Bayesian Accrual Monitoring and Prediction with Software Tools

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Background

- Slow patient accrual
  - degrades the cost/benefit ratio of a trial
  - raises critical questions for IRBs and DSMBs
  - Aware of problems in need of a solution
- Critical need tools for estimating accrual that
  - capture all the sources of uncertainty
  - Has as much mathematical rigor as currently used for sample size
- Early identification of accrual problems will allow oversight groups to propose improvements for accrual

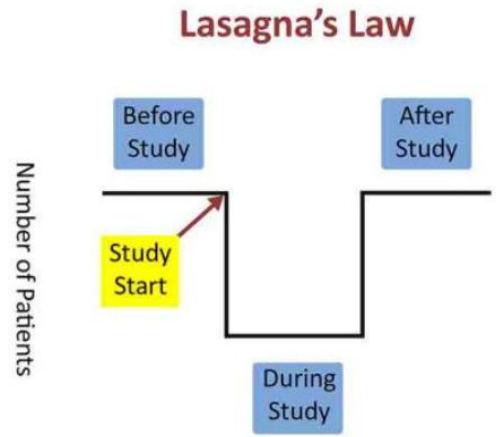
Startling Facts

In 2007 only 7% (USA) to 18% (Europe) of studies were completed on schedule. The delay was greater than 1 month in 41% (Latin America) to 70% (USA) of studies (*CenterWatch 2007*).

In the USA 57% of delays were due to slow patient recruitment and enrollment, and to protocol amendments (*Thomson CenterWatch 2007*).

Typically 30% of investigators recruit no patients or just one patient.

The number of patients predicted by investigators typically plummets by up to 90% at the start of a study (*attributed to Dr Louis Lasagna*).



"The number of patients available to join a trial drops by 90% the day a trial begins.
They re-appear as soon as the study is over."

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Long-term goal

Reduce the proportion of trials that fail to meet accrual targets by providing a tool for ethical research oversight and for ensuring equity in selecting and recruiting study populations.

Goals Today

(1) Develop and test a software program for accrual.

- interface similar to the power and sample size applets (e.g. Lenth)
- probability that the trial will finish within the planned time frame

(2) Develop a hierarchical extension to the accrual model.

- Extend previous model to include situation where investigative team “over promised”

Constant Accrual Model

- Plan: recruit *n* subjects in *T* days.
- Assumption: waiting time (*w*) for each successive patient follows an exponential distribution, $w_i \sim \exp(\theta)$
  - θ represents the average accrual time for the *i*th subject.
- Prior distribution of θ is assumed to be inverse gamma, $\theta \sim IG(nP, TP)$,
  - *P* is the investigator's confidence in the original plan, measured on a 0-1 scale.
- During the trial, *m* subjects have been collected in T_m.
- Posterior distribution for θ
  - $\theta|w \sim \mathrm{IG}(nP + m, TP + T_m)$
  - $\boldsymbol{E(\theta|w) = \left(\frac{nP}{nP+m}\right)\frac{T}{n} + \left(\frac{m}{nP+m}\right)\frac{T_m}{n}}$

    = "Prior" + "Data"

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= "Prior" + "Data"

Constant Accrual: *Predicting the Future*

- For fixed *n*, the waiting time for the rest of the rest of the waiting time is $\tau = \sum_{i=m+1}^{n} w_i$.
- Derived predictive distribution of τ
- The percentile of τ can be obtained by
  - $p(\tau) = (\mathrm{TP} + T_m)\frac{p(B)}{1-p(B)}$
  - p(B) ~$beta(n-m, nP+m)$
- $T_p = T_m + \tau$.

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  Observed + Future

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(1) Develop and test a software program for accrual

- R *accrual* package, three major functions and a graphical user interface that provides menu driven access
- web-based calculator
- smartphone application

Example

- In a clinical trial, the researcher's original proposal is to
  - recruit n=300 patients in 3 years
  - T=36 months.
  - Assuming that the investigator is 50% confident that the accrual can be done within the planned time
  - P=0.5.
- accrual.gui()

R

- Packages-> Load Packages
- Select one-> accrual
- library(“accrual”)
- accrual.gui()

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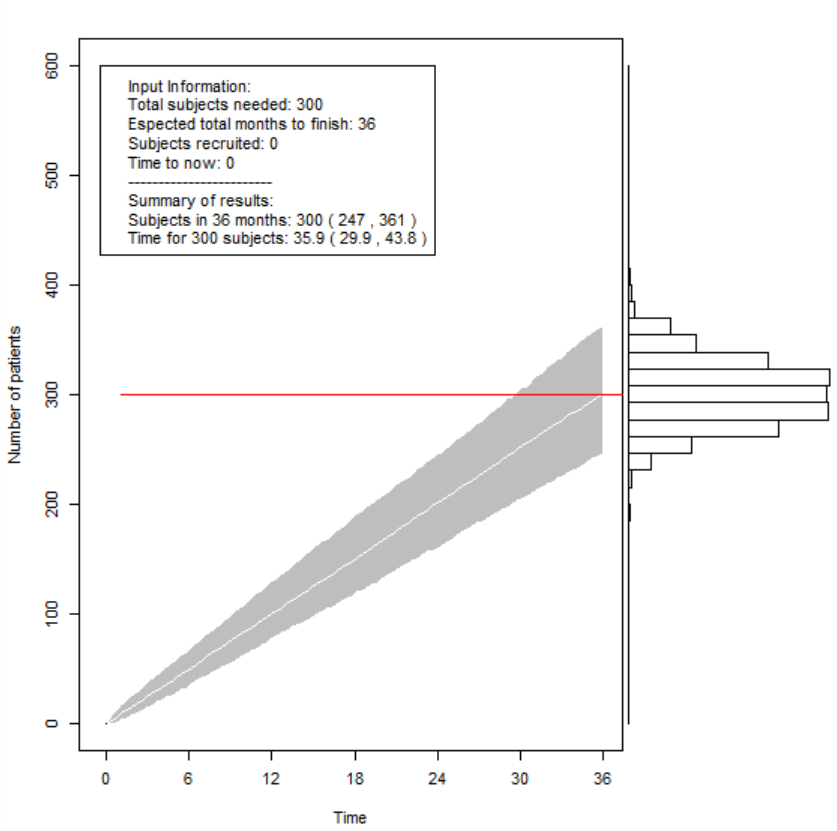

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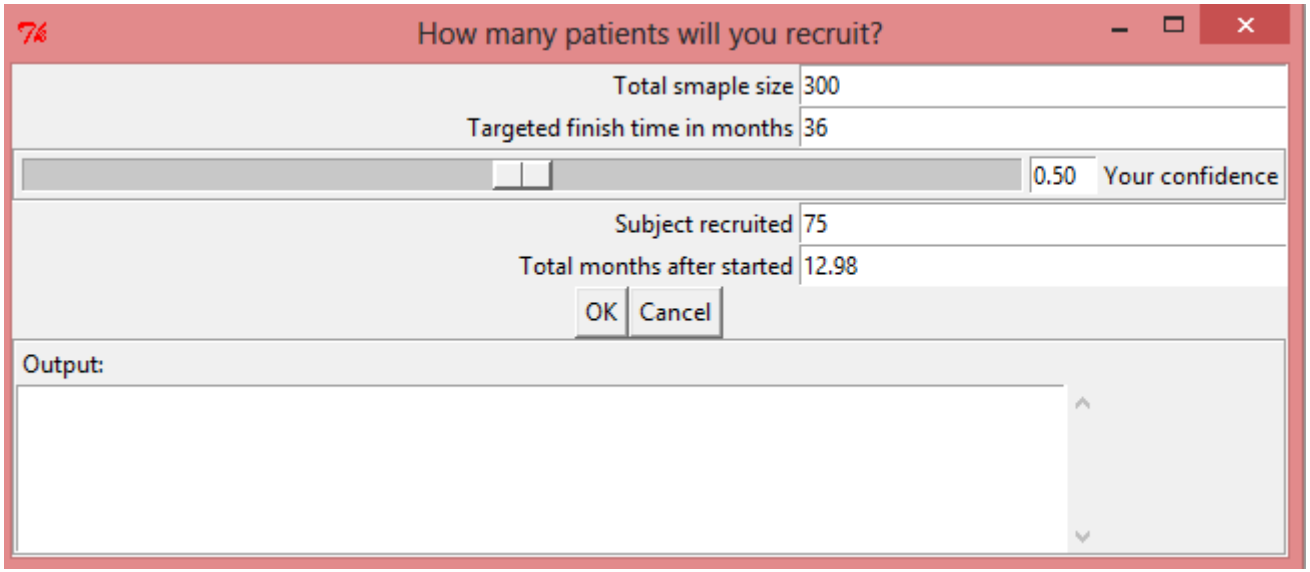

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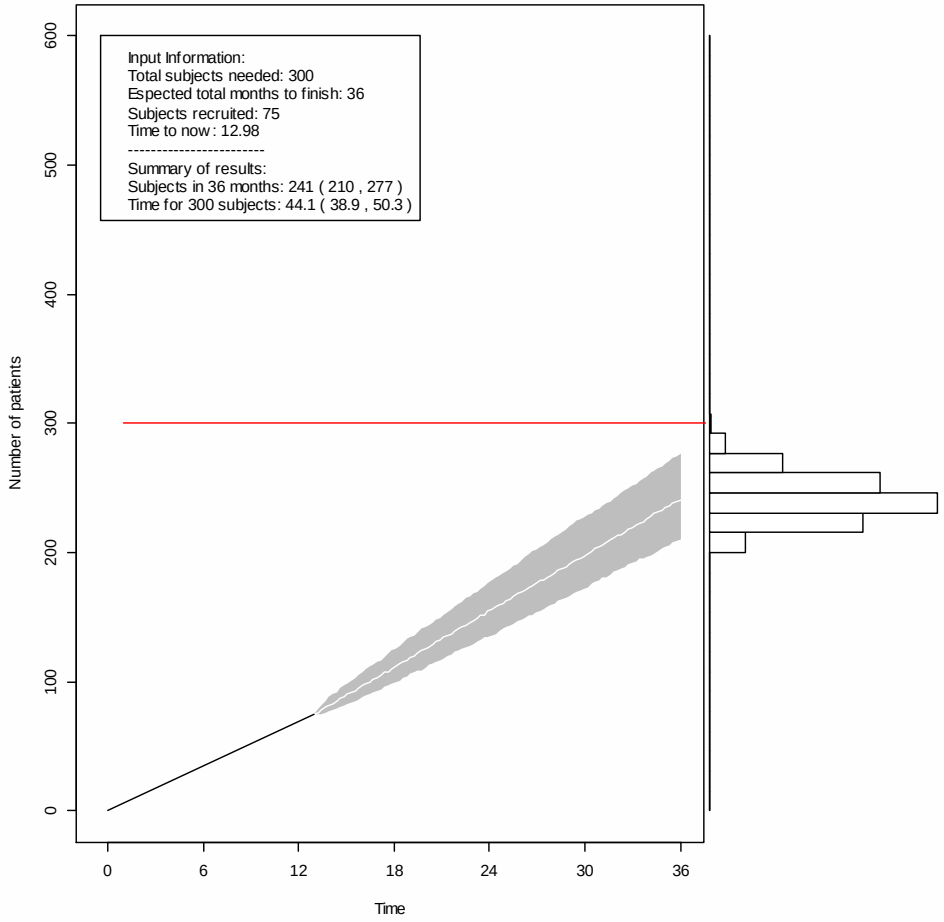

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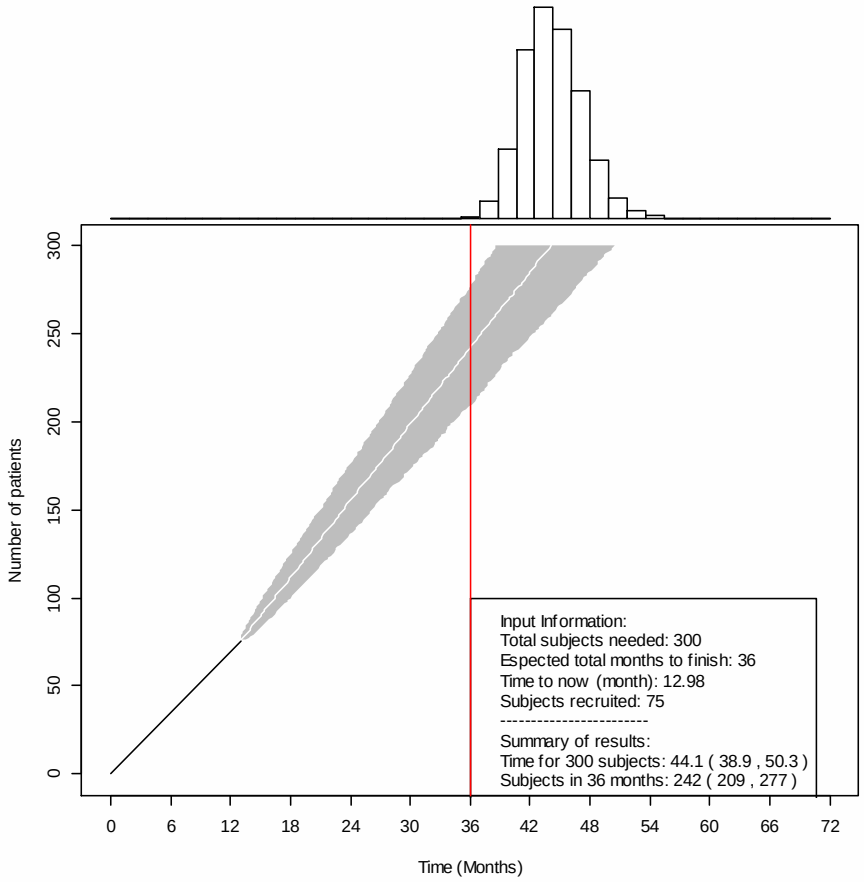

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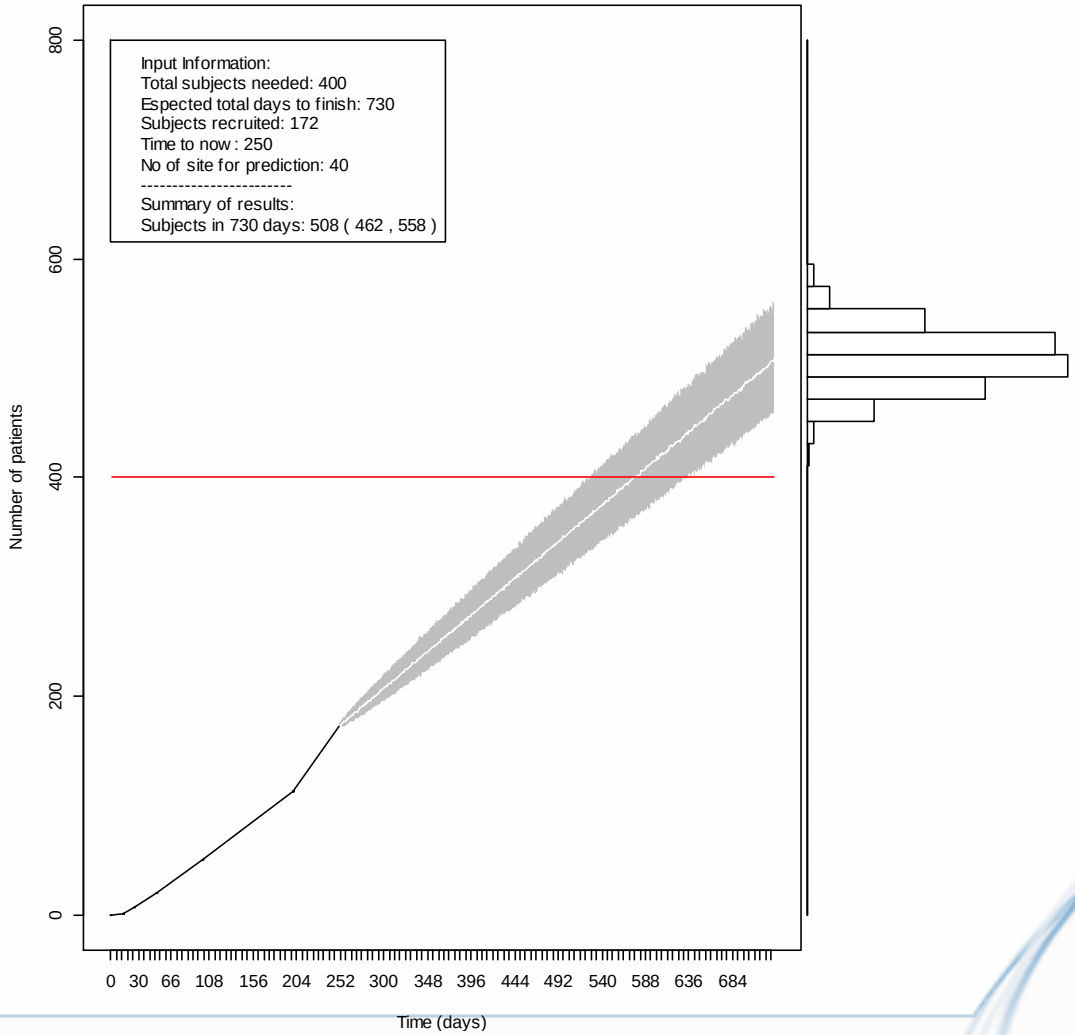
Multi-site version



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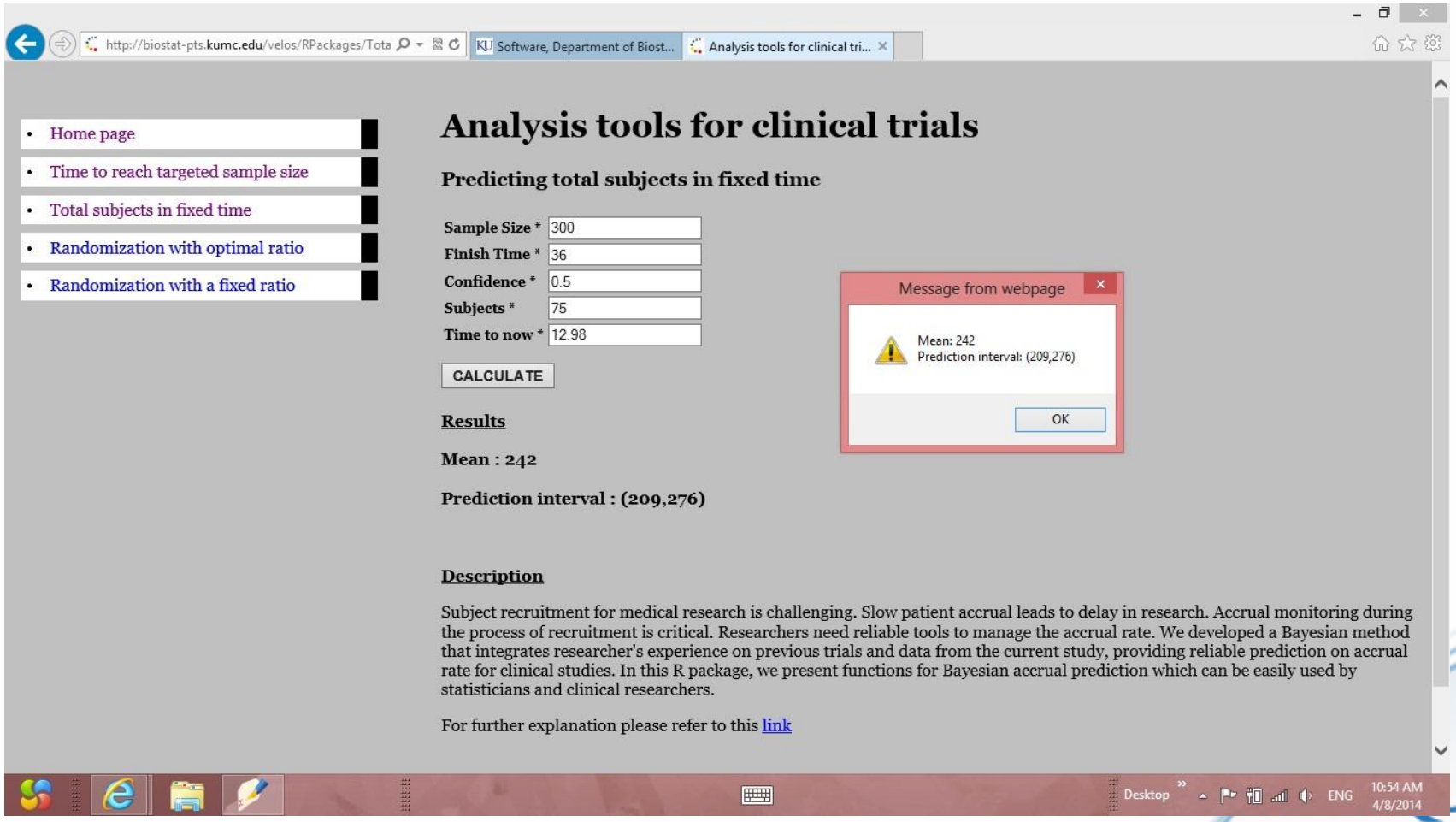
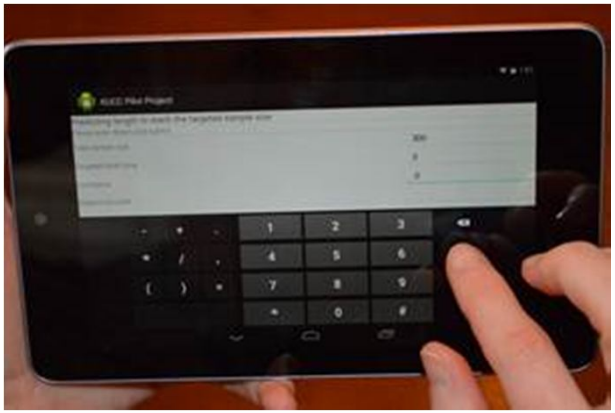
Web-based Calculator

- biostatistics.kumc.edu
  - Software
  - **Software Tools for Clinical Trial Design and Accrual Monitoring**
  - Total subjects in fixed time

Web-based Calculator



Smartphone Application



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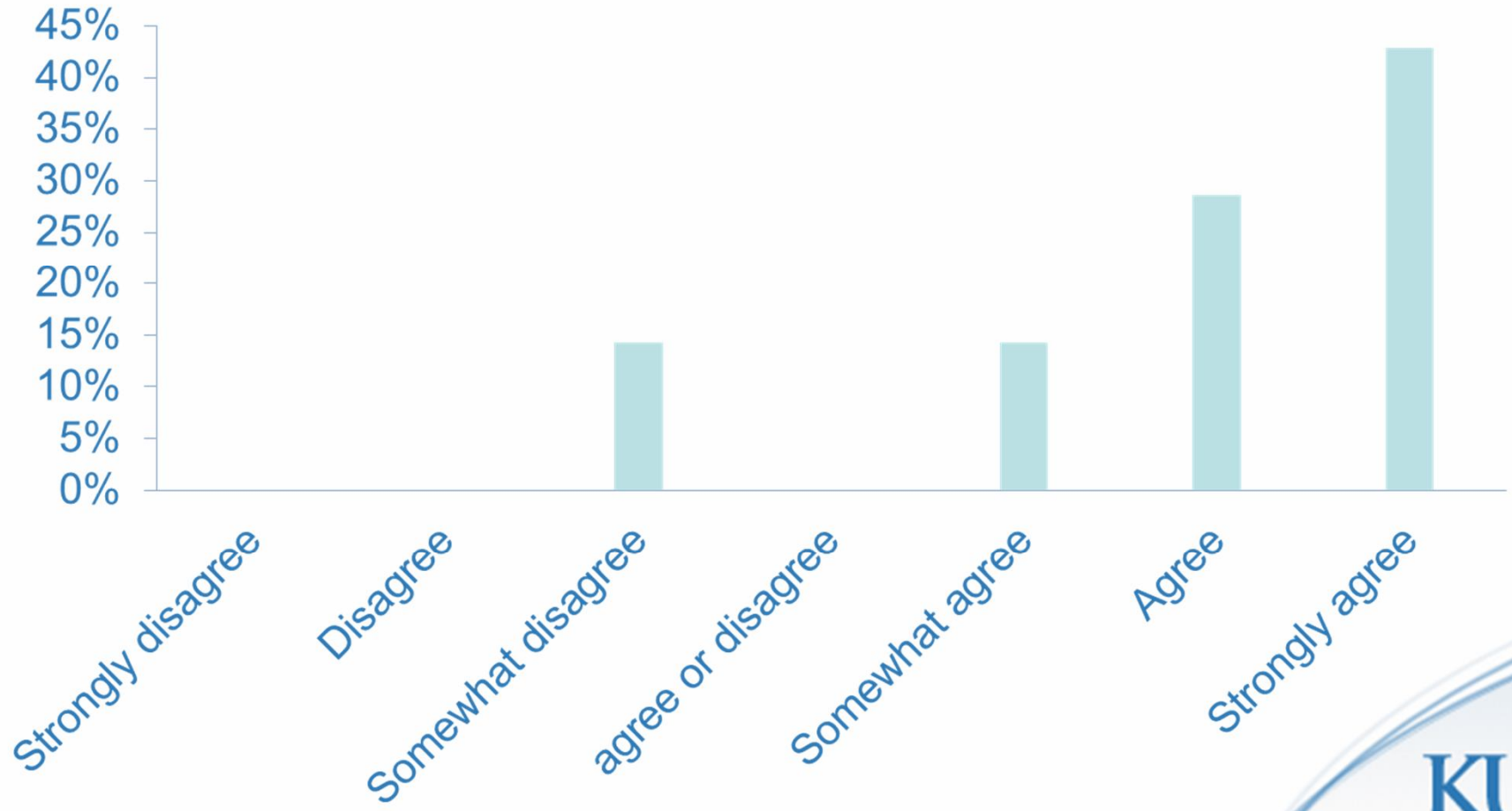
From clinical investigators:

"I would recommend this software to other researchers"



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(2) Develop a hierarchical extension to the accrual model

- What if the researcher provides a strongly informative prior distribution that is substantially off target?
  - "Bad" Prior+Data ≤ Data ≤ "Good" Prior+Data
    - David Draper
- Two Possible Fixes
  - Accelerated Prior
  - Hedging Prior

Accelerated Prior (AP)

- $P = 1 - \frac{m}{n}$
- In the beginning of the trial, m=0 and P=1, the posterior distribution of θ relies entirely on the prior specification.
- As more accrual data is collected, the value of P will shrink, and place less weight on the prior distribution as more data is collected.
- When m is equal to n, P will be 0 and the posterior estimation of θ will only be based on data.

Hedging Prior (HP)

- P presents the similarity of the current trial with historical information.
- Prior distribution for P: uniform (0, 1).
- Hedging prior (HP)

$$\pi(\theta, P|n, T) = \frac{(\mathrm{TP})^{\mathrm{nP}}}{\Gamma(\mathrm{nP})}\left(\frac{1}{\theta}\right)^{nP+1} e^{-\frac{TP}{\theta}}$$

- If the trial is off target, the distribution of P downward, downweighting of the strength of the prior distribution.

Hedging Prior (HP)

- Hedging prior is a special case of modified power prior
  - $\pi(\theta, P|n, T) = C(P)L(\theta|n, T)^P \pi_0(\theta)\pi(P)$
  - $C(P) = \frac{1}{\int L(\theta|n,T)^P \pi_0(\theta) d\theta} = \frac{(\mathrm{TP})^{\mathrm{nP}}}{\Gamma(\mathrm{nP})}$
  - $\pi(\theta, P|n, T) = C(P)L(\theta|n, T)^P \pi_0(\theta)\pi(P) = \frac{(\mathrm{TP})^{\mathrm{nP}}}{\Gamma(\mathrm{nP})}\left(\frac{1}{\theta}\right)^{nP+1} e^{-\frac{TP}{\theta}}$
- Posterior distribution

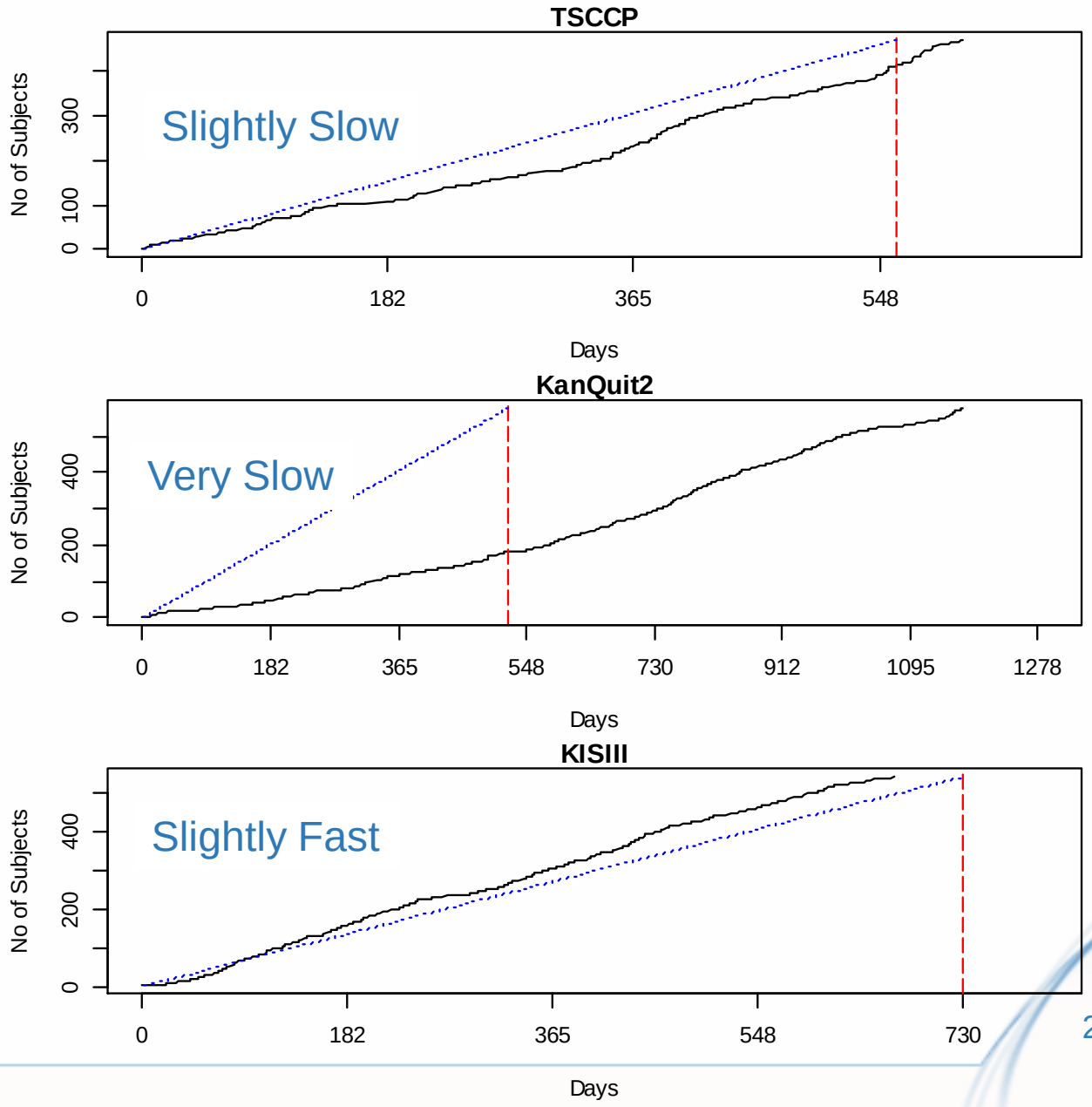
$$\pi(\theta, P|n, T, m, T_m) \propto \frac{(\mathrm{TP})^{\mathrm{nP}}}{\Gamma(\mathrm{nP})}\left(\frac{1}{\theta}\right)^{nP+m+1} e^{-\frac{TP+T_m}{\theta}}$$

$$\pi(P|n, T, m, T_m) = \frac{(\mathrm{TP})^{\mathrm{nP}}\Gamma(\mathrm{nP} + \mathrm{m})}{\Gamma(\mathrm{nP})(TP + T_m)^{nP+m}}$$

Application in three randomized clinical studies

- Colorectal Cancer Prevention (TSCCP)
  - Accrual slightly slow
- Treat hospitalized smokers (KanQuit2)
  - Accrual very slow
- Evaluates the efficacy of new intervention for smoking cessation among urban African American light smokers (KISIII)
  - Accrual slightly fast

Accrual data



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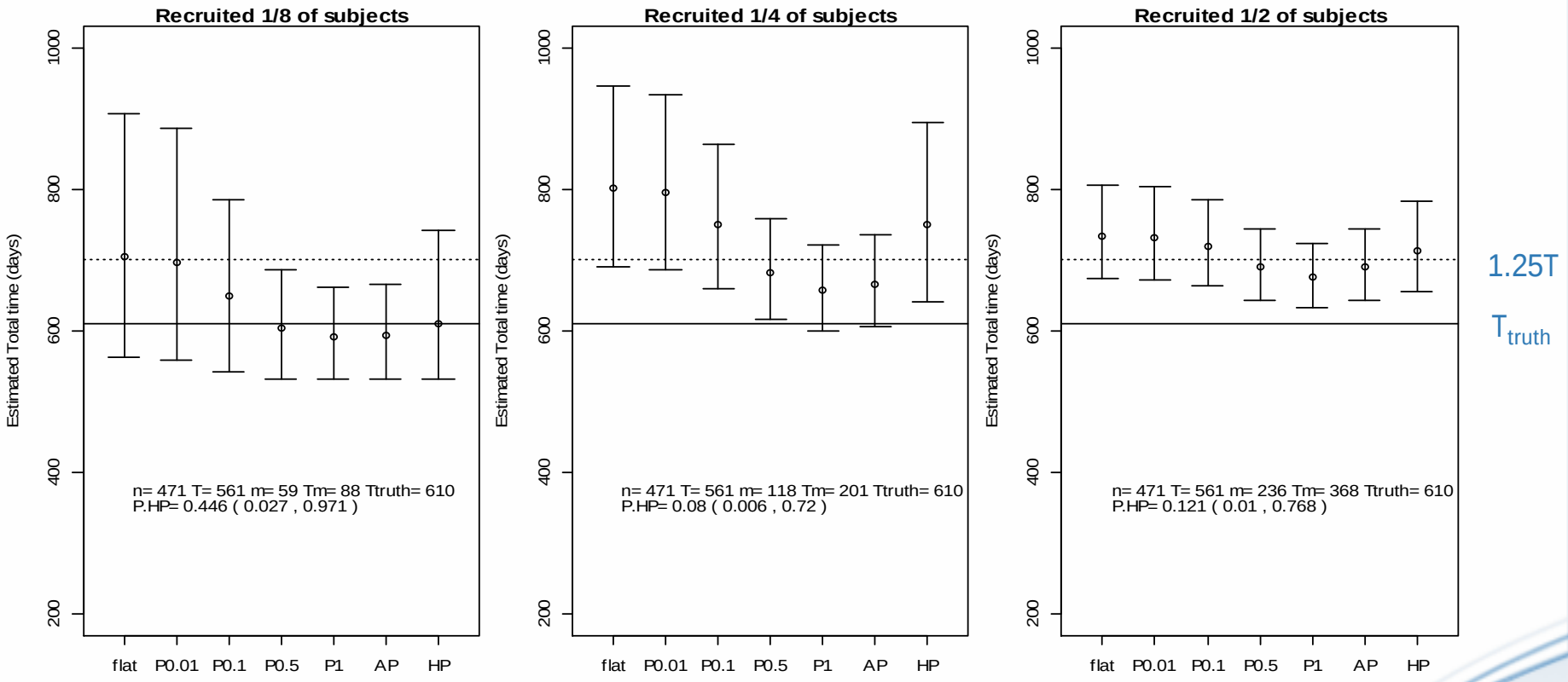
Methods and the evaluation

- Investigate different priors
  - Fix P=0, 0.01, 0.10, 0.50, or 1.00
  - Accelerated Prior (AP)
  - Hedging Prior (HP)
- For each prior, given data at different points, what is the Decision Making ability? Does a 95% interval predict off by 25% of the protocol accrual goal (1.25T)?

TSCCP –Slightly Slow

(95% intervals)



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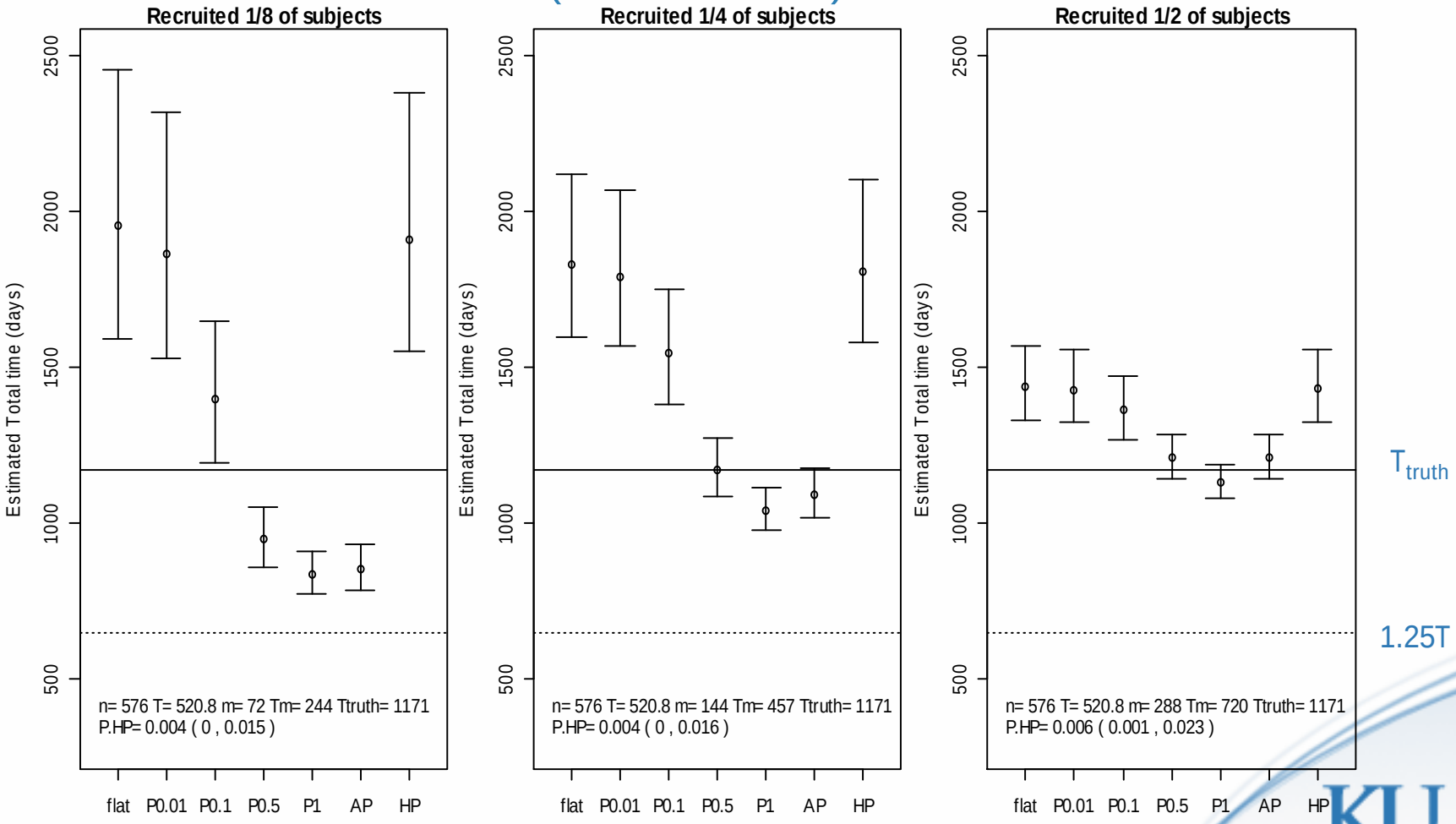
KanQuit2—Very Slow

(95% intervals)



T_{truth}

1.25T

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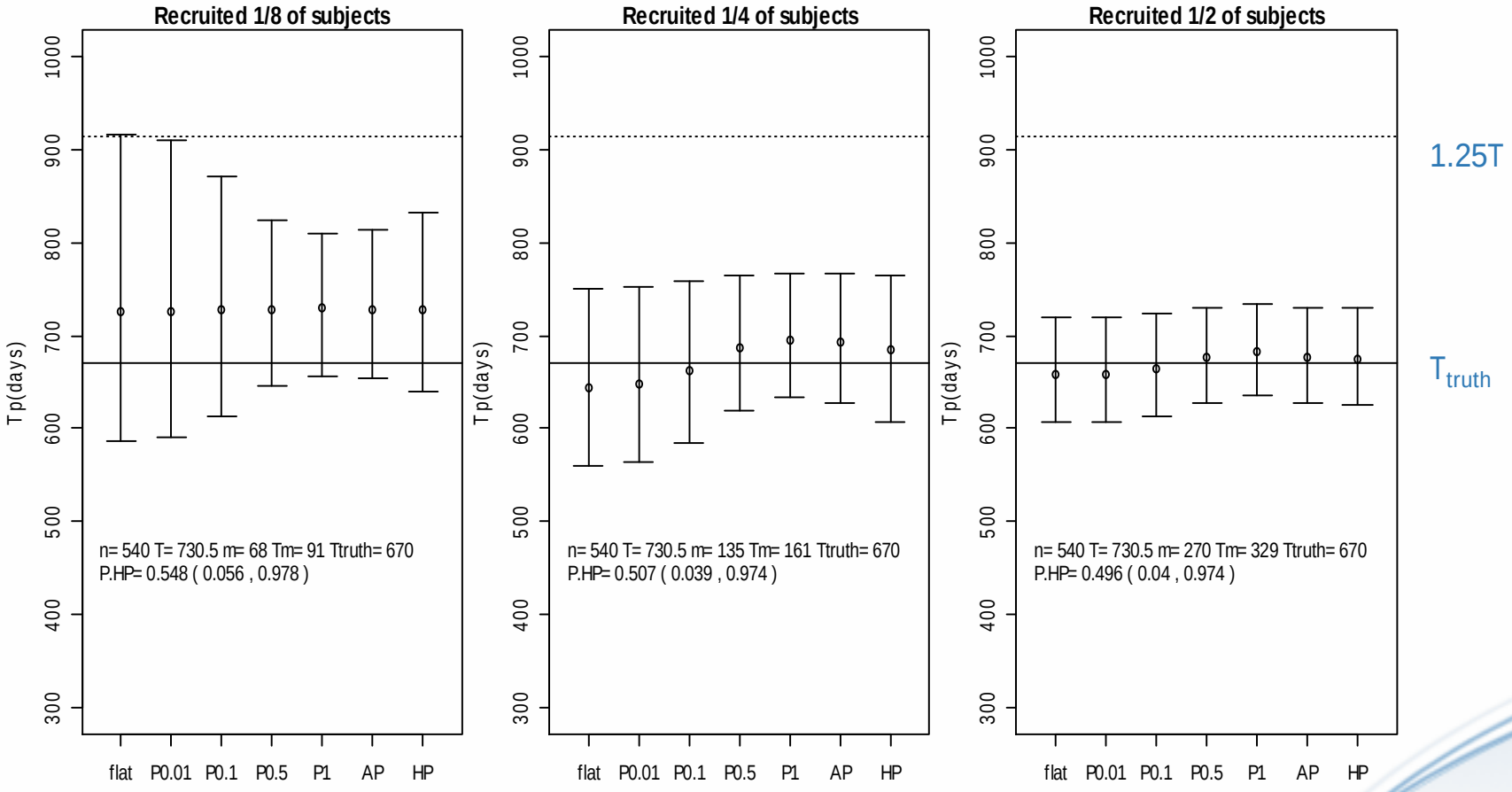
KISIII—Slightly Fast

(95% intervals)



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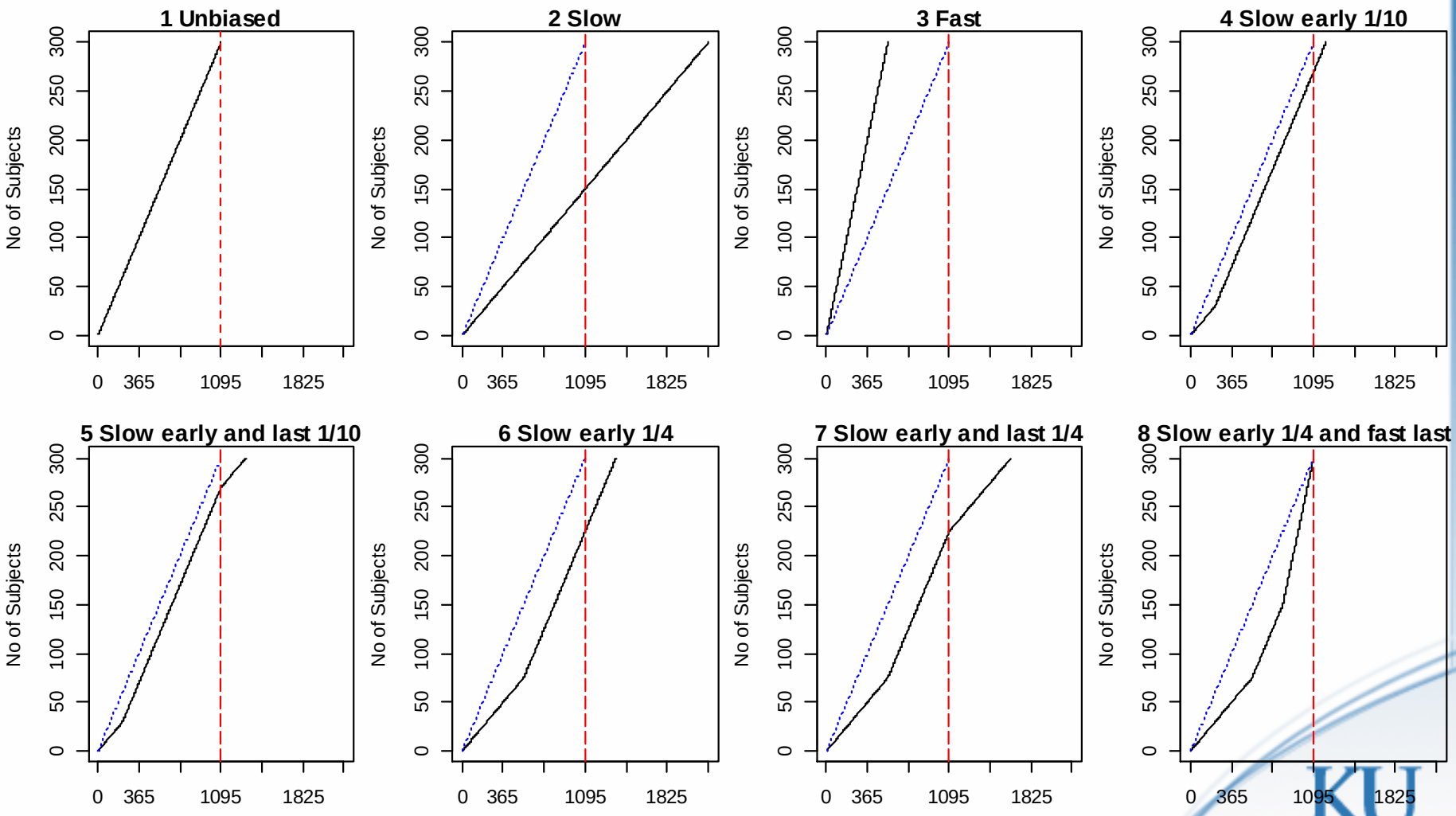
Summary of Clinical Studies

- All methods recognize early that the trial is off schedule.
- Accelerated prior behaves similar to strong informative priors.
- Hedging prior did seem to adapt its behavior somewhat, behaving more like a weak prior when the accrual was substantially off target, but like a strong prior when the accrual was only slightly off target.
- Variations in accrual rates can complicate the evaluation of these models. Need further evaluated in simulation.

Design of the simulation study



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Simulations

- Methods used for accrual prediction:
  - P=0, P=0.01, P=0.1, P=0.5, P=1, AP, HP
  - Prediction of Tp when 1/8, 1/4, and 1/2 subjects recruited
- Methods for evaluation

Let's be Practical

  - Percentage of Correct Decision:

$$CDj = I(\hat{T}_{0.025} > \delta T)\, I(Ttruth_j > T) + I(\hat{T}_{0.025} \le \delta T)\, I(Ttruth_j \le T)$$

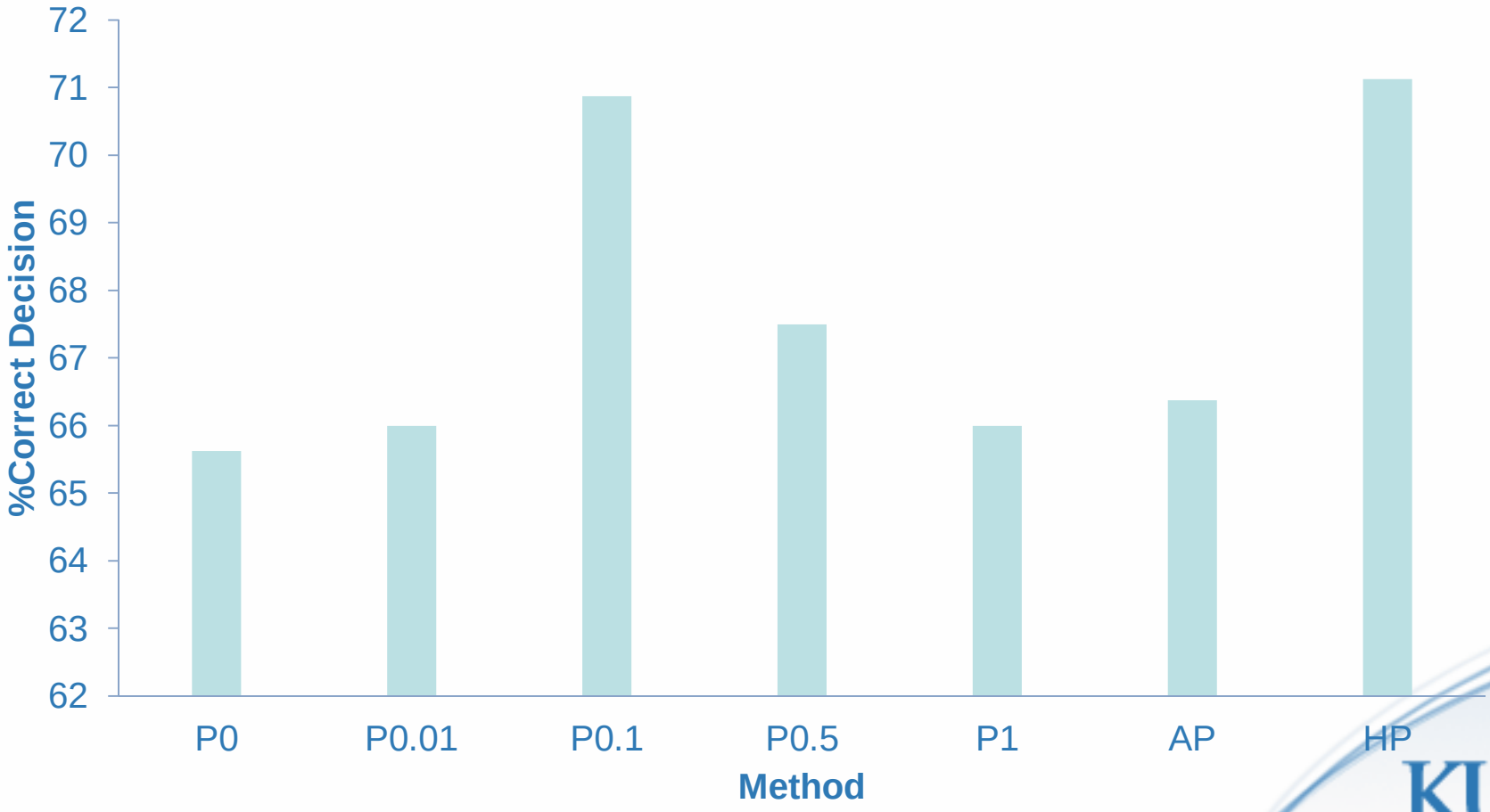
NOGO GO

$$CD = \frac{1}{1000} \sum_{j=1}^{1000} CD_j \times 100\%$$

Correct decisions

	Method	Unbiased	Slow	Fast	Slow early 1/10	Slow early and last 1/10	Slow early ¼	Slow early and last ¼	Slow early ¼ and fast last ½
		1	2	3	4	5	6	7	8
1/8	P0	100	87	100	31	48	59	84	16
	P0.01	100	85	100	33	49	60	83	18
	P0.1	100	61	100	66	71	69	60	40
	P0.5	100	9	100	97	76	57	8	93
	P1	100	1	100	99	76	52	1	99
	AP	100	2	100	99	76	53	2	99
	HP	100	57	100	70	73	69	56	44
1/4	P0	100	99	100	75	76	50	99	1
	P0.01	100	99	100	77	77	50	99	1
	P0.1	100	98	100	88	80	52	97	3
	P0.5	100	78	100	98	76	69	77	23
	P1	100	55	100	99	76	78	54	47
	AP	100	65	100	99	76	75	65	36
	HP	100	96	100	91	79	54	95	5
1/2	P0	100	100	100	97	78	70	78	22
	P0.01	100	100	100	97	78	70	78	23
	P0.1	100	100	100	98	77	75	73	28
	P0.5	100	100	100	99	76	84	54	46
	P1	100	100	100	99	76	83	41	59
	AP	100	100	100	99	76	84	54	46
	HP	100	100	100	99	77	78	68	32

Average Across Scenarios (1/8 of data)



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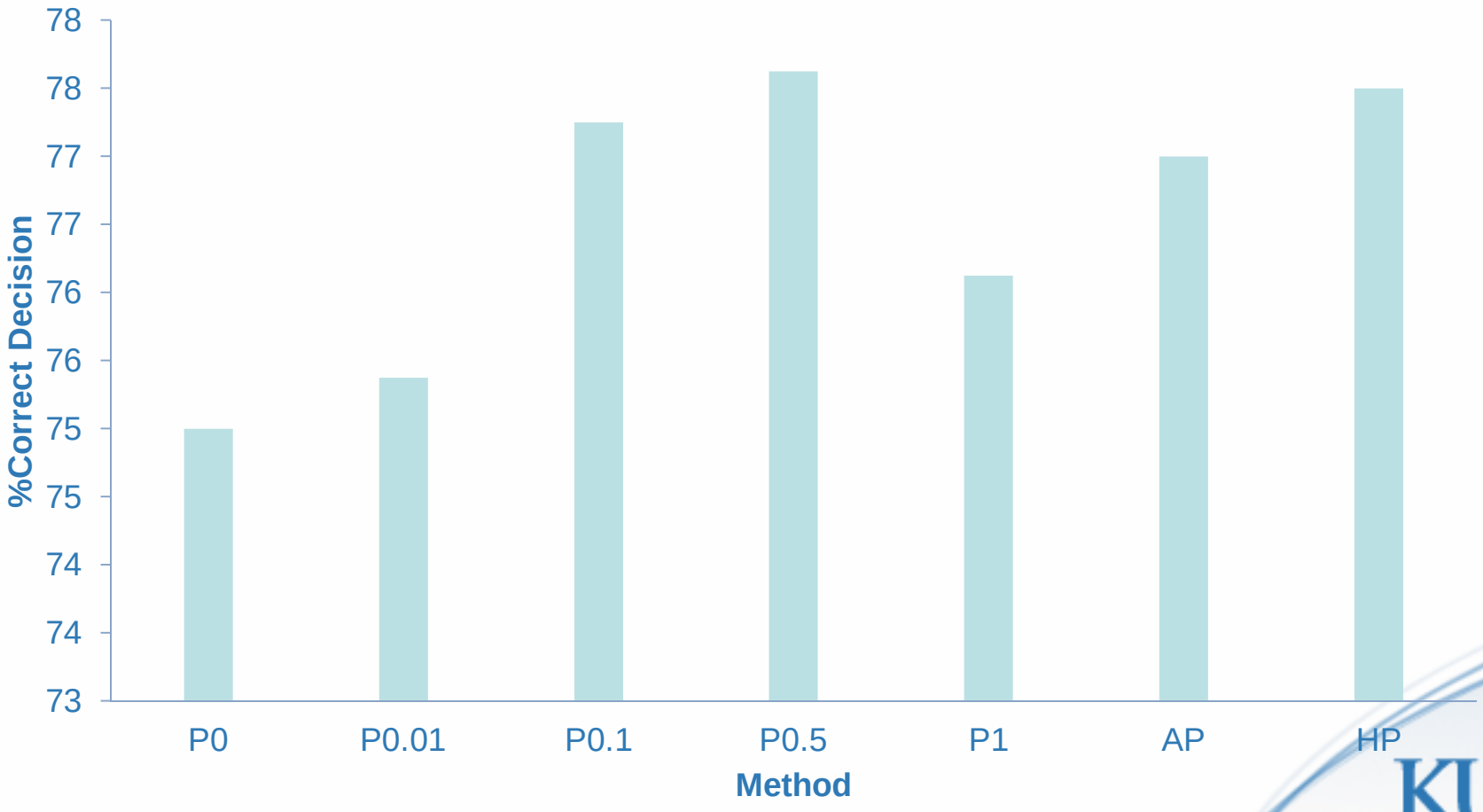
Average Across Scenarios (1/2 of data)



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Summary

- Strongly informative priors works well when accrual is on-target or slightly off
- Flat or weakly informative priors provide protection against on off-target trials, but are less efficient when the accrual is on-target.
- The accelerated prior performs similar to a strong prior.
- The hedging prior performs much like the weak priors when the accrual is extremely off-target, but closer to the strong priors when the accrual is on-target or only slightly off-target.

Next work? Submitted an NCI grant:

- **Goal 3: To thoroughly model and evaluate variation in accrual rates, especially slow accrual at the start of a clinical trial.**
- **Goal 4: To expand the accrual model to monitor accrual within patient strata.**
- **Goal 5: To broaden and generalize the accrual model to account for screen failures.**
- **Goal 6: To develop, test and disseminate software for accrual models**.

*It is our **expectation…***

…that study investigators and ethical oversight groups will have the needed and appropriate tools for monitoring accrual to either fix poorly accruing trials or to shut down trials that cannot accrue a reasonable number of patients in a reasonable time frame—a troubling ethical issue for investigators and oversight committees alike.

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