Effective Implementation of Bayesian Adaptive Randomization in Early Phase Clinical Development

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Acknowledgement

Joint work with

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Overview

- Oncology Proof Of Concept Trials: Some Considerations
- Bayesian Adaptive Randomization methodology
- Case Study
- Summary of Simulation Results
- Discussion and Conclusions

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Oncology Proof Of Concept Studies

OBJECTIVES:

- **Activity**: determine whether the treatment is sufficiently promising to proceed in further development
- **Safety**: better characterize the safety profile of the compound
- **Doses**: determine the best dose (efficacy / safety)
- **Biomarkers**: for stratification or prediction of response
- **Strategy**: Add-on strategy or replacement strategy

Challenging design and studies given their limited size and duration !

Oncology Proof Of Concept Studies

SINGLE ARM STUDIES

- Endpoint: Response Rate or rates of PFS/OS at predefined timepoint
- Early stopping rules for futility (Simon two-stage design)
- Designed for cytotoxic compounds, not fitting with compounds with different Mode Of Action
- Designs characteristics not consistent with phase III program
  - Not comparative with efficacy hypothesis testing based on historical control
  - Endpoints not used in phase III programs
  - Selection bias
- Difficult assessment of add-on therapies

Oncology Proof Of Concept Studies

SCREENING DESIGNS

- Design characteristics similar to phase III studies
  - Time To Event Endpoints used (PFS more frequently than OS)
  - Comparative ➡ Treatment effect (HR)
    Hypothesis testing procedure (Log-rank)
  - Randomized ➡ Selection bias better controlled
- Sample Size smaller than phase III trials but wider than single arm studies (150 / 300 subjects)

➡ Inflation of type I and II error rates ➡ alpha 10% - 30%; power ~ 80%

➡ Not optimal decision making process

➡ Limited to address dose-response or biomarker questions

Oncology Proof Of Concept Studies

MAIN CHALLENGES

- Learning phase of development ➡ still limited knowledge on compound characteristics during study planning
- Classical study designs
  - Fixed treatment allocation
  - No changes allowed during the trial
  - Design independent of data generated during the study
- In studies of limited size, many subjects exposed to control may not be informative (e.g. for safety or for predictive biomarkers)

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  - Workflow
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Bayesian Adaptive Randomization

- CONCEPT

  - Trial design: randomized & comparative
  - Adapt the randomization ratio during the study favoring treatment arm(s) showing best performance
  - Intermediate data of activity available during the study will be used to perform the adaptation
  - Implement efficient stopping rule for futility as soon as the drug shows no activity

Bayesian Adaptive Randomization

- Fewer subjects assigned to less effective treatment arms
- Keep flexible design during a learning / exploratory phase of development
- Use prior information on the compound and specific indication setting (Bayesian)
- More information on experimental treatment arm (if active)

  ➡ increased precision in the point estimates of activity within arm

  ➡ more safety information

  ➡ improve dose selection

- Improve decision making process

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Bayesian Adaptive Randomization: workflow

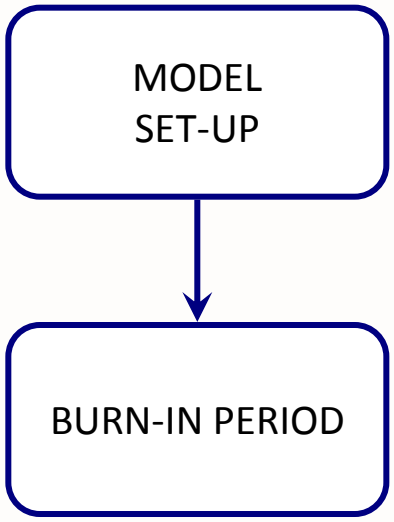
MODEL SET-UP

Step 0: Preliminary activity before start of the study

- Feasibility of the design
- Definition of prior information to be included in the model
- Fine tuning of model parameters
- Evaluation of operating characteristics versus standard designs

TOOL: SIMULATIONS

Bayesian Adaptive Randomization: workflow

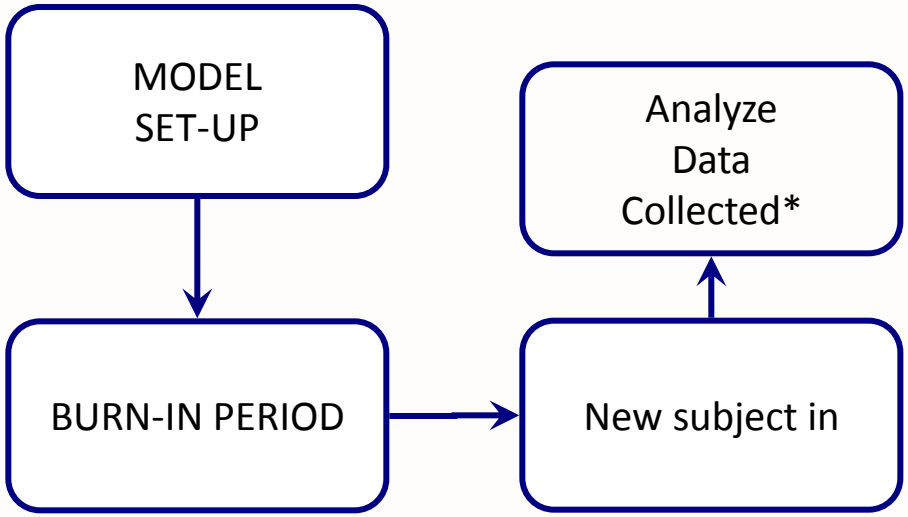


STUDY START:

Step 1: BURN-IN PERIOD

- First group of subjects is assigned to treatment arms according to standard procedures (block randomization with equal allocation ratio)
- Allows model to incorporate enough information to adapt the randomization in a robust way

Bayesian Adaptive Randomization: workflow

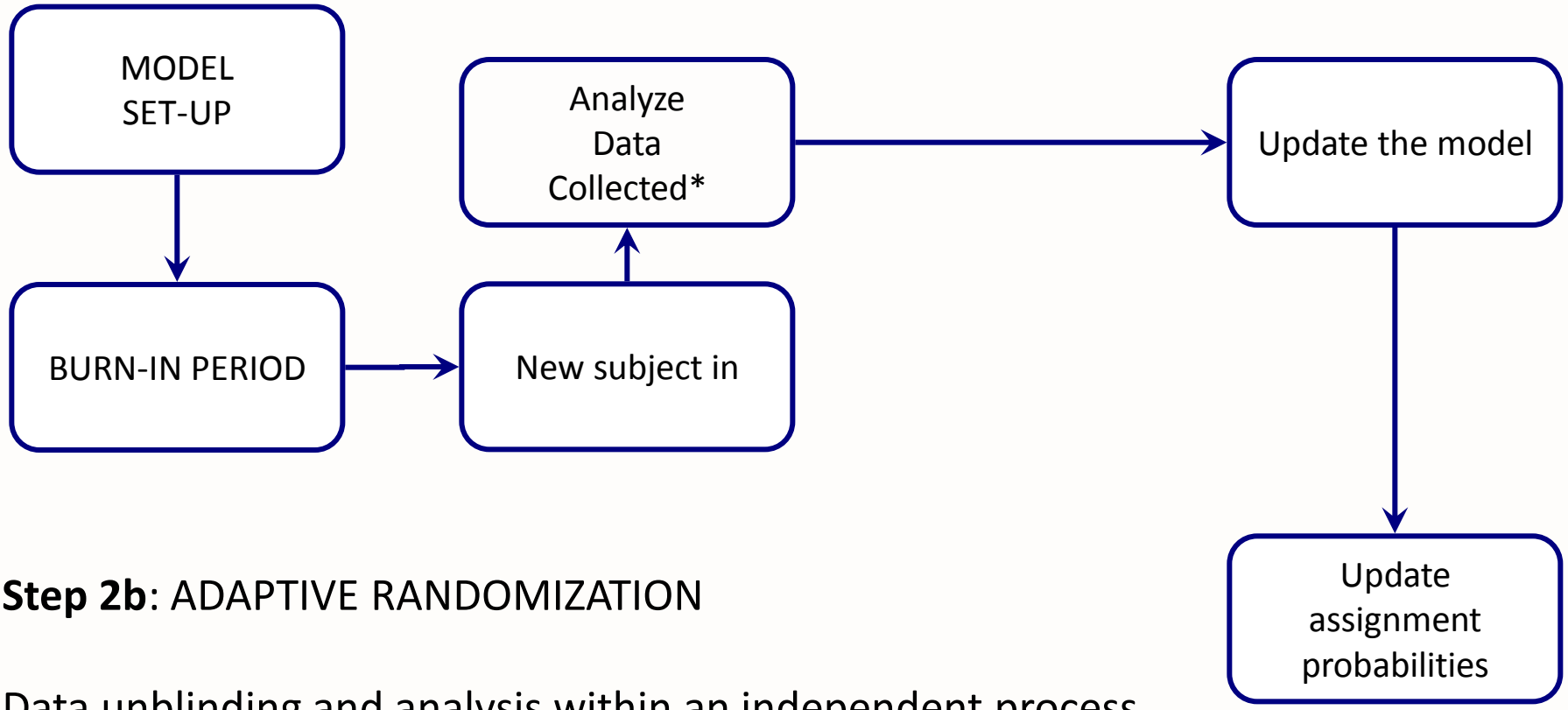


Step 2a: ADAPTIVE RANDOMIZATION

At the completion of the burn-in period before new subject is randomized

Data are transferred from the clinical database to IVRS supplier

Bayesian Adaptive Randomization: workflow

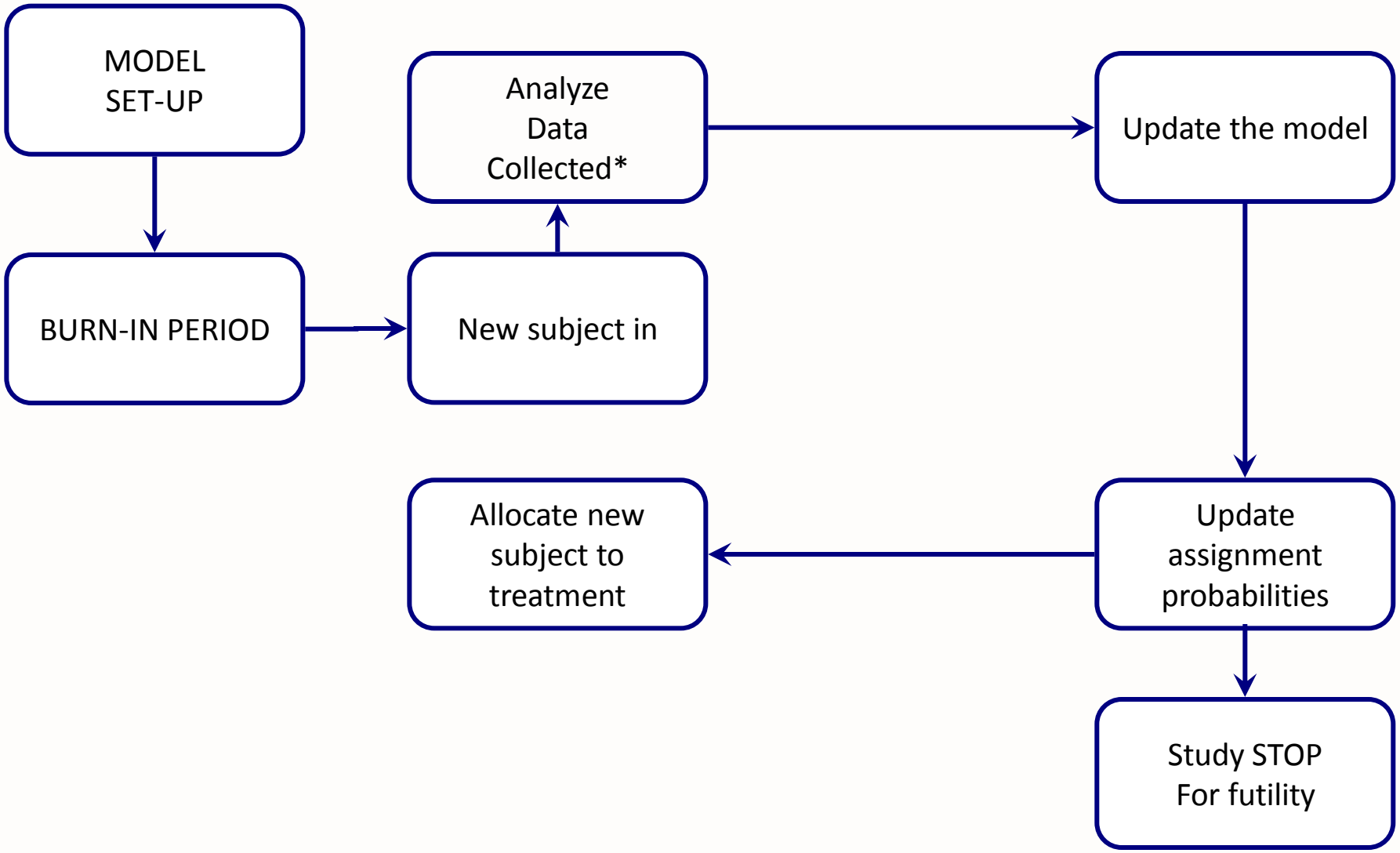


Step 2b: ADAPTIVE RANDOMIZATION

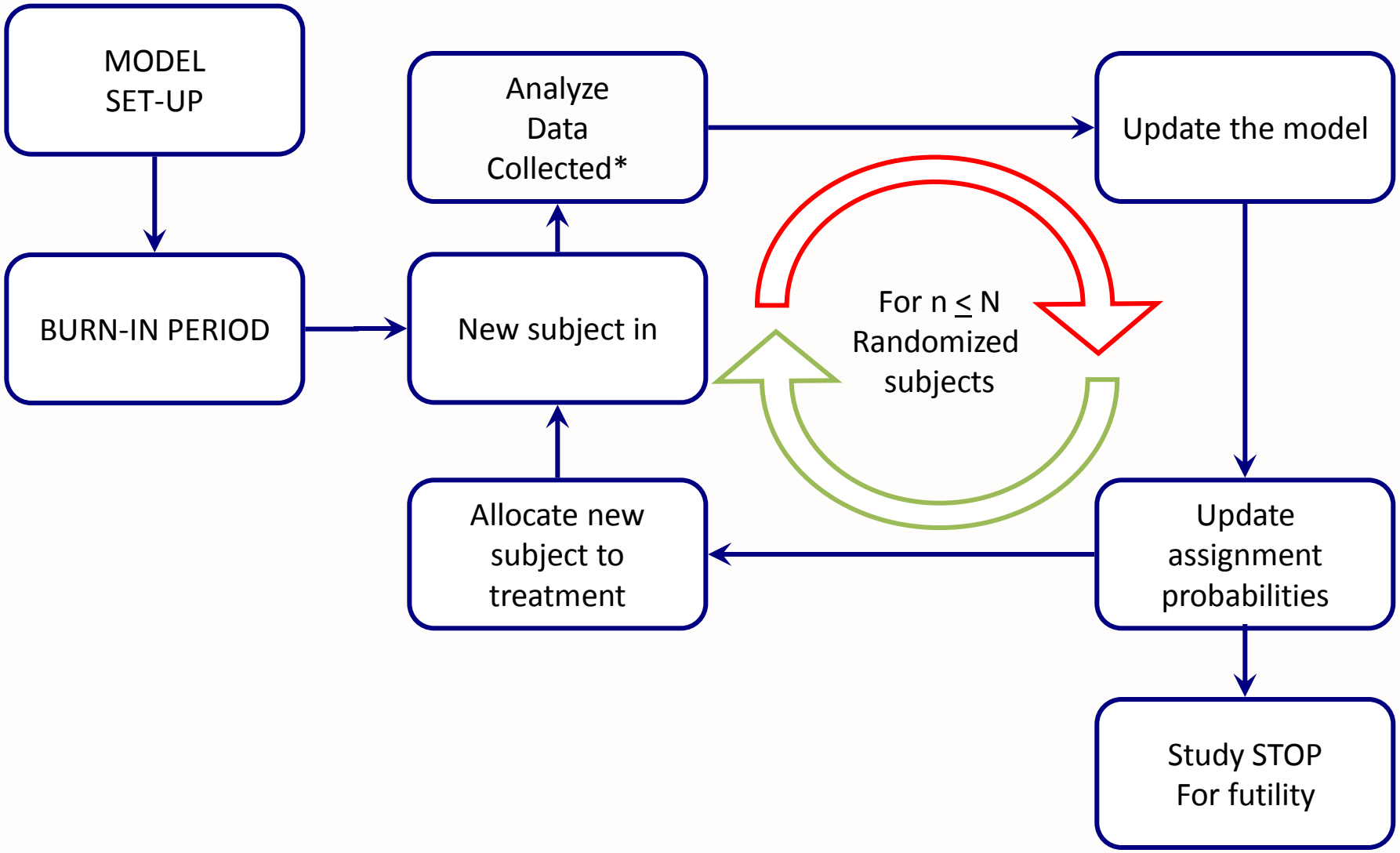
Data unblinding and analysis within an independent process

Trial Team and sponsor blinding should be adequately insured

Bayesian Adaptive Randomization: workflow



Bayesian Adaptive Randomization: workflow



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A Bayesian model

- Assignment probabilities are derived by combining prior information with observed data
  - Guarantees that observed likelihood does not exclusively drive the adaptive randomization.
- Prior information
  - Summarizes previous knowledge on the control arm (literature data) and on the experimental treatment arm (previous trials / preclinical / expectations)
  - Priors should not favor the experimental arm ➡ bias the randomization process.

Model specification: the statistical engine

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Evolution of the randomized "play the winner" design

Model links the chance of assigning a subject to one treatment arm [γ] to the probability that that treatment has the best performance over the other(s) [π]

$\gamma_j(i)$ = Probability [subject *i* is randomized to treatment *j*]

π_j = Prob ($\eta_j > \max(\eta_k)$ | data, prior) for $k \neq j$

Posterior Prob [primary endpoint in treatment *j* > all other arms]

$\gamma_j(i) = \pi_j(i)^\lambda / \Sigma_j \pi_j\ (i)^\lambda$

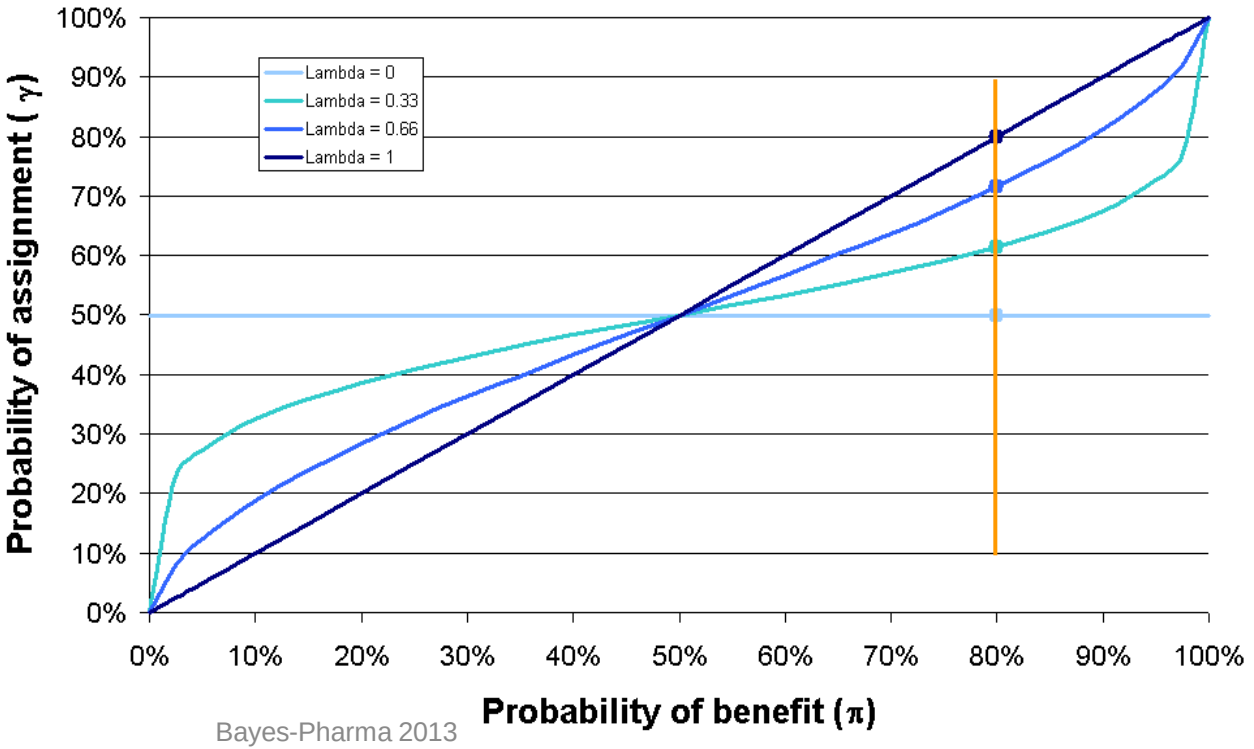
Model specification: the statistical engine

$\gamma_j(i) = \pi_j(i)^\lambda / \Sigma\pi(i)^\lambda$

λ = tuning parameter controlling the degrees of freedom of the process

- $\lambda = 0$ ➡ balanced randomization
- $\lambda = 1$ ➡ $\gamma_j(i) = \pi_j(i)$

The value of lambda based on simulation results before study start



Decision making tool

π_{SoC} = Probability (Standard Of Care > Experimental Treatment Arm(s))

Direct measure of drug activity to be used for decision making

- During the study High $\pi_{SoC} \geq c_1$

  Stop for futility for weak drug activity

- Final analysis Low $\pi_{SoC} \leq c_2$

  Claim drug activity within a hypothesis testing framework

- Simulation results will pre-define proper values for c_1 and c_2 leading to adequate control of type I and II error

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Trial Insights

- Cytostatic compound (monoclonal antibody) with not established dose-response curve (monotonic or bell-shaped)
- Phase II randomized
  - Standard Of Care (SoC)
  - SoC + “LOW” dose
  - SoC + “HIGH” dose
- Primary endpoint: Progression Free Survival
- Study Objective
  - **Primary**: *Evaluate Drug activity*
  - **Secondary**: *Choose the best dose*

Trial Insights

Standard solution not completely satisfactory as

- Two parallel looks to data lead to multiplicity issues inflating alpha and increasing the power
  - the overall false positive rate (alpha) equal to 23%
  - power > 90% in case both arms are equally active
- Not feasible to have clearer and more robust decision rule for selection of the best dose
- Performance of Bayesian Adaptive Randomization evaluated through simulations

Trial Insights: Simulation plan

- Simulations were run to
  - Evaluate model operating characteristics versus standard design
  - Define the model parameters (burn-in period, tuning parameter, priors, futility stopping rule, rejection region definition)
- Scenarios of activity:
  - Negative
  - No drug activity
  - One arm active (mild / strong activity)
  - Dose response (mild / strong activity)
  - Both arms equally active (mild / strong activity)

Simulation scenaria

Scenario 1					
Negative	**Hypothesis**		$\lambda_P > \lambda_L = \lambda_H$		
	Median(months)		2.76	2.30	2.30
	HR		120%	120%	
	λ	3.98	3.32	3.32	
Scenario 2					
Null	**Hypothesis**		$\lambda_P = \lambda_L = \lambda_H$		
hypothesis	Median(months)		2.76	2.76	2.76
	HR		100%	100%	
	λ	3.98	3.98	3.98	
Scenario 3.1					
Only one	**Hypothesis**		$\lambda_P = \lambda_L < \lambda_H$		
arm	Median(months)		2.76	2.76	3.68
moderately	HR		100%	75%	
active	λ	3.98	3.98	5.31	
Scenario 3.2					
Only one	**Hypothesis**		$\lambda_P = \lambda_L < \lambda_H$		
arm highly	Median(months)		2.76	2.76	4.14
active	HR		100%	66.7%	
	λ	3.98	3.98	5.97	

Used for estimation of type I error

Used for estimation of power

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Summary of results: Model parameter

- **Burn-in period**: 81 subjects randomized (37% of sample size)
- Dynamic tuning parameter = (2/3) * (number or subjects randomized / max sample size)
- Futility rule: study stopped anytime for futility when
  - π_{SoC} = P[SoC > experimental arms] > 0.6 and
  - $\geq$ 150 subjects randomized (2/3 of sample size)
- Null Hypothesis of "No drug effect" rejected ➡ if $\pi_{SoC} < 0.095$

Summary of results: Priors

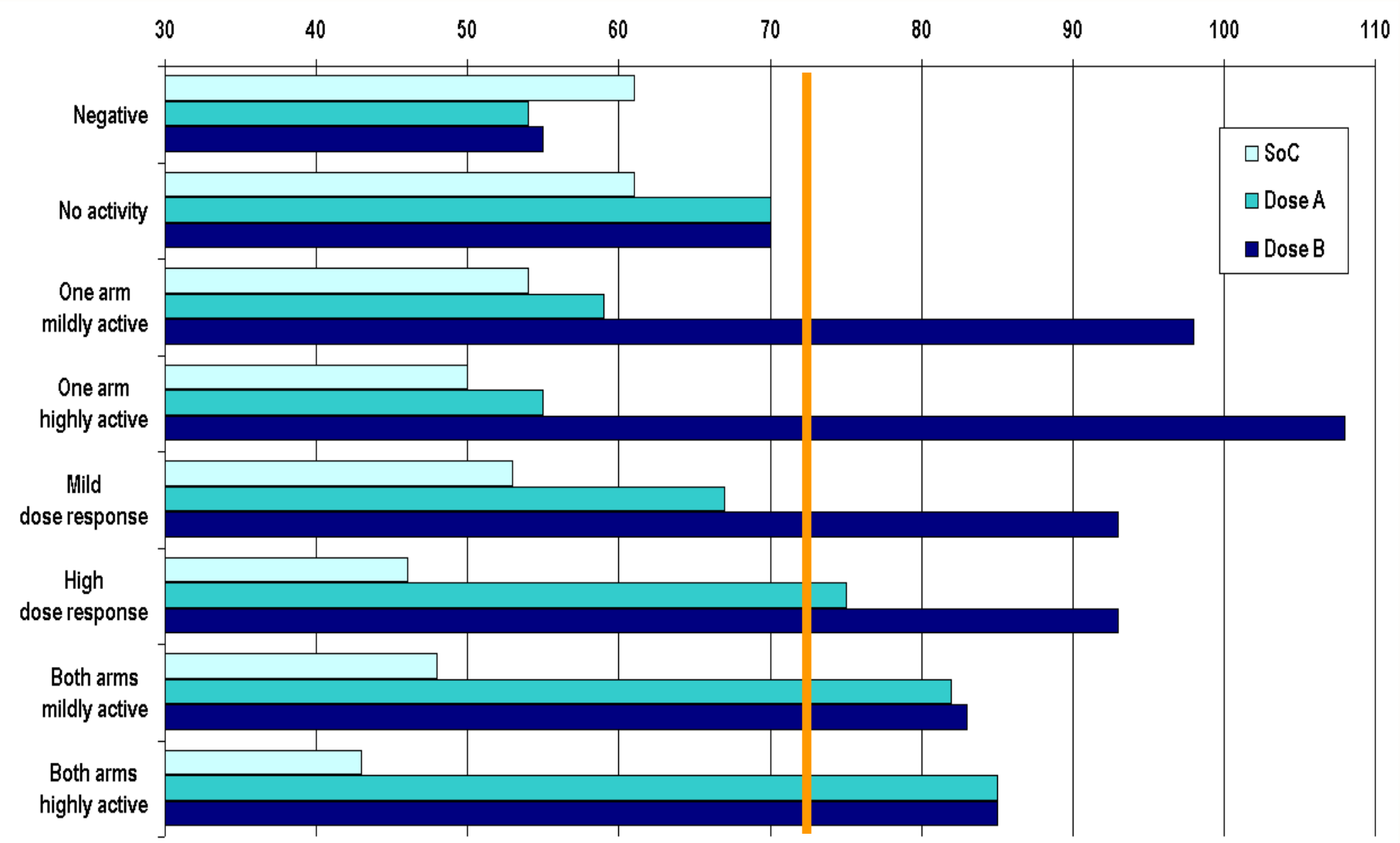
Choice of the Priors

- Standard Of Care
  - Point estimate and 95% confidence interval of most recent and relevant pivotal studies in the same setting.
- Experimental treatment
  - Same expected point estimate ➡ no drug activity assumed in order not to bias the randomization
  - Higher variability reflecting the uncertainty of performance

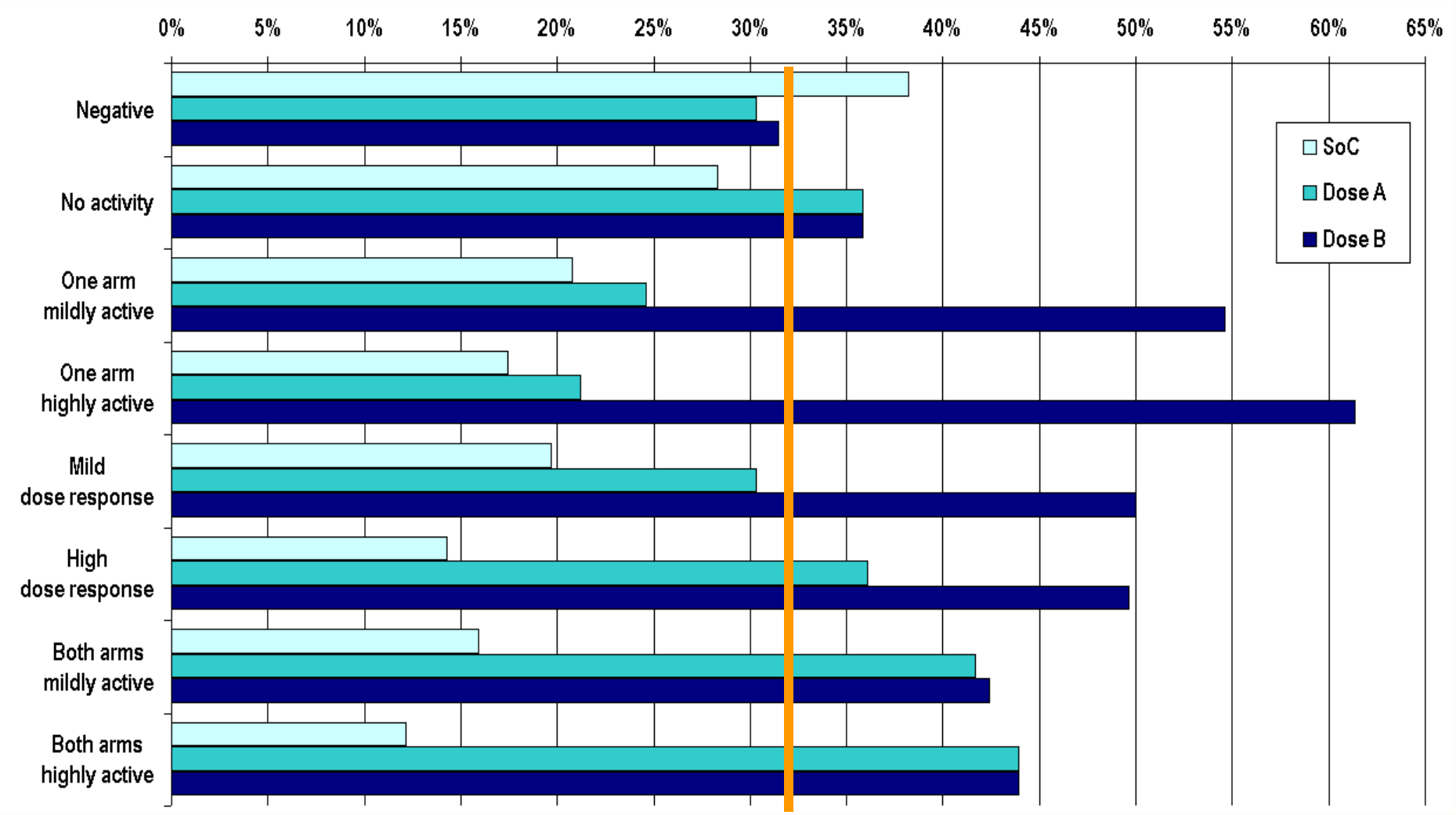
Probability of stopping for futility

SCENARIO	**P(Futility)**
Negative	69.0%
No drug activity	27.9%
One arm mildly active	5.3%
One arm highly active	2.4%
Mild dose response	3.9%
High dose response	0.6%
Both arms mildly active	1.4%
Both arms highly active	0.3%

Expected Number of Subjects Randomized



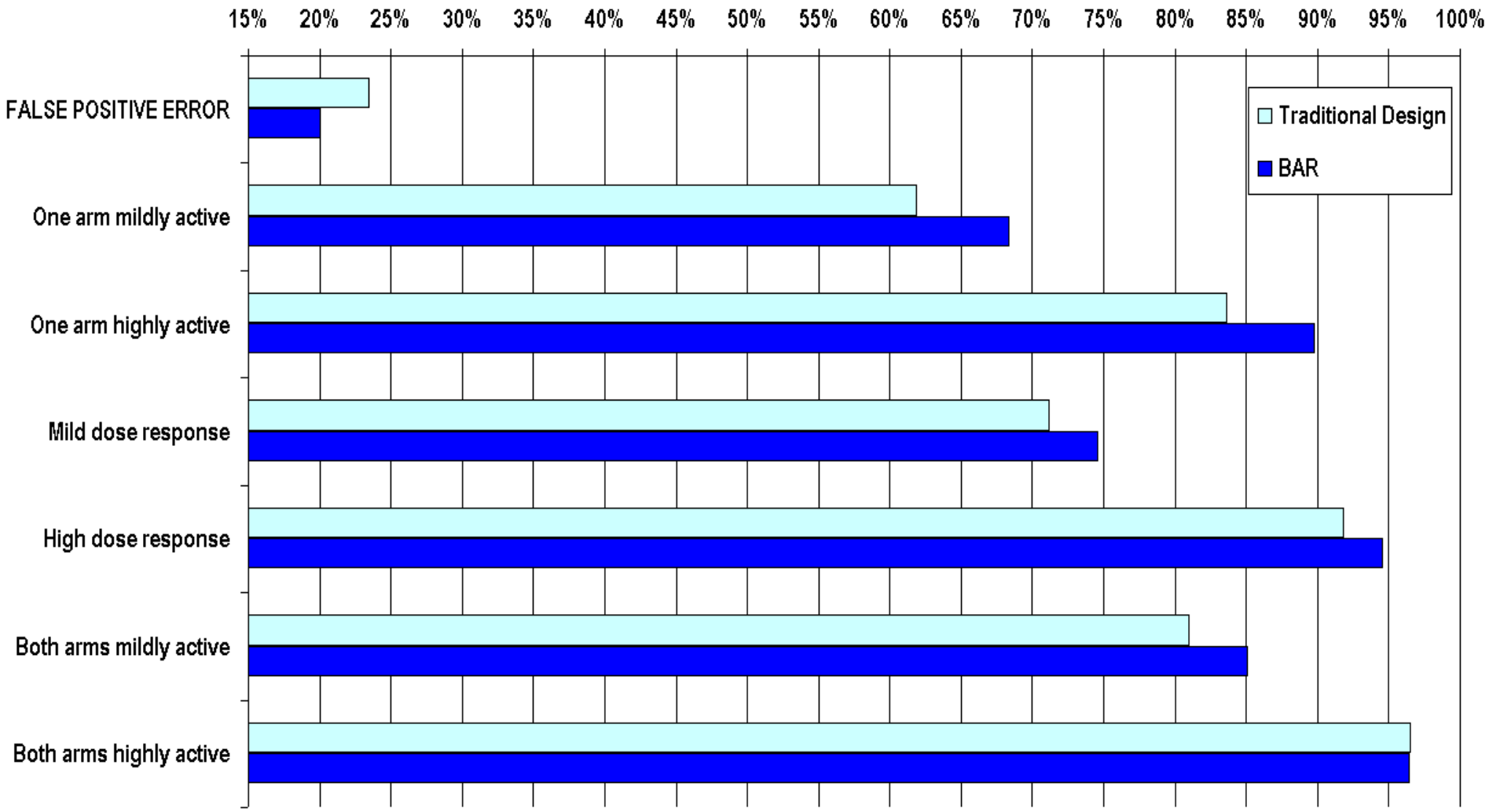
% Number of Subjects Randomized without Burn-In Period



Final π_{SoC} (mean)

SCENARIO	π_{SoC}
Negative	57.1%
No drug activity	33.0%
One arm mildly active	10.3%
One arm highly active	4.8%
Mild dose response	8.8%
High dose response	2.6%
Both arms mildly active	4.7%
Both arms highly active	1.6%

Alpha and Power



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Discussion and Conclusions

- Bayesian Adaptive Randomization could be alternative design for Proof-Of-Concept studies in oncology
- Key points to consider when planning such designs:
  - Median Time to event / Recruitment rate
  - Schedule of assessment (PFS)
  - Control of covariates / Presence of treatment predictive factors
  - Model does not take into account safety
  - Operational burden (eCRF, blinding, etc)
- Simulations are of key importance to evaluate the applicability and the expected benefit of this design.

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THANK YOU !

BACKUP SLIDES

The model: Likelihood

- Primary outcome is Progression Free Survival (PFS) time (measured in months)

- X_{ij} the theoretical PFS time for patient *i* on therapy *j*, where *j* = *1,2,3* and *i* = *1,2,…* n_j

- We assume that X_{ij} has an exponential distribution with median η_j and corresponding mean λ_j

$$f(x_{ij}) = \frac{1}{\lambda_j} e^{-x_{ij}/\lambda_j} \equiv \frac{\ln 2}{\eta_j} e^{-x_{ij} \ln 2/\eta_j}.$$

The model: Prior distributions

- The median parameters, η_1, η_2 and η_3 follow independent inverse gamma distributions with shape parameters α_j and scale parameters β_j

- The data for each patient consist of a pair of the form (Z_{ij}, δ_{ij}) where Z_{ij} is the observed PFS time for patient *i* under treatment *j*, and δ_{ij} is the indicator variable taking the value 1 if the event is observed and 0 if the patient is censored. The likelihood then becomes:

$$L(Z;\eta_j) = \left(\frac{\ln 2}{\eta_j}\right)^{E_j^+} \exp\left(-\frac{\ln(2)\, T_j^+}{\eta_j}\right)$$

- where $T_j^+ = \sum_{i=1}^{n_j} Z_{ij}$ and $E_j^+ = \sum_{i=1}^{n_j} \delta_{ij}$

The model: Posterior distributions

- The combination of the exponential likelihood along with the Inverse Gamma priors result in the posterior distribution of the η_j parameters,
  - i.e., $\pi(\eta_j | Z)$ being independent Inverse Gamma distributions as well with
  - shape parameters $\alpha_j + E_j^+$ and scale parameters $\beta_j + \ln(2)\, T_j^+$

Choice of Priors

- The prior distribution of median PFS time (η_P) for the placebo arm chosen based on results of publications (see Small 2006) in the same setting, where the median PFS time for active treatment was 11.7 weeks (95% CI, 9.1 to 16.6) and 10.0 weeks (95% CI, 8.7 to 13.1) for placebo-treated patients.
- Hence, assumed a prior distribution of the median PFS time for placebo with an expected median PFS of 2.76 months (12weeks) and a 95% confidence interval of 1.86 to 4.09 months (8.06 to 17.7 weeks). This corresponds to:

$$\eta_P \sim IG(25.0836;\ 66.4708)$$

- For the active treatments we assumed the same expected value but a higher variance in order to reflect the uncertainty over the drug.

$$\eta_{exp} \sim IG(17.2352;\ 44.809152)$$