Exposure outcome model II

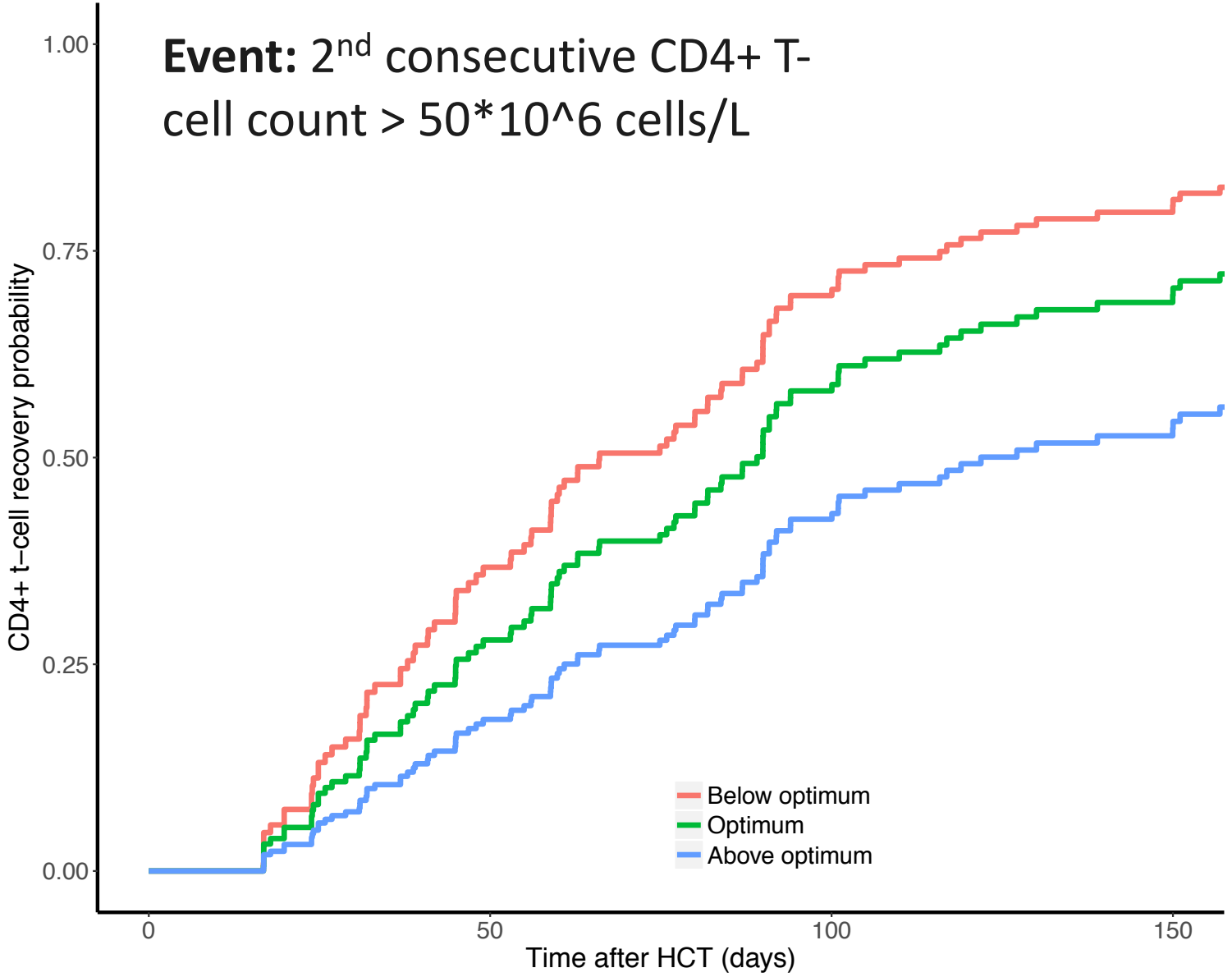


CD4 reconstitution: adjusted



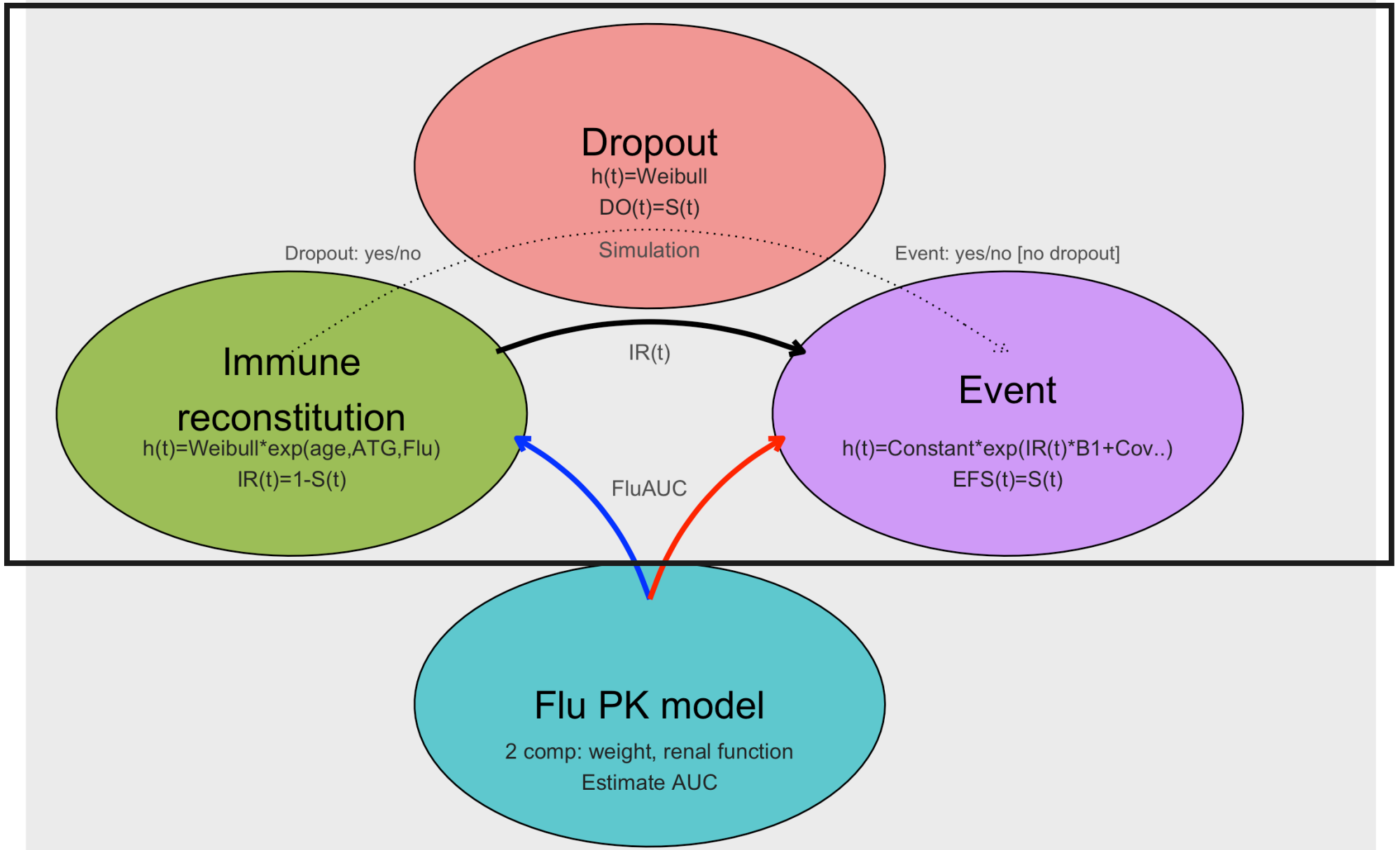
CD4 reconstitution: adjusted

Event: 2nd consecutive CD4+ T-cell count > 50*10^6 cells/L



Parameter	Hazard ratio	P-value (deletion)
Flu AUC (lin: 0-max)	0.11	<0.001
ATG postTx-AUC (lin: 0-max)	0.047	<0.001
Age$^{\theta}$	-0.19=θ	<0.001

Exposure outcome model III



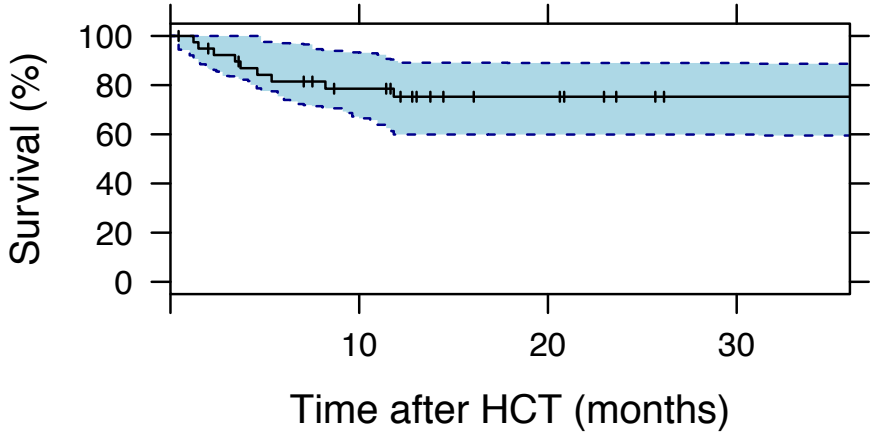
Parameter estimates

Parameter	Estimate	RSE	P-value
$Lambda_{tx\text{-}1year}$	0.0456	30%	
$Lambda_{1year\text{-}\infty}$	0.0049	70%	0.078
Immune Reconstitution probability (HR: 0-100%)	**0.68**	**104%**	**<0.001**
Optimum AUC (13-21 mg*h/l)	1		
Above optimum (>21 mg*h/l)	**1.9**	**42%**	**0.0082**
Below optimum (<13 mg*h/l)	**2.9**	**56%**	**0.12**
Leukemia / Lymphoma	1.00		
Benign	0.59	69%	0.051
MDS	1.4	98%	0.31
Multiple Myeloma	1.4	91%	0.34

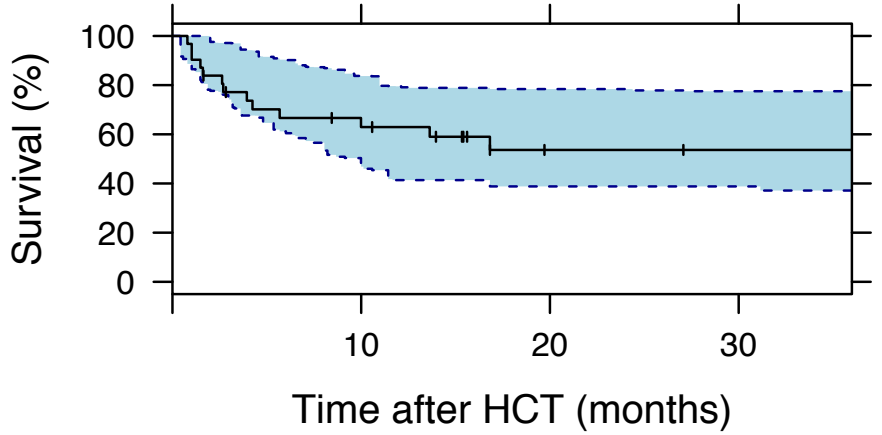
Model Evaluation

Visual predictive check

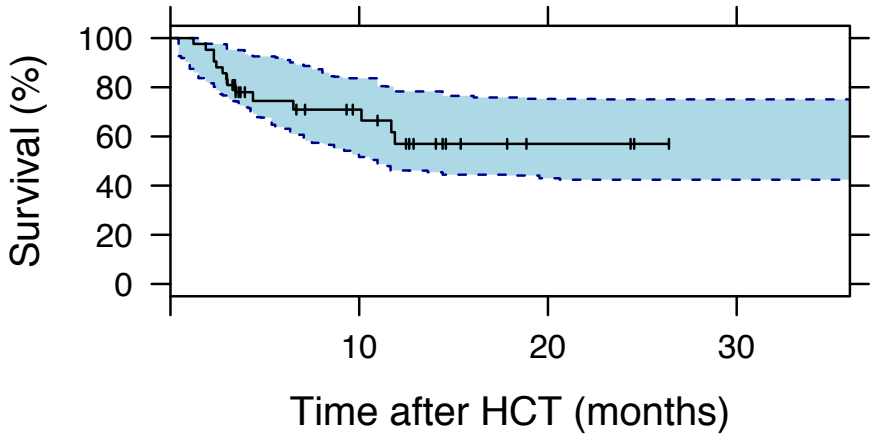
Children: inside target



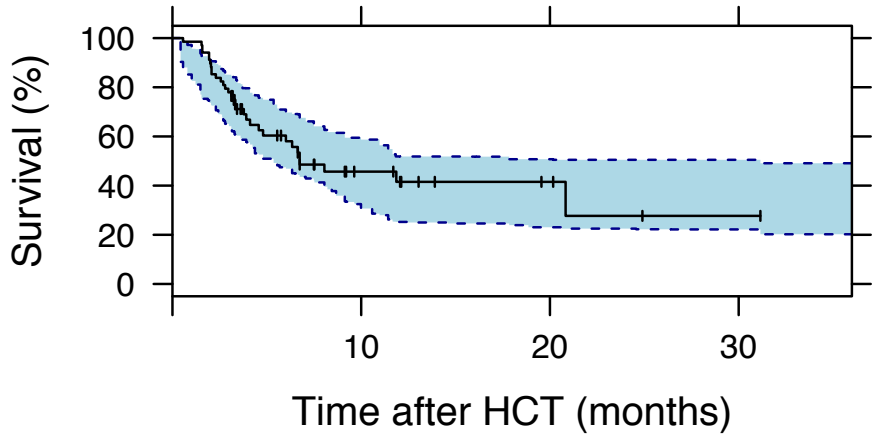
Children: outside target



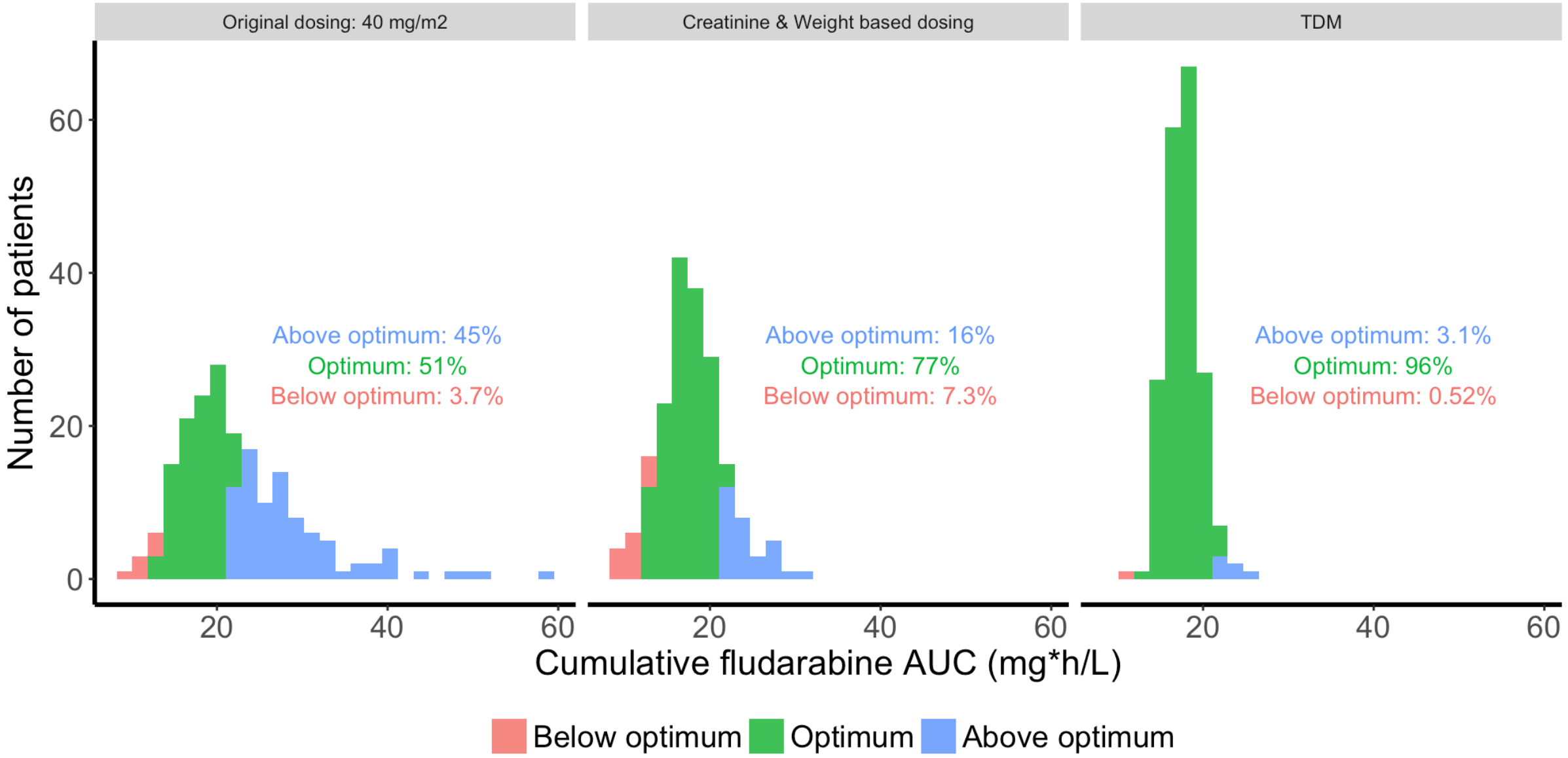
Adults: inside target



Adults: outside target



Alternative dosing regimen simulations



Summary

- We successfully derived a pharmacokinetic target for fludarabine at 17 mg*h/L (13-21) for all ages and indications
  - High fludarabine exposure is associated with higher mortality rate
  - Low fludarabine exposure is associated with failure of the treatment
  - Fludarabine exposure hampers immune recovery

- Faster immune recovery predicts for better survival

- Individualizing fludarabine exposure by better dosing and/or TDM could improve EFS after HCT

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