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Optimizing clinical study designs for CAR-T cell therapy: Development of an efficient sampling strategy through optimal experimental design

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Optimizing clinical study designs for CAR-T cell therapy: Development of an efficient sampling strategy through optimal experimental design

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Model & analysis code: github.com/Kloft-Lab/Klima-et-al-2026-CART-OptimalDesign

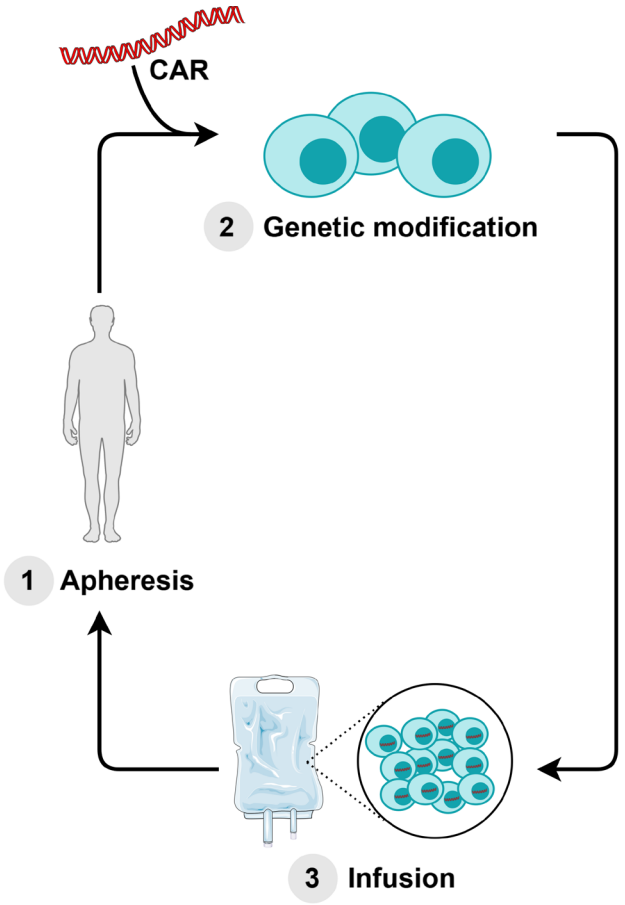
Designing efficient studies for emerging therapies

- Three obstacles tend to defeat locally-optimal design — and they appear together for many novel therapies:
  1. Uncertain priors: The design criterion depends on parameter values we do not yet know , estimated from a tiny first-in-class dataset.
  2. Between-subject variability: Large heterogeneity between patients and even between candidate study populations shifts where information sits.
  3. Infeasible fixed schedules: Clinic logistics, ethics and assay cost rule out exact sampling times; a schedule must tolerate some “wiggle room”.
- This talk: a robust, flexible optimal-design framework that tries to handle all three at once, and yield a schedule a clinic can run.

CAR-T cell therapy: a “living drug”

A patient’s own T cells are re-engineered to attack their cancer.

T cells are collected, transduced to express a **chimeric antigen receptor (CAR)** against a tumour-surface antigen (here **CD19** on B-cell malignancies), expanded, and re-infused.

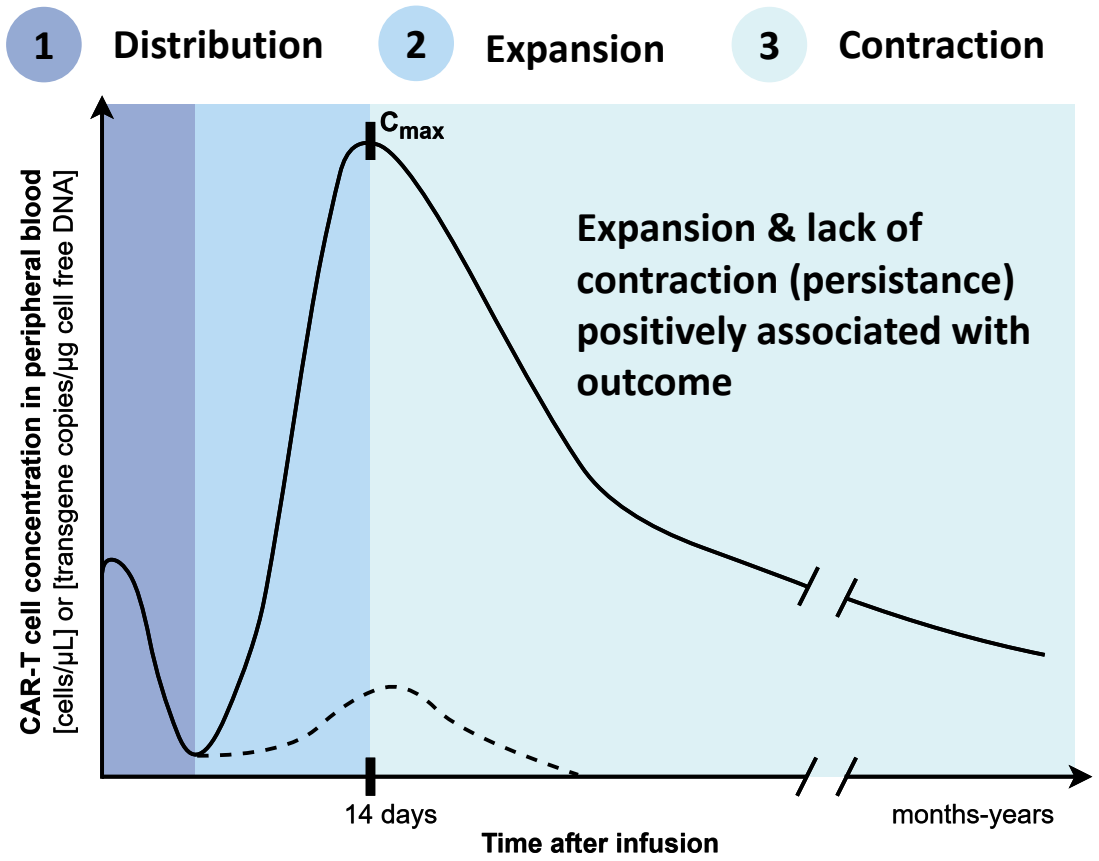


- Vastly improved overall survival (complete remission) in many patients
- 40-60% of patients without long-term response

WHY A STATISTICIAN SHOULD CARE

- **No absorb-and-clear PK.** The dose self-amplifies in vivo, then contracts, then persists, exposure is not dose-proportional.
- **Target-coupled dynamics.** Expansion is driven by the tumour the cells are killing, a feedback loop, not a one-way input.
- **A genuinely nonlinear system.** The “living” behaviour makes information about parameters cluster in narrow, unknown time intervals.

The pharmacokinetics (PK) are why the design problem is hard



A single infusion produces a multiphasic profile spanning ~4 orders of magnitude.

Consequences for design

- Information about kinetic parameters is concentrated in short, parameter-dependent windows — uniform sampling wastes most samples.
- Peak timing and persistence carry the parameters tied to clinical outcome yet vary widely between patients.

...and the data are scarce

Rare indications: few eligible patients per centre

High treatment cost: small trials, sparse sampling

Costly bioanalysis: CAR-T phenotyping limits samples/patient

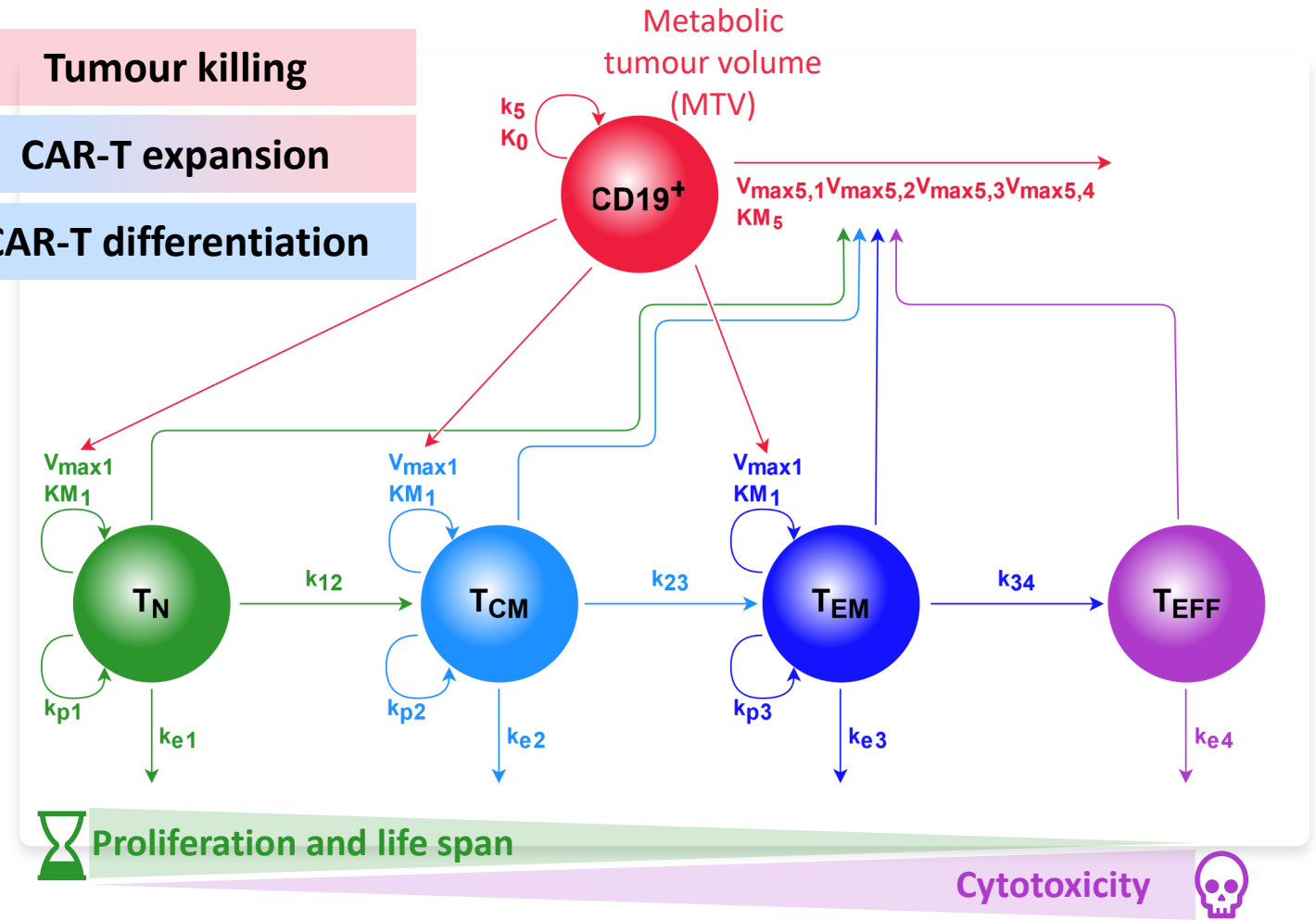
A mechanistic nonlinear mixed-effects model

Published QSP model (Mueller-Schoell et al., 2021), fit to 19 r/r non-Hodgkin lymphoma patients on axicabtagene ciloleucel.

Tumour killing

CAR-T expansion

CAR-T differentiation



STRUCTURAL (ODE system)

Disposition: first-order differentiation k_{12},k_{23},k_{34}, proliferation k_p, death k_e

Expansion: tumour-driven, saturable (Michaelis–Menten); 2-component mixture on V_max (ref / low)

Killing: saturable, phenotype-specific (V_max5,j, K_M5); logistic tumour growth (k_5, K_0)

STOCHASTIC

IIV (η ~ N) on V_max,ref and V_max5,2

Subpopulation membership ~ Bernoulli

Residual error: proportional (+ small additive — see later slide)

OBSERVATIONS · 2 outputs

y_1 CAR-T phenotype conc. (flow cytometry) · y_2 MTV (PET/CT)

≈ 12 structural parameters to identify

Robust D-optimal design on the population FIM

OBJECTIVE & INFORMATION

Design ξ: CAR-T sampling times; MTV times fixed by imaging schedule.

Criterion: D-optimality, maximize ln(det M(ξ, Θ)) over the population Fisher information matrix M.

Approximation: M has no closed form for a nonlinear mixed-effects model. We use the first-order (FO) linearization in PopED.

No GET for nonlinear mixed-effect models, so every conclusion is re-checked by simulation/estimation (later slide).

ROBUSTNESS

A local design is optimal only at the assumed Θ. We robustify over two sources:

Between-population variability — 100 replicate virtual populations (covariate samples for initial tumour burden, mixture membership).

Prior parameter uncertainty — Θ drawn from the SIR posterior of the original 19-patient fit.

Windows — optimize per scenario, then take the 5th–95th percentile of the optimal times as a sampling window.

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Workflow

Model + prior Θ

SIR posterior, 19 pts

→

100 virtual populations

tumour burden, mixture

→

Approx. population FIM (FO, PopED)

per scenario

→

RSE / efficiency / optimal times

summarise over reps

How many patients?

Minimal population size to identify every parameter at target precision.

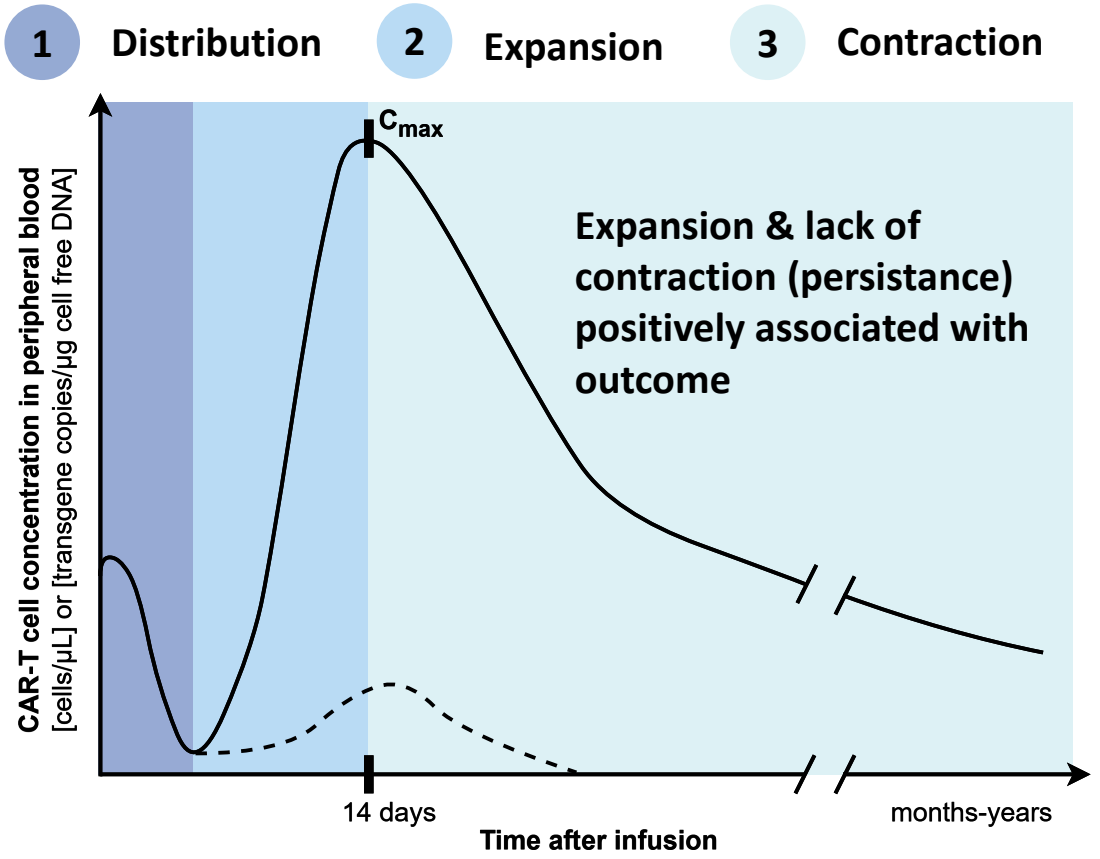
Which samples, when?

Optimize CAR-T sample times

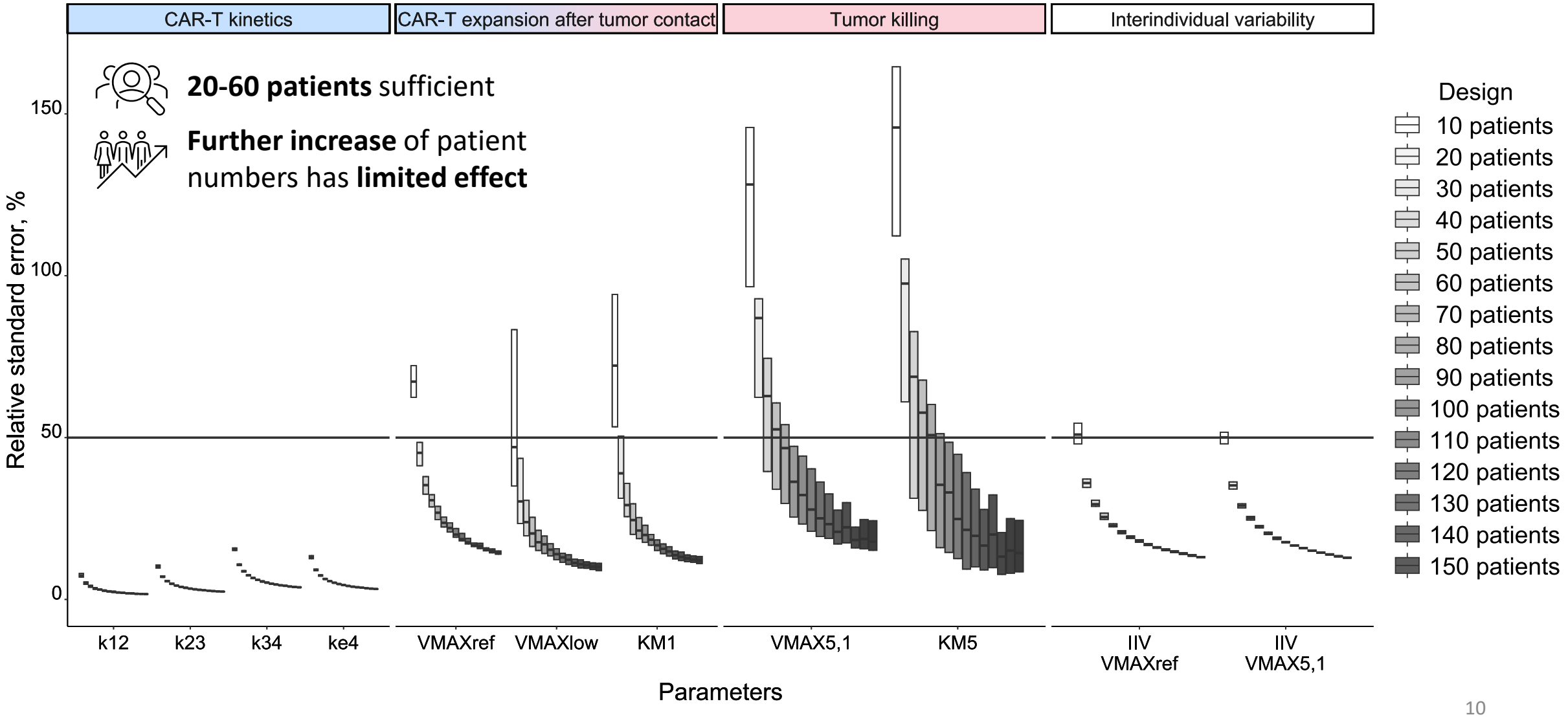
Fixed times or windows?

Convert per-scenario optima into clinically feasible, robust sampling windows.

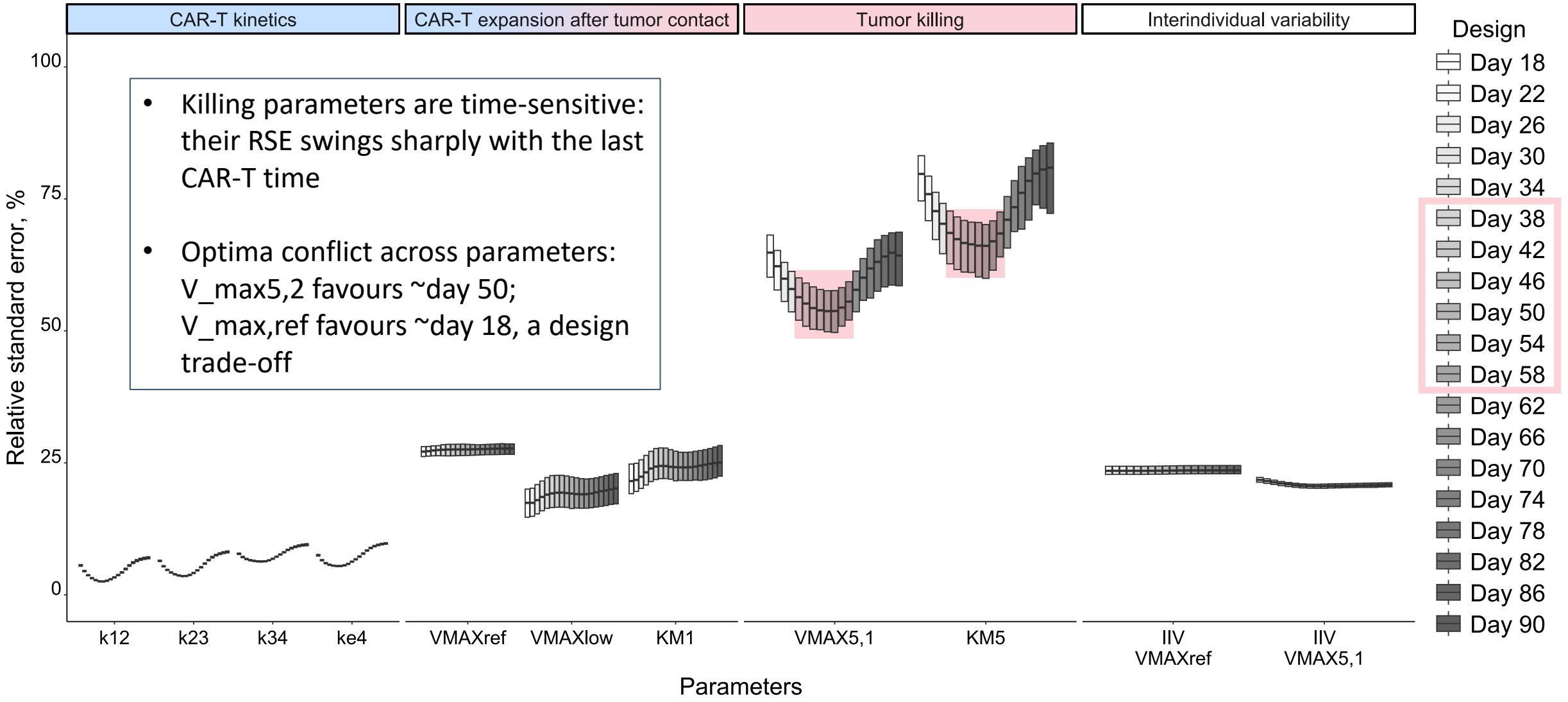
Reference design



The model is identifiable at a feasible sample size



Evaluating the FIM at different sampling schedules



- Killing parameters are time-sensitive: their RSE swings sharply with the last CAR-T time
- Optima conflict across parameters: V_max5,2 favours ~day 50; V_max,ref favours ~day 18, a design trade-off

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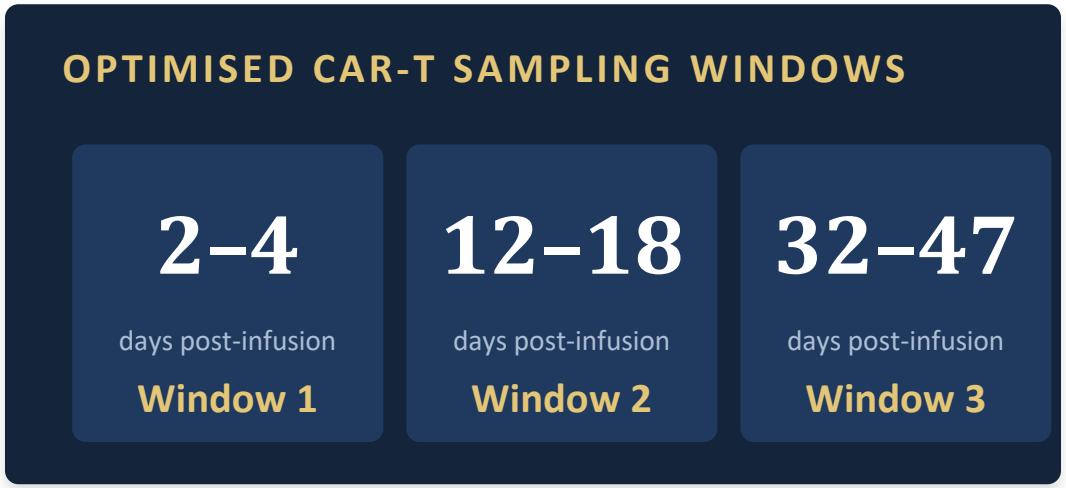
Sampling windows

How the windows are built

1. **Optimise per scenario** D-optimal CAR-T times for each population replicate × parameter draw.
2. **Take the spread** For each sample, the 5th–95th percentile of optimal times becomes a window.
3. **Compare uncertainty sources** Population variability alone → narrow windows; adding parameter uncertainty → the wide, realistic windows.



111%

D-efficiency vs. reference

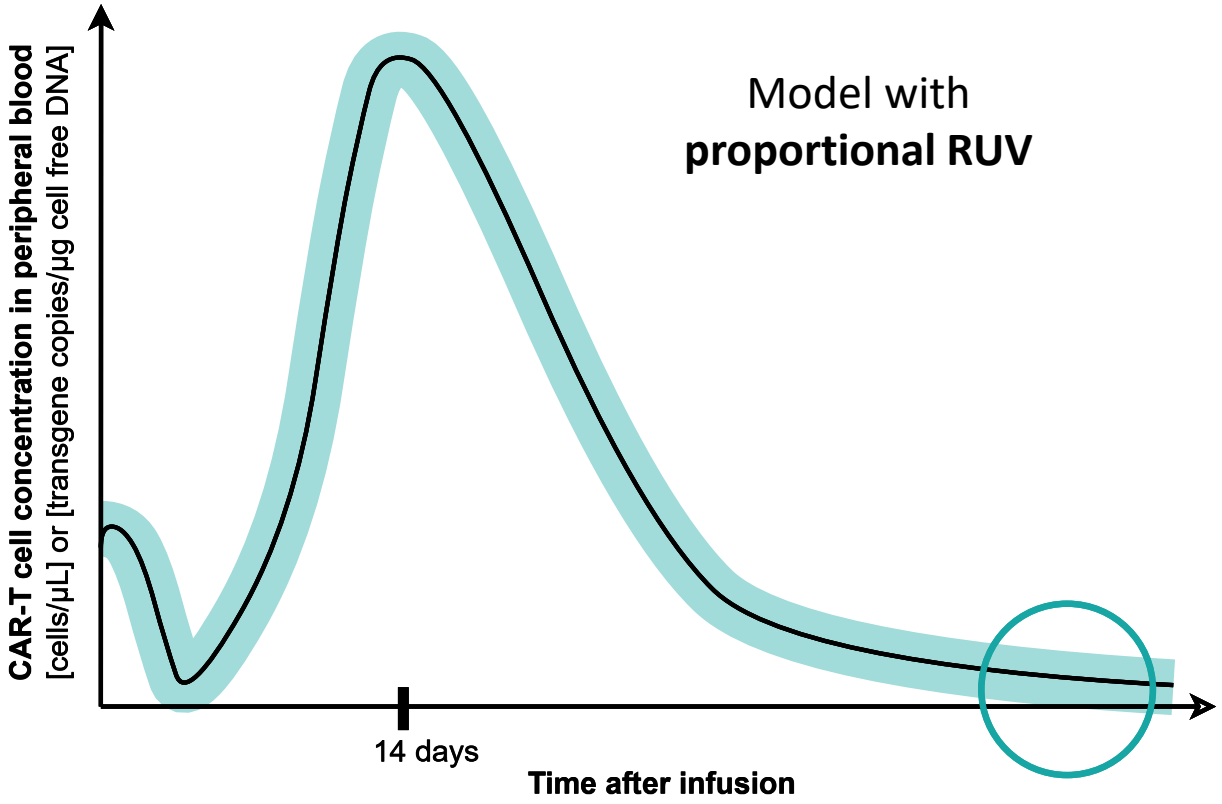
[90% CI 106–118%]

≈11%

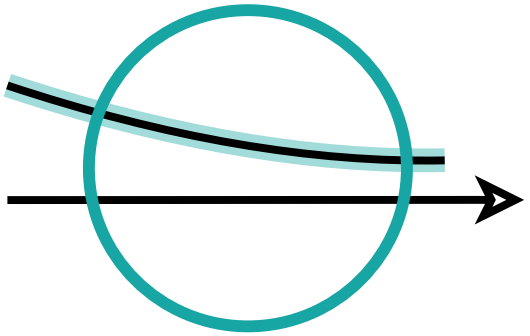
fewer patients

for equal precision

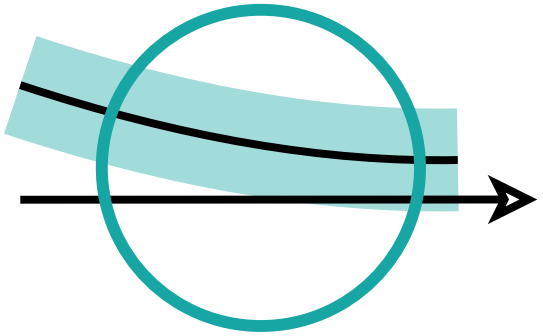
Only proportional RUV in model can lead to implausible results



Model with
proportional RUV



Low concentrations appear informative

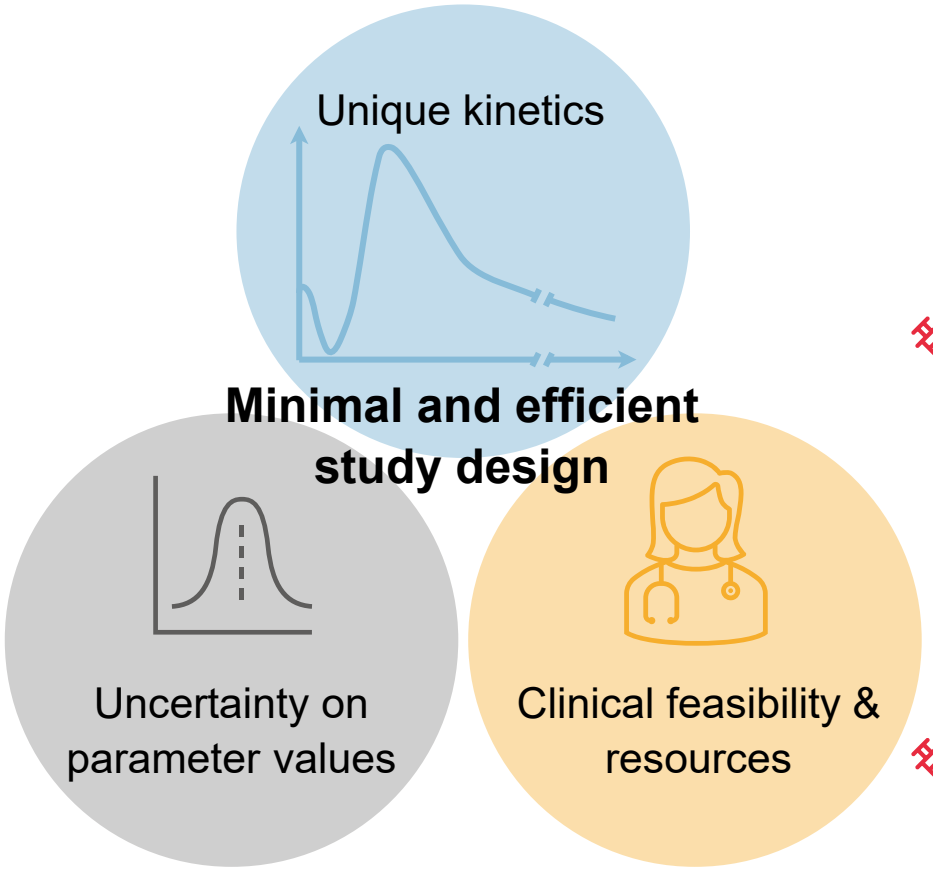


Additive RUV accounts for bioanalytical constraints

PAGE 21 (2012) Abstr 2578 [www.page-meeting.org/?abstract=2578]

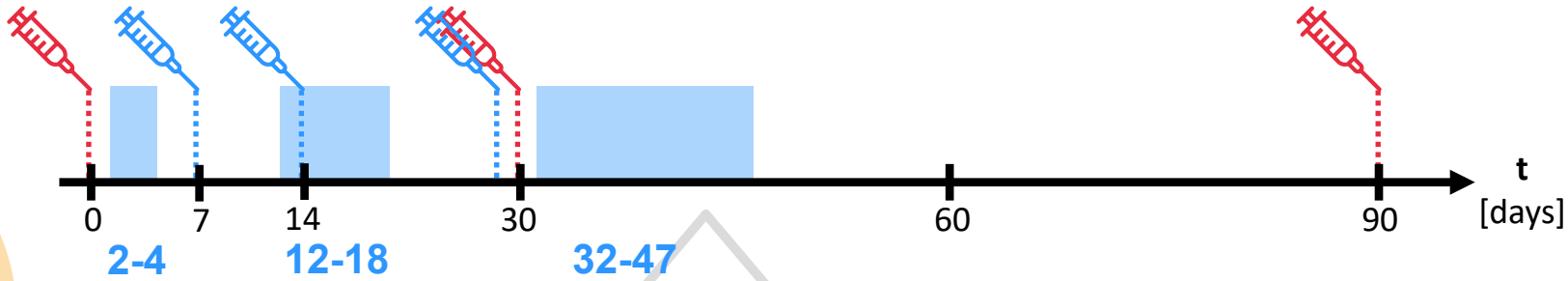
RUV Residual unexplained variability

Efficient study design for clinical CAR-T cell data

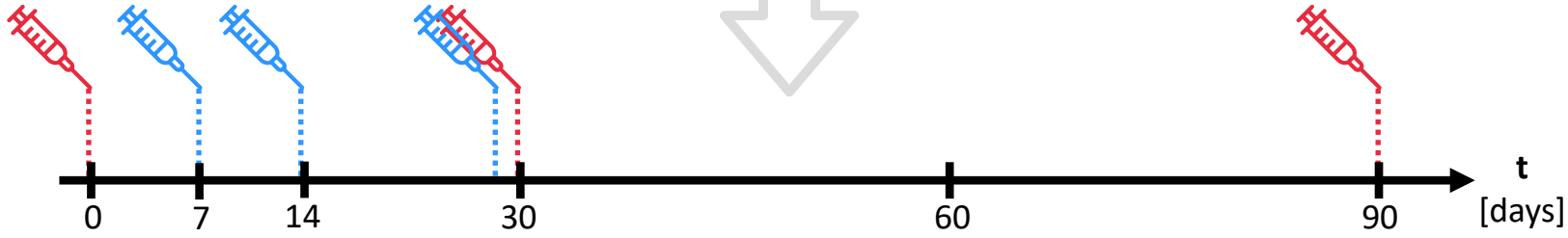


≥20-60 patients sufficient

Informative **sampling windows**



Stochastic simulation & estimation (SSE)
with parameter uncertainty, n=500



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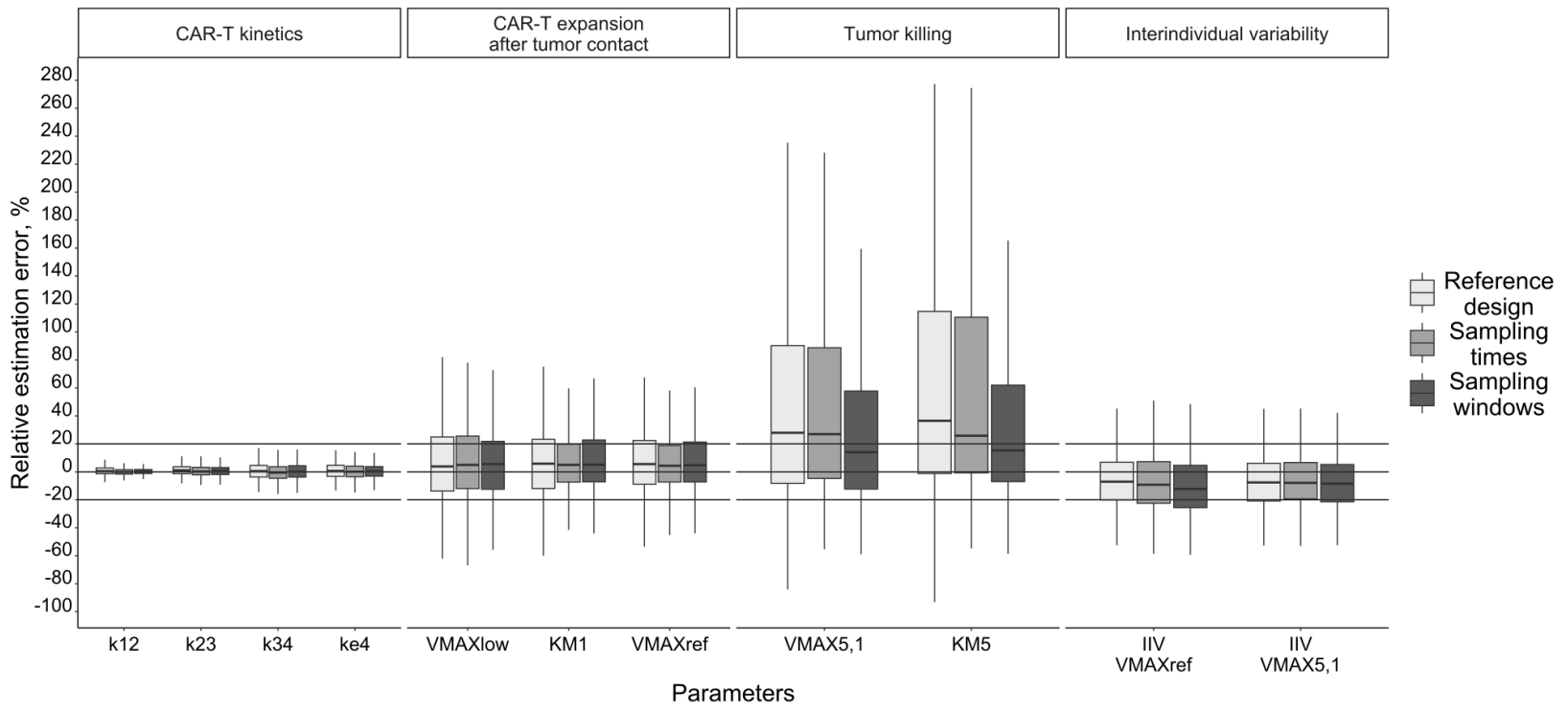
Do the asymptotic predictions hold in finite samples?



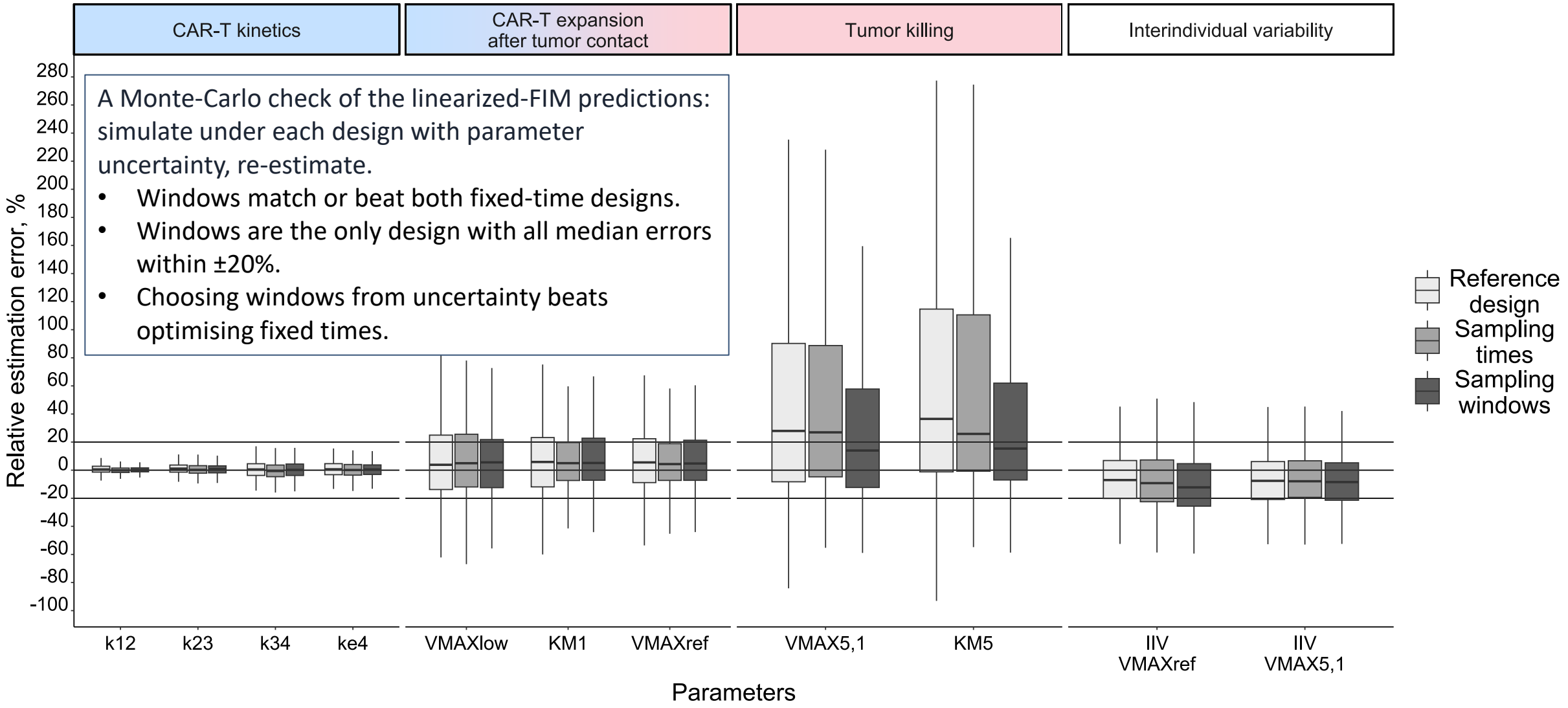
Relative estimation error, 500 simulate-and-refit replicates with parameter uncertainty. Reference vs. fixed-optimal times vs. windows.

Stochastic simulation & estimation

A Monte-Carlo check of the linearised-FIM predictions: simulate under each design, re-estimate, inspect bias & precision.

- Windows match or beat both fixed-time designs.
- Windows are the only design with all median errors within ±20%.
- Choosing windows from uncertainty beats optimising fixed times.

Do the asymptotic predictions hold in finite samples?



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Takeaways

- Robust + flexible beats local + fixed: Designing windows from parameter uncertainty out-performed optimizing exact timepoints, even under a simulation check, and even when the fixed times were themselves optimal.
- The error model is part of the design: A proportional-only residual model gives a degenerate D-optimum; a small additive floor regularizes it. Specify the observation error before trusting the optimizer.
- Approximate, then verify: FO-based optimization allows us to optimize for NLME models; need to pair it with simulate-and-refit evaluation.
- It produced an implementable schedule: 60 patients, 3 fixed tumor assessments, 3 CAR-T windows (days 2–4, 12–18, 32–47), the first OED applied to a cellular immunotherapy.