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?

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Overview of the Decision Analysis method

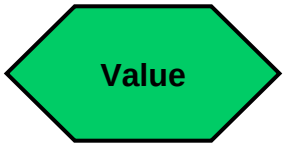
What is needed for a Decision Analysis model

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

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

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



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

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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

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Decisions

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

Strategies

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

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Information

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

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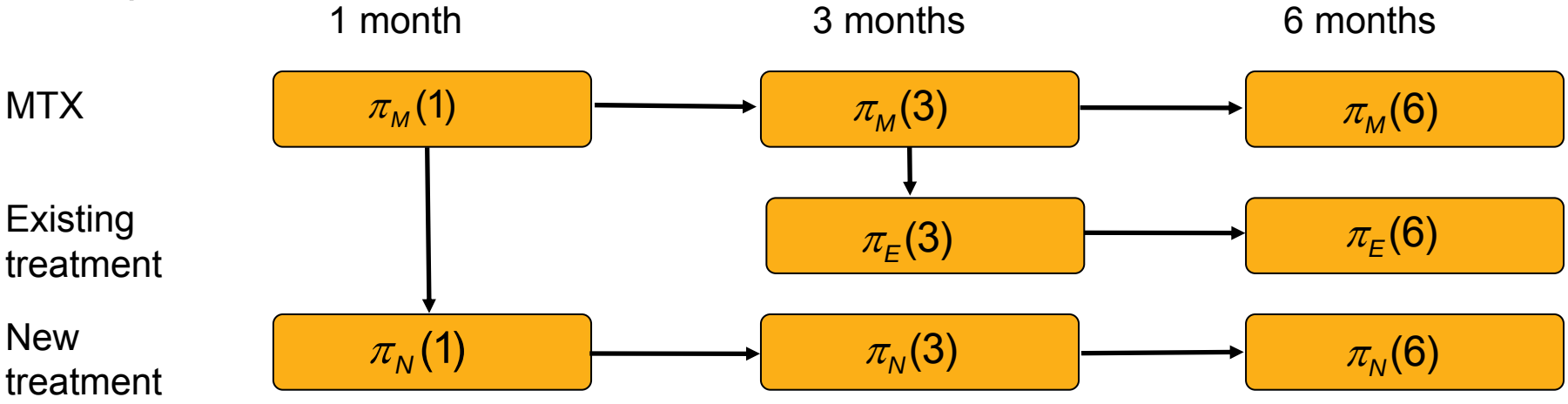
Information

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



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Information

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

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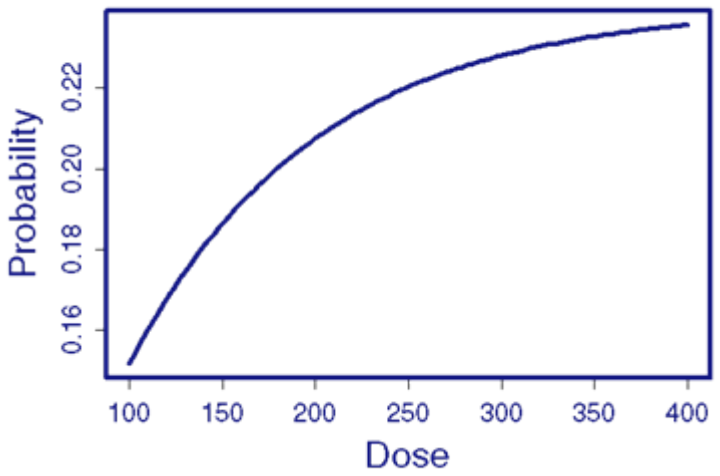
Safety concern 1 distributions

Elicited because there is no data

Information

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

- 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

$$\frac{1-\exp(-\{M1\}\beta)}{1-\exp(-\{H\}\beta)} \sim Beta(16.1,8.2)$$

  - So get an (implicit) distribution for β

- Risk of withdrawal if given MTX + {M1}mg $\quad \gamma\left(1-\exp(-\{M1\}\beta)\right) \sim Beta(2.2,59.7)$

  - So get an (implicit) distribution for γ

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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

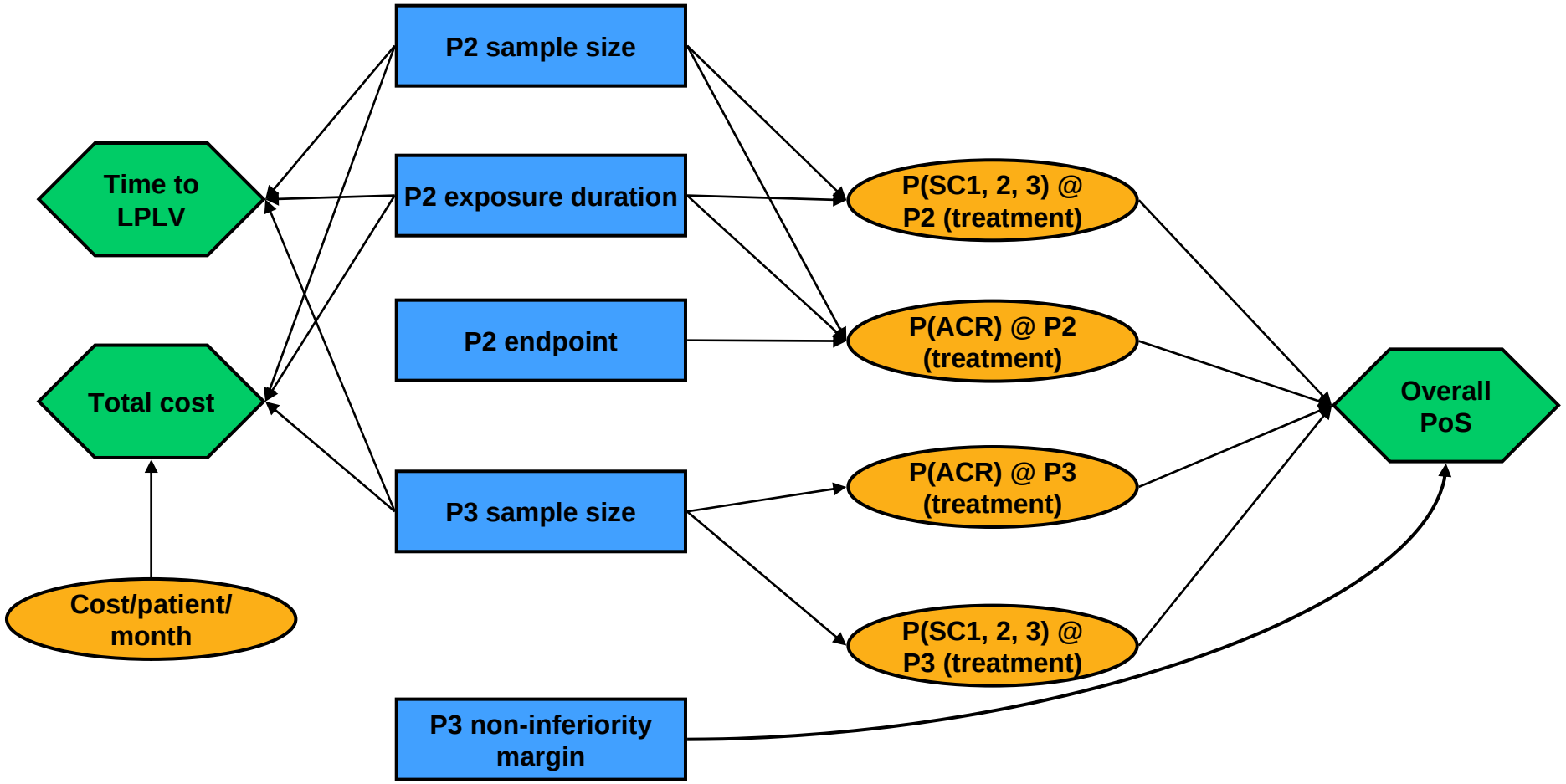
$$(F_{a,b}(0.1)-0.05)^2+(F_{a,b}(0.2)-0.5)^2+(F_{a,b}(0.35)-0.95)^2$$

CFD of a beta distribution

Find a Beta(5.8, 22.3) distribution

Study simulation model

How decisions, information and values are linked



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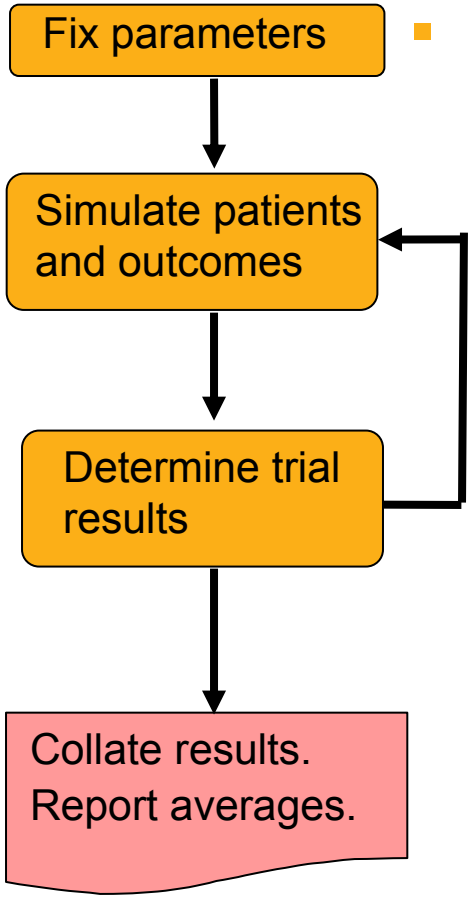
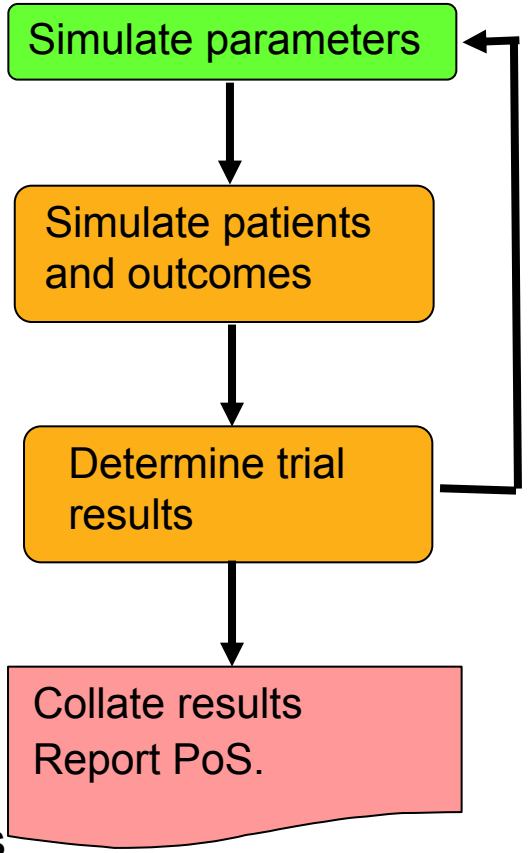
Clinical Trial Simulation vs Bayesian Clinical Trial Simulation



- 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**

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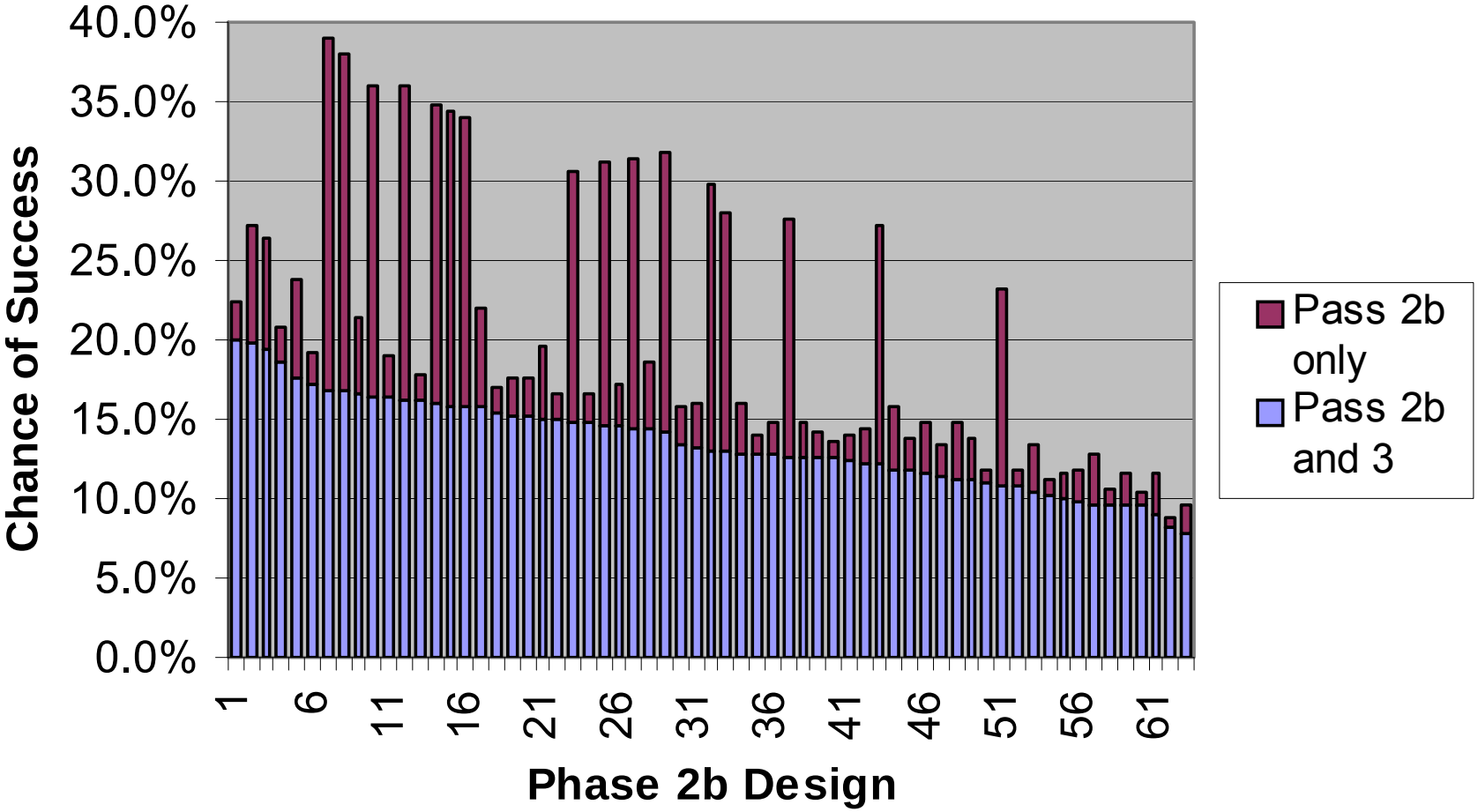
Probability of success depends on design

Could pick a design that gives maximum PoS

Value



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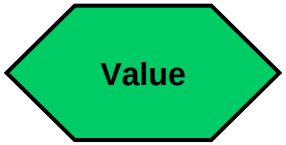
Study results

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

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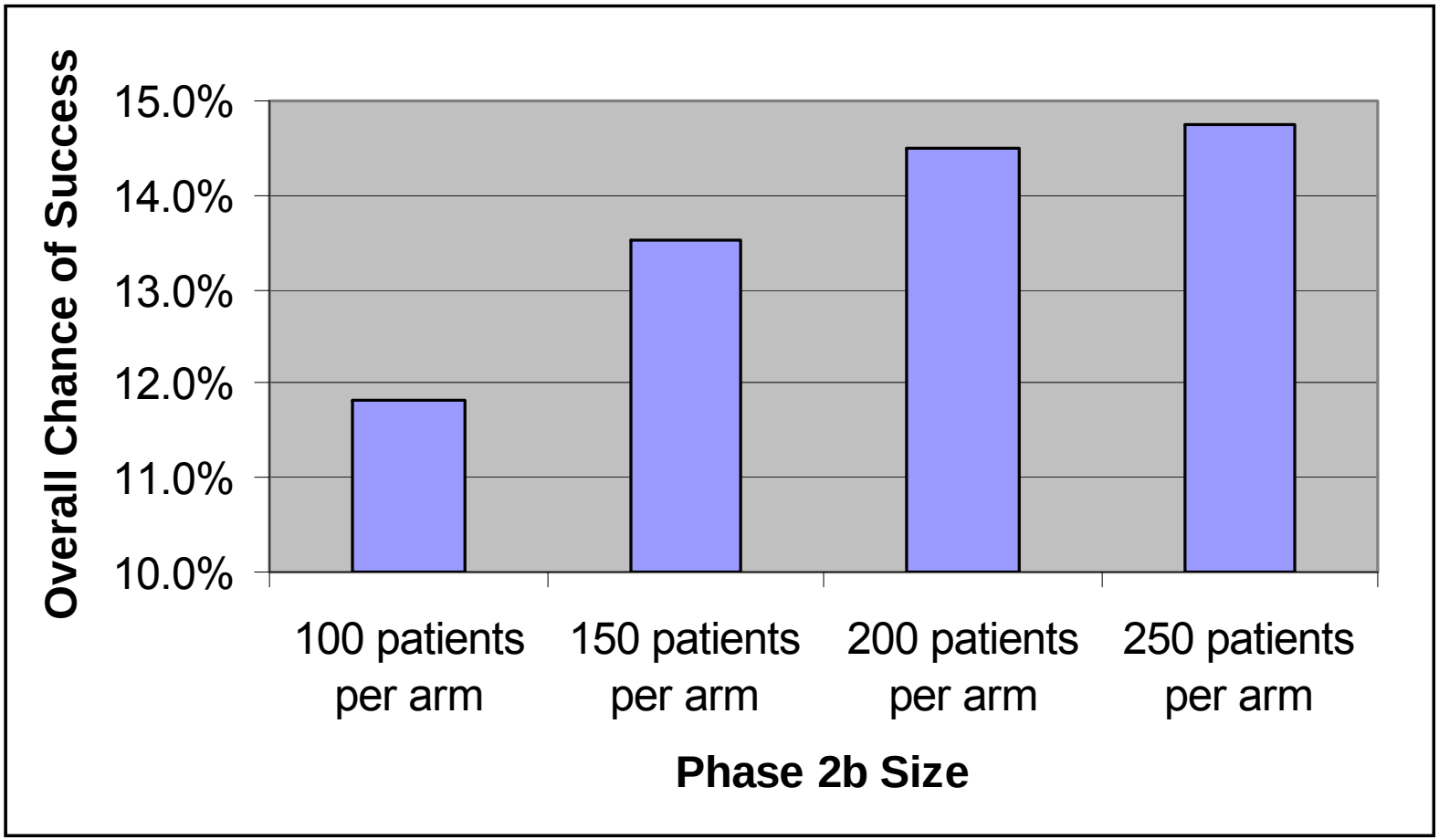
Impact of larger Phase IIb trials

Size of the Phase IIB is key driver of PoS

Value



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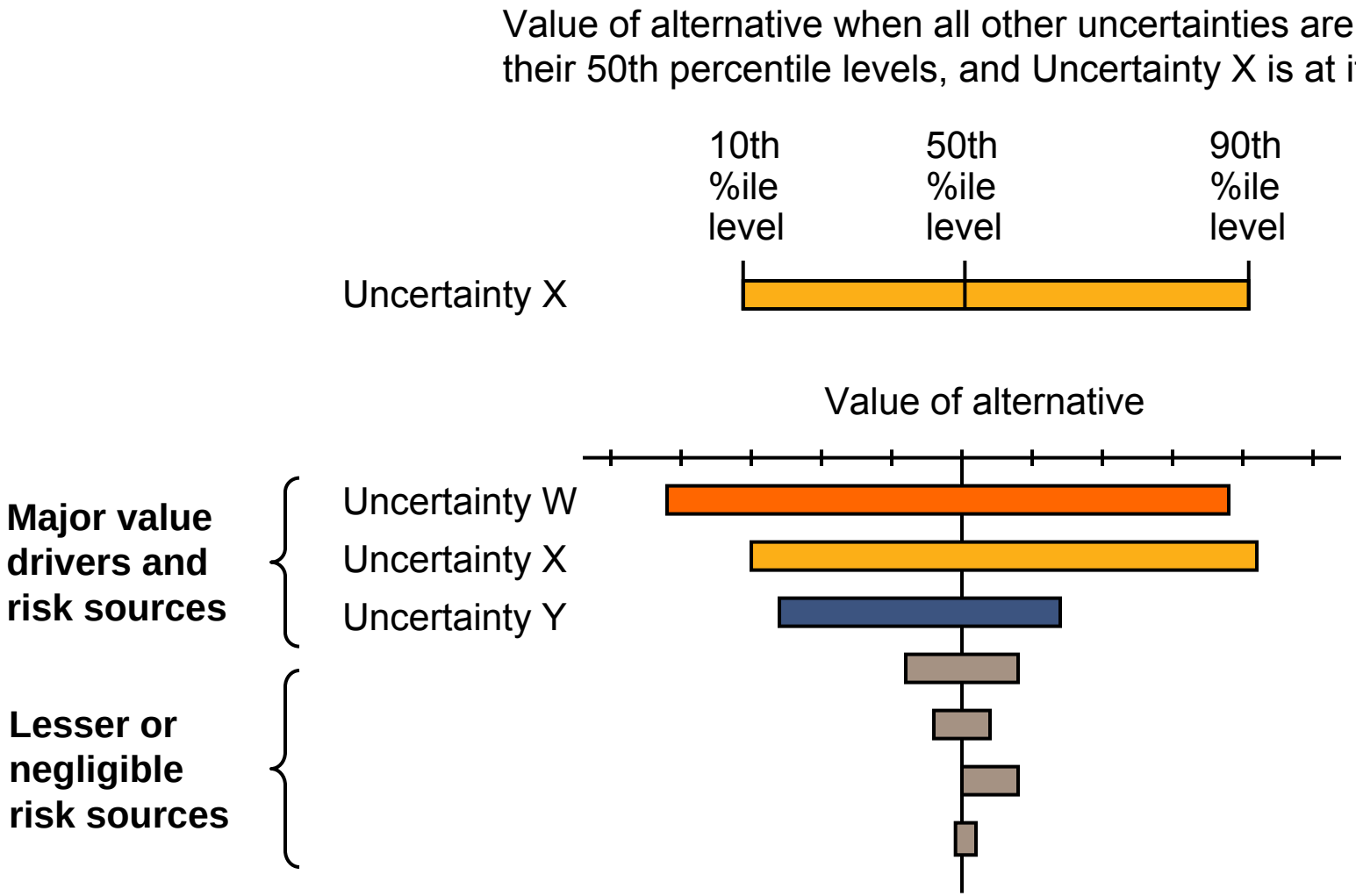
Sensitivity analysis: the Tornado Diagram

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



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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

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