Optimal Sequential Predictive Probability Designs for Early Phase Expansion Cohorts

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Cleveland Clinic

This work was part of a joint effort

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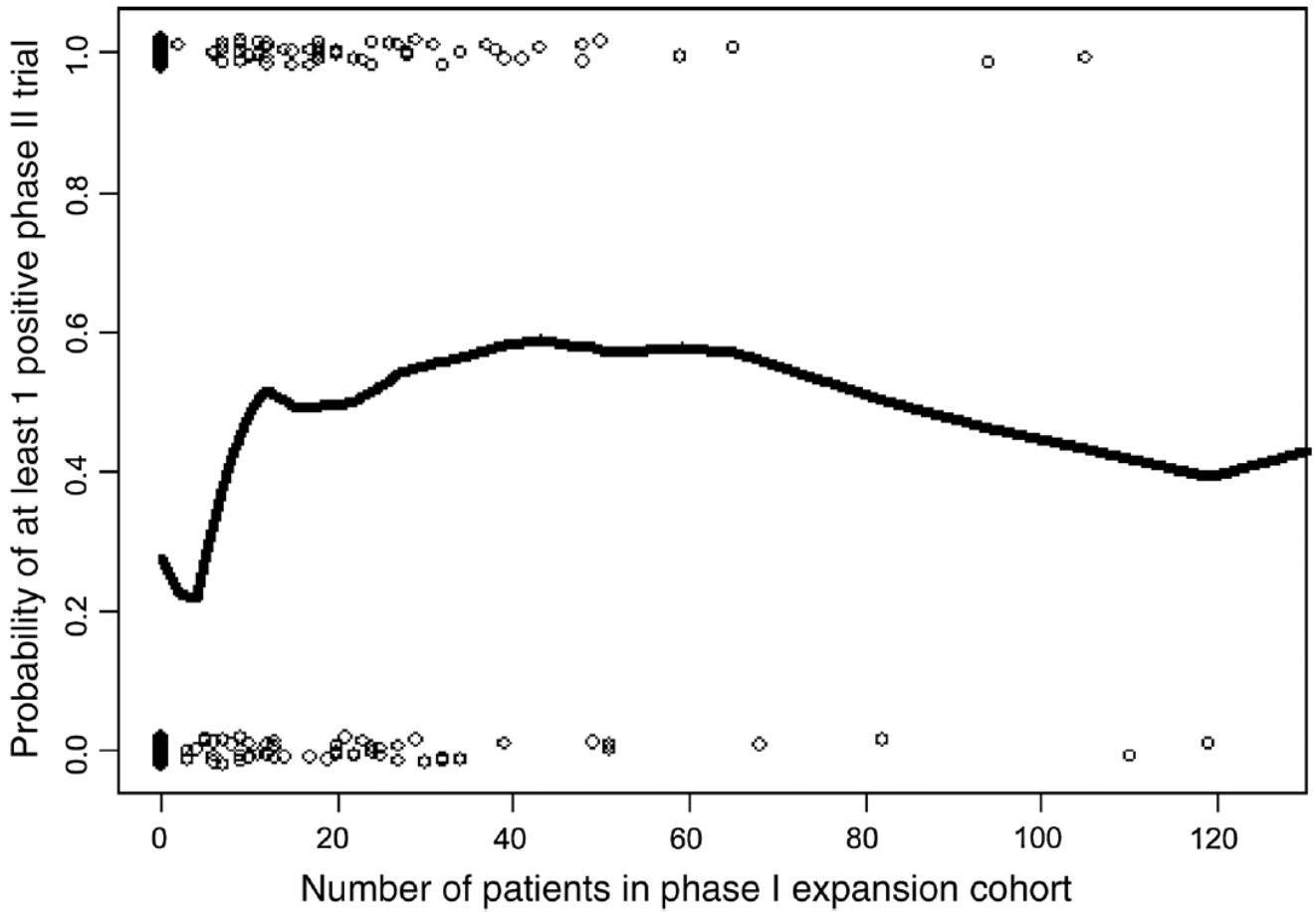
The use of expansion cohorts in phase I oncology trials is increasing over time

Table 2. Univariable Analysis of Relationship Between Trial Characteristics and Use of Expansion Cohort (N = 611)

Characteristic	No.	Use of EC		OR	95% CI	*P**
		No.	%			
Year						
2006	90	11	12	1.4	1.2 to 1.6	< .001
2007	81	12	15			
2008	100	20	20			
2009	100	20	20			
2010	132	45	34			
2011	108	41	38			

Manji et al. Evolution of clinical trial design in early drug development: systematic review of expansion cohort use in single-agent phase I cancer trials. J Clin Oncol. 2013 Nov 20;31(33):4260-7.

Trials with expansion cohorts have higher rate of phase II success; larger trials not necessarily better



Bugano et al. Use of Expansion Cohorts in Phase I Trials and Probability of Success in Phase II for 381 Anticancer Drugs. Clin Cancer Res. 2017 Aug 1;23(15):4020-4026.

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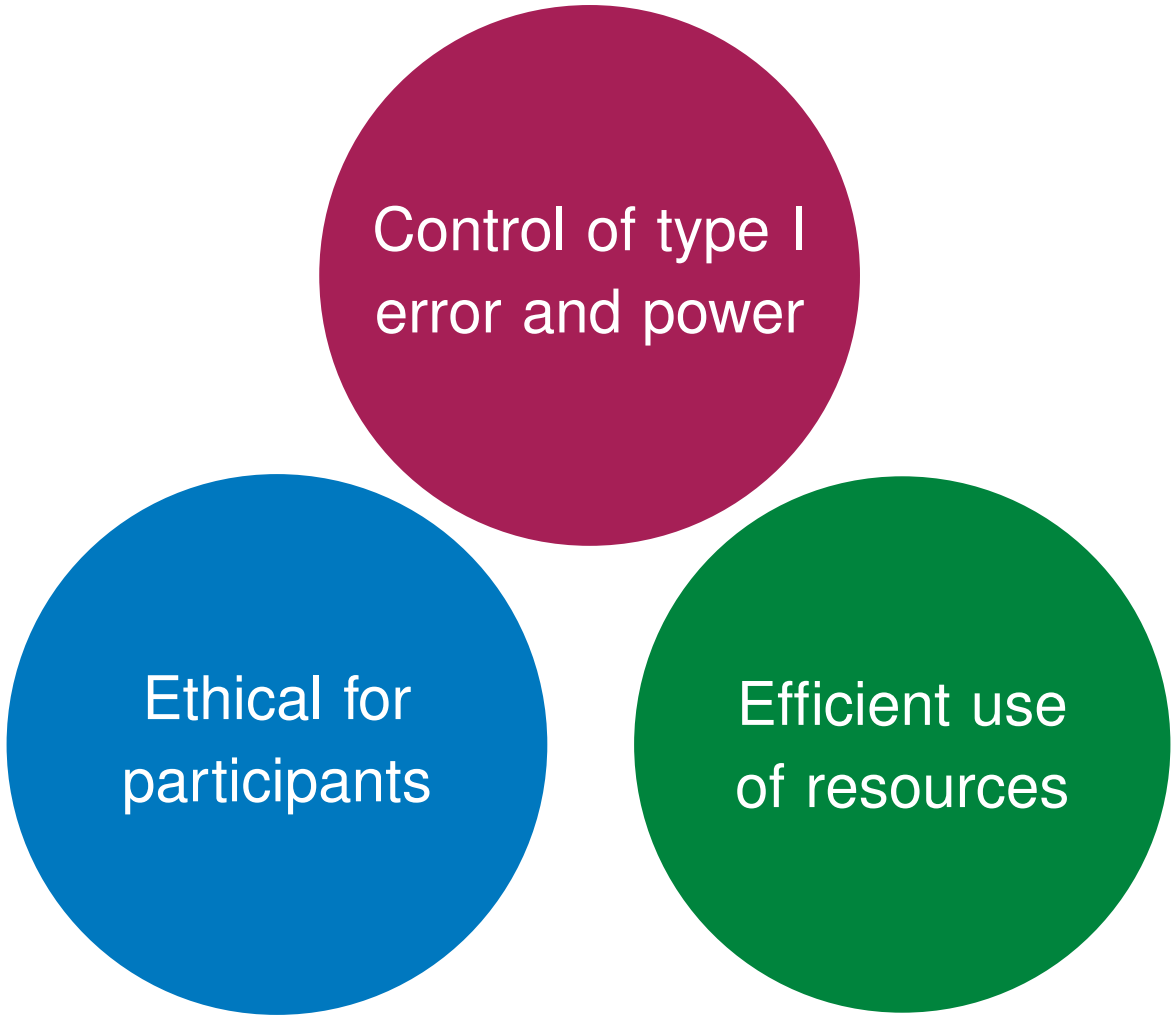
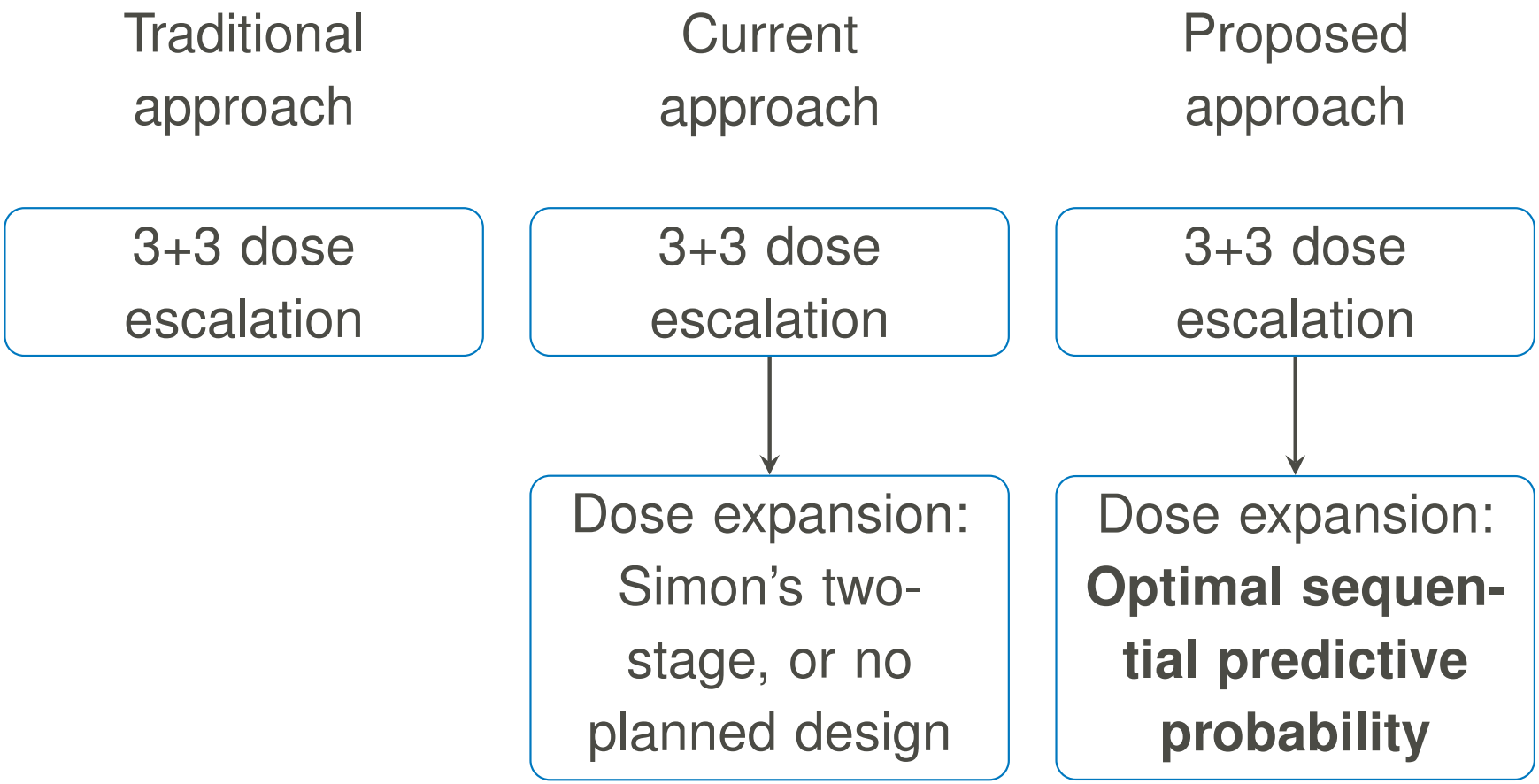
Futility stopping can be used as a mechanism to achieve multiple phase I expansion cohort goals



Optimal sequential predictive probability design is ideal for this setting



Consider the setting of a one-arm clinical trial with a binary response endpoint

Each patient i either has the outcome(or not) such that $x_1 = 1(0)$. Then $X = \sum_{i=1}^{n} x_i$ is the total number of responses out of n patients observed so far of N patients total.

We test:

$$H_0 : p \leq p_0$$

vs

$$H_1 : p \geq p_1$$

Bayesian statistical paradigm is the basis for sequential statistical learning

Prior: $\pi(p) \sim Beta(a_0, b_0)$ [Specifically $Beta(0.5, 0.5)$ here]

Likelihood: $L_x(p) \propto p^x(1-p)^{n-x}$

Posterior: $p|x \sim Beta(a_0 + x, b_0 + n - x)$

The treatment is efficacious at posterior threshold θ if:

$$Pr(p > p_0|X) > \theta$$

Predictive probability monitoring stops the trial according to a threshold

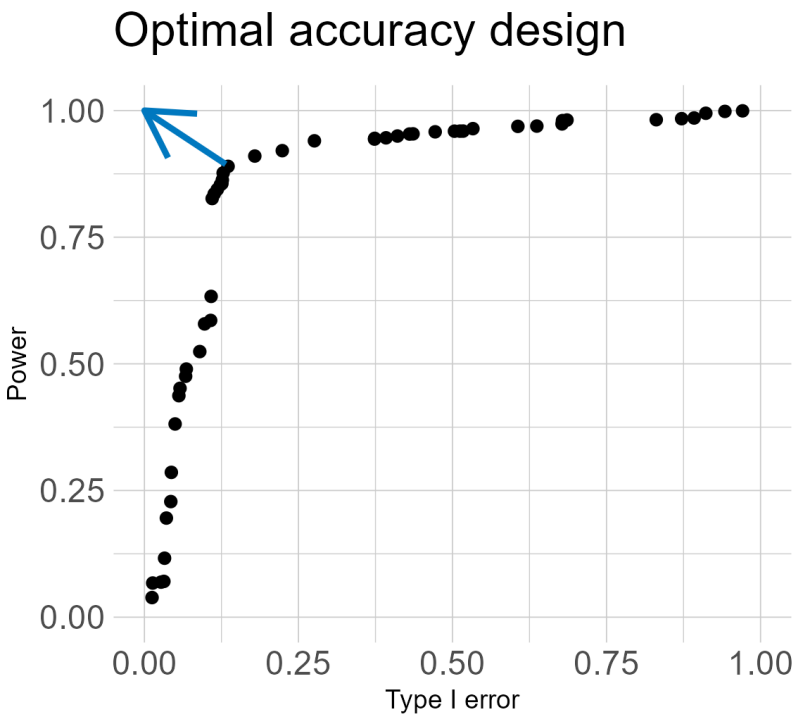
The posterior predictive distribution of the number of future responses X^* in the remaining $n^* = N - n$ future patients follows:

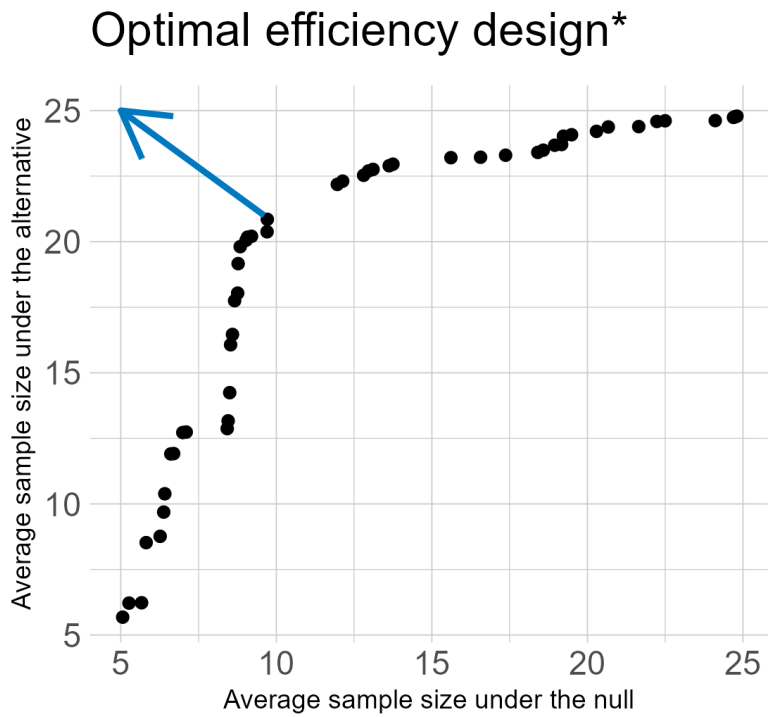
$$Beta - binomial(n^*, a_0 + x, b_0 + n - x)$$

$$PPP = \sum_{x^*=0}^{n^*} Pr(X^* = x^*|x) \times I(Pr(p > p_0|X, X^* = x^*)$$

We stop for futility at predictive threshold θ^* if $PPP < \theta^*$.

Two optimization criteria are proposed to calibrate posterior and predictive thresholds





*Subject to constraints on type I error and power

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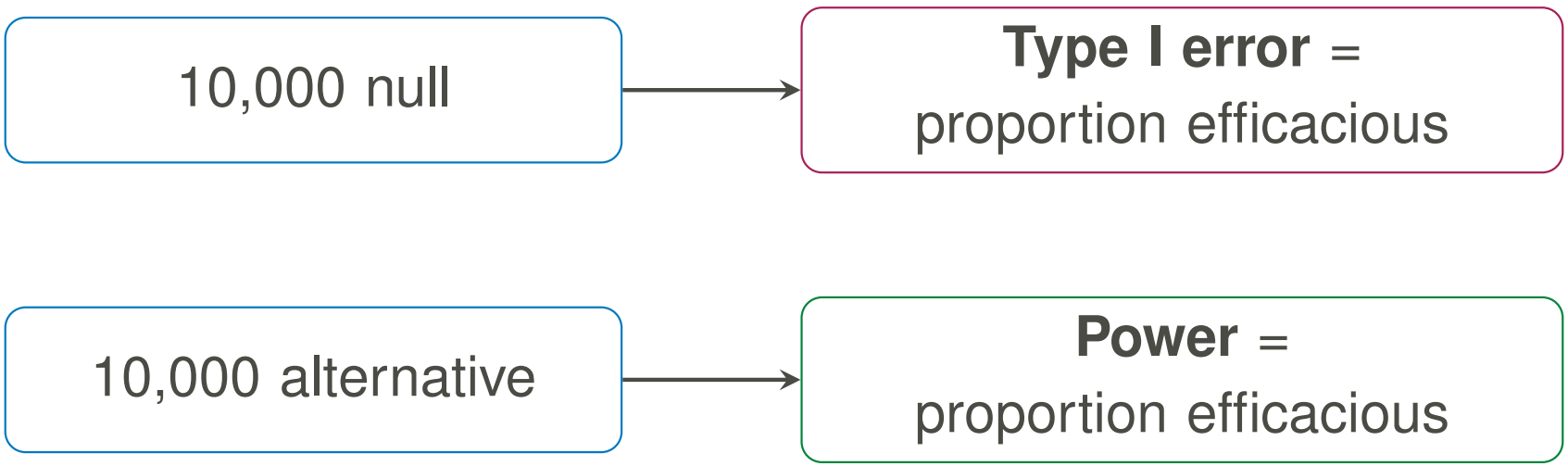
Operating characteristics of all designs are estimated in a simulation study

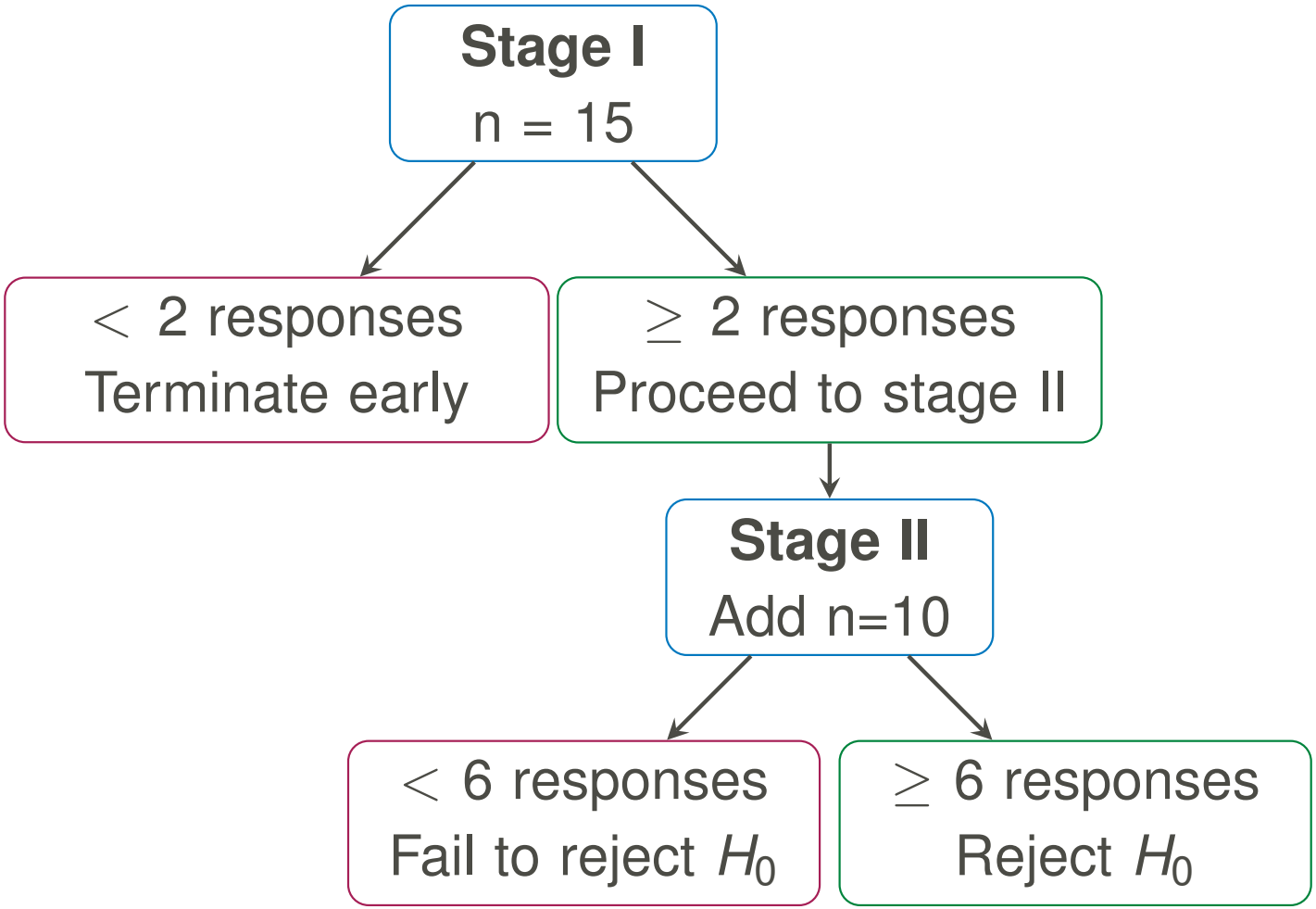
$$H_0 : p \leq 0.1$$
$$H_1 : p \geq 0.3$$



Proposed design is compared to two other common expansion cohort designs

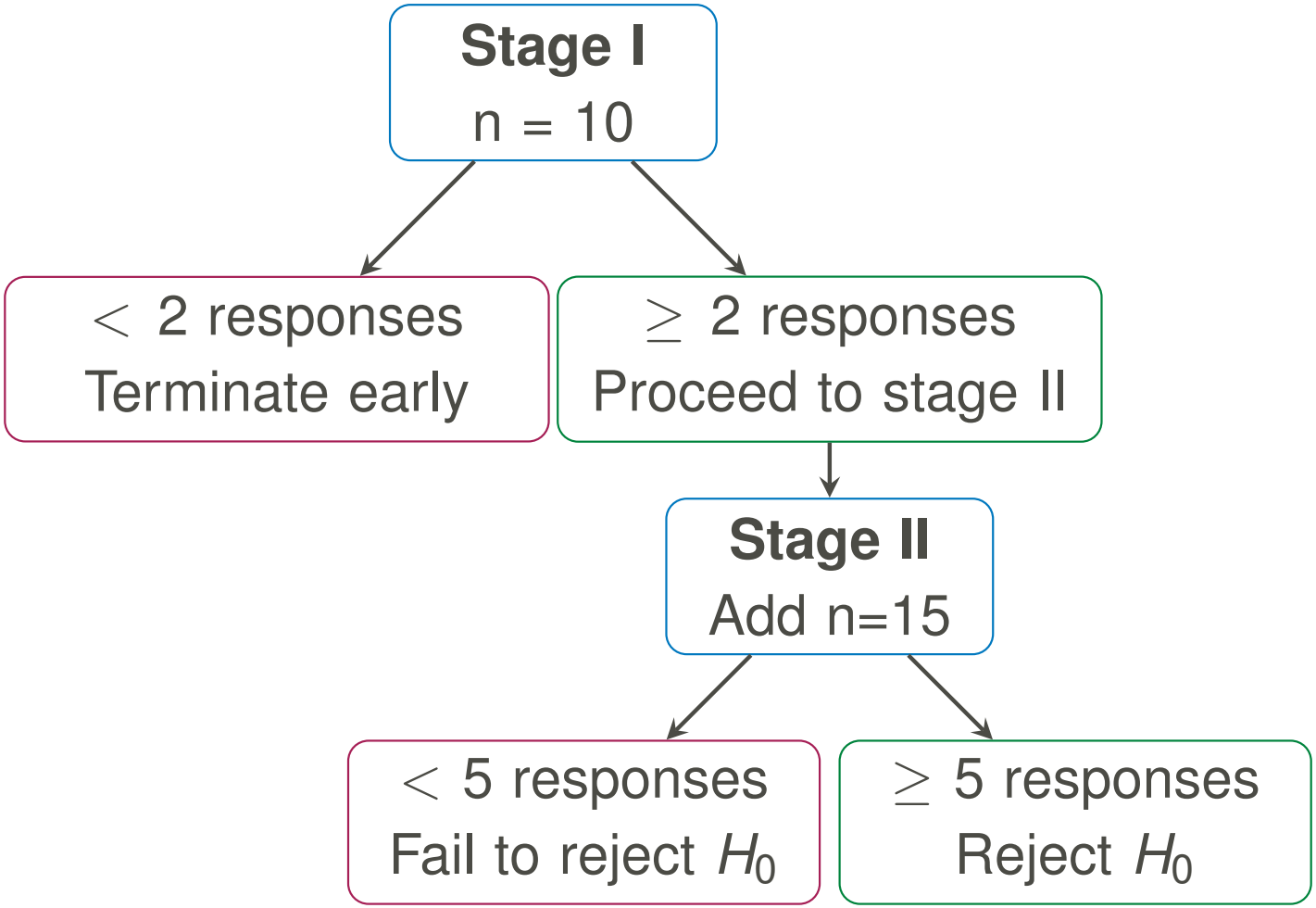
1. Optimal sequential predictive probability
2. Simon's two-stage
   - Optimal
   - Minimax
3. Posterior probability monitoring

Simon's minimax assumes a type I error of 0.05 and power of 0.8



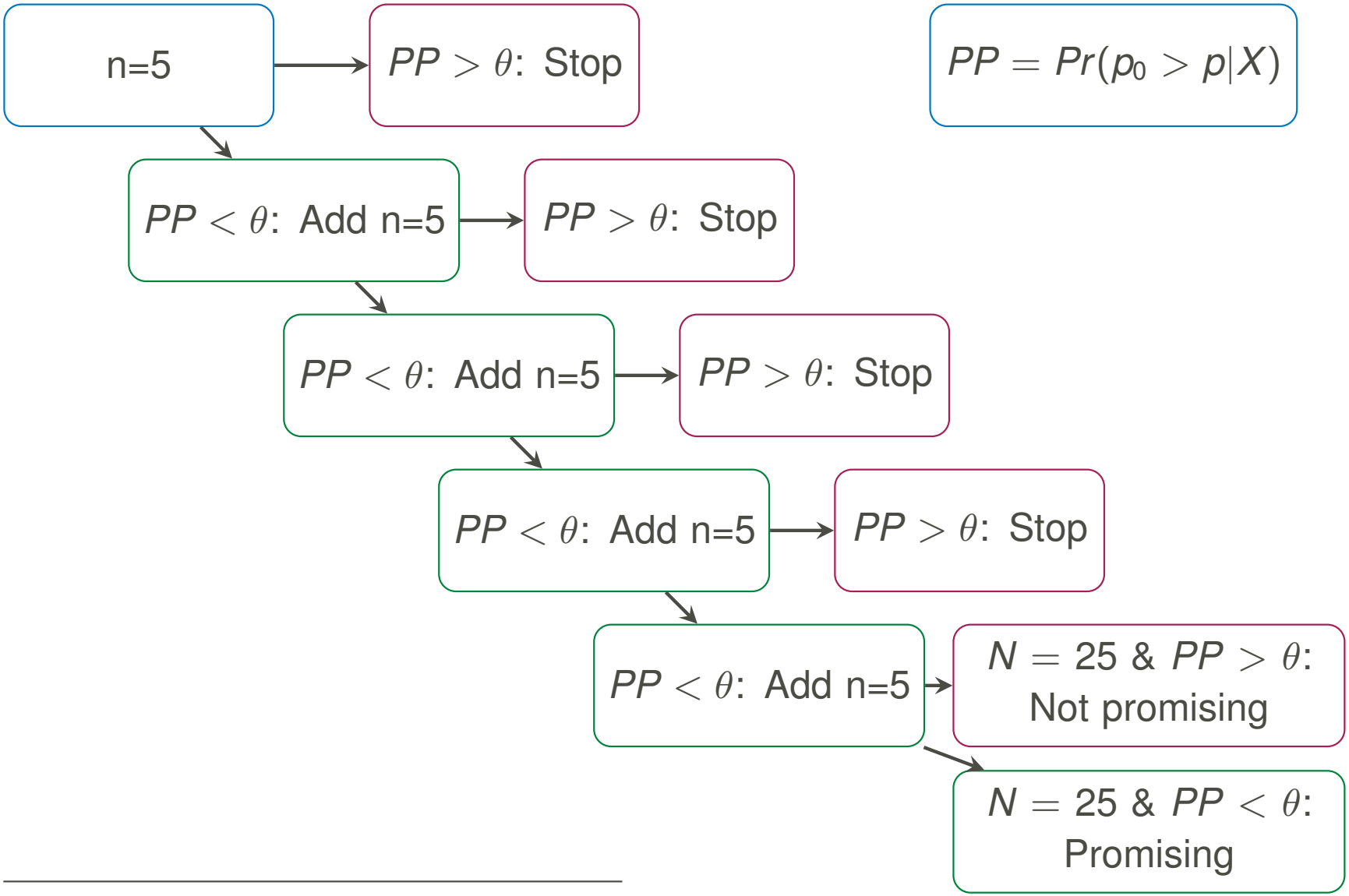
Venkatraman E. Seshan and Karissa Whiting (2022). clinfun: Clinical Trial Design and Data Analysis Functions. R package version 1.1.0. https://CRAN.R-project.org/package=clinfun

Simon's optimal assumes a type I error of 0.075 and power of 0.8 to achieve N=25



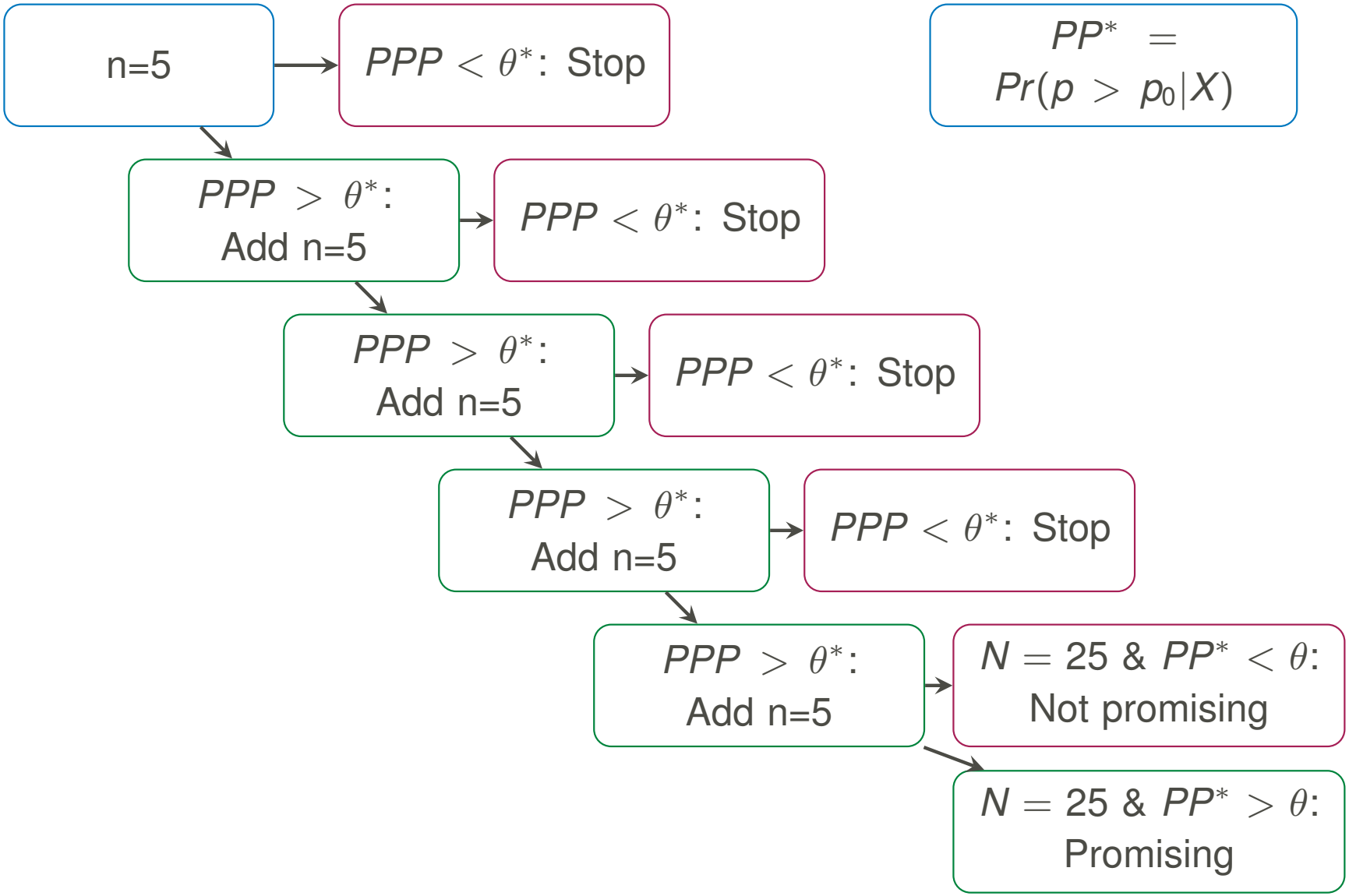
Venkatraman E. Seshan and Karissa Whiting (2022). clinfun: Clinical Trial Design and Data Analysis Functions. R package version 1.1.0. https://CRAN.R-project.org/package=clinfun

PP design examines 19 static PP thresholds



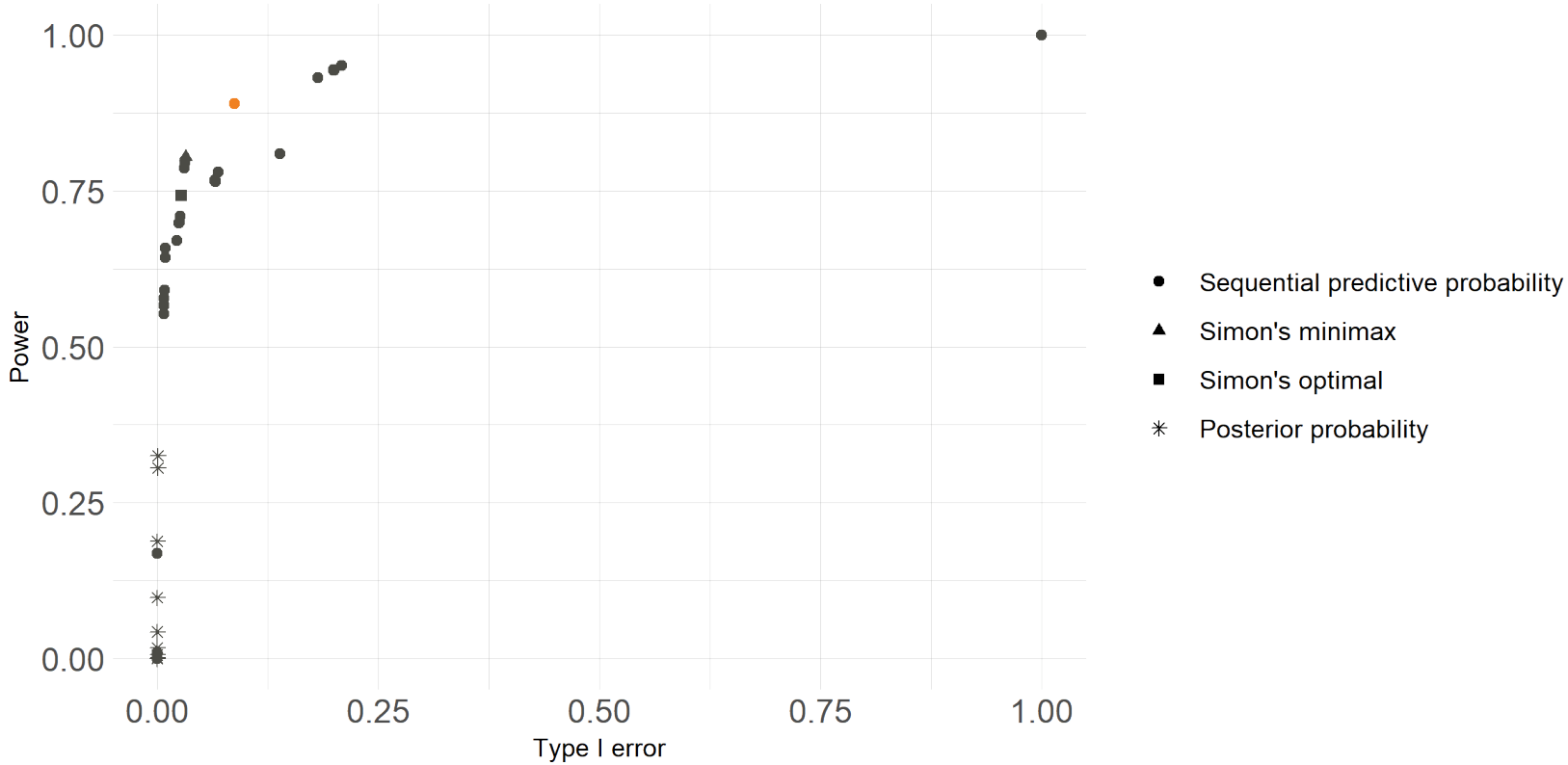
https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware/Index/12

PPP design examines 19 PP and 4 PPP thresholds



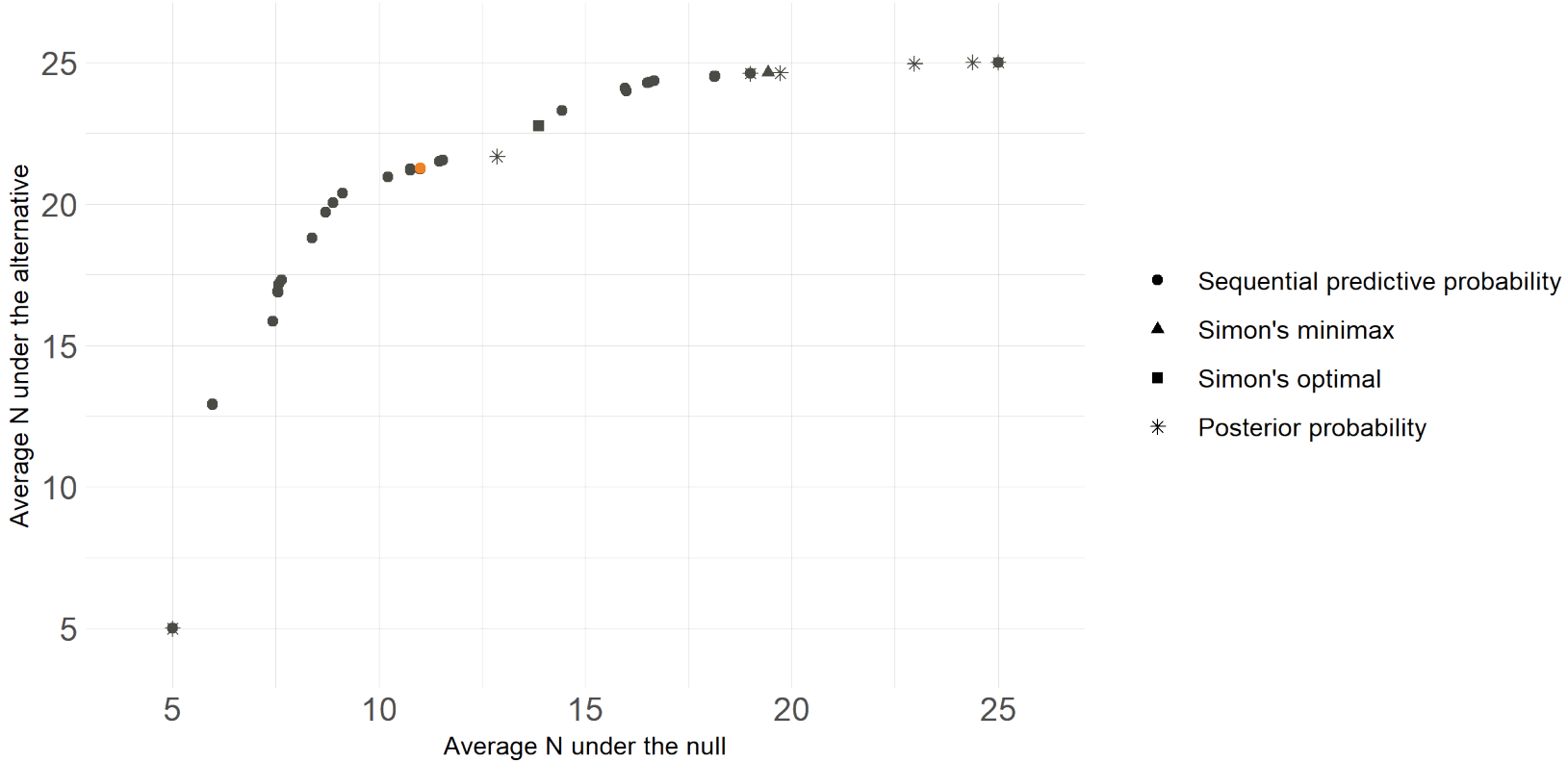
Zabor EC, Hobbs, BP and Kane, MJ. (2021). http://www.emilyzabor.com/ppseq/

The OA design has type I error 0.087 and power 0.89



- Sequential predictive probability design with posterior threshold 0.93 and predictive threshold 0.1

The OE design has type I error 0.065 and power 0.77



- Sequential predictive probability design with posterior threshold 0.86 and predictive threshold 0.2
- Average 11 and 21.3 under null and alternative, respectively

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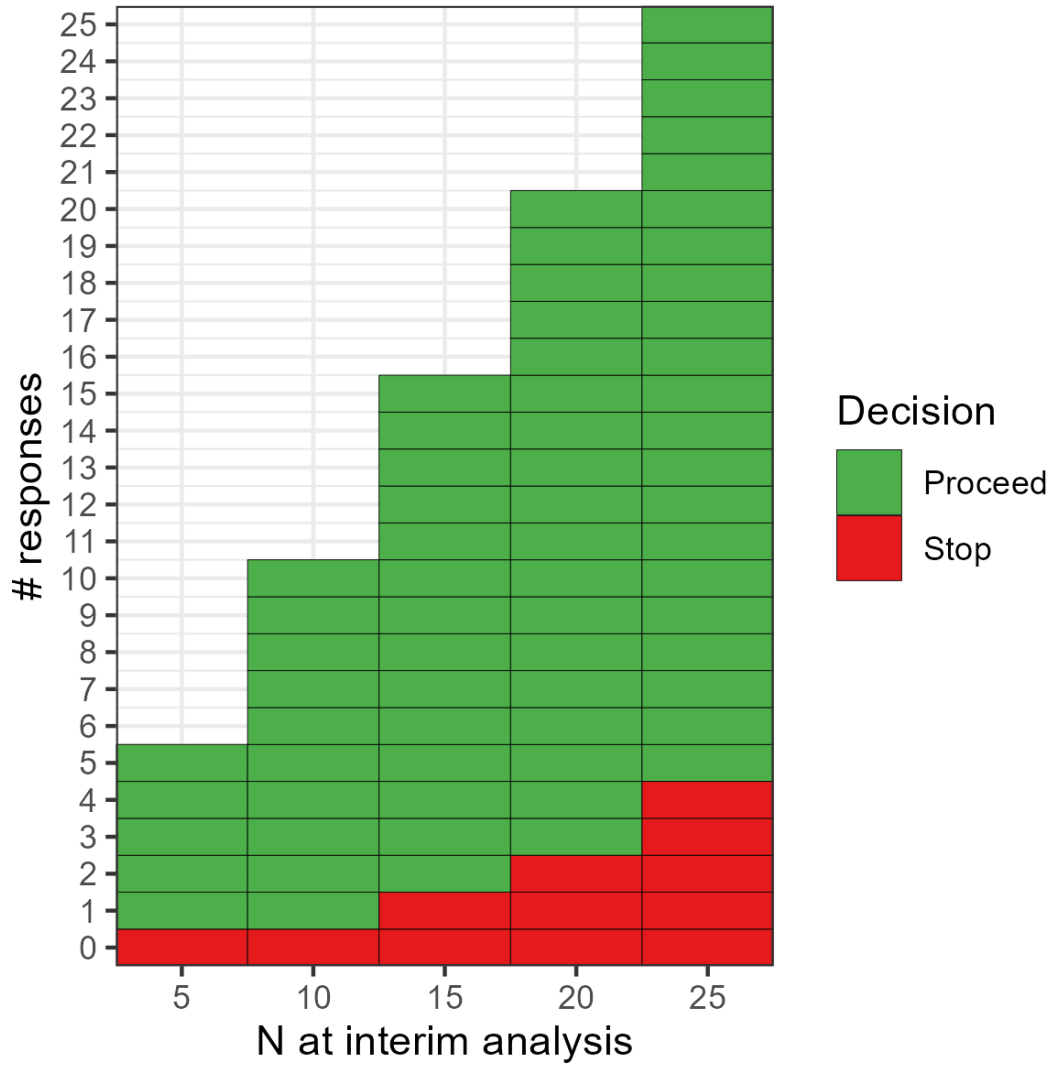
The selected design's thresholds can be mapped to a set of decision rules for easy implementation



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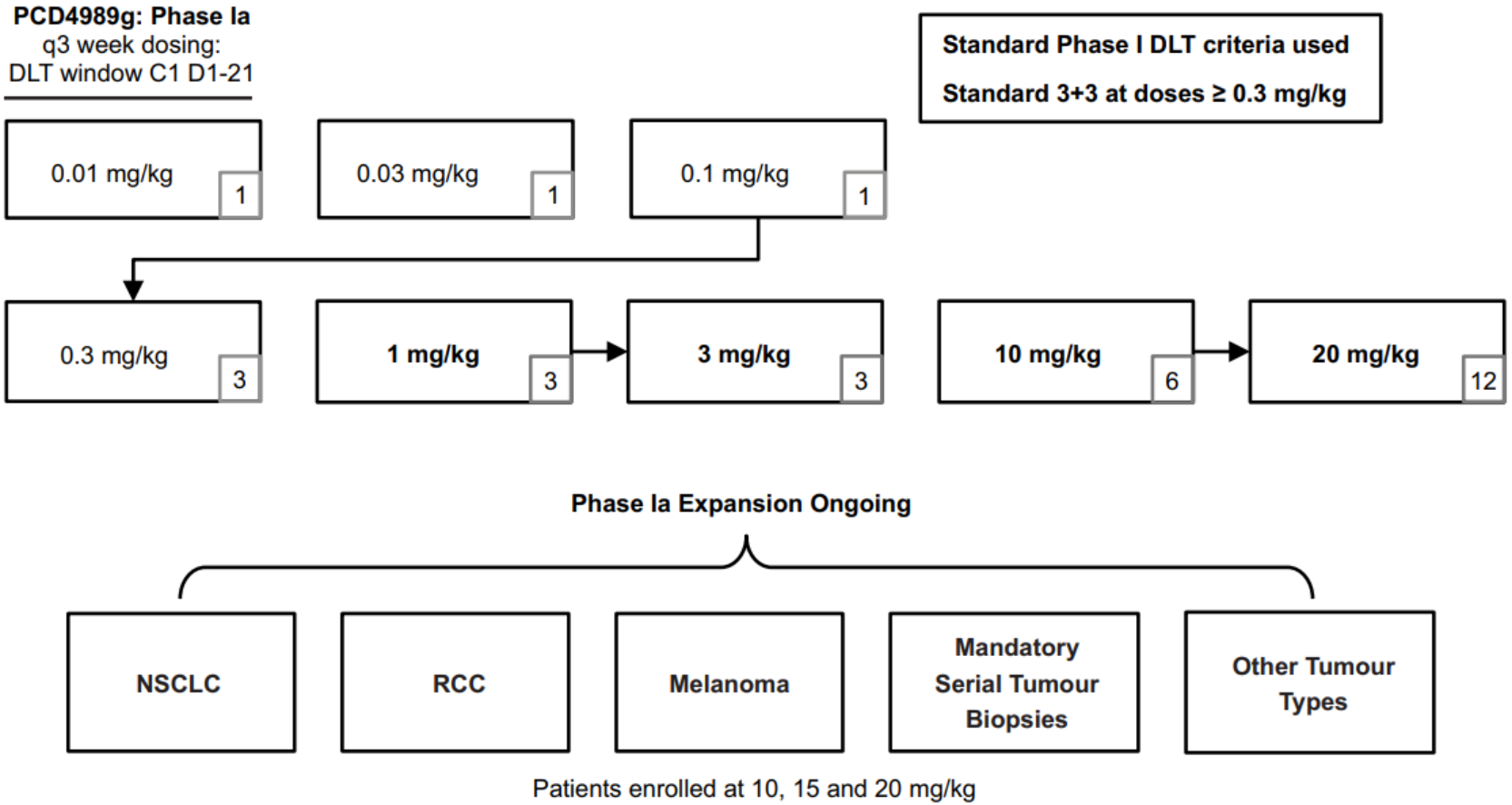
Phase I trial of atezolizumab planned three expansion cohorts; metastatic urothelial carcinoma added later



Herbst et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014 Nov 27;515(7528):563-7.

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The planned design of the mUC expansion cohort was not clear

Original expansion cohort design:

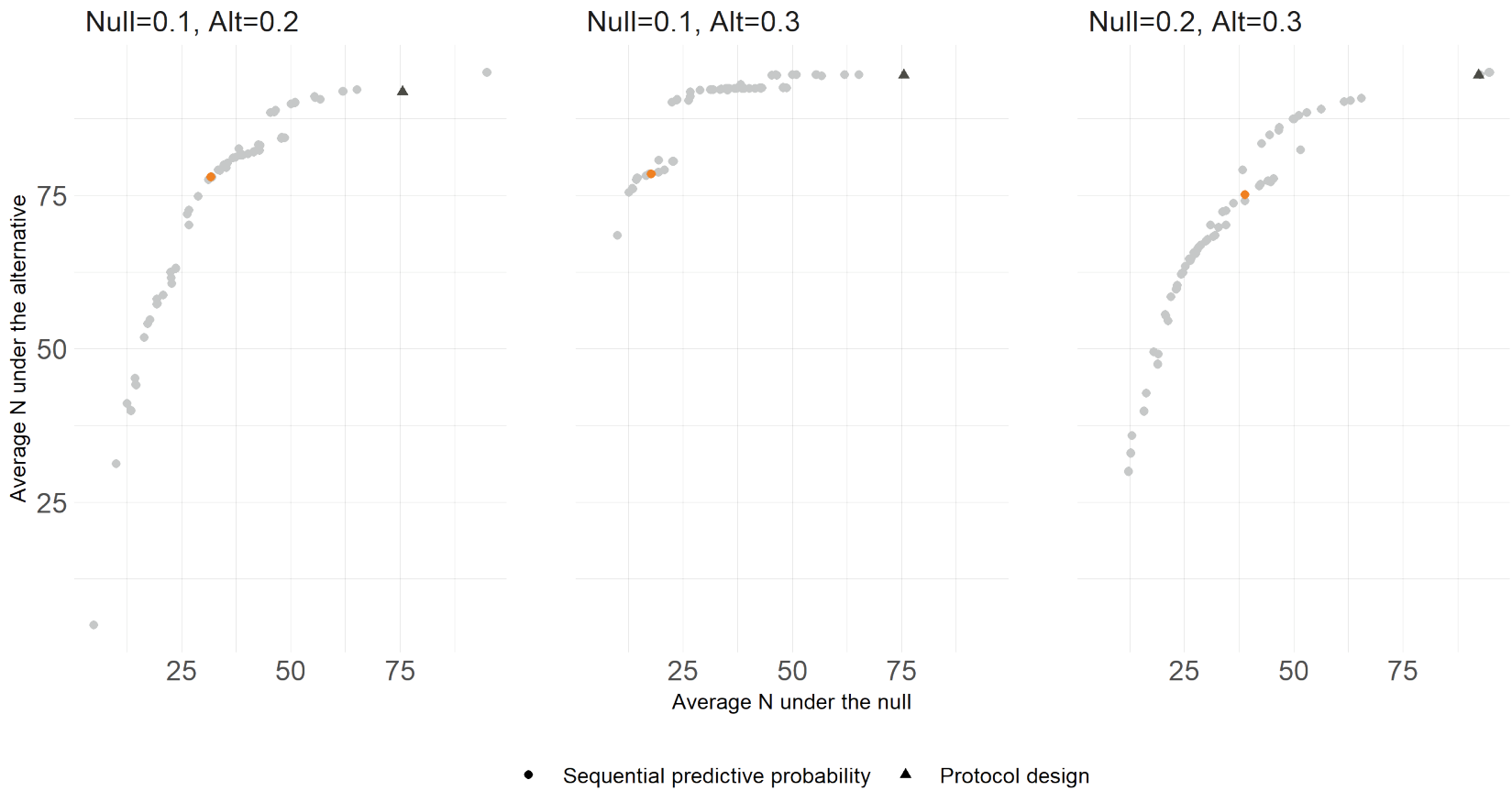
- Total sample size of 40
- Single interim futility look: stop the trial if 0 responses in first 14 patients
- 4.4% chance of stopping if true response rate $\geq 20\%$

But mUC cohort enrolled 95 patients...

Six simulation settings were investigated based on the original/inferred atezolizumab trial design

Null response rate	Alternative response rate	N
0.1	0.2	95
0.1	0.3	95
0.2	0.3	95
0.1	0.2	40
0.1	0.3	40
0.2	0.3	40

OE designs have higher power and lower average sample size under the null than protocol designs



*For N=95

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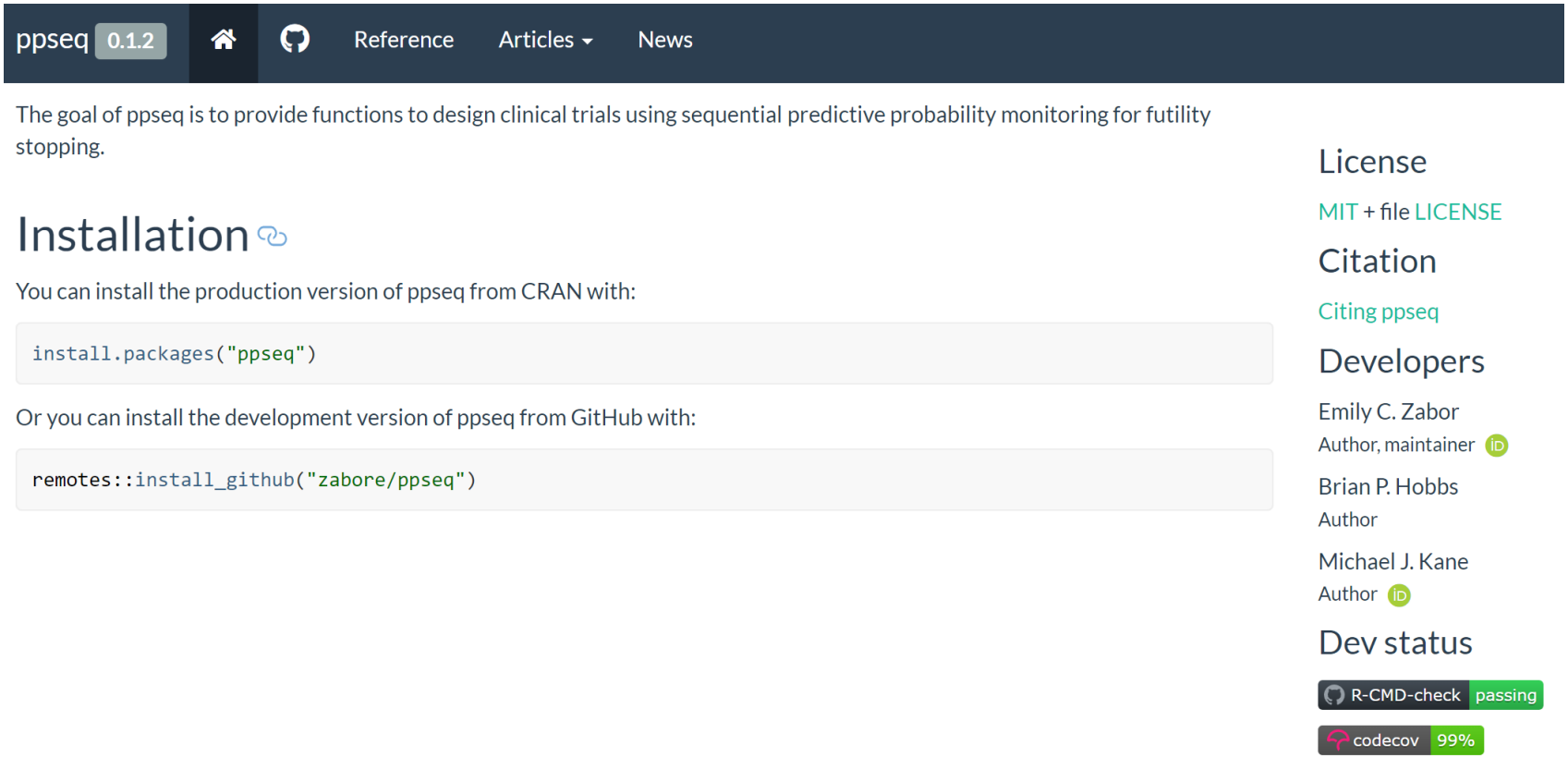
Protocol designs have type I error < 0.01 and power around 50% when N=95

Null	Alt	Design	Post	Pred	α	$1-\beta$	$\bar{N}$ Null	$\bar{N}$ Alt
0.1	0.2	OA	0.90	0.05	0.072	0.883	51	90
0.1	0.2	OE	0.95	0.15	0.041	0.723	32	78
0.1	0.2	Protocol	NA	NA	0.005	0.528	76	92
0.1	0.3	OA	0.96	0.05	0.029	0.992	45	95
0.1	0.3	OE	0.97	0.20	0.018	0.814	18	79
0.1	0.3	Protocol	NA	NA	0.000	0.499	76	95
0.2	0.3	OA	0.82	0.05	0.141	0.874	56	89
0.2	0.3	OE	0.86	0.10	0.081	0.703	39	75
0.2	0.3	Protocol	NA	NA	0.009	0.499	92	95

*For N=95

R package {ppseq} implements optimal sequential predictive probability design



ppseq 0.1.2 | Reference | Articles | News

The goal of ppseq is to provide functions to design clinical trials using sequential predictive probability monitoring for futility stopping.

Installation

You can install the production version of ppseq from CRAN with:

```
install.packages("ppseq")
```

Or you can install the development version of ppseq from GitHub with:

```
remotes::install_github("zabore/ppseq")
```

License

MIT + file LICENSE

Citation

Citing ppseq

Developers

Emily C. Zabor
Author, maintainer

Brian P. Hobbs
Author

Michael J. Kane
Author

Dev status

R-CMD-check passing

codecov 99%

Zabor EC, Hobbs, BP and Kane, MJ. (2021). http://www.emilyzabor.com/ppseq/

Thank you! Questions?

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