Dose-Finding Clinical Trials in Stan

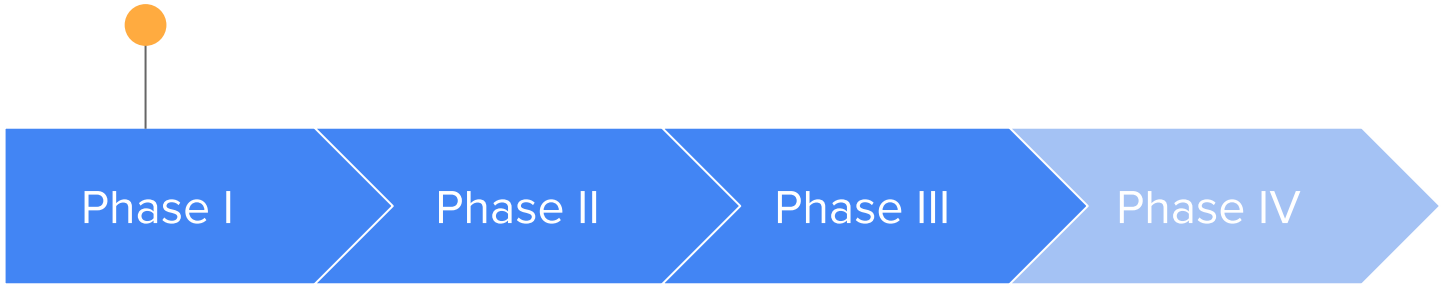
Kristian Brock, StanCon Helsinki, 30-Aug-18


Phase I
Phase II
Phase III
Phase IV

What dose?

Not too toxic…but

High enough to be effective



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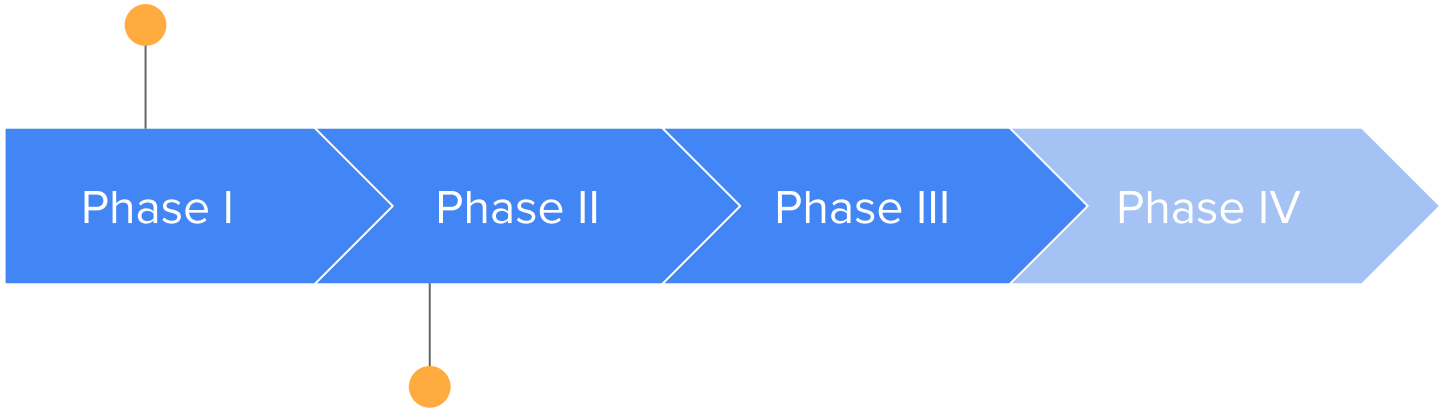

Is it any good?

Does it do something desirable?

What dose?

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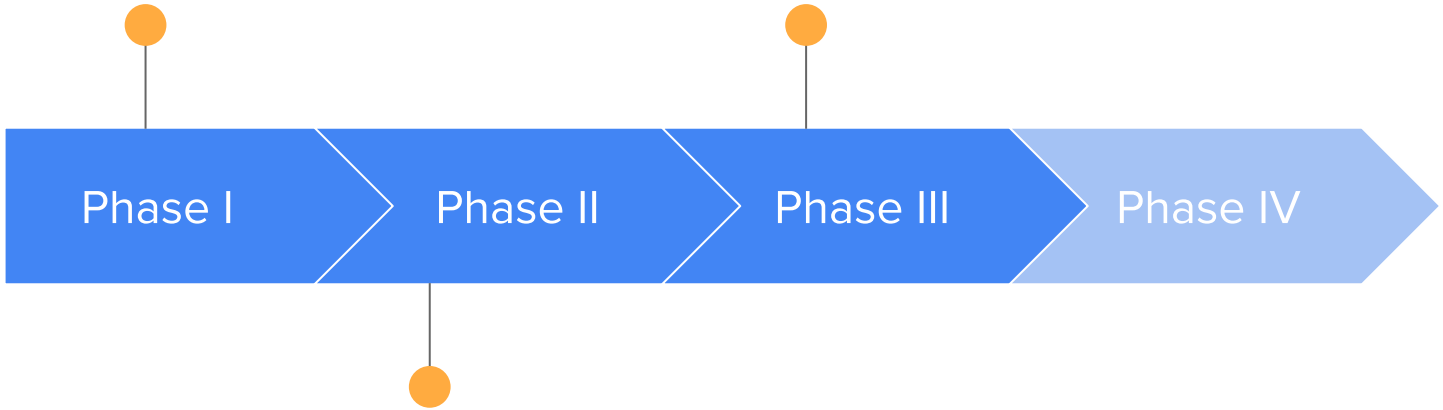
Pivotal study

The challenger vs the standard of care



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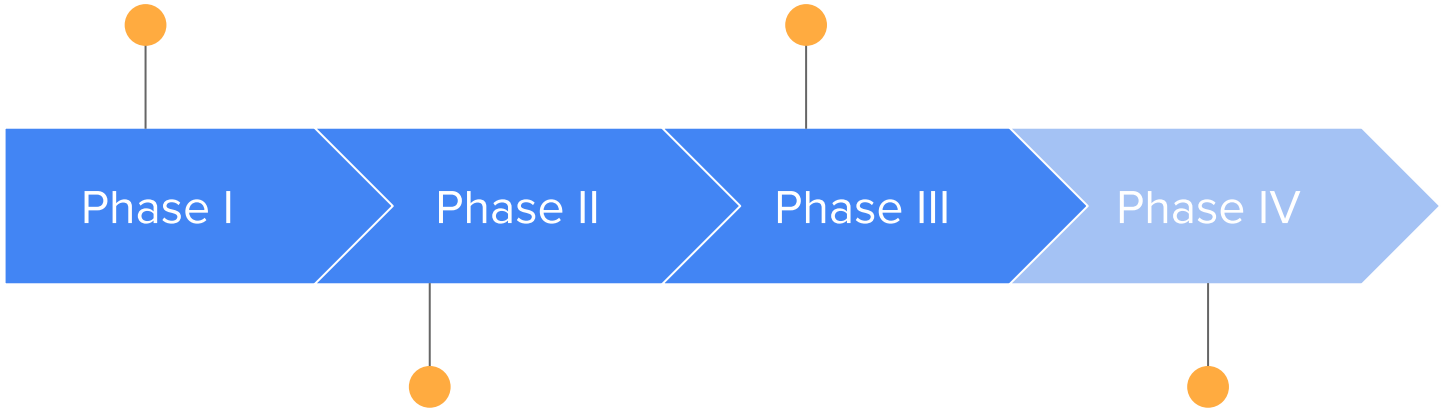


Is it any good?

Does it do something desirable?

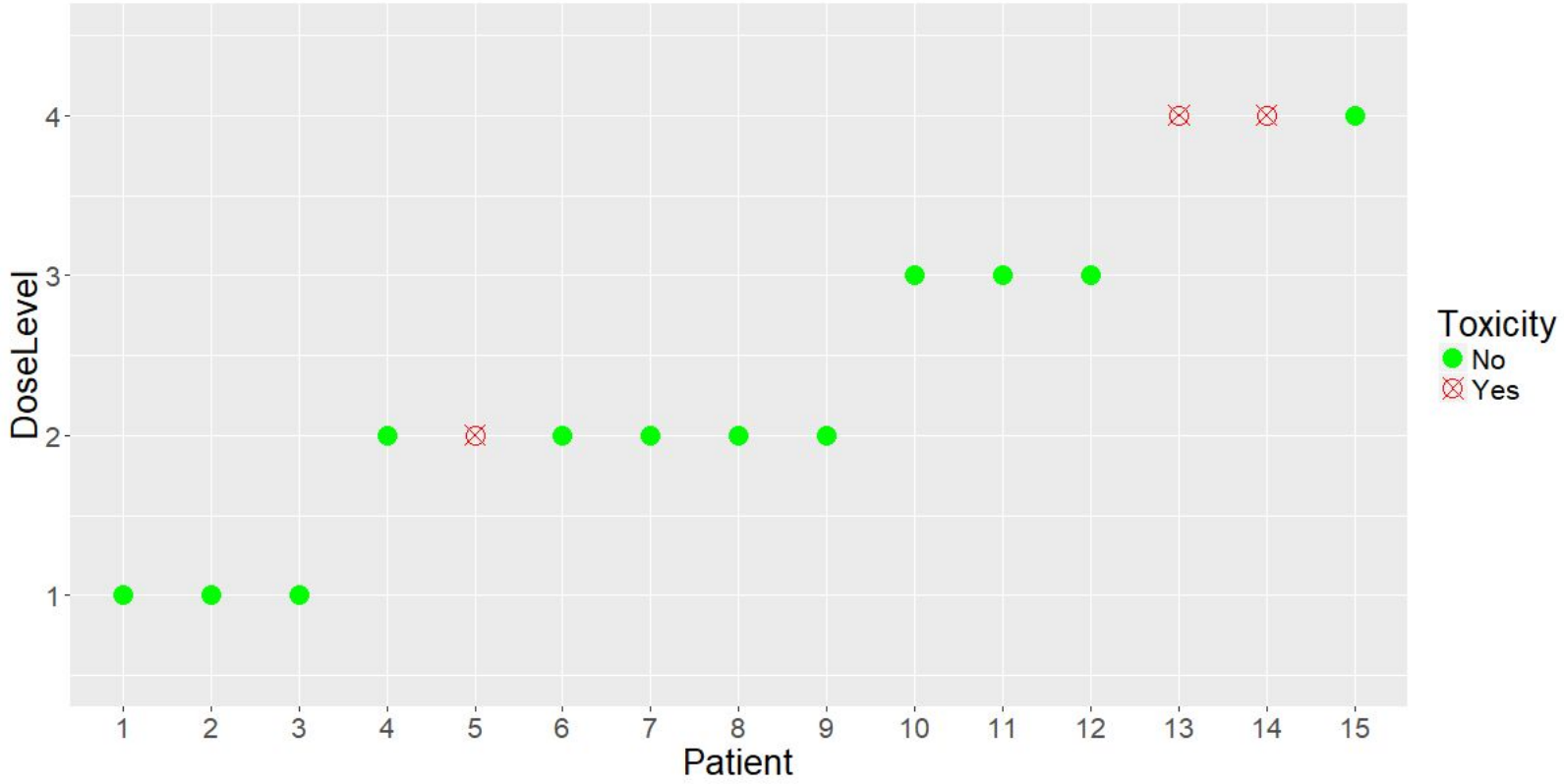
Post-marketing

We'll use it...

But let's keep an eye on it

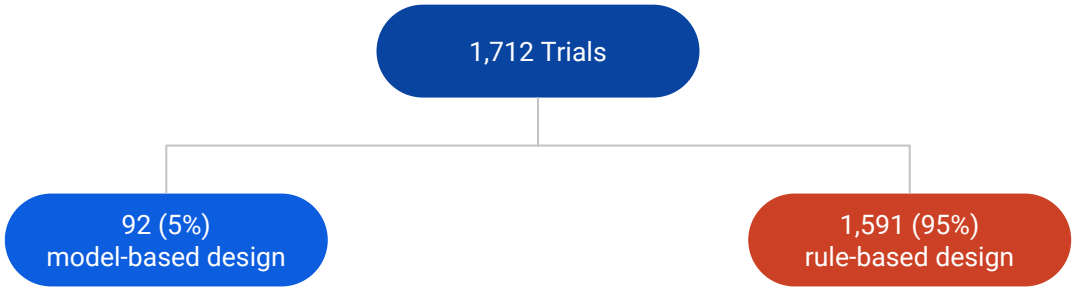
Dose-finding by toxicity

Dose Finding and the 3+3 Method



Surely folk use statistical models these days?

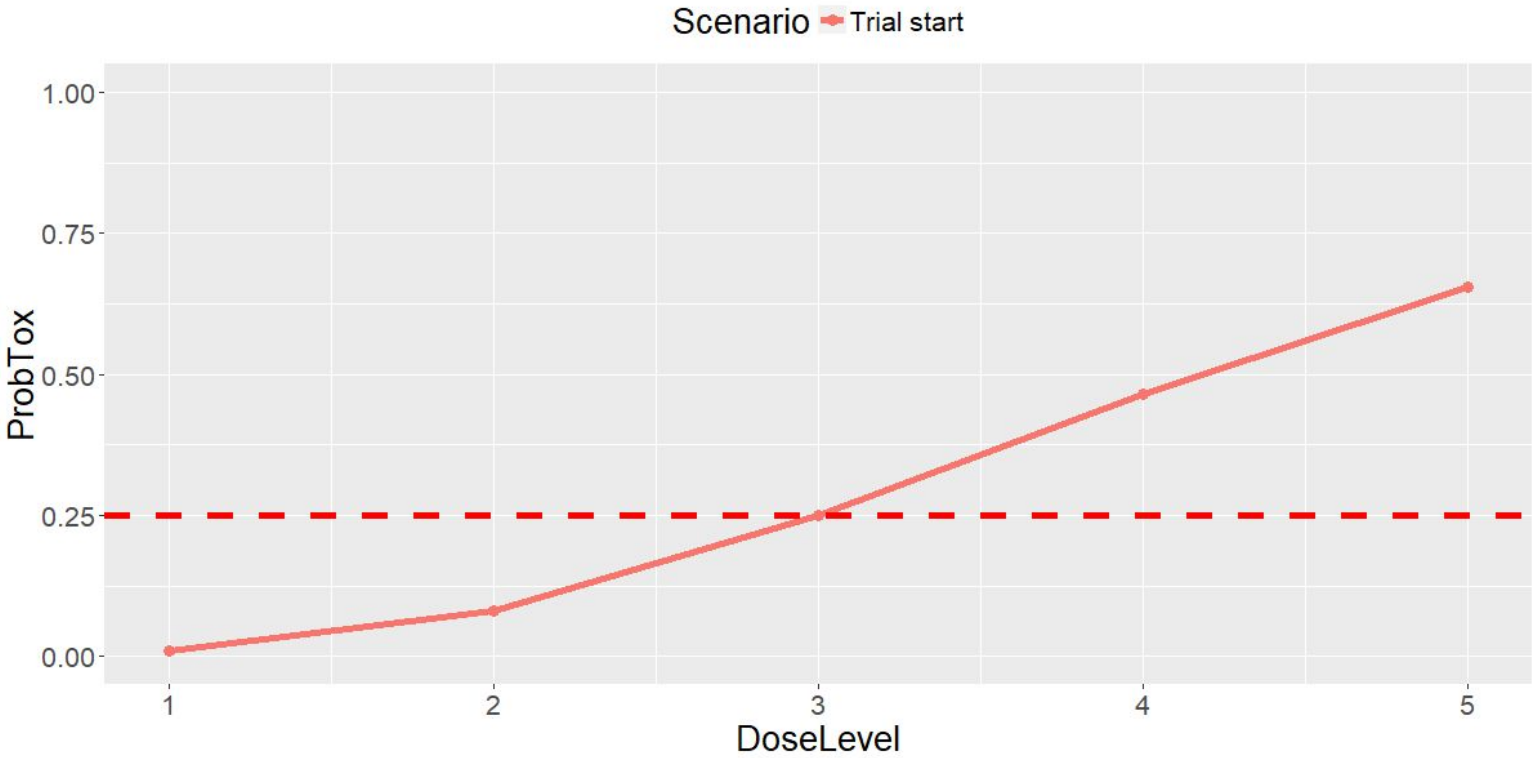
- Chiuzan *et al.* (2017) conducted systematic review of dose-finding methods
- Cancer trials published between 2008 and 2014



"adoption of [model-based] designs continues to remain low"

Chiuzan, *et al.* (2017). Dose-finding designs for trials of molecularly targeted agents and immunotherapies. Journal of Biopharmaceutical Statistics, https://doi.org/10.1080/10543406.2017.1289952

Continual Reassessment Method (CRM)



O'Quigley, Pepe, and Fisher (1990). Continual Reassessment Method: A Practical Design for Phase 1 Clinical Trials in Cancer. Biometrics. https://doi.org/10.2307/2531628.

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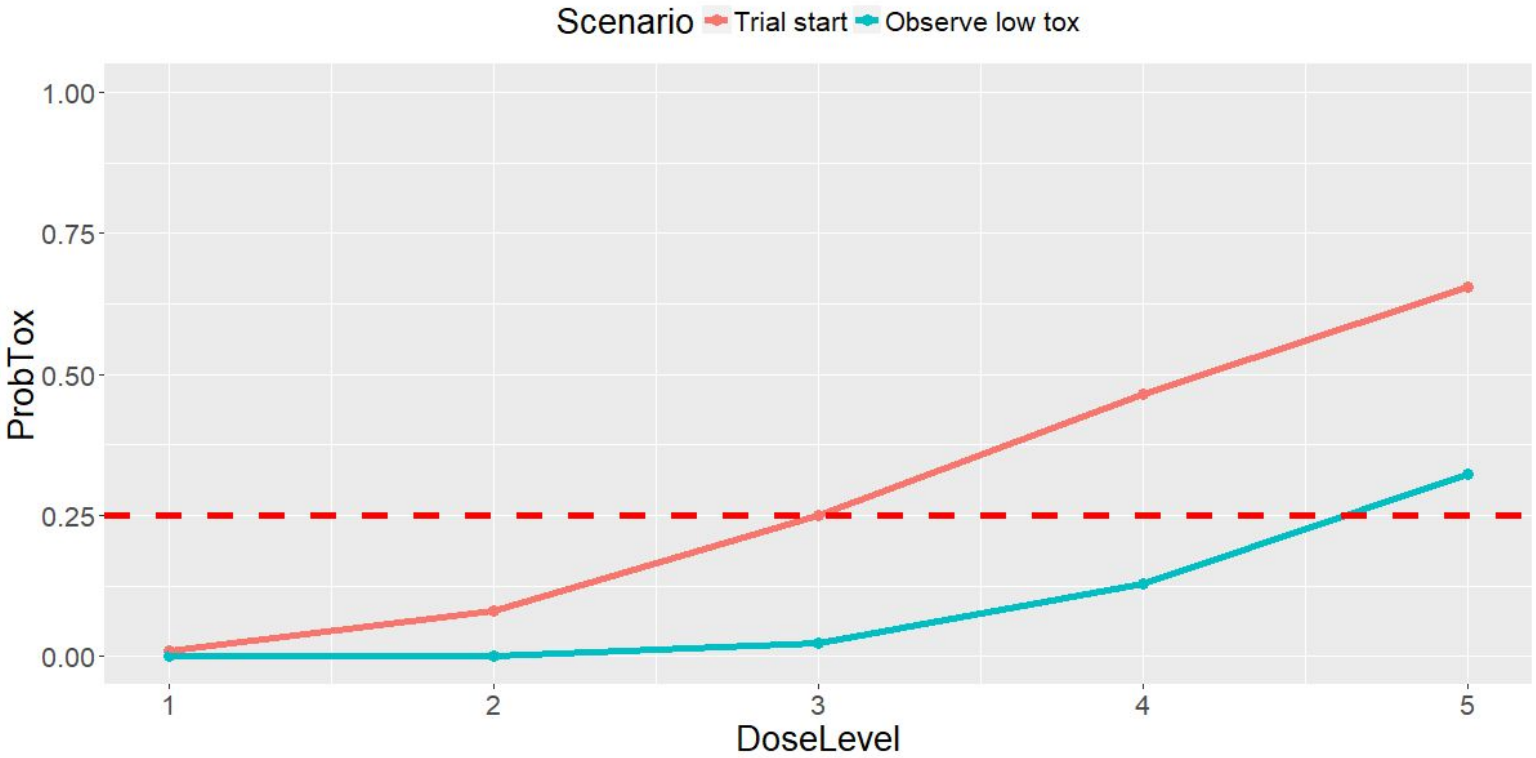

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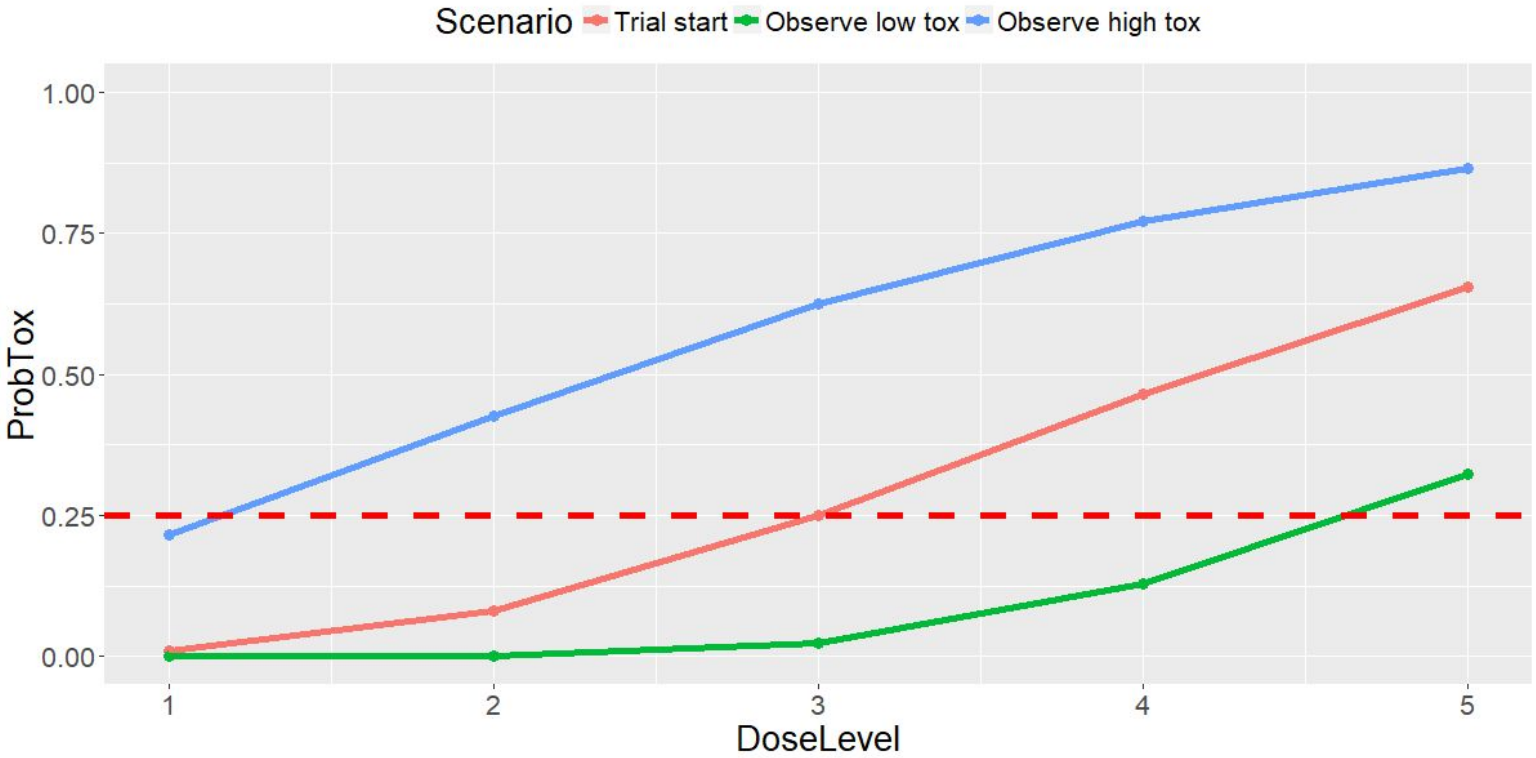

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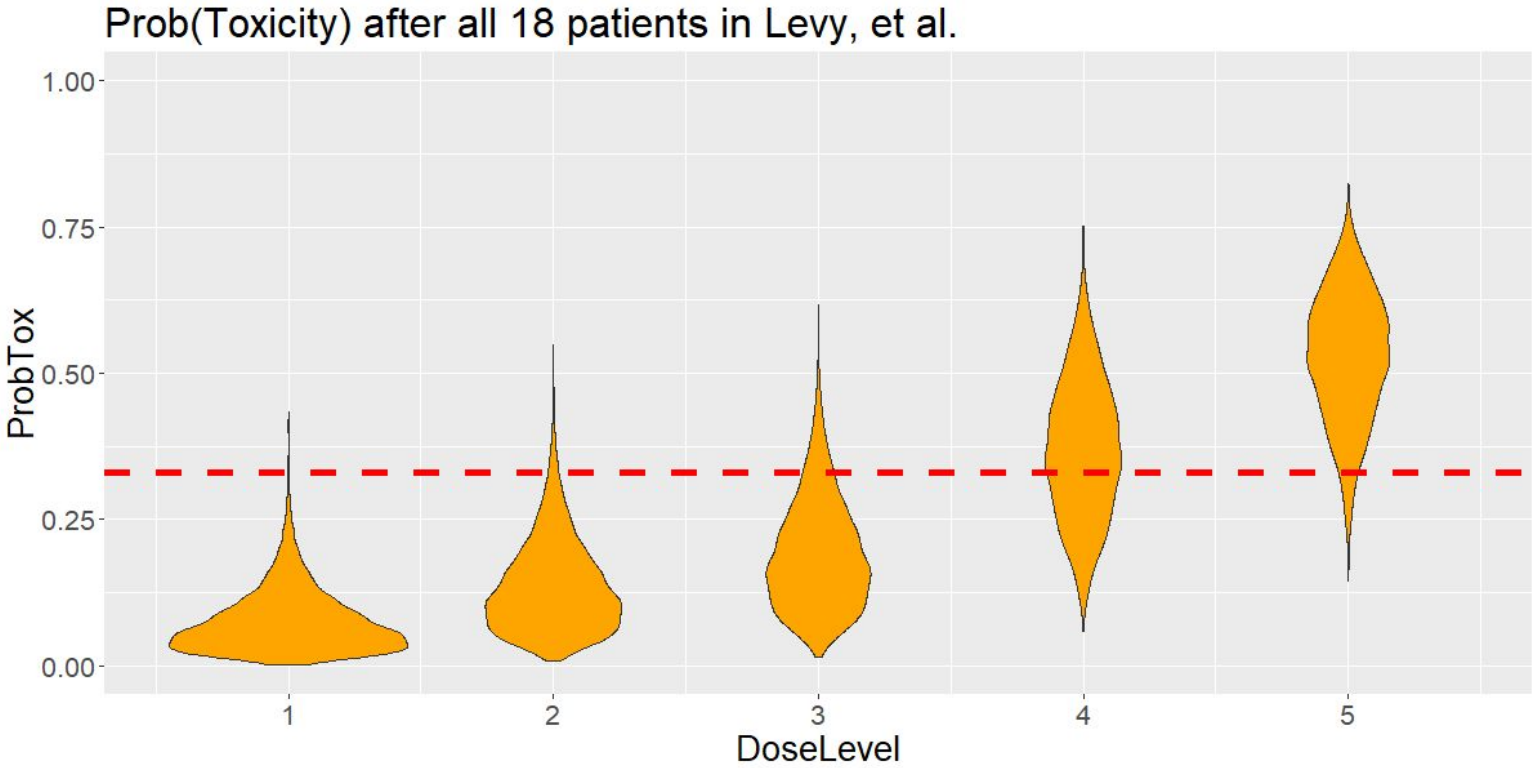
Levy *et al.* - ssHHT in leukaemia



Levy, et al. A Phase I Dose-Finding and Pharmacokinetic Study of Subcutaneous Semisynthetic Homoharringtonine (ssHHT) in Patients with Advanced Acute Myeloid Leukaemia. BJC. https://doi.org/10.1038/sj.bjc.6603265.

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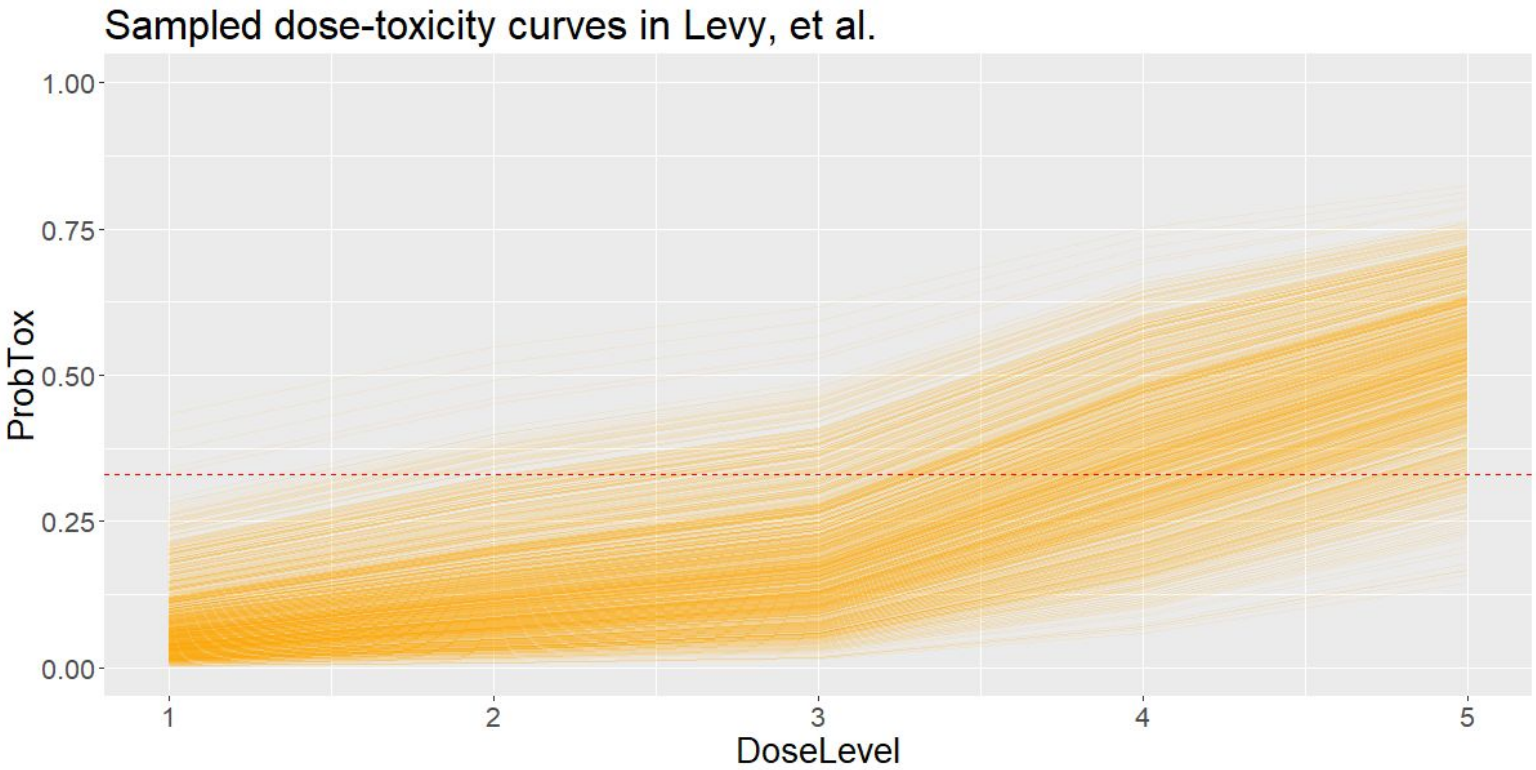

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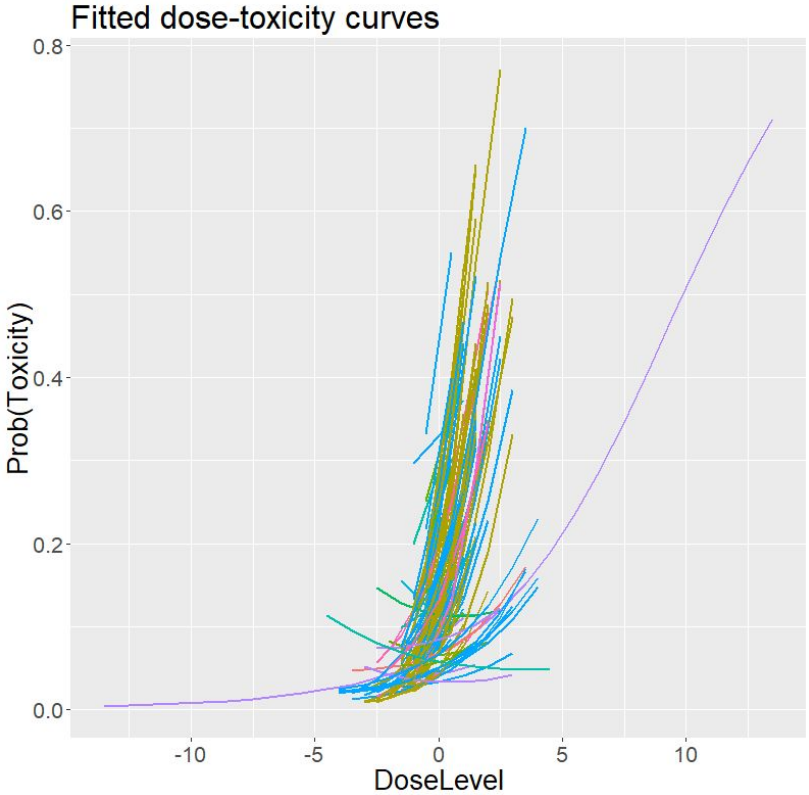
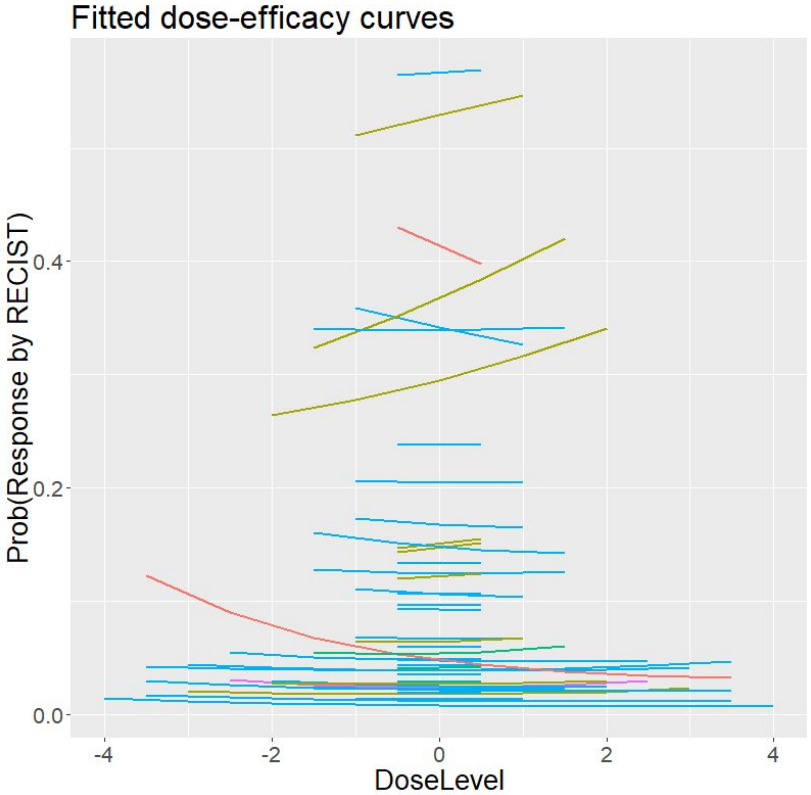
Dose-finding by toxicity & efficacy

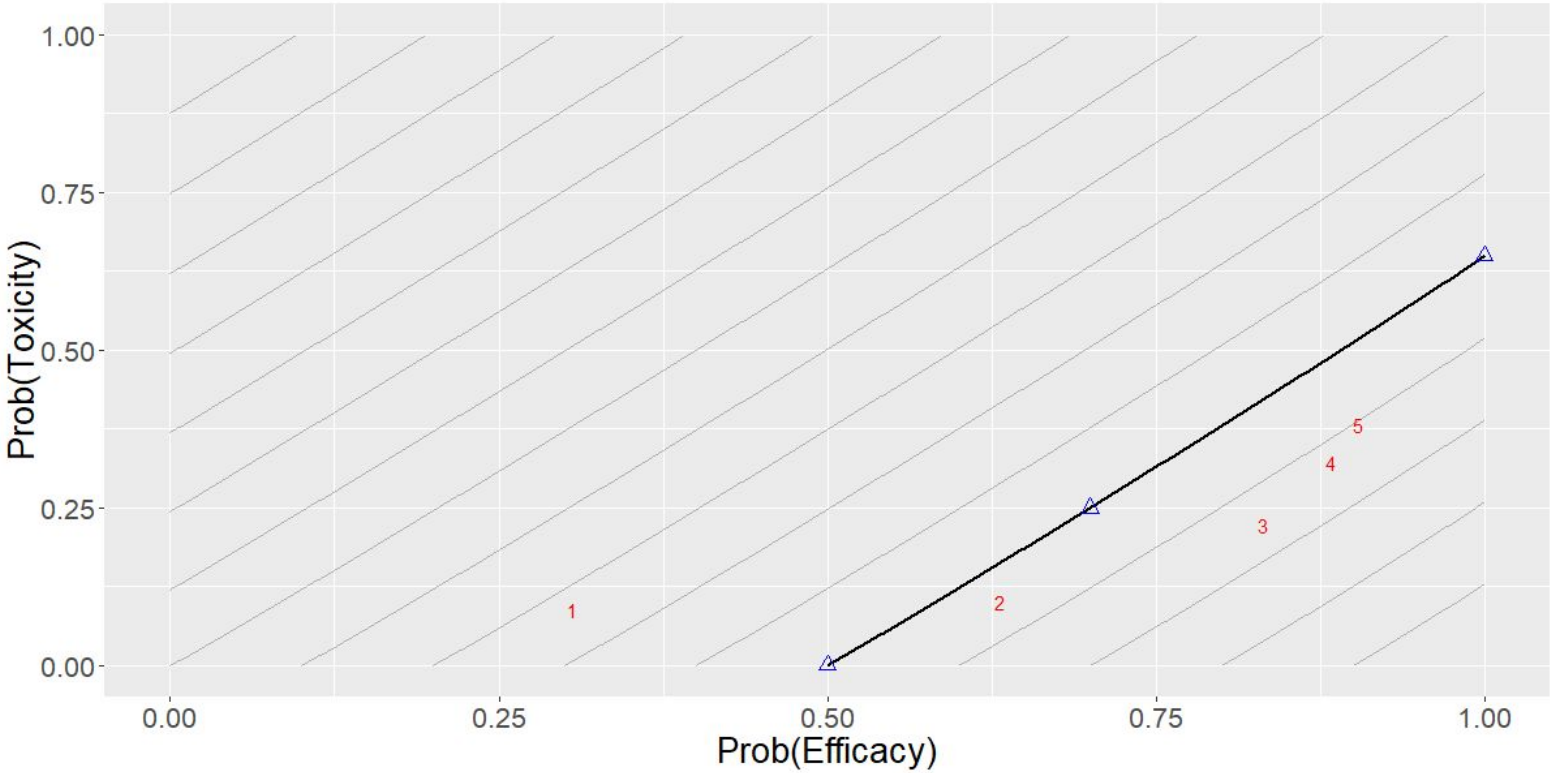
Dose-toxicity & efficacy in modern therapies





Brock, *et al.* (unpublished). Meta-analysis of the dose-toxicity and dose-efficacy curves in the manuscripts in the Chiuzan (2017) review paper.

EffTox - dose-finding based on efficacy & toxicity trade-offs



Thall, PF, and JD Cook. Dose-Finding Based on Efficacy-Toxicity Trade-Offs. Biometrics 60, no. 3 (2004): 684–93.

Posterior beliefs on attractiveness

Prob("dose in column is more attractive than dose in row")

Dose	1	2	3	4	5
1		0.92	0.86	0.82	0.8
2			0.75	0.68	0.64
3				0.58	0.54
4					0.52
5					

trialr - clinical trial designs in R & Stan

```r

# Install
devtools::install_github('brockk/trialr')
# Or
install.packages('trialr')

# CRM
levy ← '1NNN 3NNT 4NNT 4NNN 4NTN 4TNT'
skeleton ← c(0.05, 0.10, 0.15, 0.33, 0.5)
target ← 0.33
levy_mod ← stan_crm(levy, skeleton = skeleton, target = target,
                    model = 'logistic_gamma', a0 = 4,
                    beta_shape = 1, beta_inverse_scale = 1,
                    seed = 123, control = list(adapt_delta = 0.95))

# EffTox
outcomes ← '1NEN 2NBE'
mod2 ← stan_efftox_demo(outcomes, seed = 123)
# That is short-hand for
mod2 ← stan_efftox(outcomes,
                   real_doses = c(1.0, 2.0, 4.0, 6.6, 10.0),
                   efficacy_hurdle = 0.5, toxicity_hurdle = 0.3,
                   p_e = 0.1, p_t = 0.1,
                   eff0 = 0.5, tox1 = 0.65,
                   eff_star = 0.7, tox_star = 0.25,
                   alpha_mean = -7.9593, alpha_sd = 3.5487,
                   beta_mean = 1.5482, beta_sd = 3.5018,
                   gamma_mean = 0.7367, gamma_sd = 2.5423,
                   zeta_mean = 3.4181, zeta_sd = 2.4406,
                   eta_mean = 0, eta_sd = 0.2,
                   psi_mean = 0, psi_sd = 1,
                   seed = 123)

```

Future work:

- Add more trial designs :-)
- Plumb it to work with tidybayes
- More visualisation via bayesplot
- Scrutinise fit by shinystan, etc
- Automated documents via Flexdashboards?

The End

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