UMC Utrecht

Cause-specific hazard models with Markovian elements to quantify the fludarabine exposure-response relationship

from learning to confirming in allogeneic hematopoietic cell transplantation

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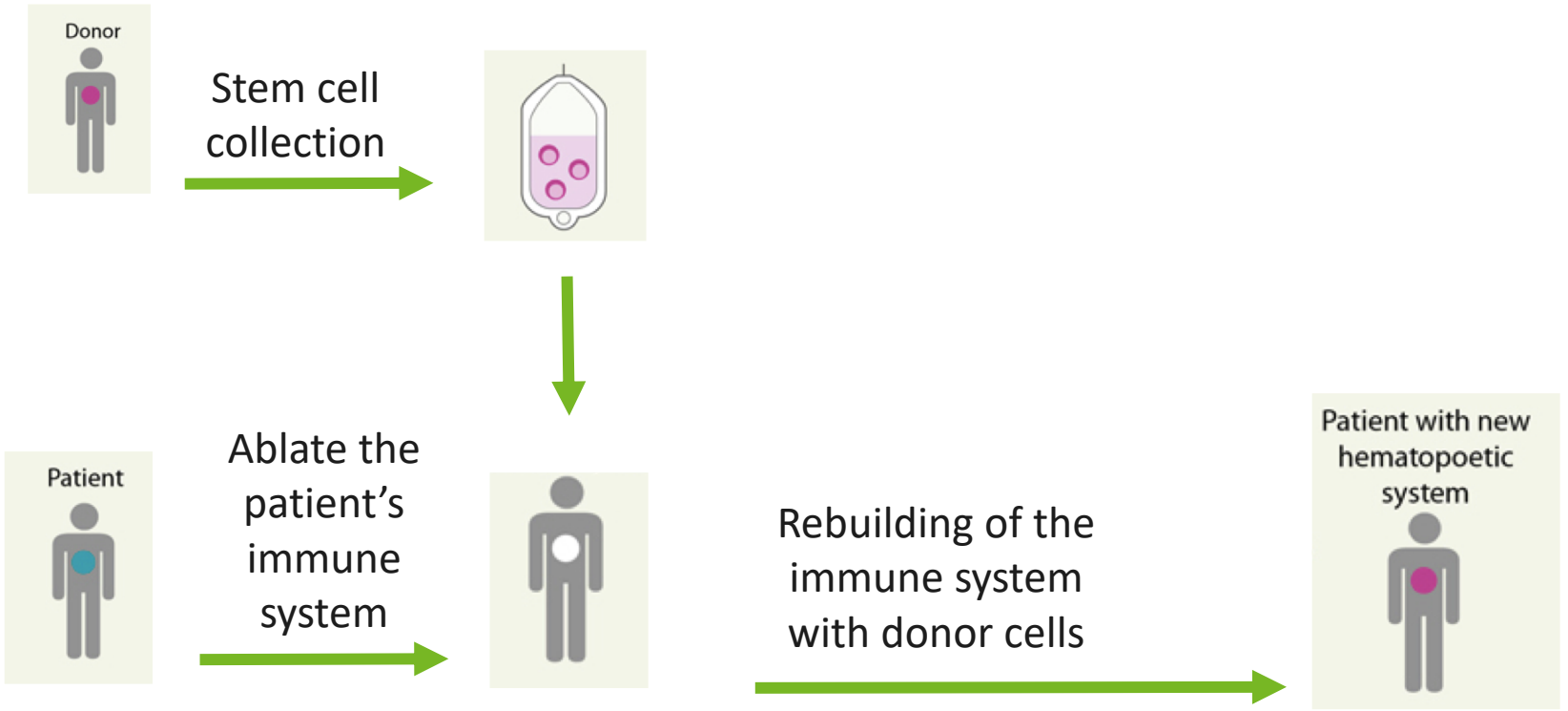
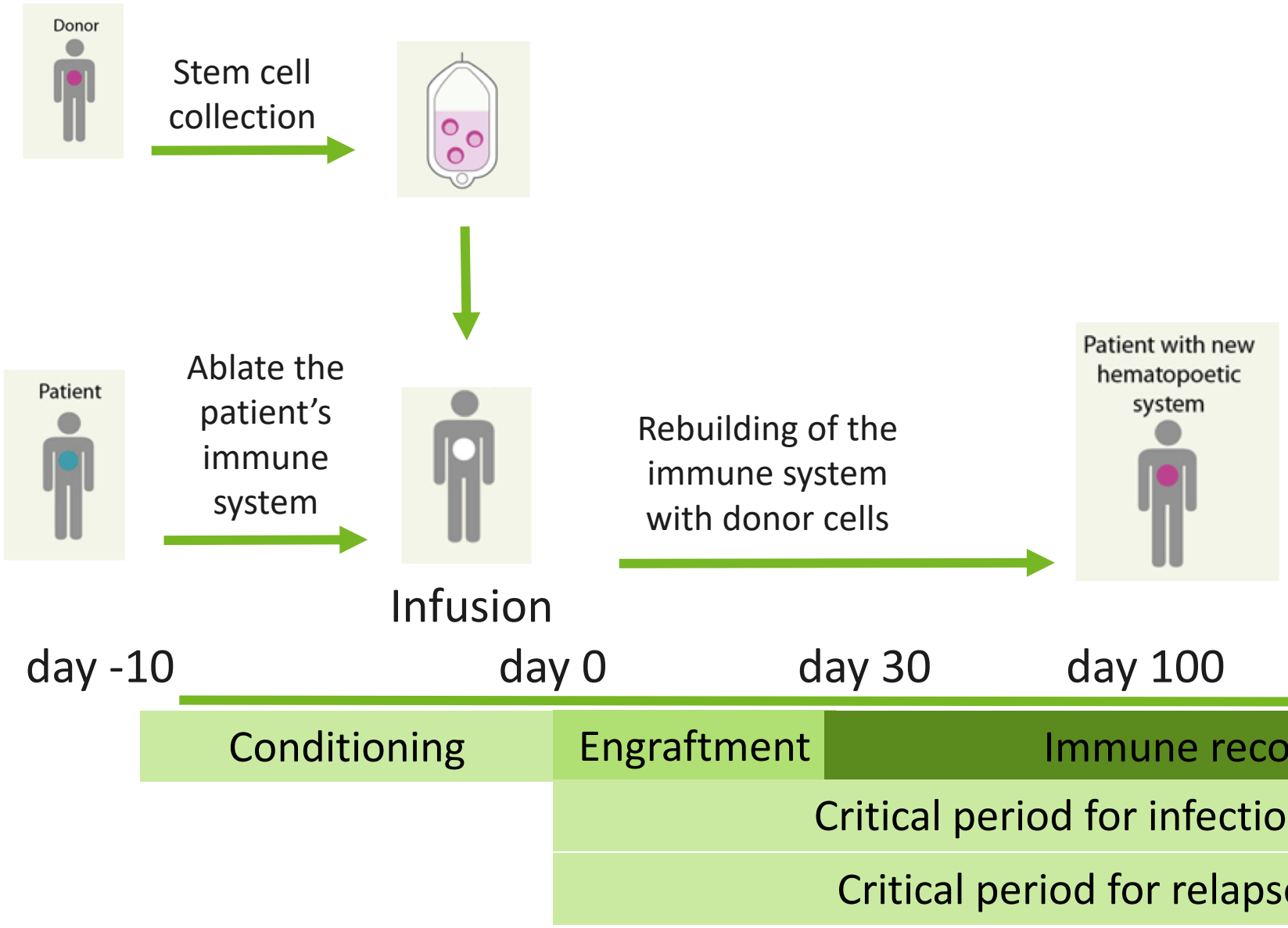
Allogeneic hematopoietic cell transplantation (HCT)



Indications:

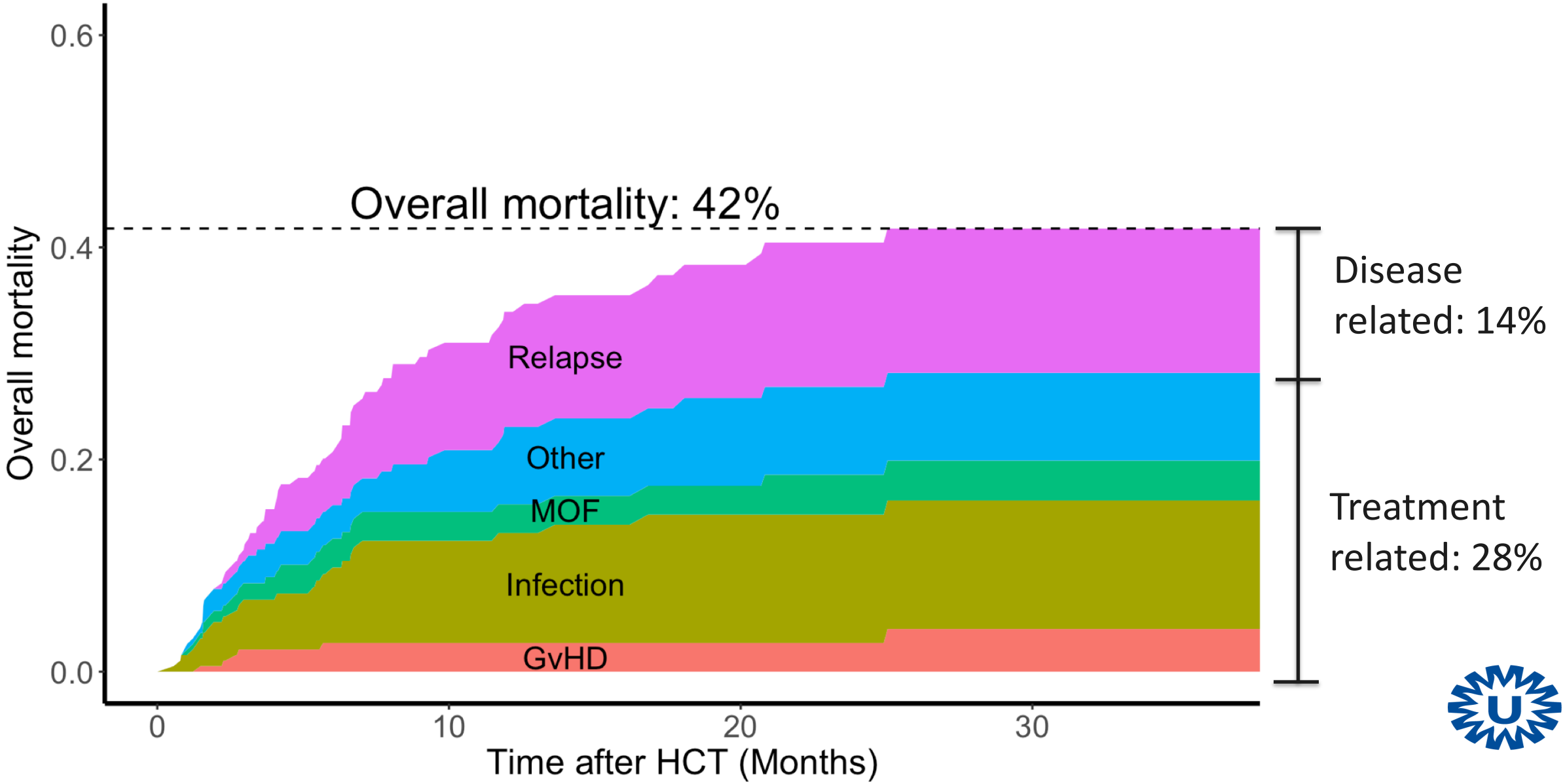
Malignancies
Immune deficiencies
Metabolic/inborn errors
Autoimmune disease
Bonemarrow failure

Allogeneic hematopoietic cell transplantation (HCT)



Allogeneic hematopoietic cell transplantation (HCT)

Clinical need: current HCT prospectives



ATG-FluBu as Standard Conditioning

Lympho-depletion	Bone marrow depletion	HCT

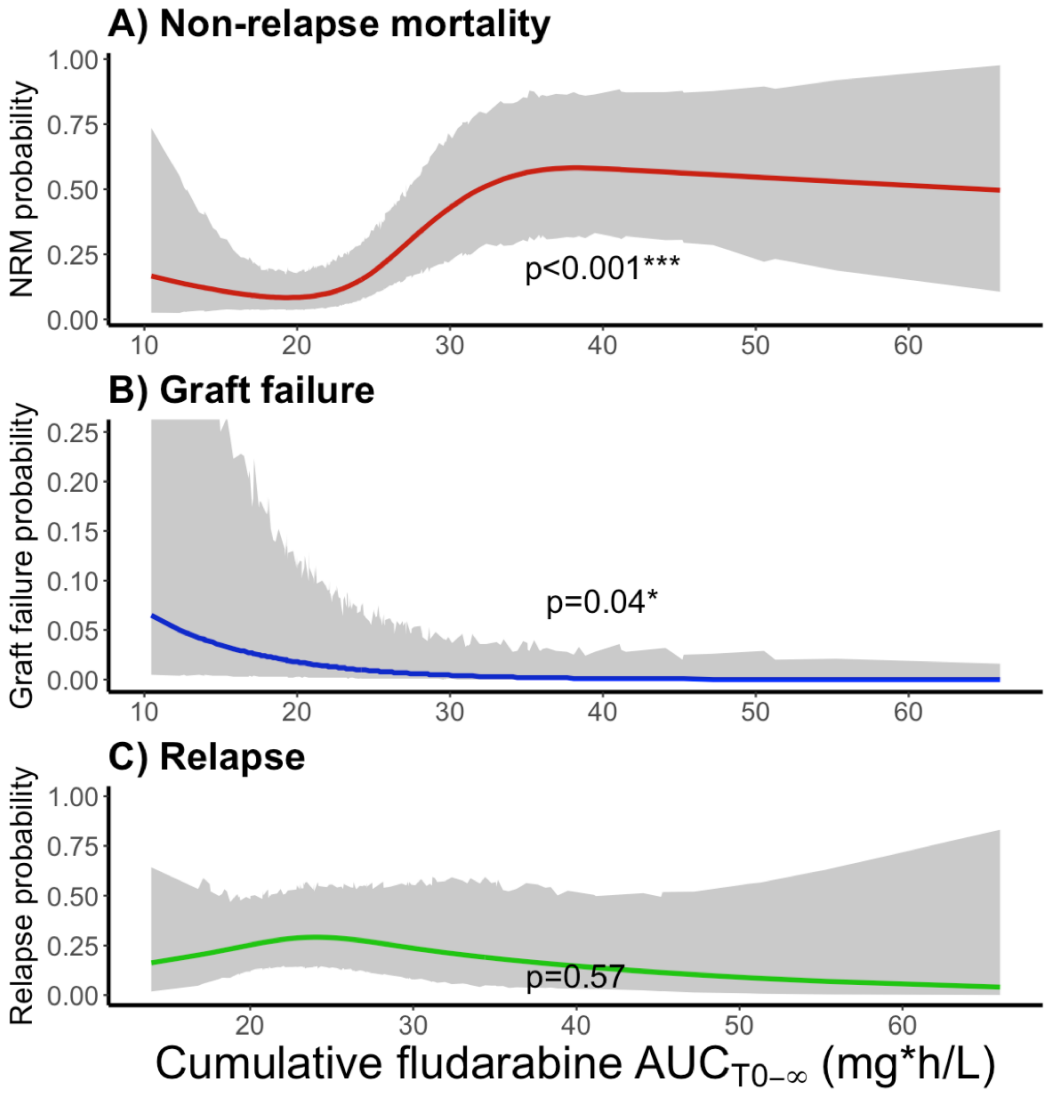
✓ **ATG:** targeted

✓ **Busulfan:** targeted

× **Fludarabine?**
- ❖ **160 mg/m2**

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

Effect of fludarabine exposure on events

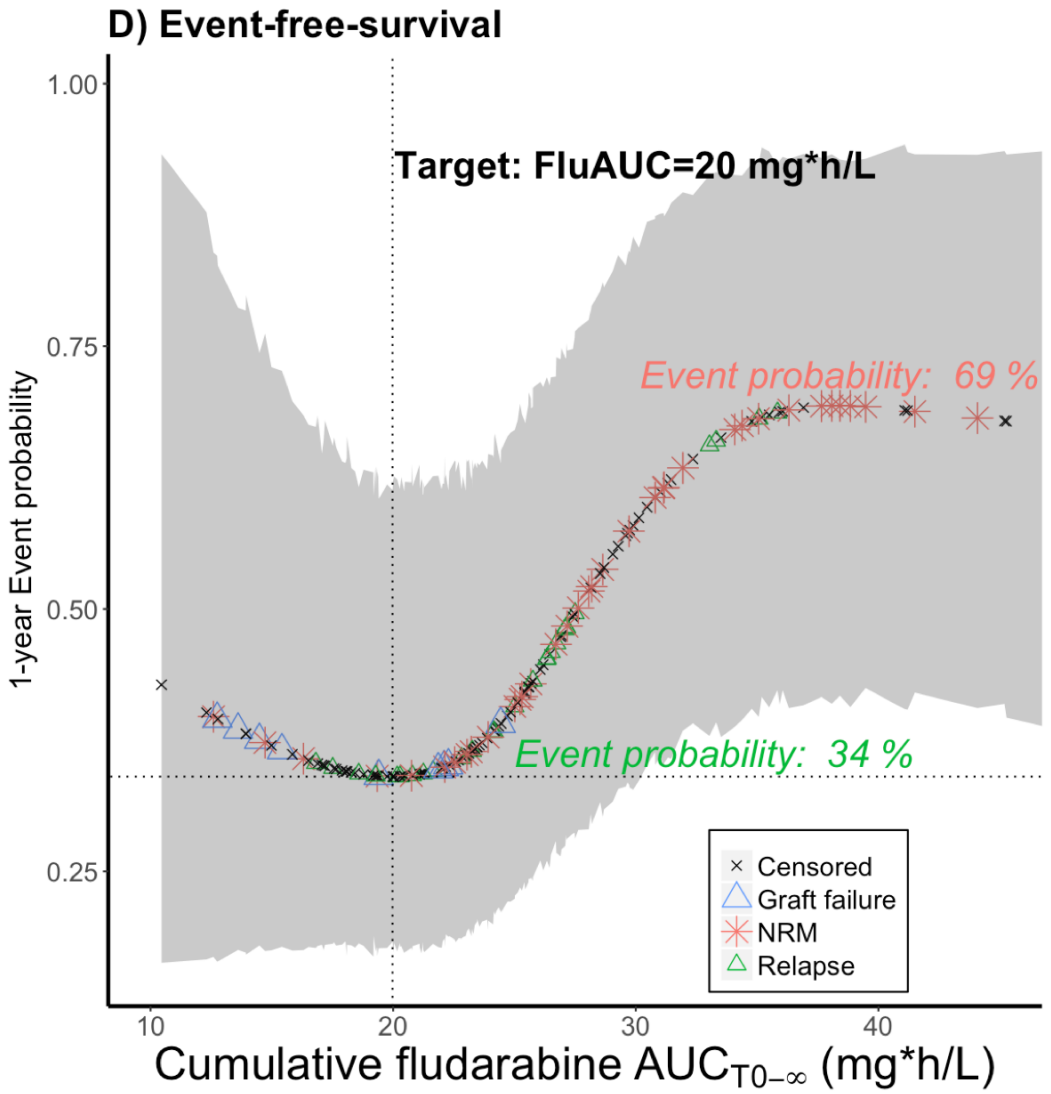


Increased NRM at AUC>20 mg*h/L

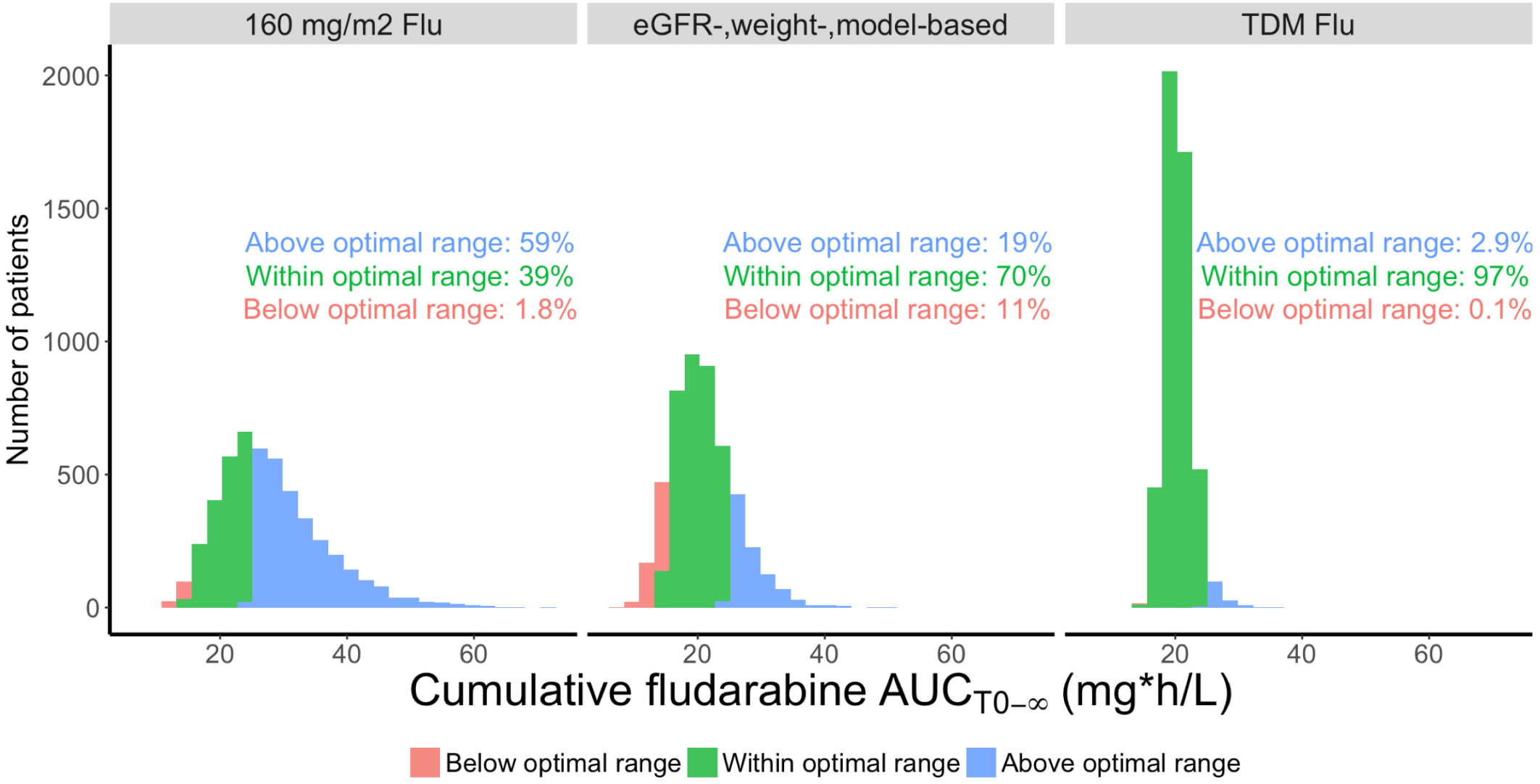
Lower AUC -> More graft failures

No relationship with relapse

Effect of fludarabine exposure on events



Alternative dosing regimens



What's next: *can we implement these findings?*

Retrospective study

- Risk for bias: are we missing a confounder?
- Not all clinicians are convinced: converting non-believers

✓ **Possible major gains**

- Preventing unnecessary over-exposure with current dosing regimen
- Omitting part of the toxicity of current dosing

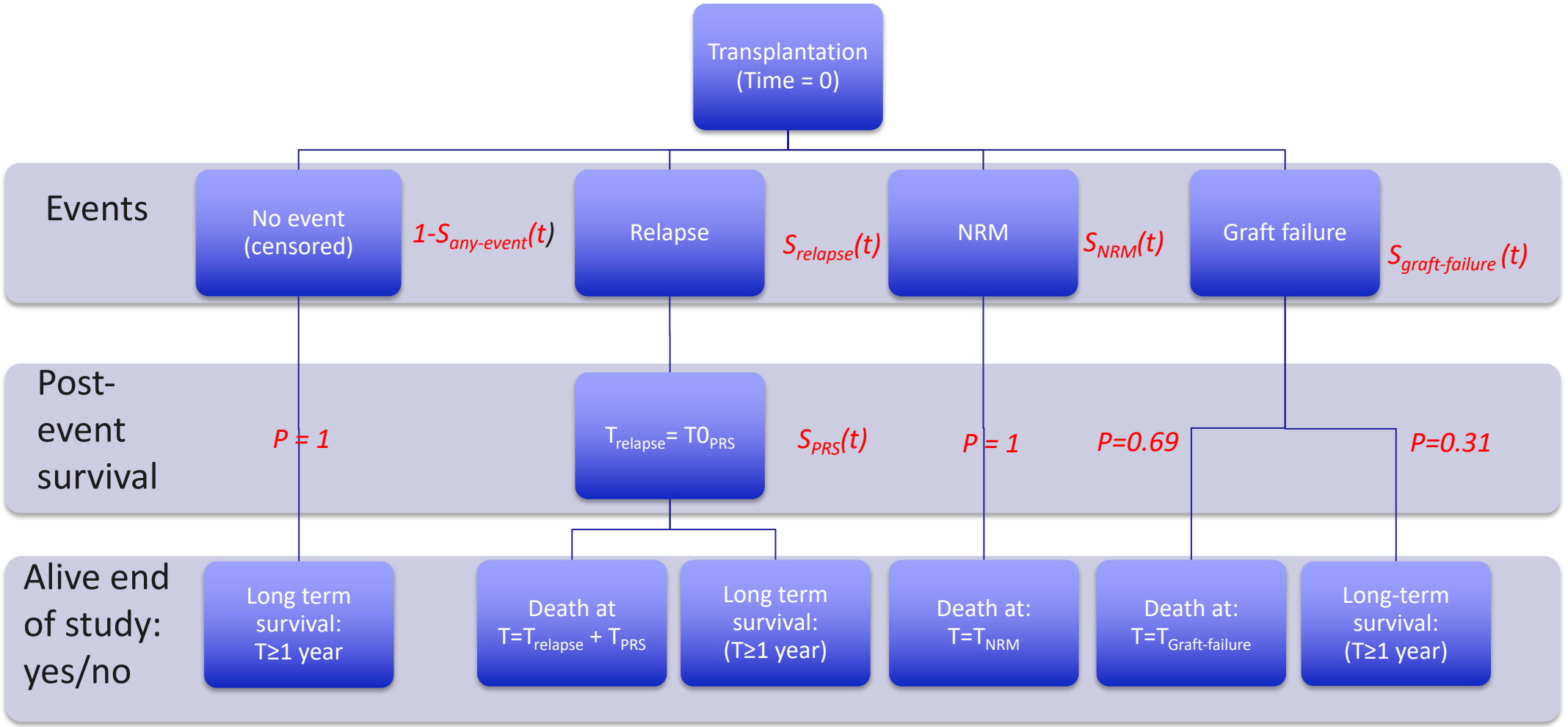
- **How could we test this prospectively in a randomized controlled trial?**

  - Aim: **optimize trial size** & **estimate expected results**
  - Simulations of RCT:

    Current dosing ~ Model-based dosing

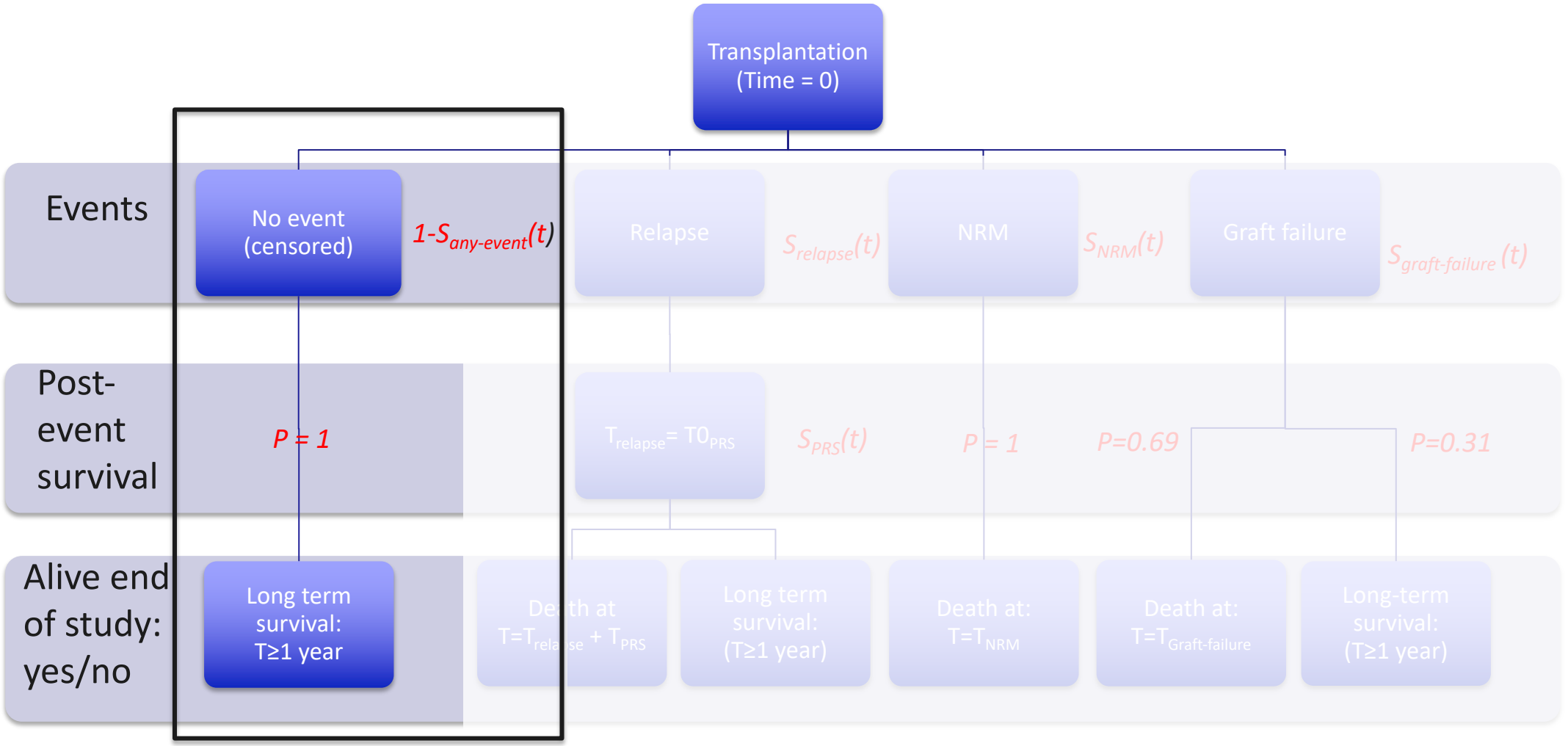
    Current dosing ~ TDM

Survival simulation model



- *PRS = post-relapse survival*
- *NRM = Non-relapse mortality*

Survival simulation model



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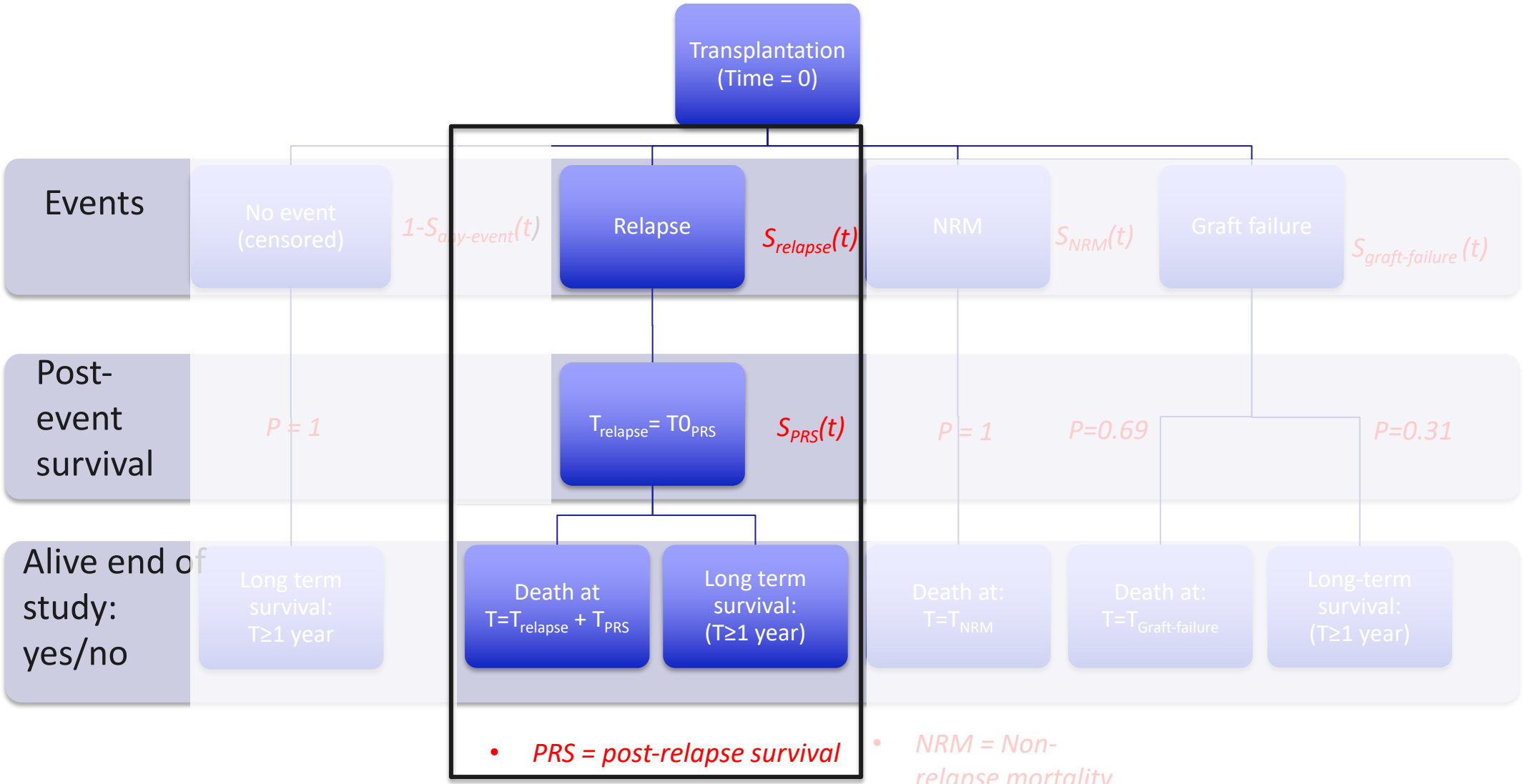
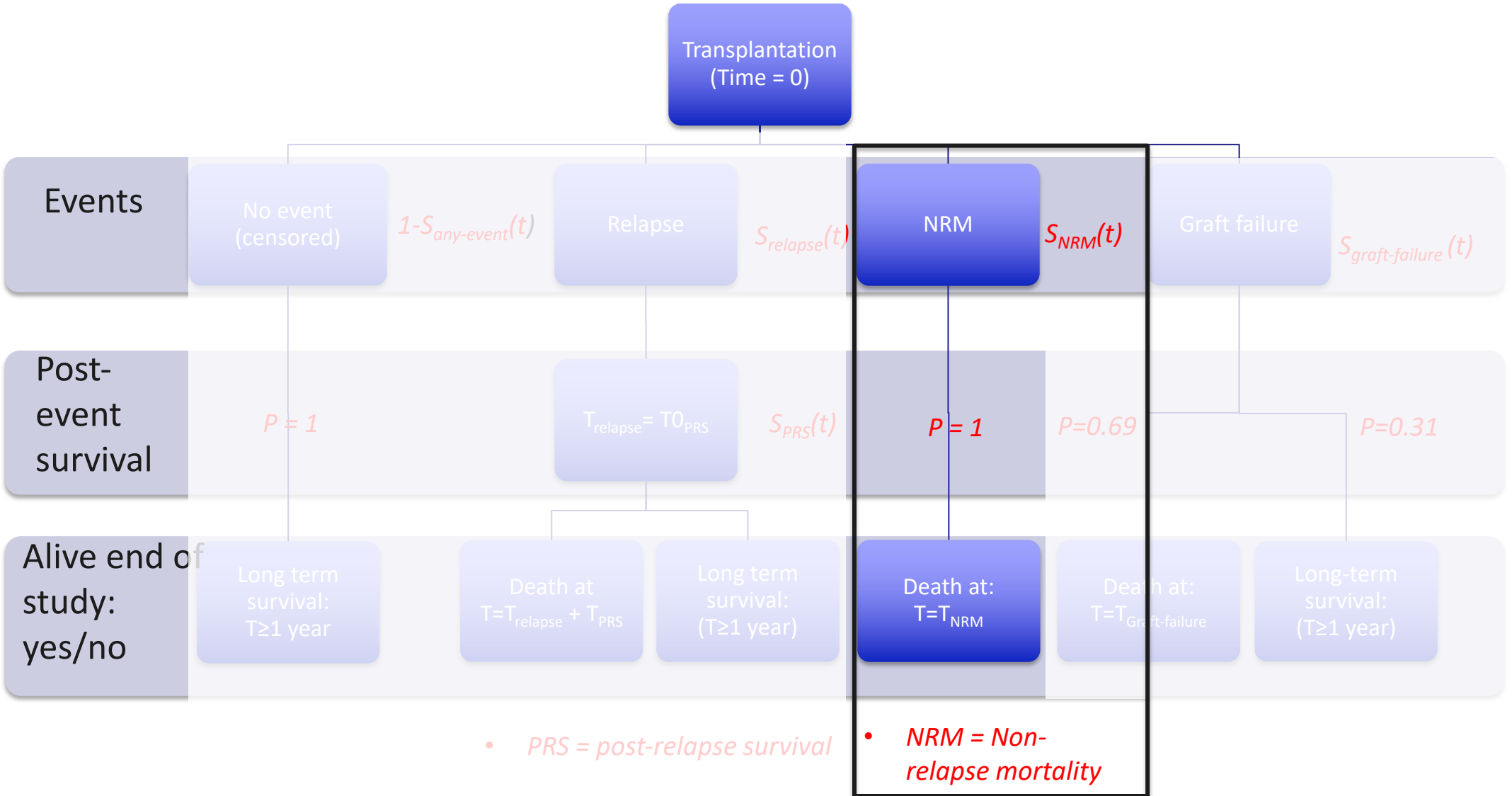
Survival simulation model



Survival simulation model



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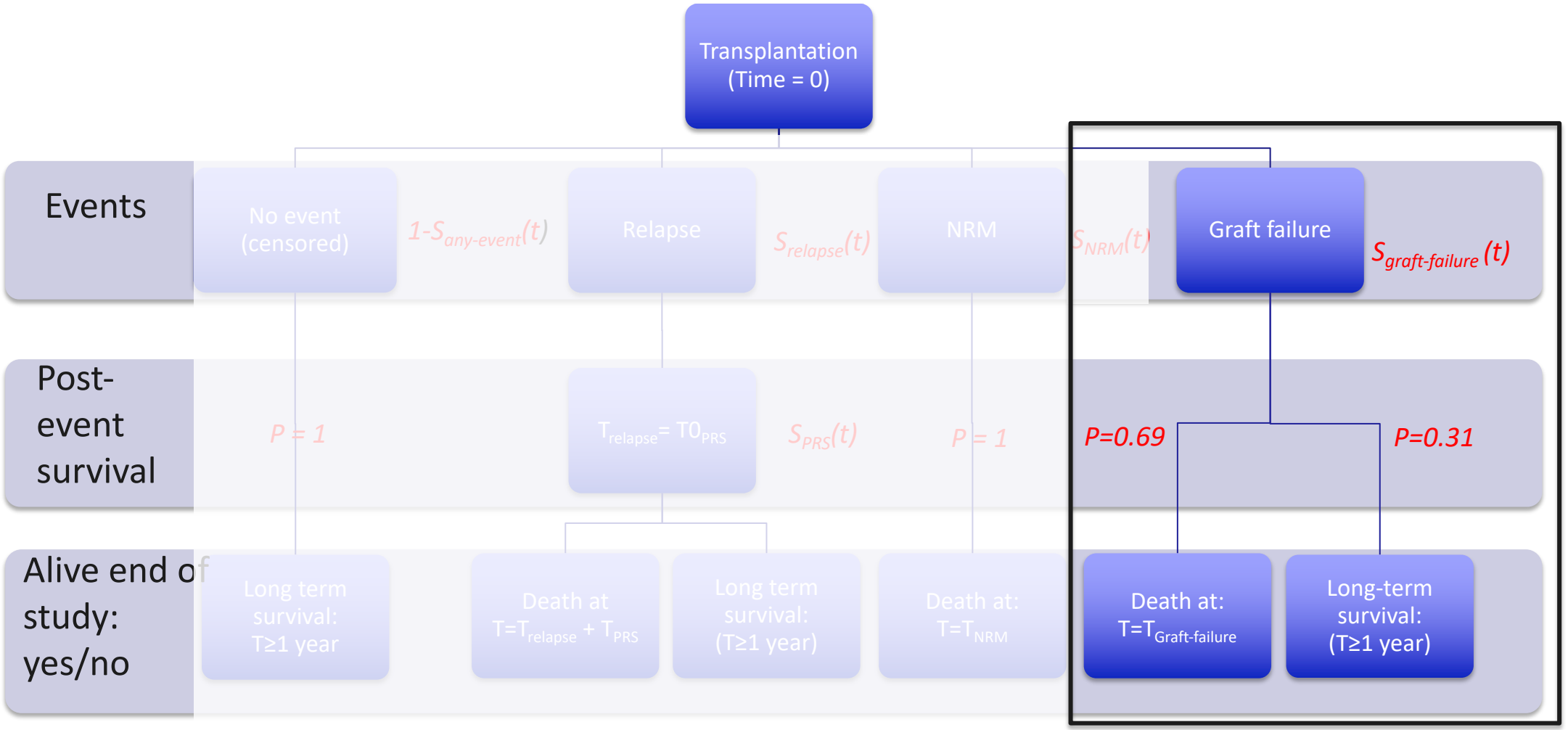

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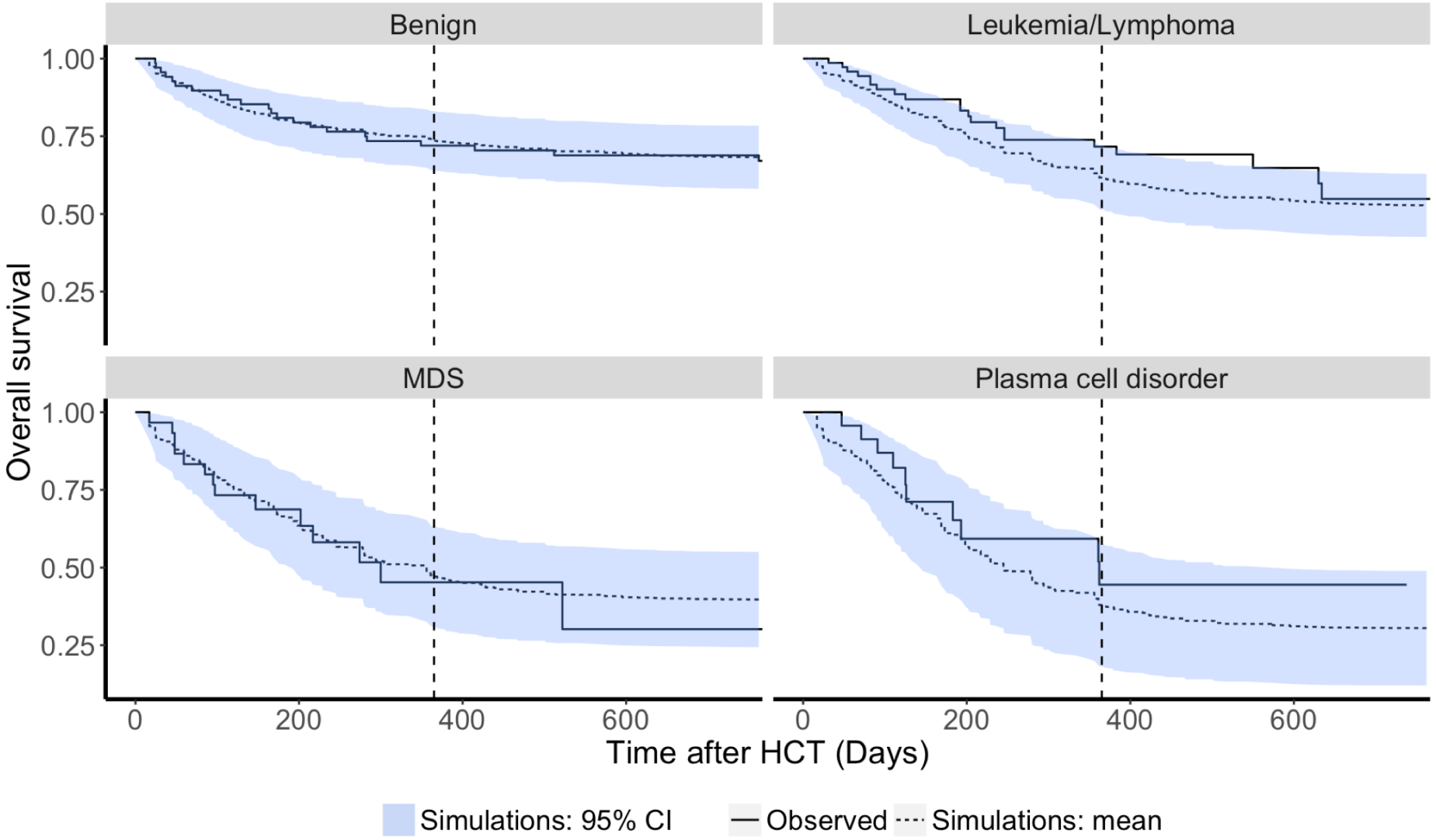
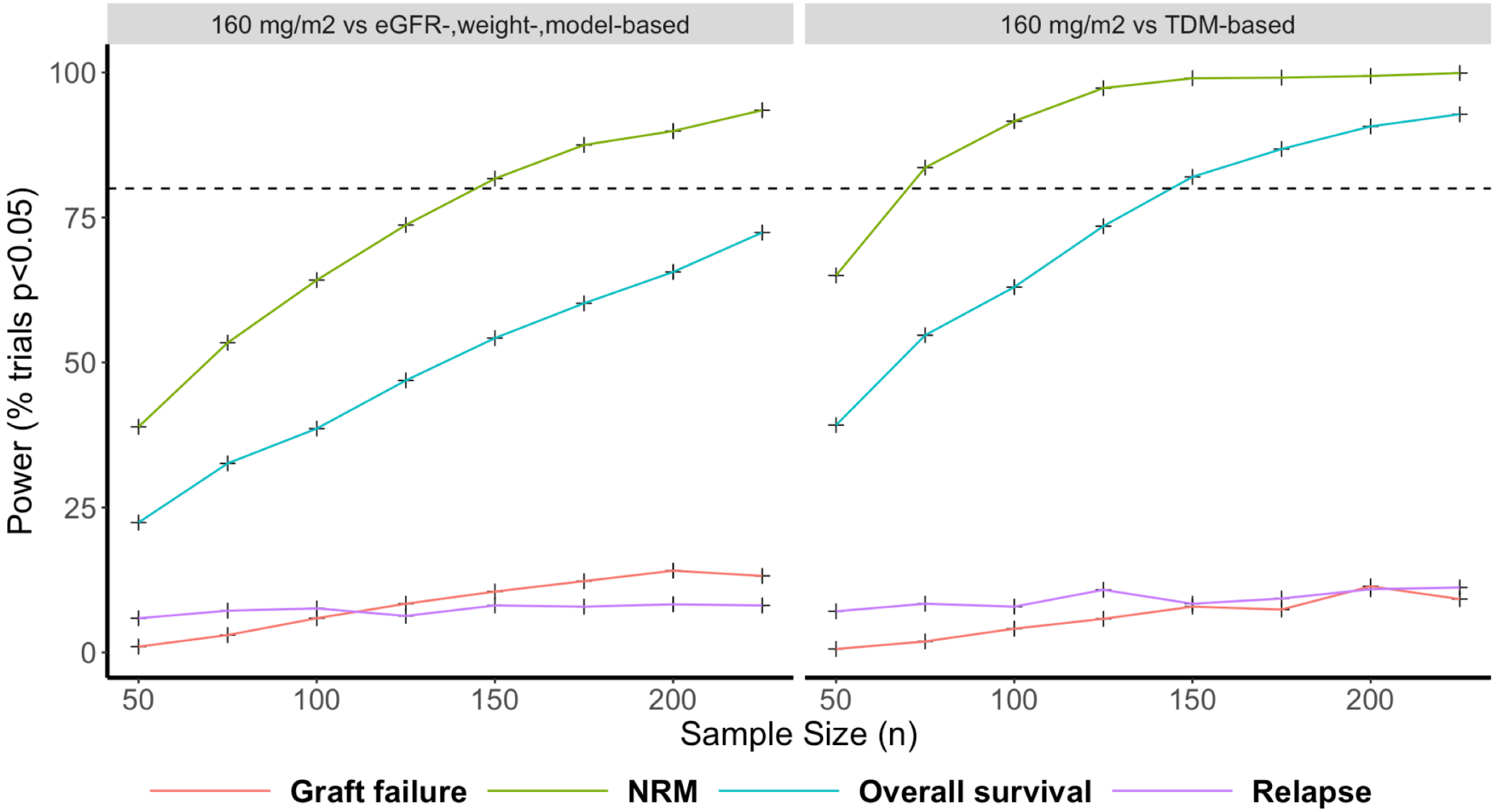
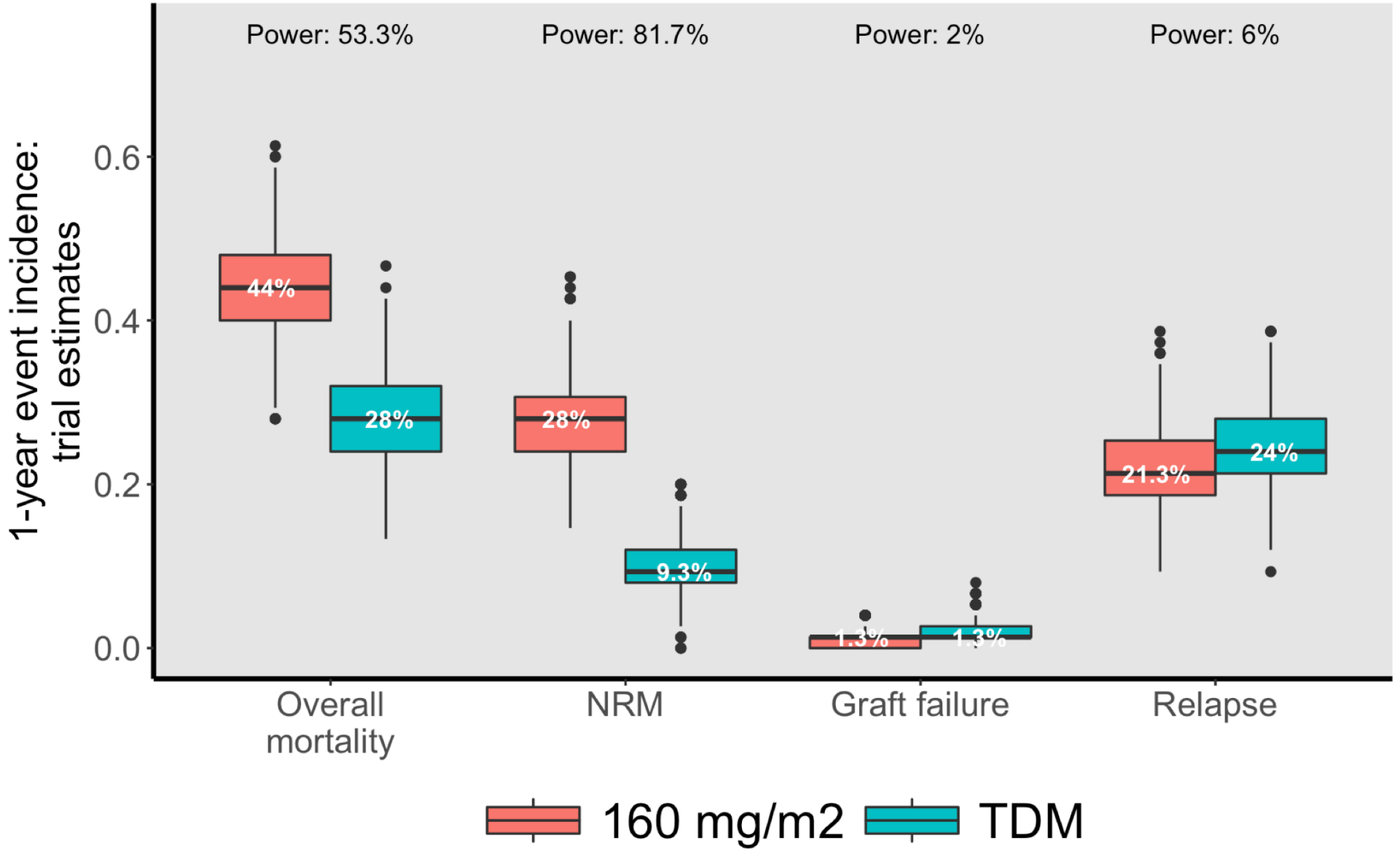
Visual predictive check: *full simulation model*



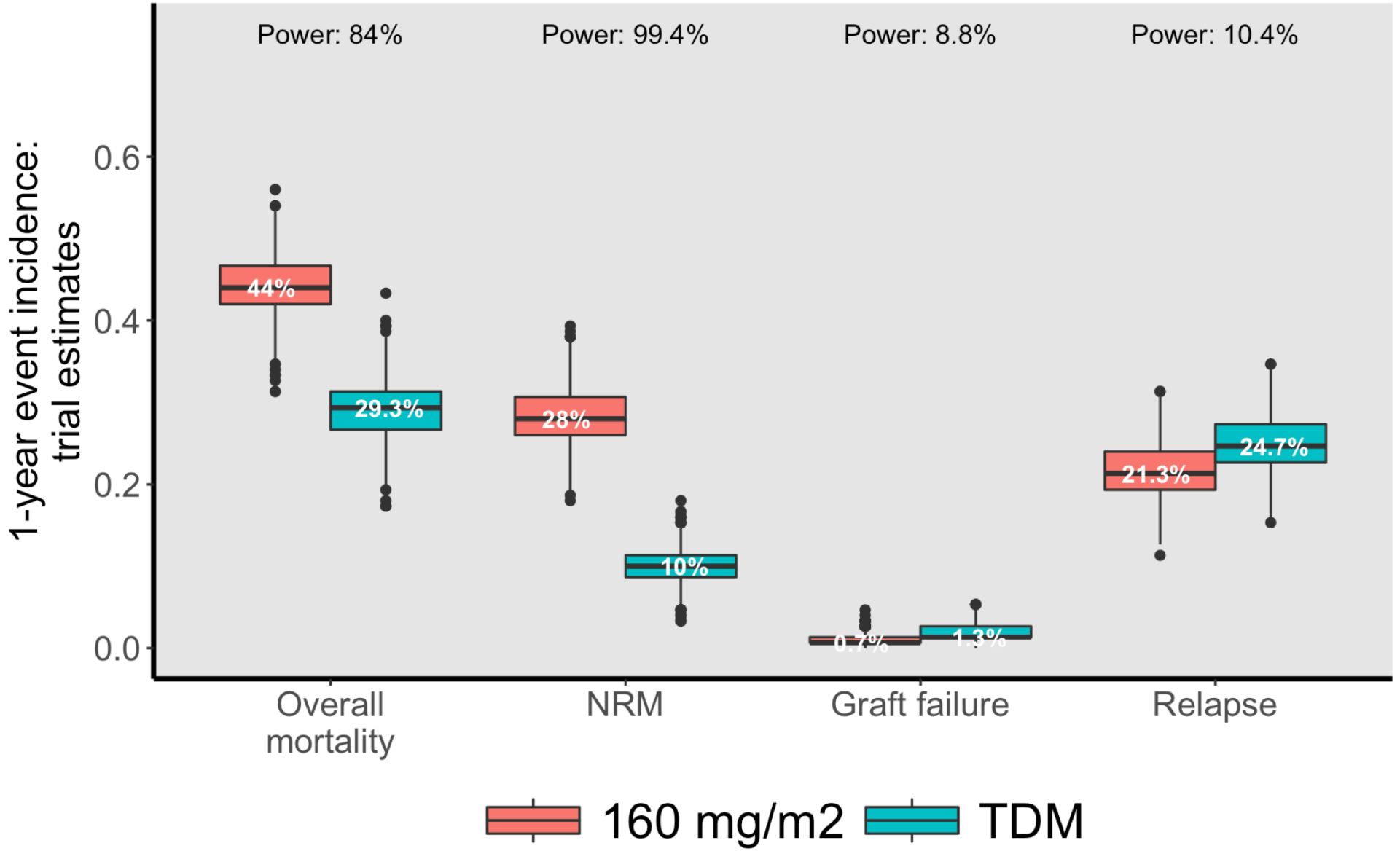
Sample size optimization



Optimal trials (1): *NRM primary end-point, N=75 each arm*



Optimal trials (2): *OS primary end-point, N=150 each arm*



Sensitivity analysis: testing uncertainty of assumptions

- Account for possible **failure of TDM** during the trial:
  - Arbitrary 90% success-rate of TDM
  - Remaining 10% get model-based dosing

- Take into account the **uncertainty** in the **fludarabine~event** relationship:
  - What if NRM probability for high exposures (>20 mg*h/L) is 10% lower than predicted
  - What if graft failure probability for low exposures (<20 mg*h/L) is 10% higher than predicted

Sensitivity analysis: results

	OS-trial (N=150 per arm)		**NRM-trial (N=75 per arm)**	
	Original power	Adjusted power	Original power	Adjusted power
TDM-failure	84%	81%	82%	79%
Model uncertainty: lower NRM effect		75%		81%
Model uncertainty: higher Graft failure effect		72%		83%

Summary

- Current simulation platform allows for simulation with various end-points (i.e. separate events, cumulative events, overall survival)
- To achieve sufficient power for a trial setting, TDM is recommended as individualized dosing arm with expected results being:
  - A decrease of NRM probability (from 28% to 10%)
  - Comparable graft failure (~1-2%)
  - An increase in relapse probability (from 21 to 24%)
  - ➢ Overall survival probability increase from 56% to 71%
- Overall survival as and end-point best reflects the overall benefit
- NRM necessitates half the patients for similar power and is less sensitive to survival model uncertainties

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