

The rheumatoid arthritis drug development model: a case study in Bayesian clinical trial simulation

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Problem statement

What decisions should be made about a Phase IIb and Phase III study for a new Rheumatoid Arthritis treatment?

- Rheumatoid Arthritis
 - A chronic, progressive, inflammatory disease which affects about 0.5% -1% of adults
 - Traditional Disease-Modifying Anti-Rheumatic Drugs - lots of them
 - Methotrexate (MTX) most effective
 - Biologic - more effective and more costly
 - Etanercept, infliximab, adalimumab (TNF- α), anakinra (IL-1 inhibitor)
 - A new drug we wish to test

- We need to make decisions about the devolvement program
 - Decisions about each study design
 - Sample sizes?
 - Exposure duration?
 - ...
 - Stopping rules for the program
 - Efficacy thresholds? Safety thresholds?

Overview of the Decision Analysis method

What is needed for a Decision Analysis model



Strategies

Collections of decisions that must be made about study design whose effects are simulated

- Sample size, comparator, endpoint, exposure, patient population, stopping rules



Information

Consequences and effects of the decisions, plus other relevant variables, which the model will incorporate

- Treatment efficacy and safety
- Recruitment rates, drop out rates, costs

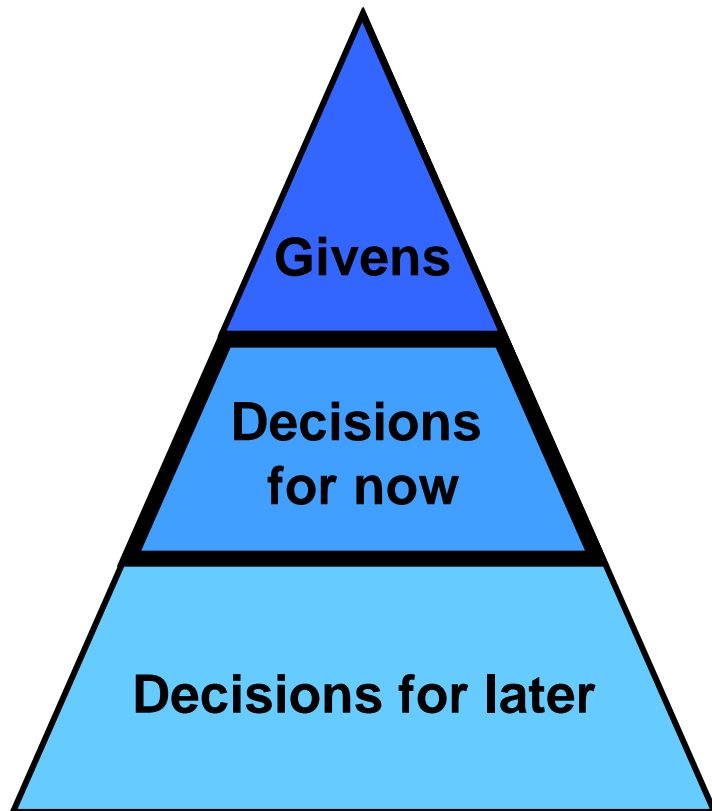


Value

The final measures of the design, which the model will calculate, and by which we will evaluate candidate strategies

- Probability of success (registration), time LPLV, cost

A decision hierarchy identifies issues to be decided and issues already decided or that can be deferred.



- Policy
- Environment
- Decisions already made

- Near- and long-term strategic direction
- Near-term significant resource commitments
- Issues that must be resolved today

- Later significant resource commitments
- Decisions for specialists
- Operational or tactical decisions

Decisions

Rows have no meaning - options from different columns may be combined

Decisions already made								
Both studies		Phase IIb			Phase III			
Average disease duration	Stopping rule: safety criteria	Comparator	Doses	Stopping rule	Comparator	Dose	Stopping rule	Exposure duration
8 years	1) SC1 withdrawal > 10% 2) SC2 withdrawal >25% 3) SC3 significantly different from MTX	MTX	L, M1, M2, H	1) Fail superiority to MTX 2) Fail non-inferiority to active comparator (indirect comparison)	MTX + Etanercept	Lowest successful dose in Phase IIb	Fail non-inferiority to active comparator	6 months

Decisions to make now				
Phase IIb			Phase III	
End point	Sample size per arm	Exposure duration	Sample size	Non-inferiority margin
ACR20	40	3 months	150	0.7
ACR50	60	6 months	200	0.8
	80		250	0.9
	100			

- (1) SC = safety criteria
- (2) ACR20, ACR50 binary outcome which indicates a 20% or 50% improvement over a given time period

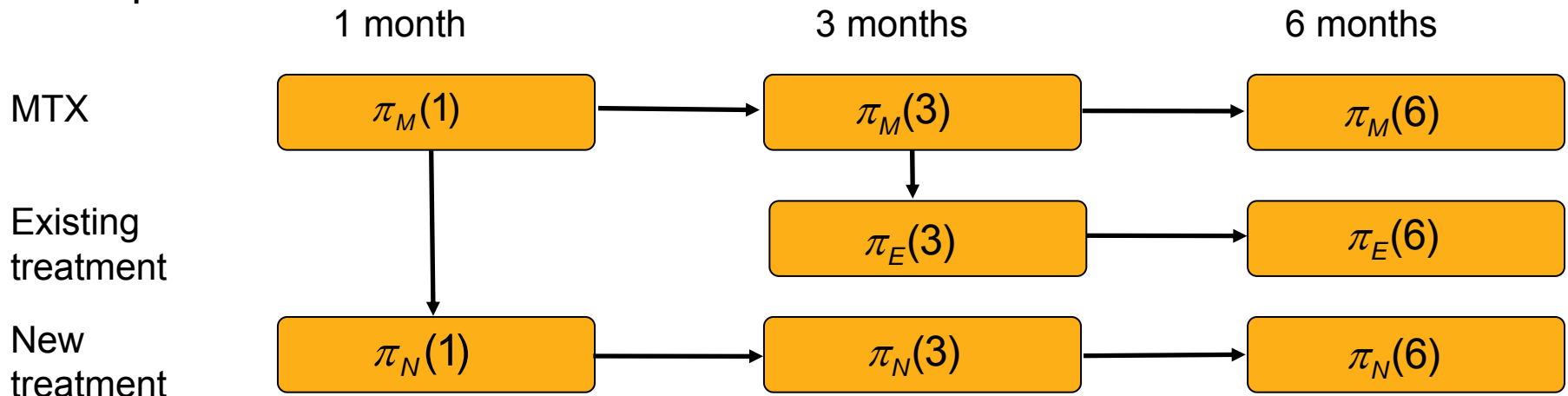
Effectiveness

- Two data sources
 - Phase 3 trials for biologics (snippet of data below)
 - Early 1 month Phase 2a trial

Drug	Regime	N	1 Month ACR50	3 Months ACR50	6 Months ACR50
Anakinra	Placebo	121	NA	6	10
	30mg day	119	NA	NA	20
	75mg day	116	NA	12	13
	150mg day	116	NA	9	22
Anakinra	MTX	251	NA	15	20
	100mg day	250	NA	33	43
Etanercept	MTX	228	10	61	91
	25mg 2wk+MTX	231	44	95	133
	25mg 2wk	223	35	79	92

Effectiveness Prediction Functions

- Use Phase III data set to estimate
 - Odds ratios between different treatments at the same time points
 - by a mixed-treatment-comparisons meta-regressions
 - Predict probability of ACR event at 3 or 6 months from 1 or 3 months
 - By logistic regression with random-effects
 - These can be functions of different treatment and disease duration
- Use Phase IIa study to predict the probability of ACR given new treatment compared to MTX



Safety Criteria Functions (SCx)

3 month withdrawal probabilities if given MTX + biologic treatment at dose d

$\pi_{sc1}(3, d)$ Probability of withdrawing because of SC1

$\pi_{sc2}(3, d)$ Probability of withdrawing because of SC2

$\pi_{sc3}(3, d)$ Probability of withdrawing because of SC3

6 month withdrawal probabilities are twice 3 month probabilities



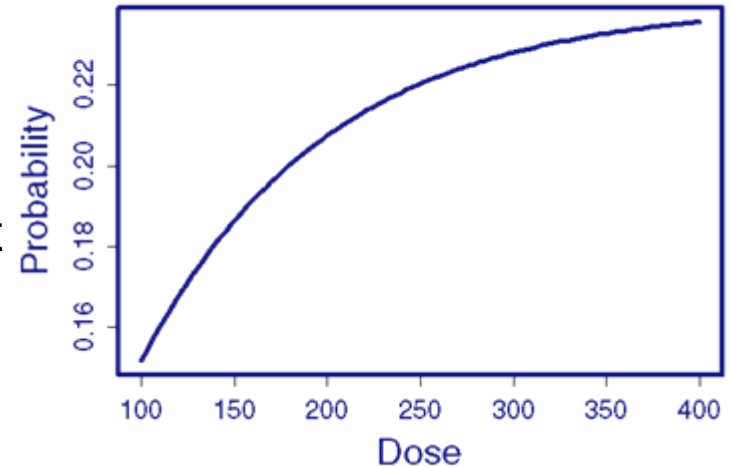
Safety concern 1 distributions

Elicited because there is no data



$$\pi_{sc1}(3, d) = \lambda(1 - \exp(-d\beta))$$

- Probability of withdrawing because of SC1 safety if given MTX + biologic treatment at dose d after 3 months



- Relative risk of withdrawal if given MTX + {M1}mg compared to MTX + {H}mg

$$\frac{1 - \exp(-\{M1\}\beta)}{1 - \exp(-\{H\}\beta)} \sim \text{Beta}(16.1, 8.2)$$
 - So get an (implicit) distribution for β
- Risk of withdrawal if given MTX + {M1}mg

$$\gamma(1 - \exp(-\{M1\}\beta)) \sim \text{Beta}(2.2, 59.7)$$
 - So get an (implicit) distribution for γ



Elicitation

- Suppose we wish to elicit a distribution for a risk
- The experts judge the percentiles of the risk to be
- Find a and b to minimize

5 th	50 th	95 th
0.1	0.2	0.35

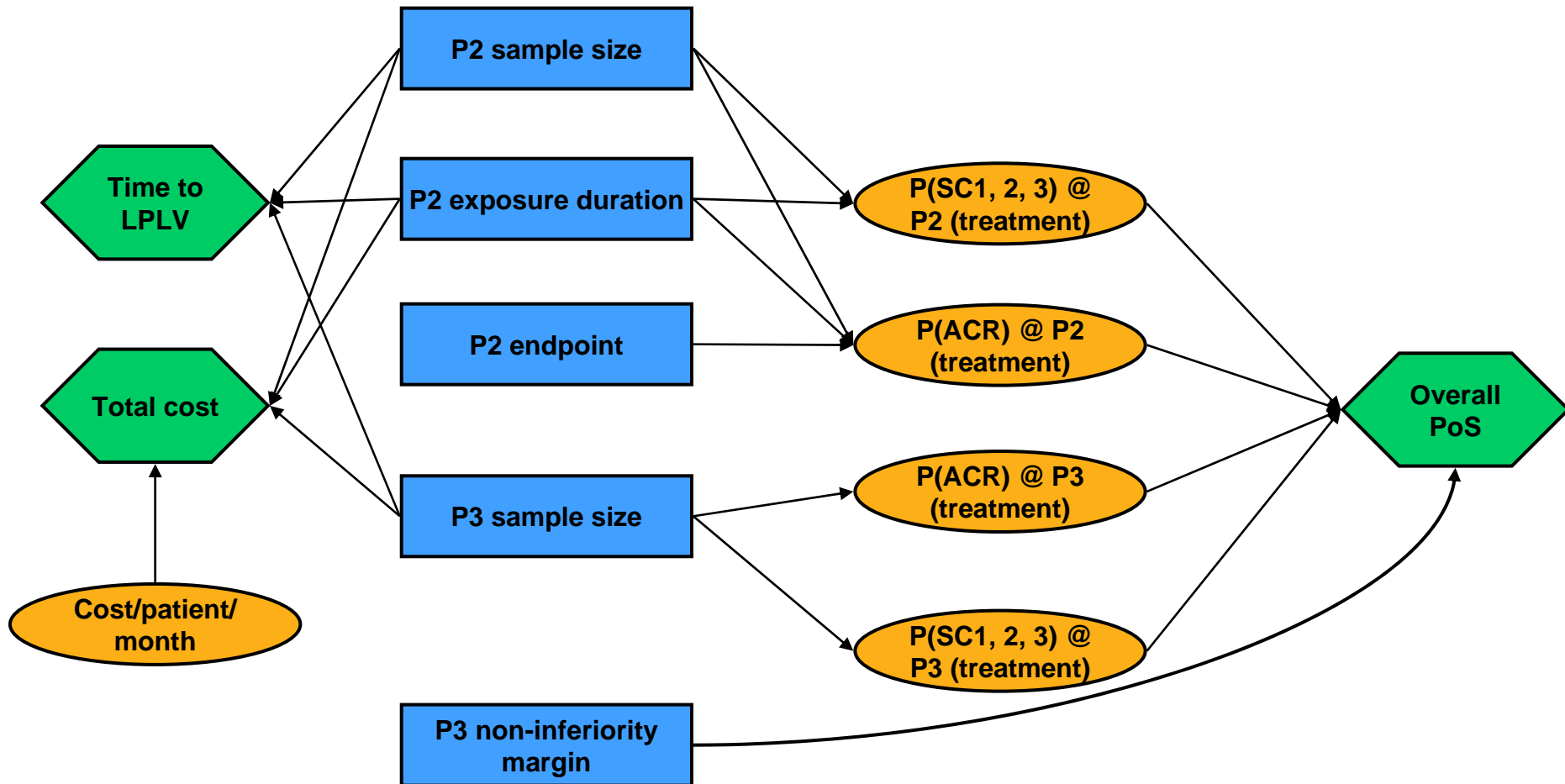
$$(F_{a,b}(0.1) - 0.05)^2 + (F_{a,b}(0.2) - 0.5)^2 + (F_{a,b}(0.35) - 0.95)^2$$

CFD of a beta distribution

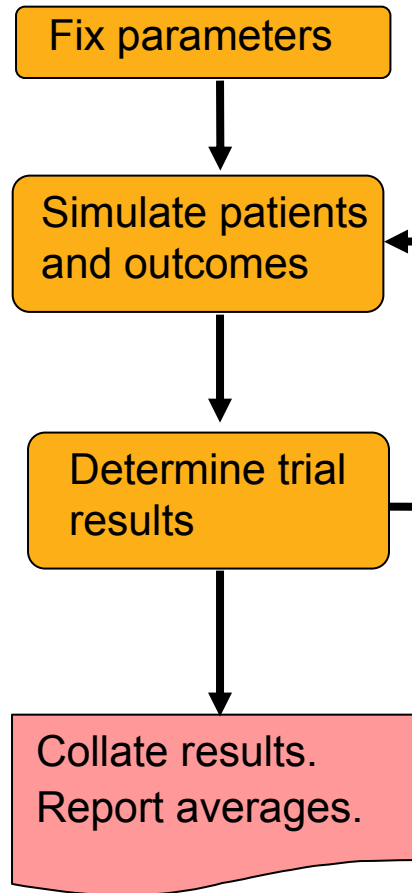
Find a Beta(5.8, 22.3) distribution

Study simulation model

How decisions, information and values are linked



Clinical Trial Simulation vs Bayesian Clinical Trial Simulation

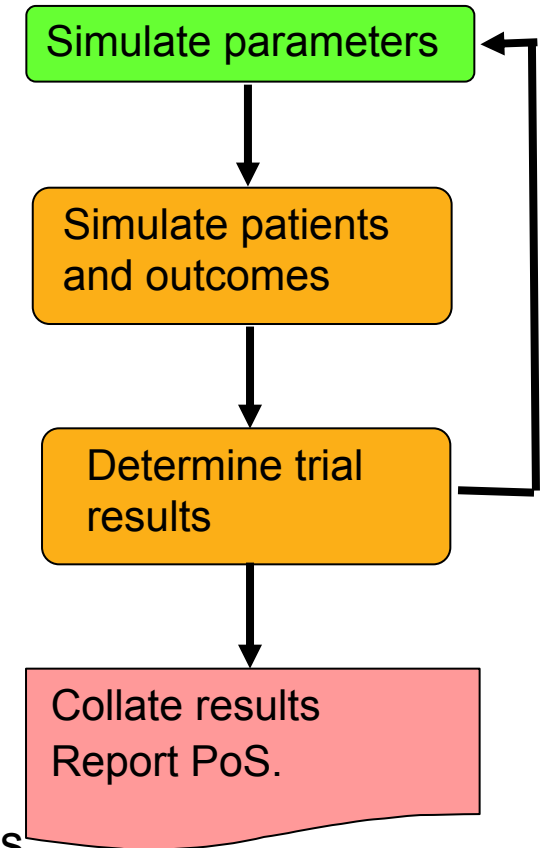


■ Clinical trial simulation

- Can estimate expected results from complex trials
- **But parameters are fixed**

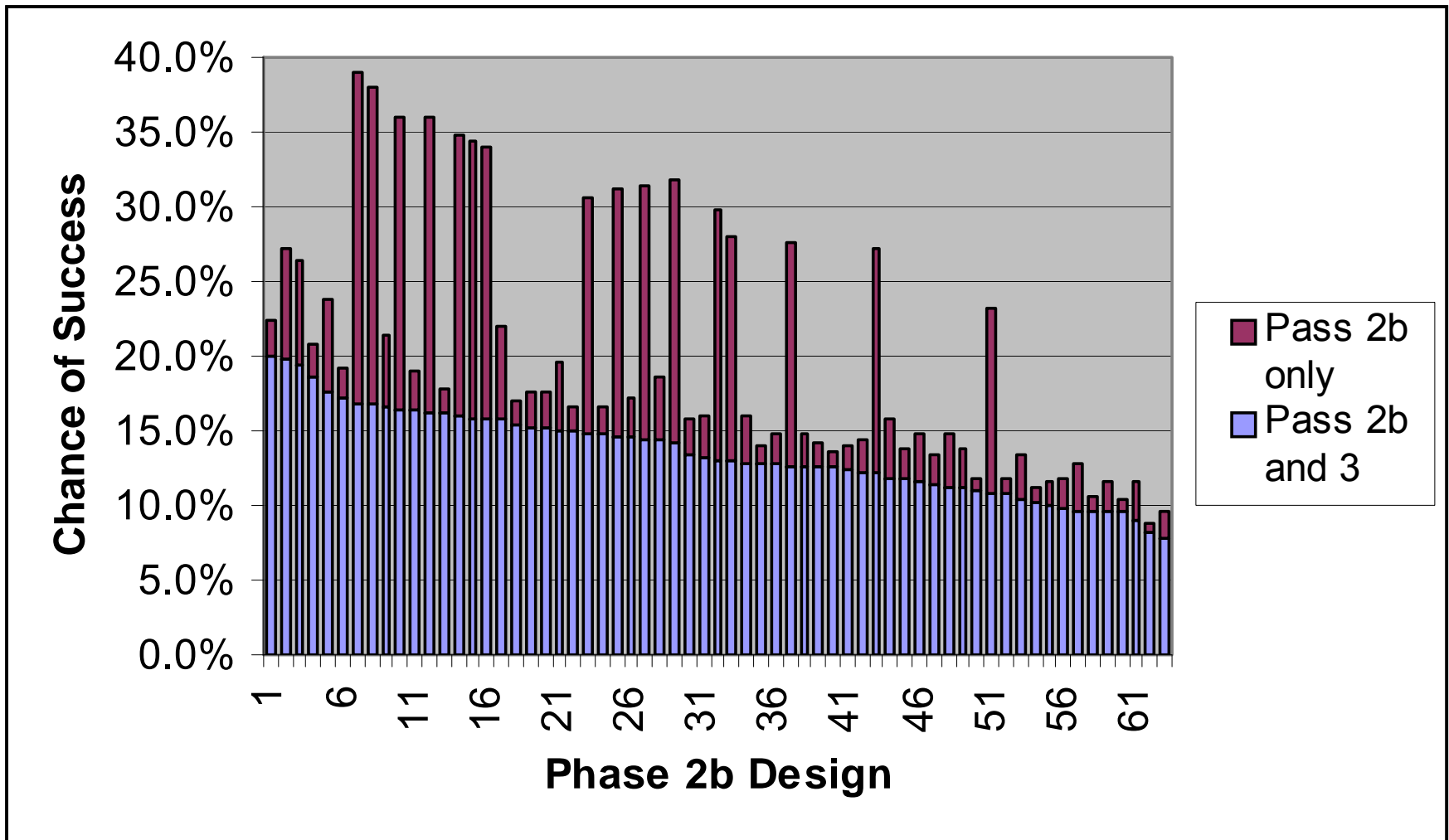
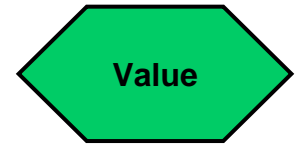
■ Bayesian clinical trial simulation

- To compute PoS we must also simulate parameters
- This is done in the same loop and needs no extra simulated trials
- **Average over the unknown parameters**



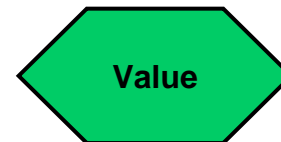
Probability of success depends on design

Could pick a design that gives maximum PoS



Study results

Dig into where studies are failing

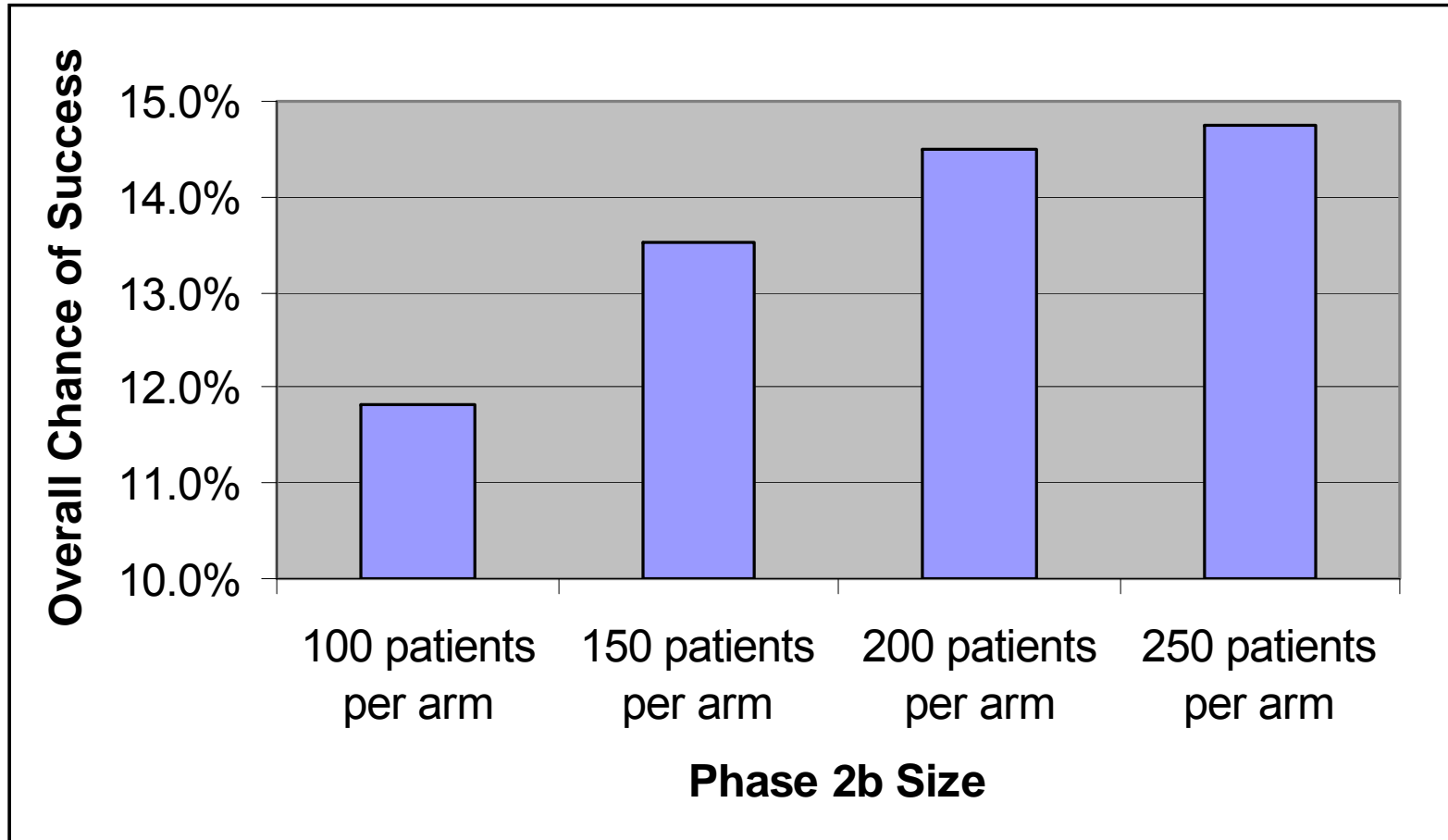
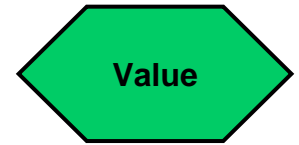


Phase IIb			Phase III		Phase IIb				Phase III		
End point	Sample size	Exposure	Sample size	Non-inferiority margin	PoS	Fail Non-inferiority	Fail Superiority	Fail Safety	PoS (Registration)	Fail Non-inferiority	Fail Safety
ACR20	80	3 months	200	0.8	7.8%	91.8%	42.6%	5.2%	4.7%	1.7%	0.16%
ACR20	80	6 months	200	0.8	6.8%	89.9%	40.1%	2.2%	4.7%	1.5%	0.02%

- The overall probability of successful drug registration is the same in both cases
 - But a 6-month study has a slightly smaller chance progression from Phase 2b to Phase 3
 - This is good as it stops the program before the expensive study

Impact of larger Phase IIb trials

Size of the Phase IIB is key driver of PoS

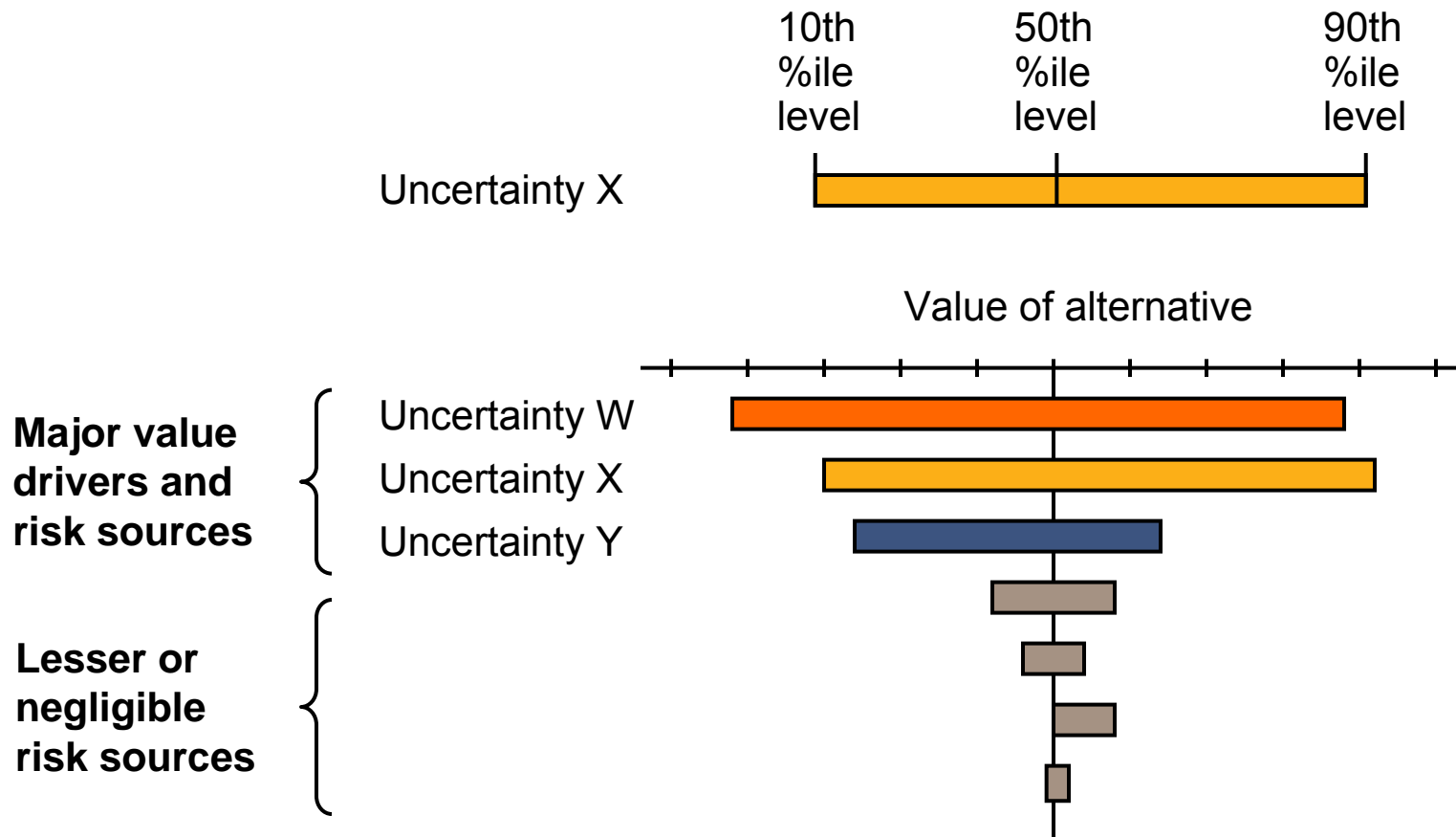




Sensitivity analysis: the Tornado Diagram

Not calculated during this work, but are a useful way of assessing which uncertainties have most influence on value

Value of alternative when all other uncertainties are at their 50th percentile levels, and Uncertainty X is at its:



What does decision analysis bring to trial design?

- Comprehensive approach that evaluates many different combinations
- Considers interactions of options
- Accounts for uncertainty in assumptions
- Evaluation of tradeoffs beyond statistical power