

Development of efficient CAR-T cell clinical study designs: Towards understanding of novel anticancer therapies through optimal experimental design

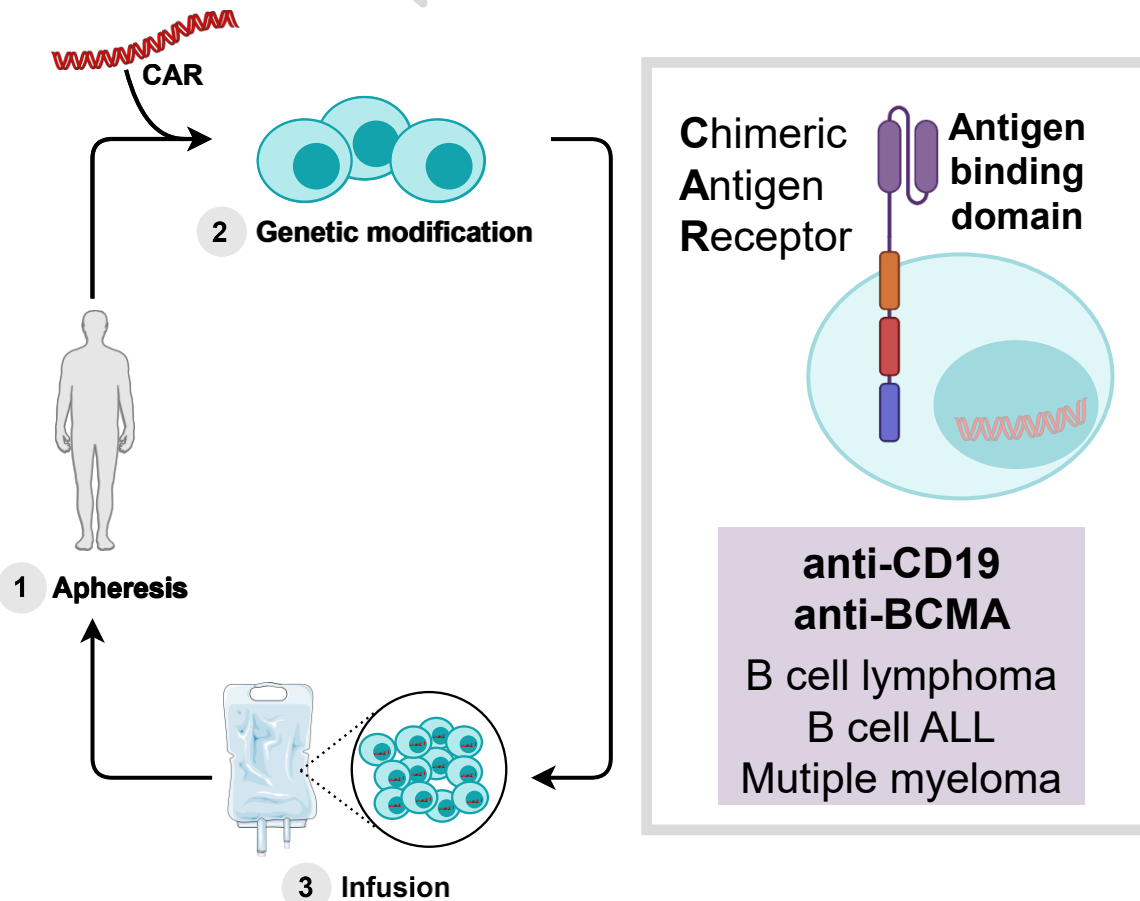
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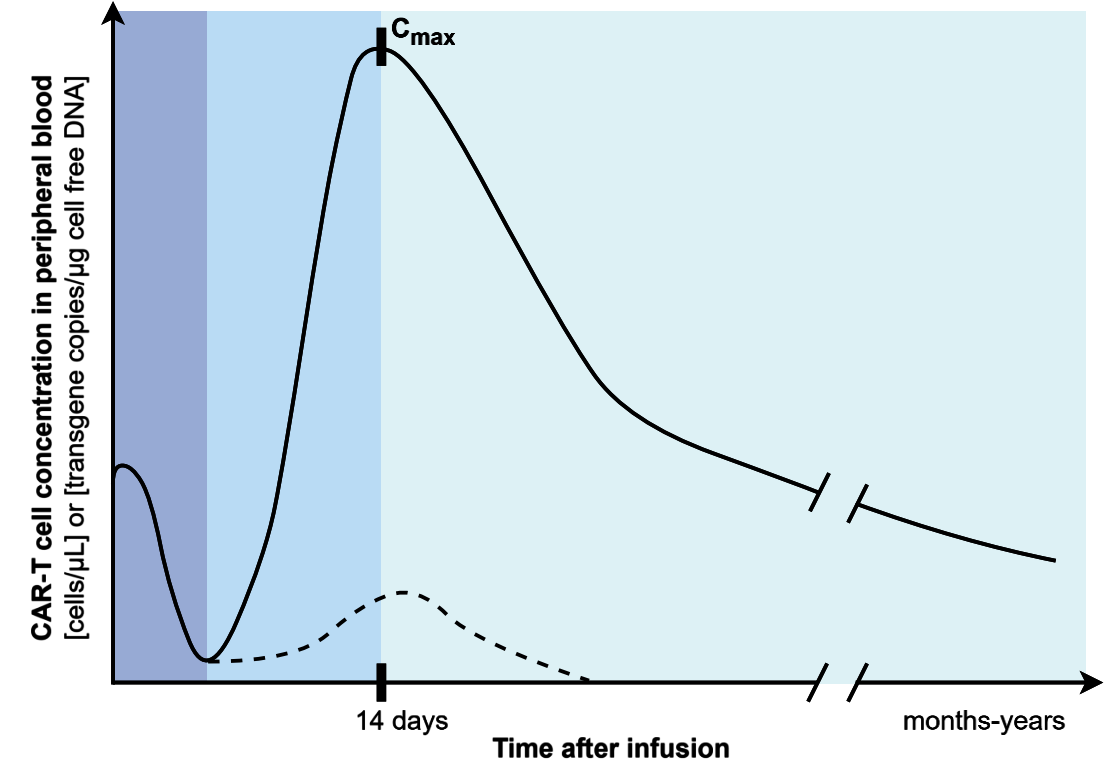
33rd PAGE meeting in Thessaloniki
05 June 2025

CAR-T cells are a promising treatment option – for some

Improved overall survival ← 40-60% of patients without long-term response



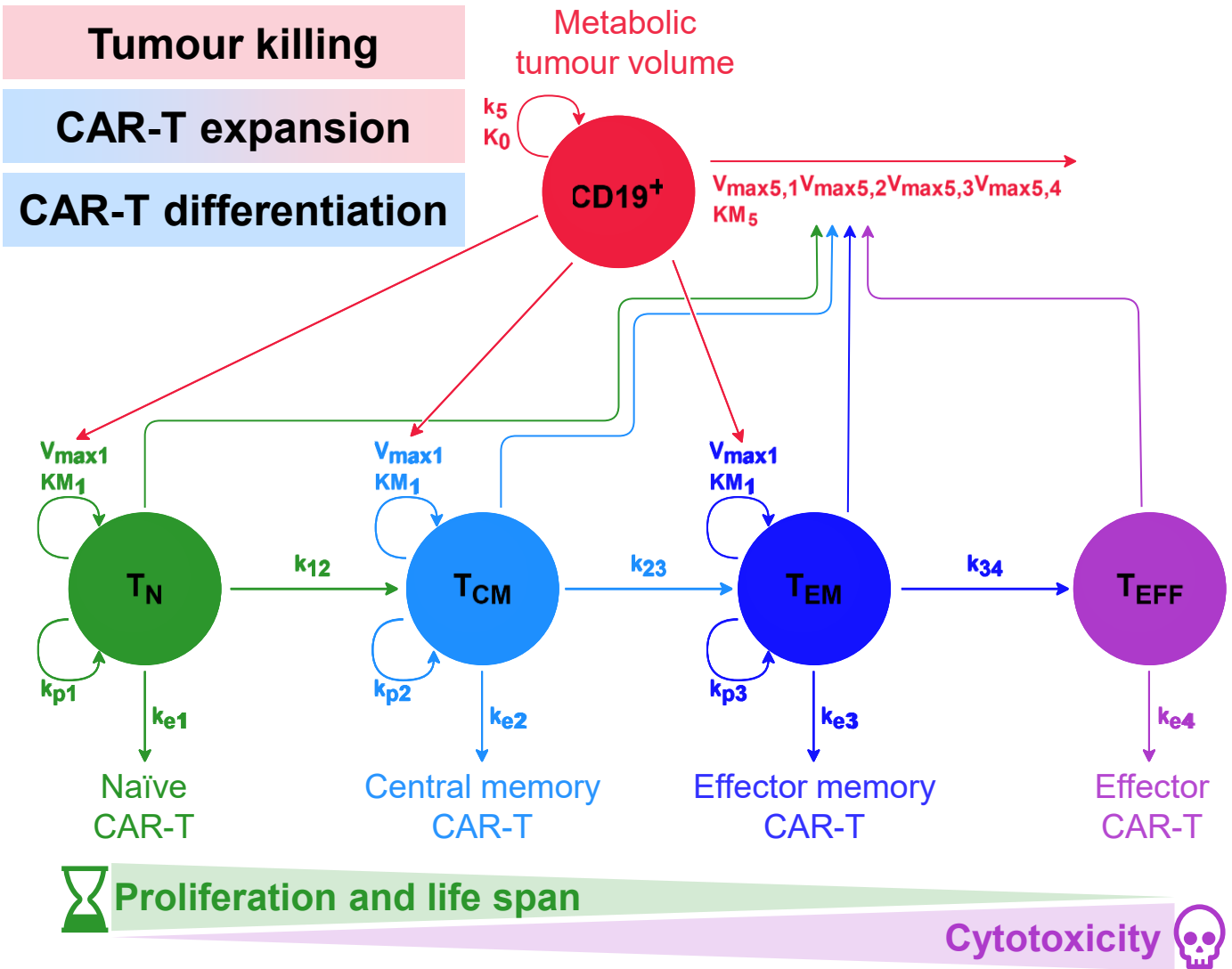
1 Distribution 2 Expansion 3 Contraction



Expansion & persistence positively associated with outcome

Dose-exposure relationship unclear

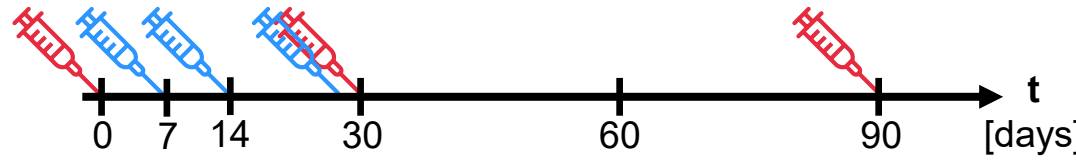
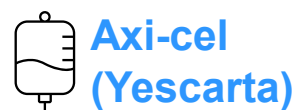
Mechanistic model of CAR-T kinetics & tumour dynamics



Mueller-Schoell et al. *Cancers* 2021



19 patients with non-Hodgkin lymphoma



Confirm model structure

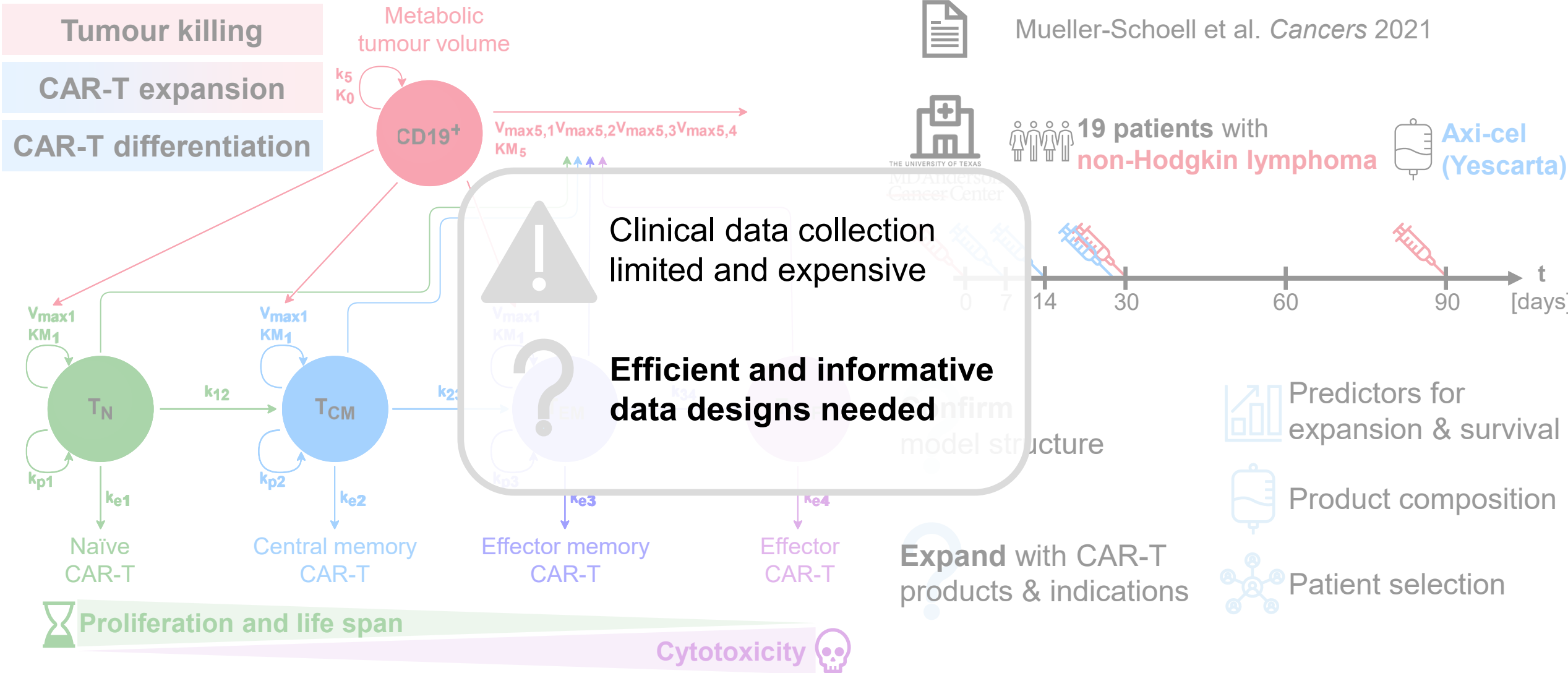
Predictors for expansion & survival

Product composition

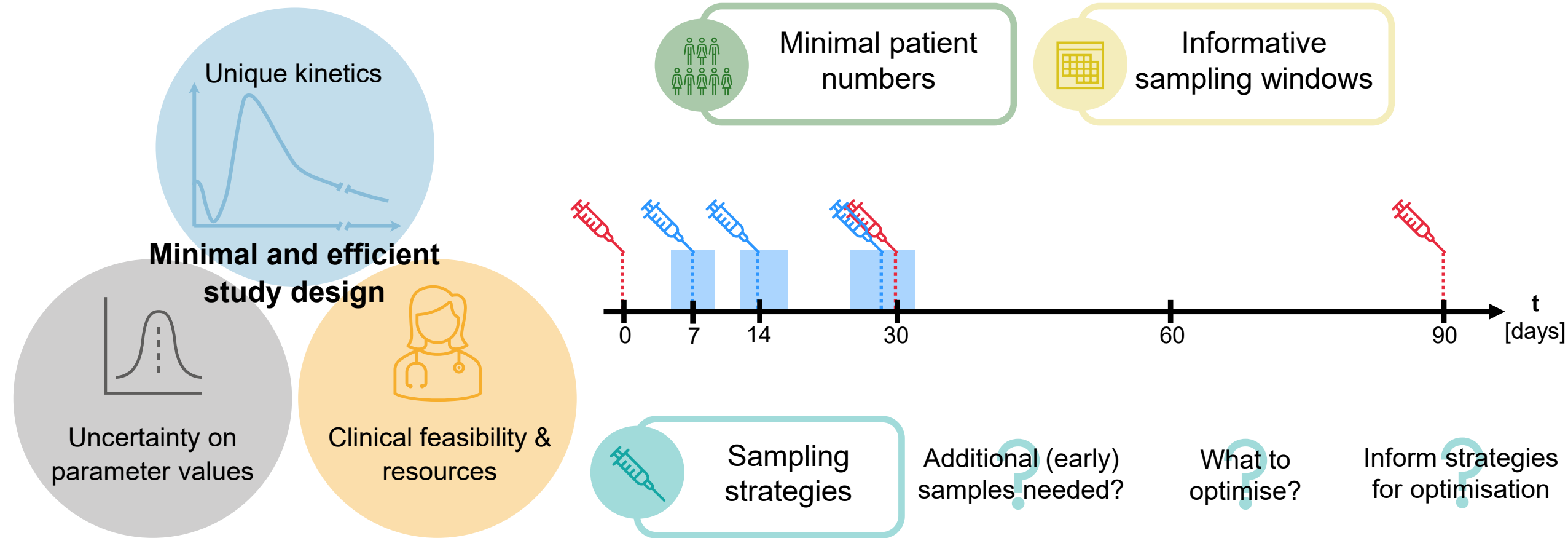
Expand with CAR-T products & indications

Patient selection

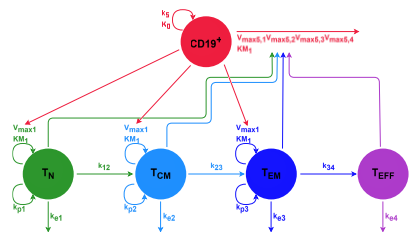
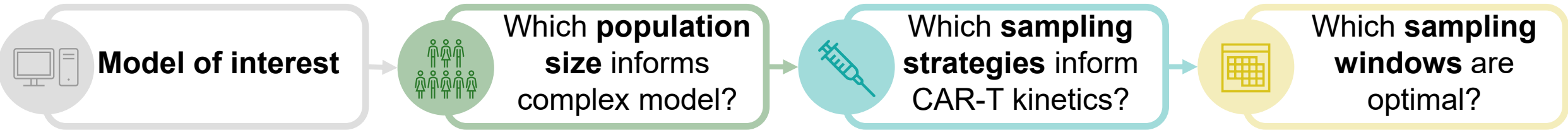
Mechanistic model of CAR-T kinetics & tumour dynamics



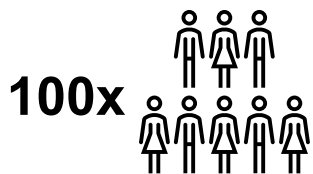
Efficient study design for clinical CAR-T cell data



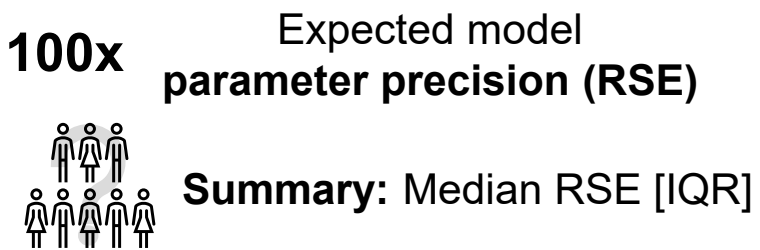
Optimal experimental design for CAR-T cell therapy



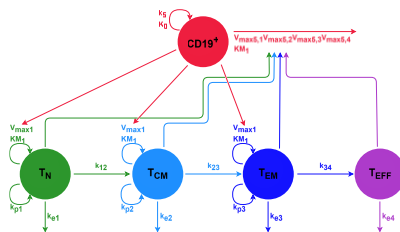
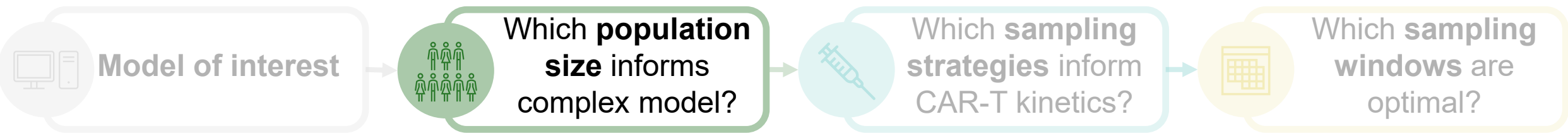
Set of model parameters



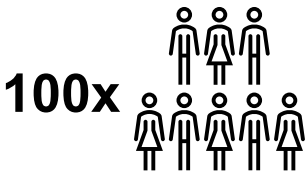
Approximation of **Fisher Information Matrix**



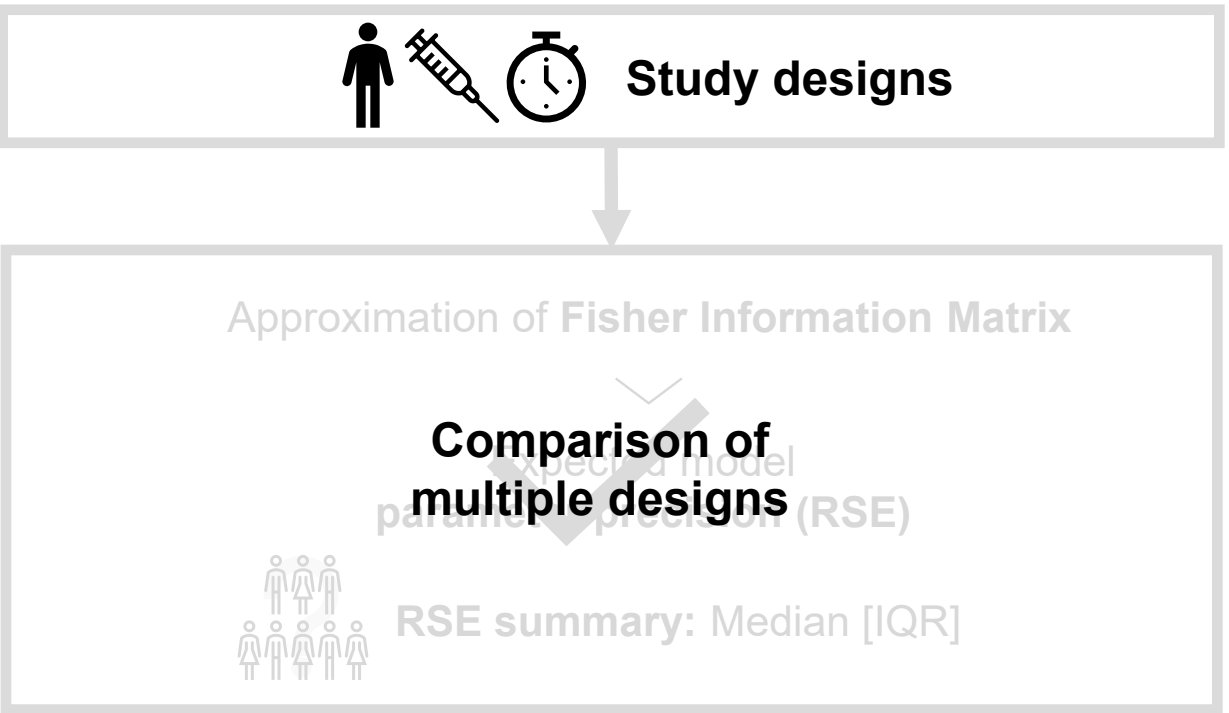
Identification of informative population size



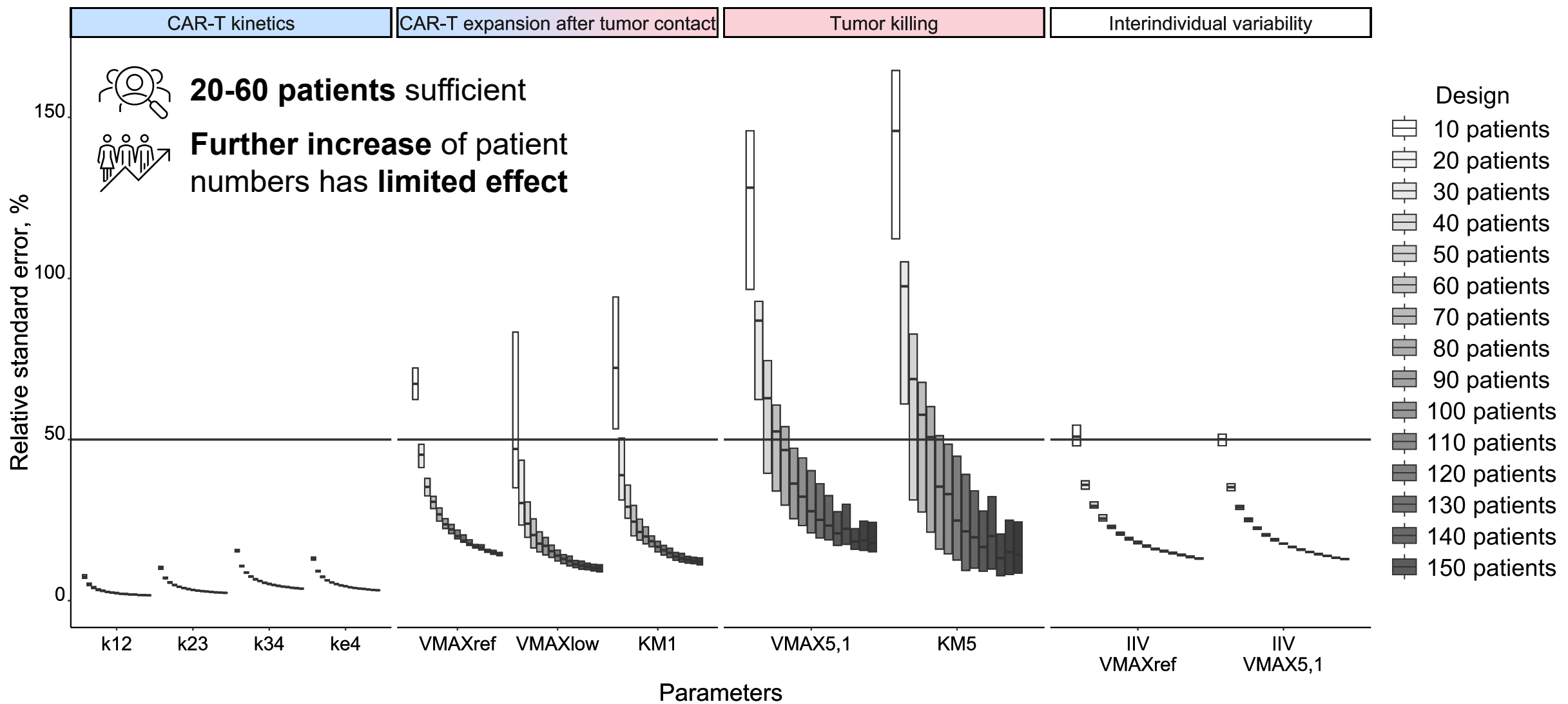
Set of model parameters



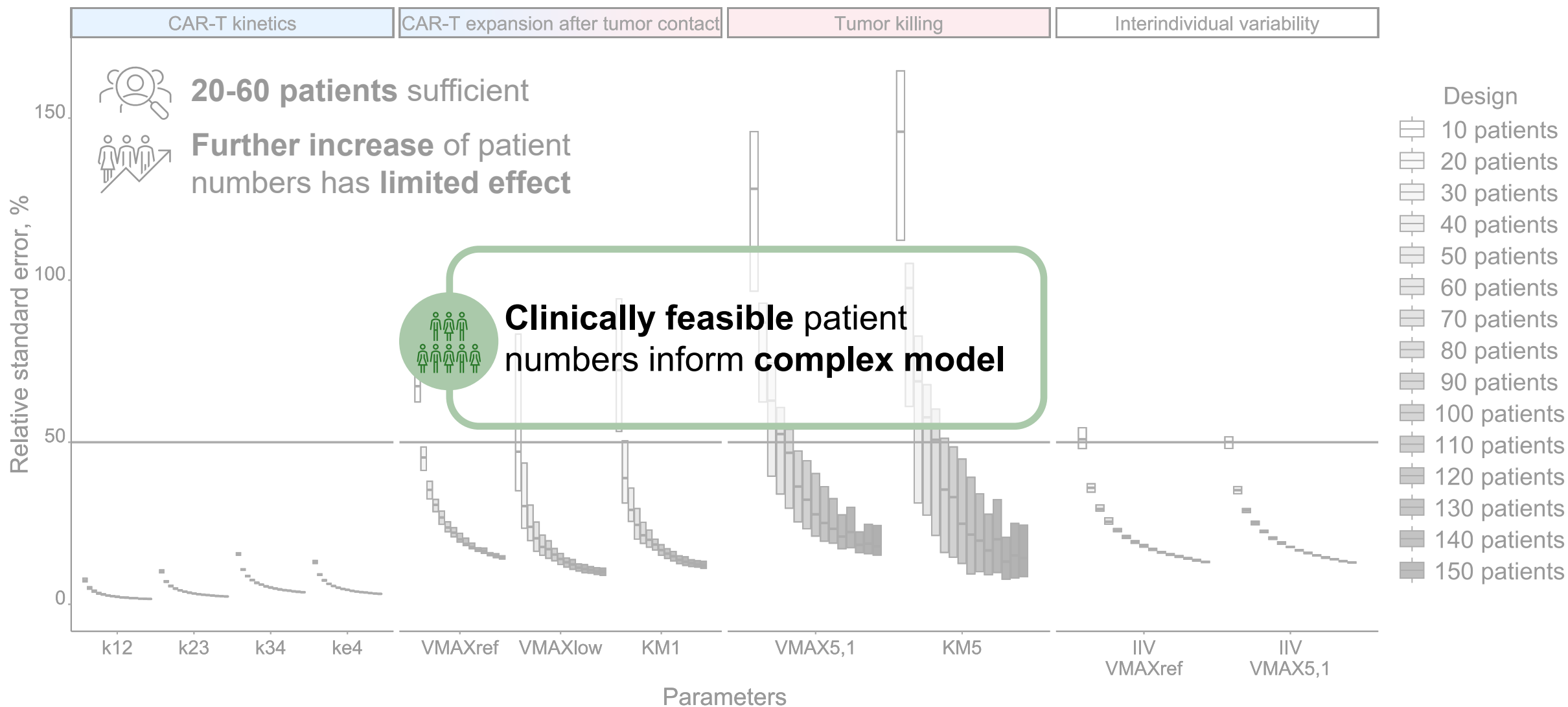
Simulated input variables (initial tumour burden)



Complex model can be informed with realistic population size



Complex model can be informed with realistic population size



Exploring CAR-T and tumour sampling strategies



Model of interest



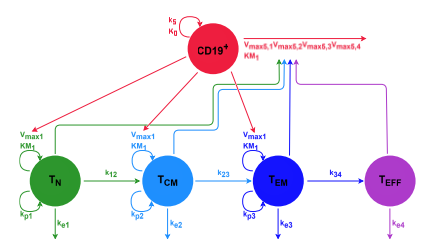
Which **population size** informs complex model?



Which **sampling strategies** inform CAR-T kinetics?



Which **sampling windows** are optimal?



Set of model parameters

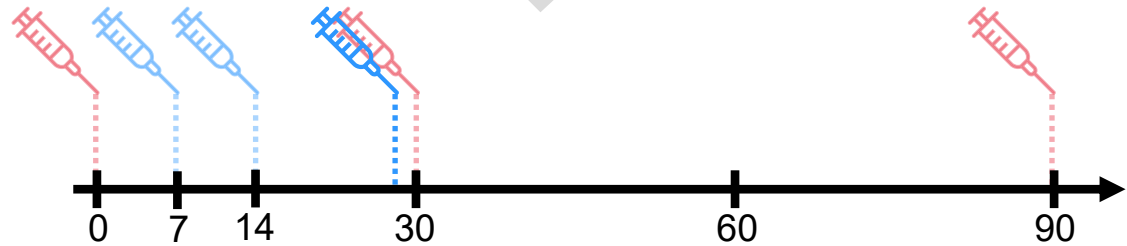


Simulated input variables (initial tumour burden)



Study designs

Comparison of multiple designs

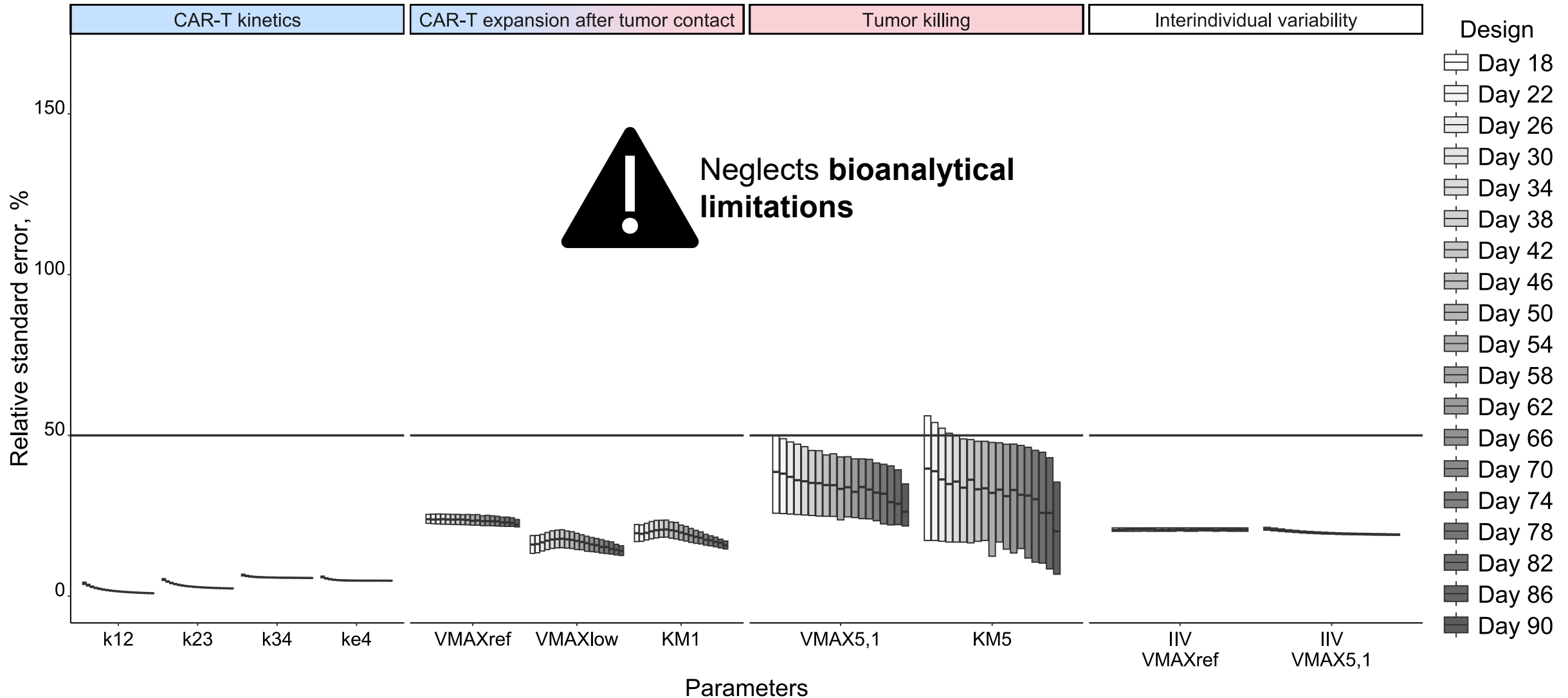


~~Additional (early) samples needed?~~

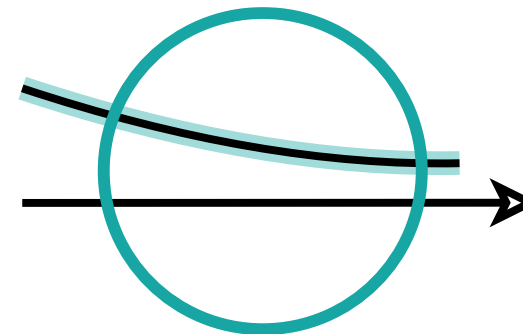
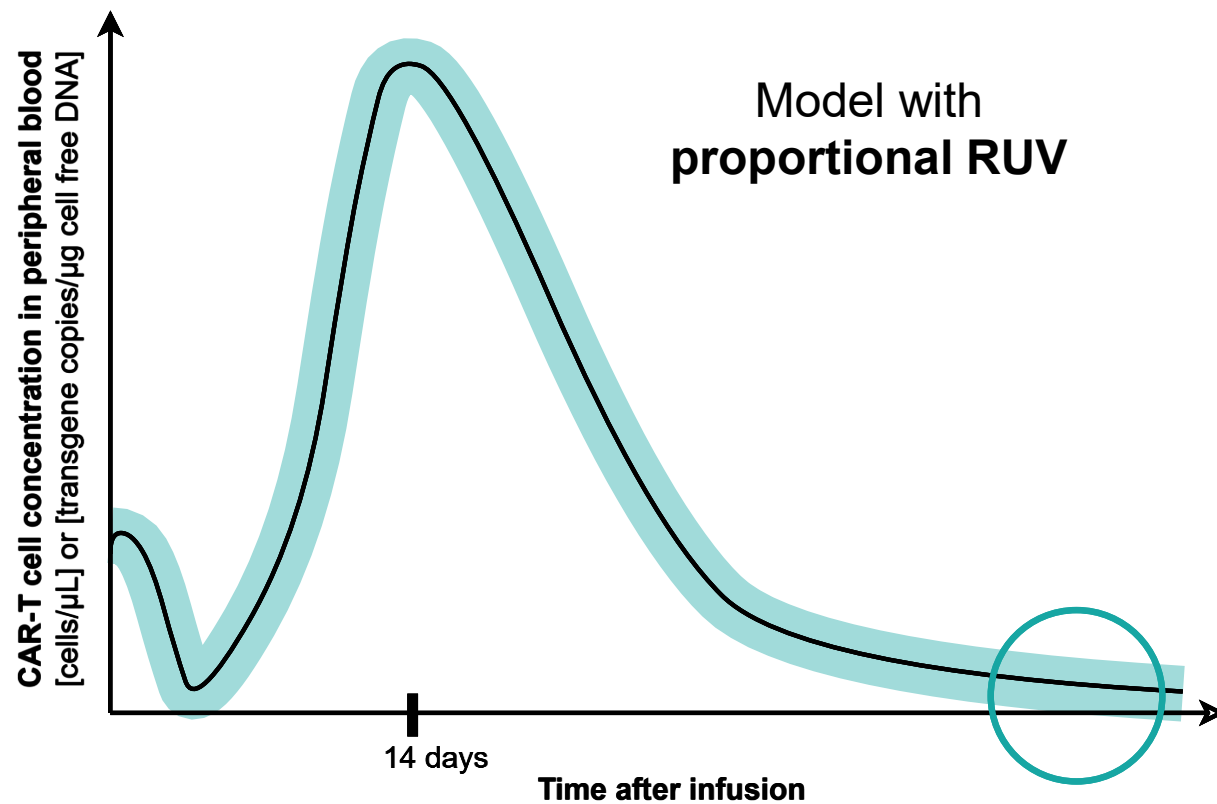
~~Where is need for optimisation?~~

Inform strategies for optimisation

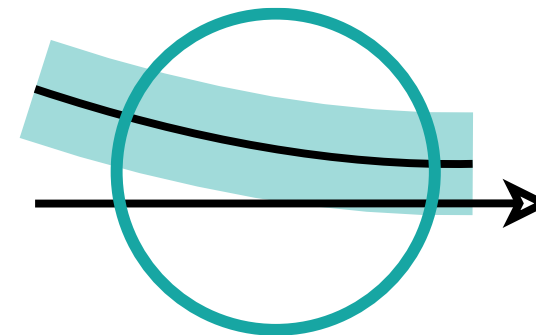
Implausible CAR-T sampling times are selected



Proportional RUV can lead to implausible results

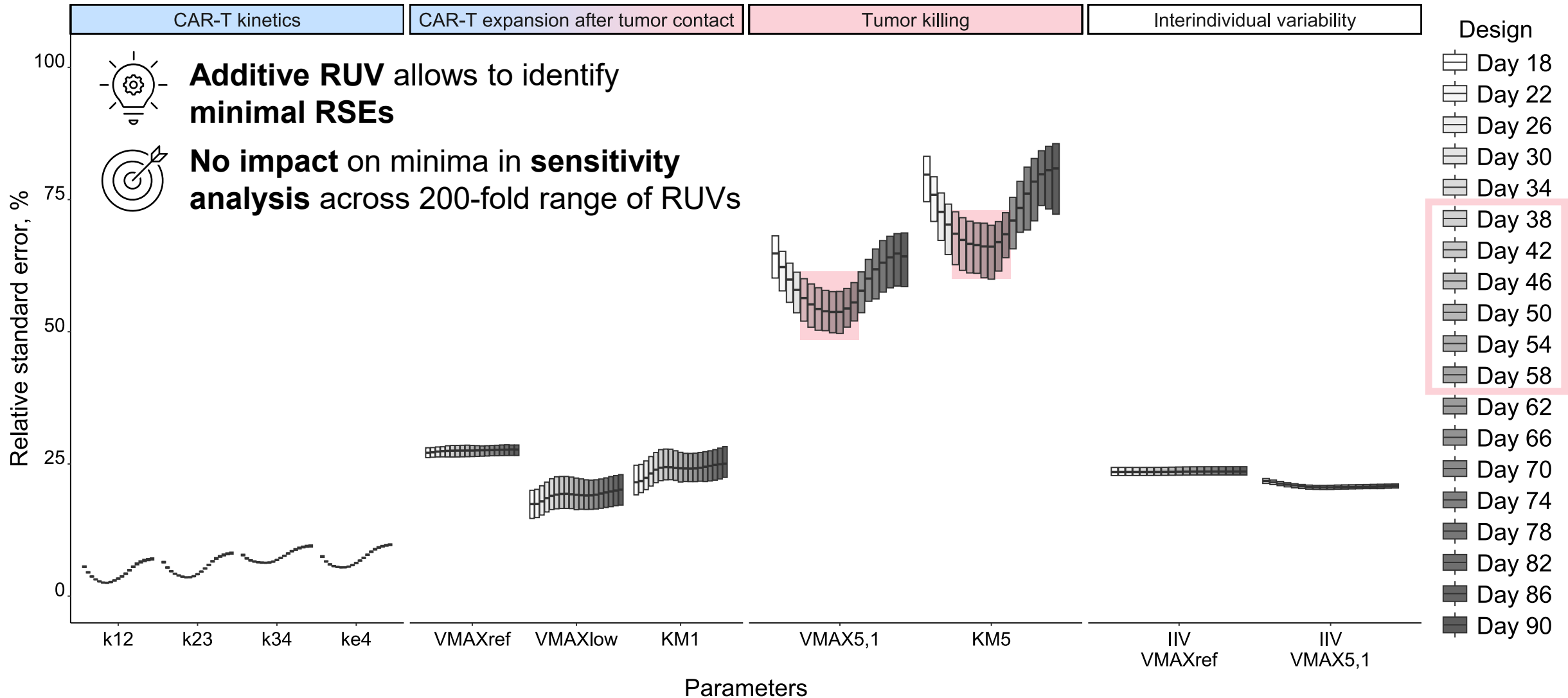


✗
Low concentrations
appear informative

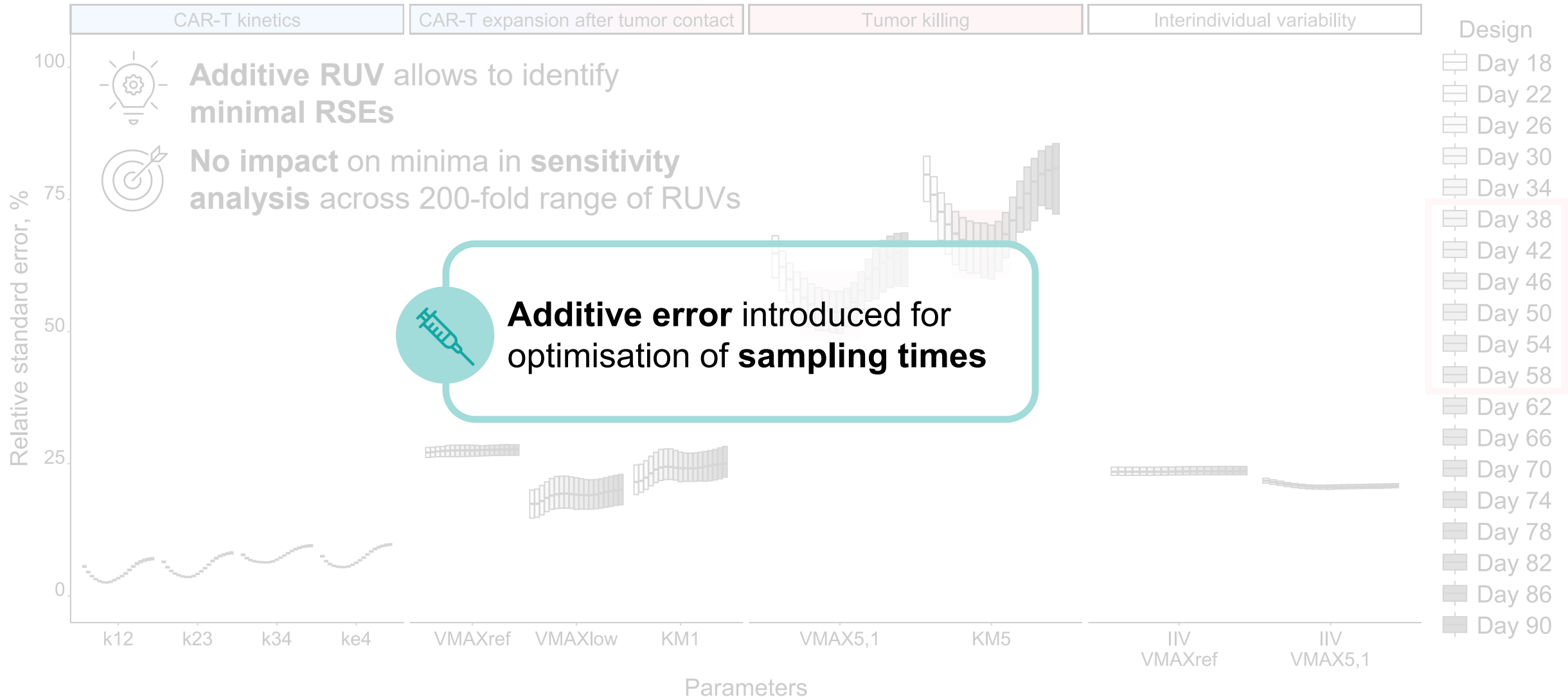


✓
Additive RUV accounts
for bioanalytical constraints

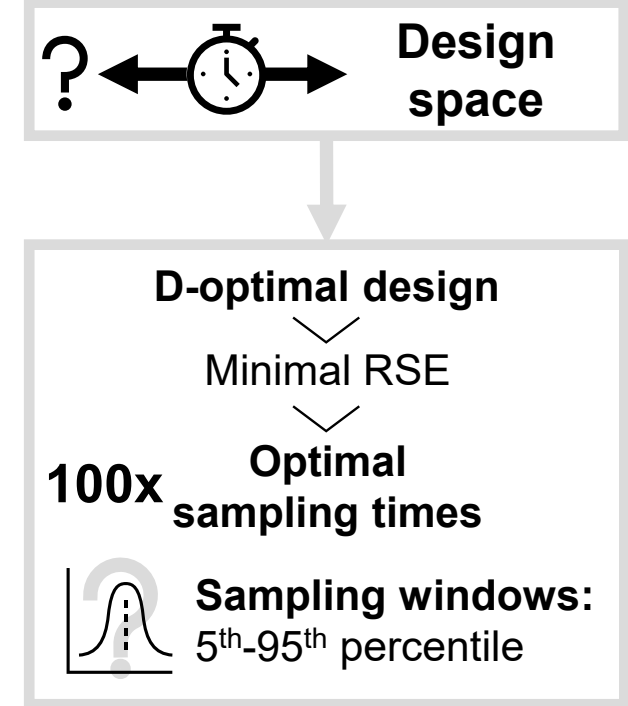
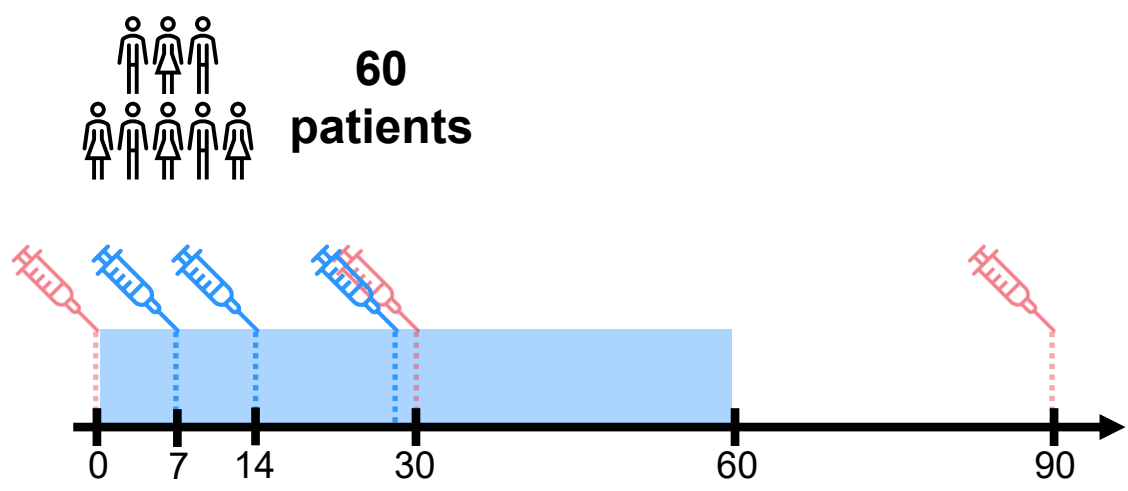
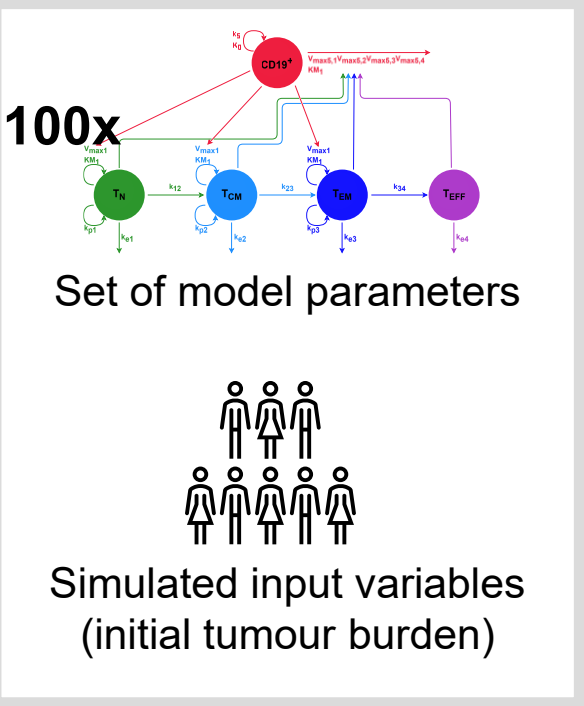
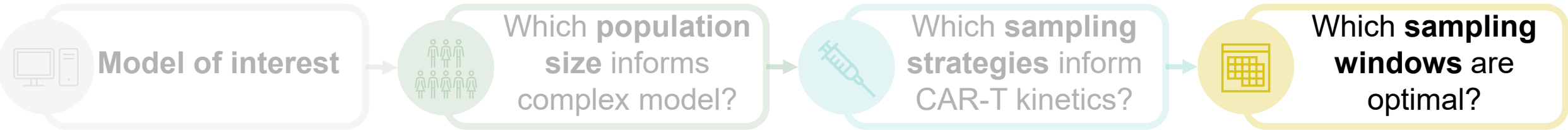
Additive RUV helps informing optimal CAR-T sampling times



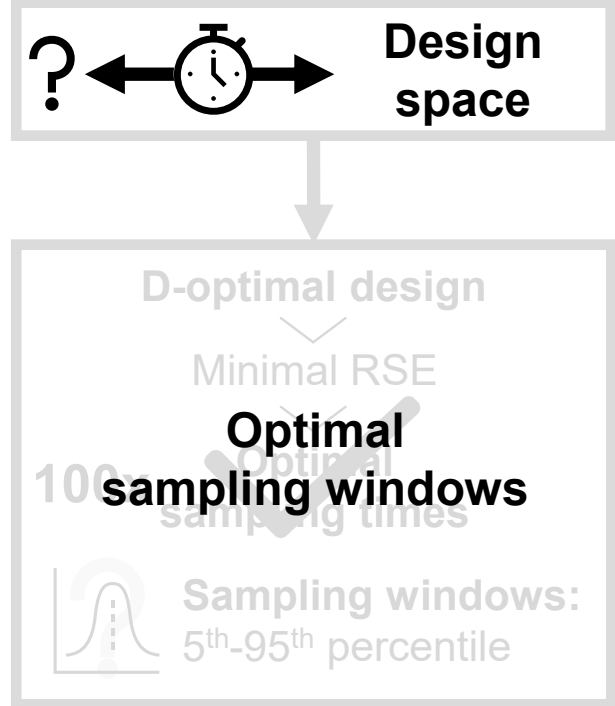
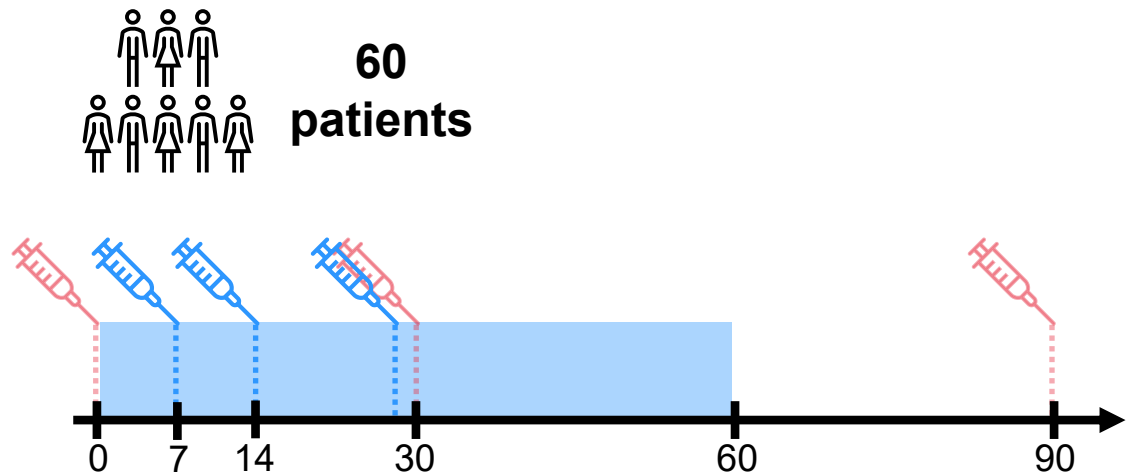
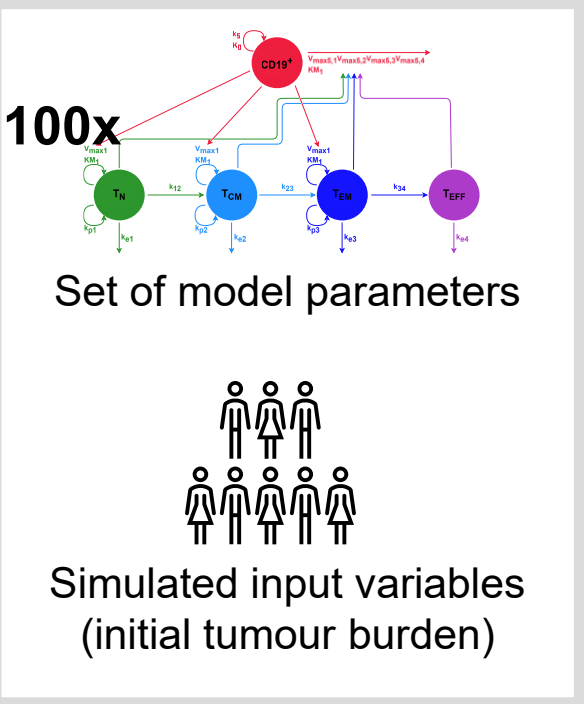
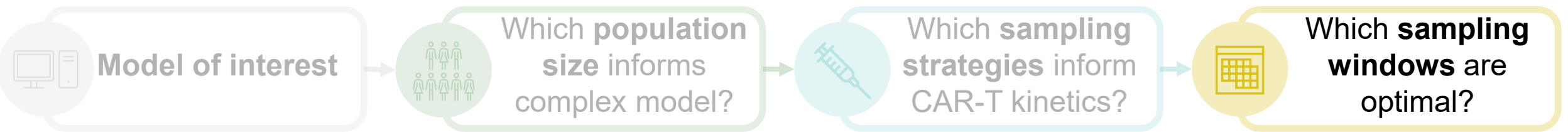
Additive RUV helps informing optimal CAR-T sampling times



Optimising CAR-T cell sampling windows

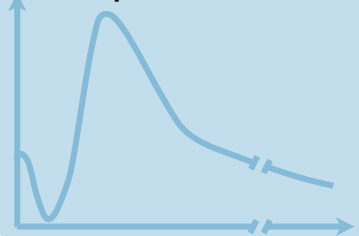


Optimising CAR-T cell sampling windows

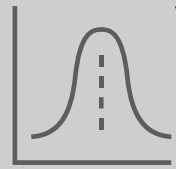


Efficient study design for clinical CAR-T cell data

Unique kinetics



**Minimal and efficient
study design**



Uncertainty on
parameter values



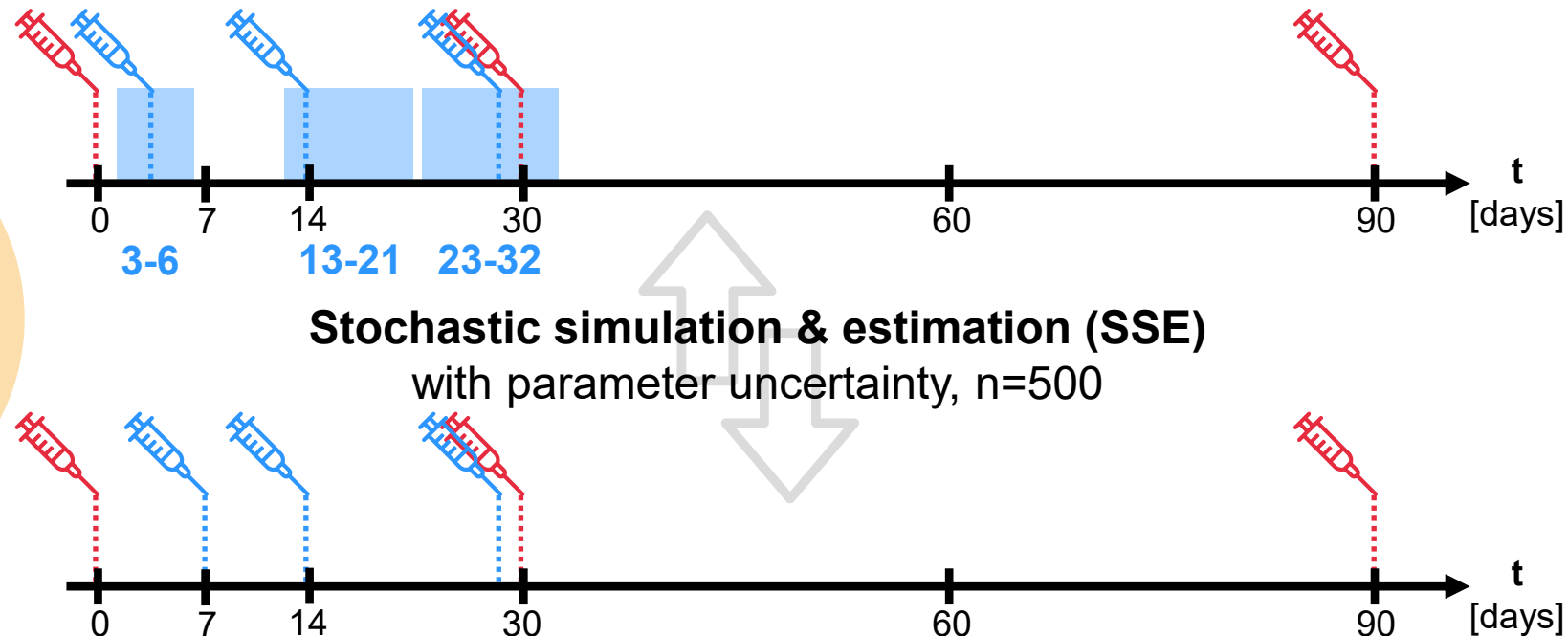
Clinical feasibility &
resources



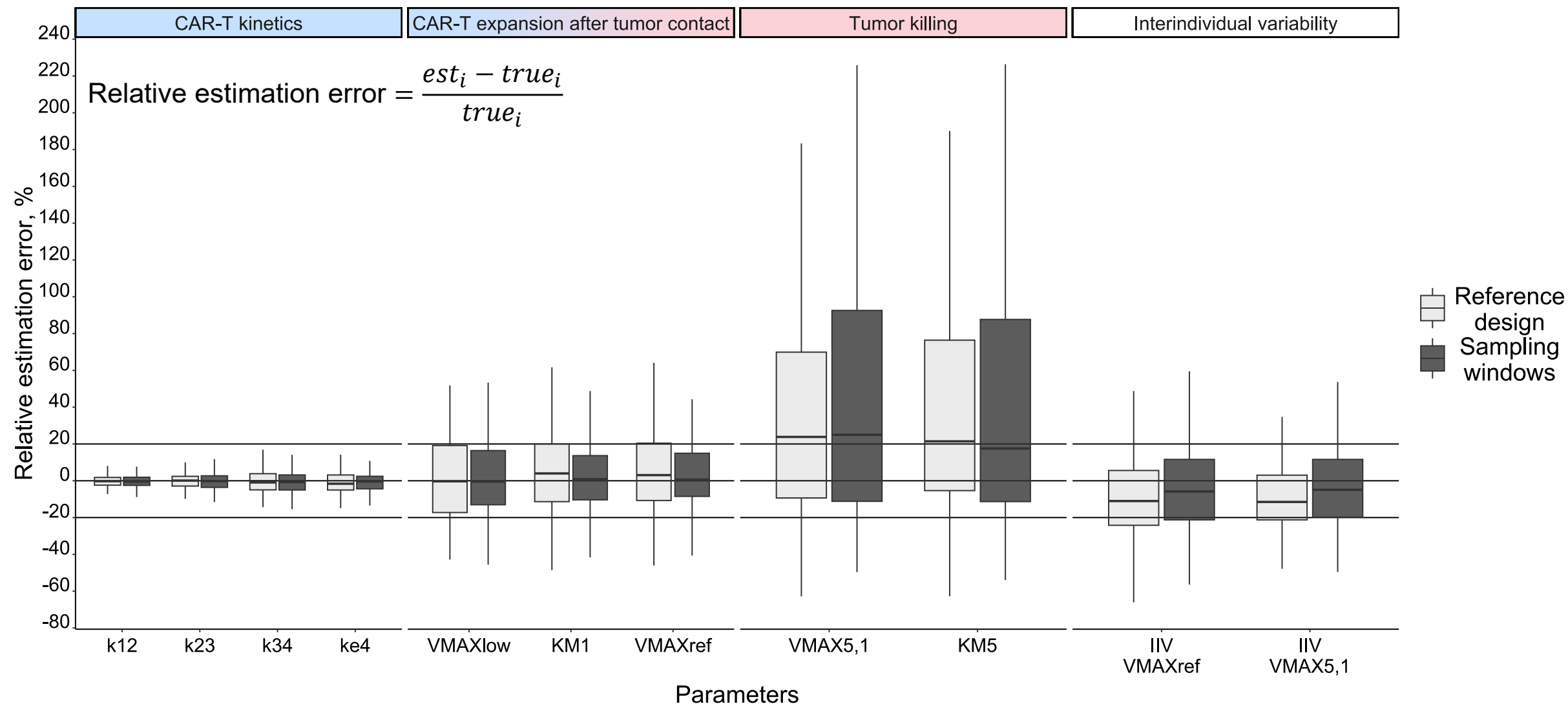
**$\geq 20-60$ patients
sufficient**



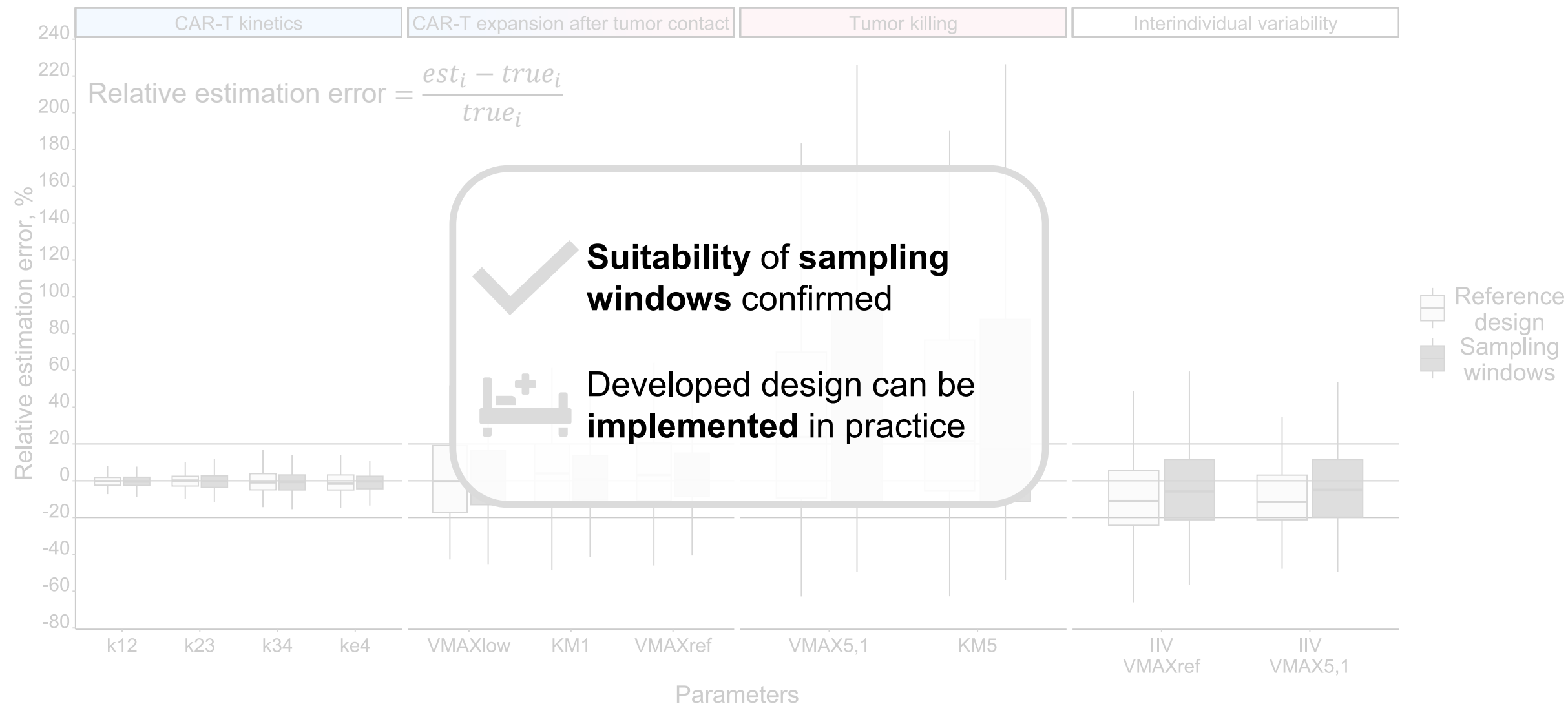
**Informative
sampling windows**



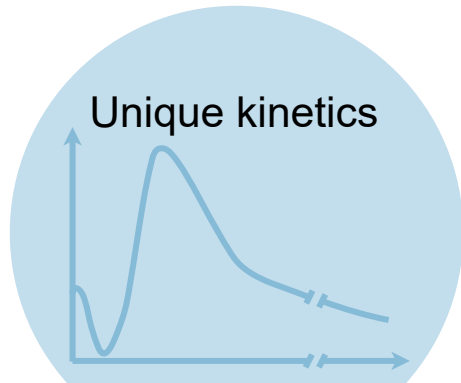
Sampling windows perform comparable to reference scenario



Sampling windows perform comparable to reference scenario



Summary and perspective



**Minimal and efficient
study design**



Clinical feasibility &
resources

**Uncertainty in
model structure**



**Implement design
for data collection**



**Understanding and
improved treatment**



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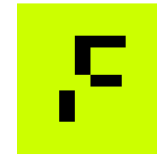
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