Statistical Modeling for Efficient and Adaptive Trial Designs Using Composite Endpoints

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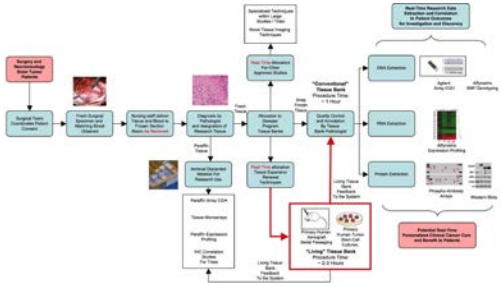
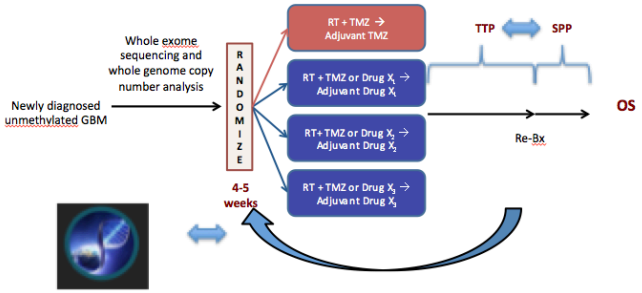
Therapeutic development continuum

Therapy does something in a patient population

Drug does something of value better than current standard

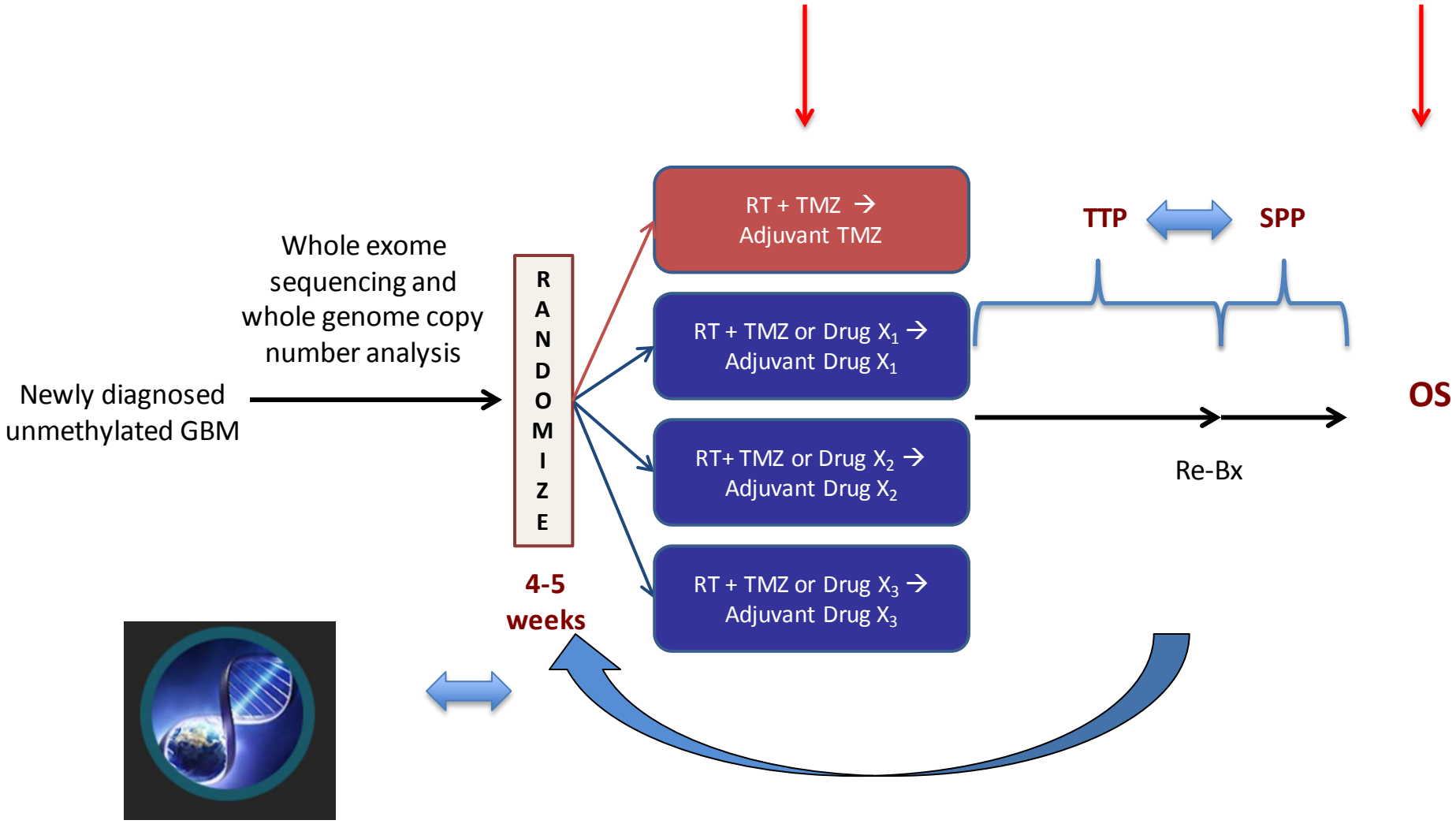




Individualized Screening trial of Innovative GBM therapy (INSIGhT)

Potential problems with phase II

- Design issues
  - Endpoints
  - Controls
- Downtime between studies
  - “Master” protocols
  - Add/drop arms
- Inefficient use of multiplex biomarker data



Individualized Screening trial of Innovative GBM therapy (INSIGhT)

Adaptive trials

- Use accumulating data to decide how to modify a study in a pre-specified manner
- Types of adaptations
  - Adaptive randomization
  - Dropping arms
  - Surrogate endpoints
- Likelihood principle makes Bayesian designs natural for adaptive trials

Frequentist example

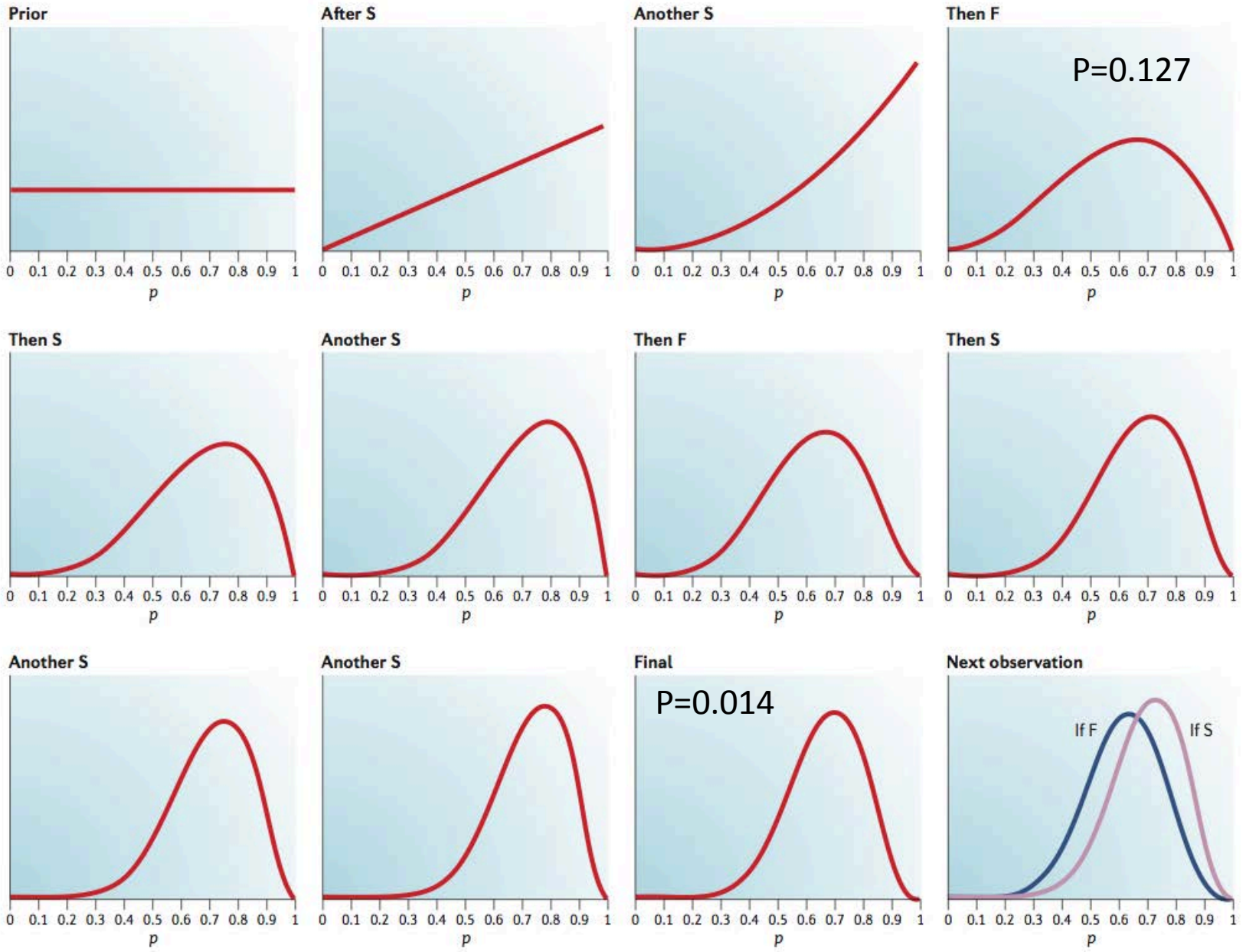
- Consider and experiment testing a probability of success of 0.35
  - SSFSSFSSSF
- Trial design for 10 observations→ p=0.026 (one sided)

Successes	0	1	2	3	4	5	6	7	8	9	10
$p = 0.35$	0.013	0.072	0.176	0.252	0.238	0.154	0.069	**0.021**	0.004	0.001	0.000
$p = 0.70$	0.000	0.000	0.001	0.009	0.037	0.103	0.200	**0.267**	0.233	0.121	0.028

Figure 1 | **Probabilities for a hypothetical clinical trial.**

- Alternative trial design of proceeding until 3 failures→ p=0.004

Berry. *Nat Rev Drug Discov* 2006



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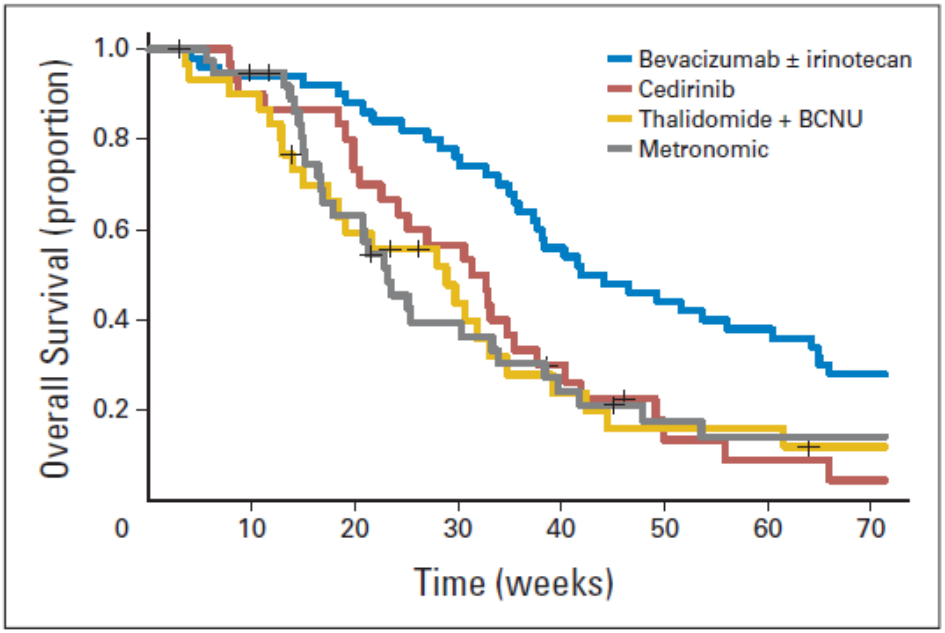
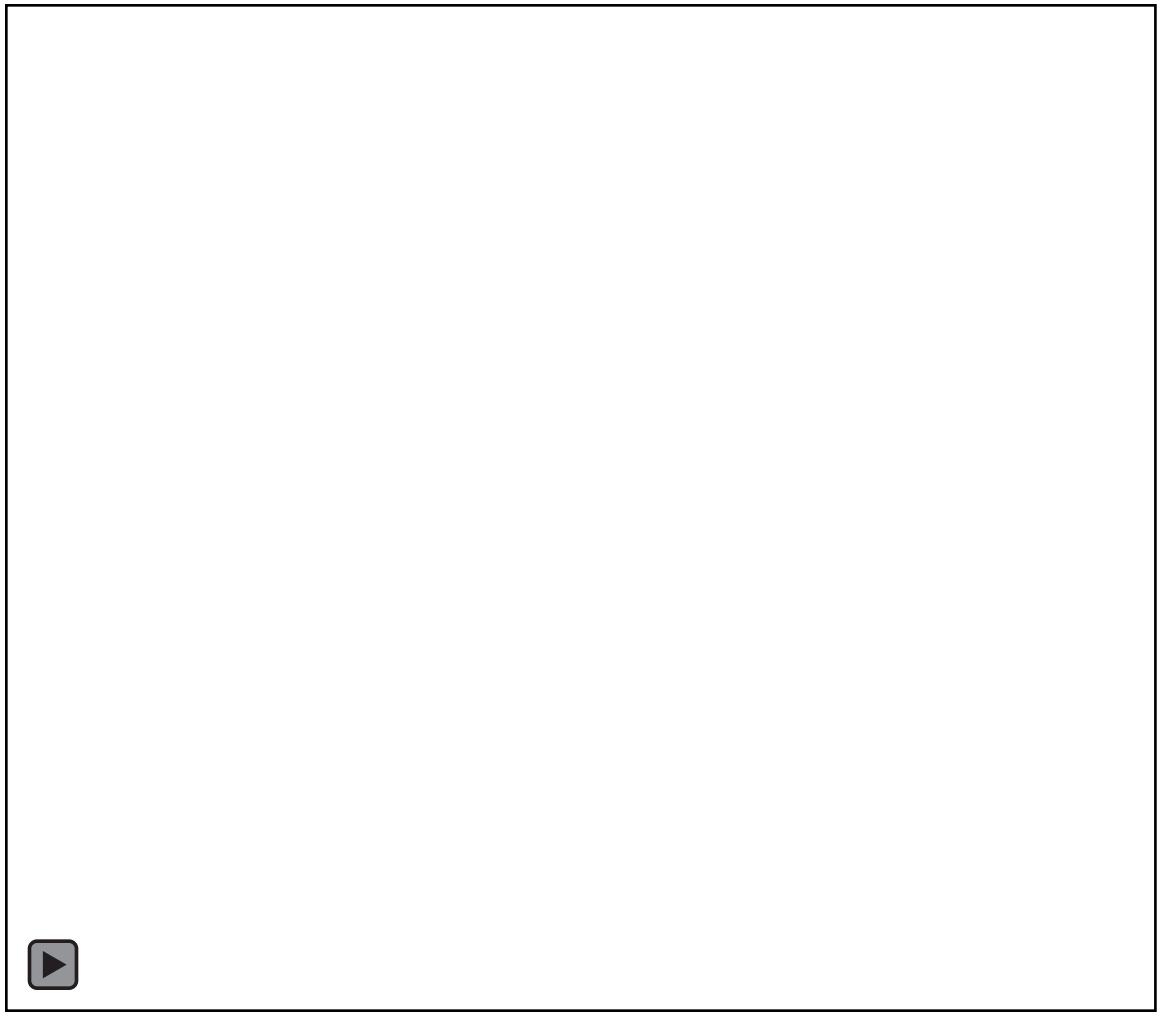
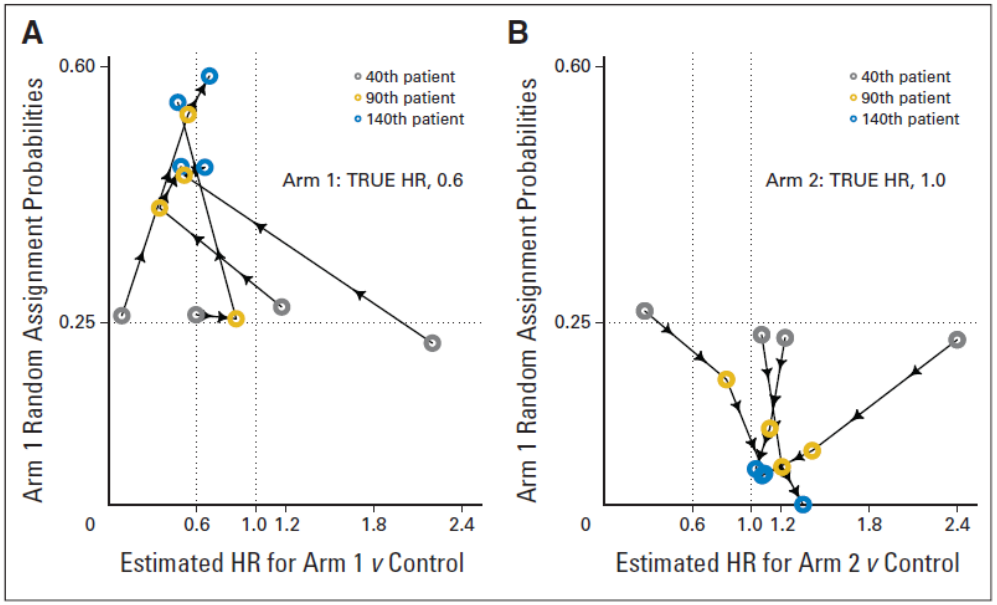


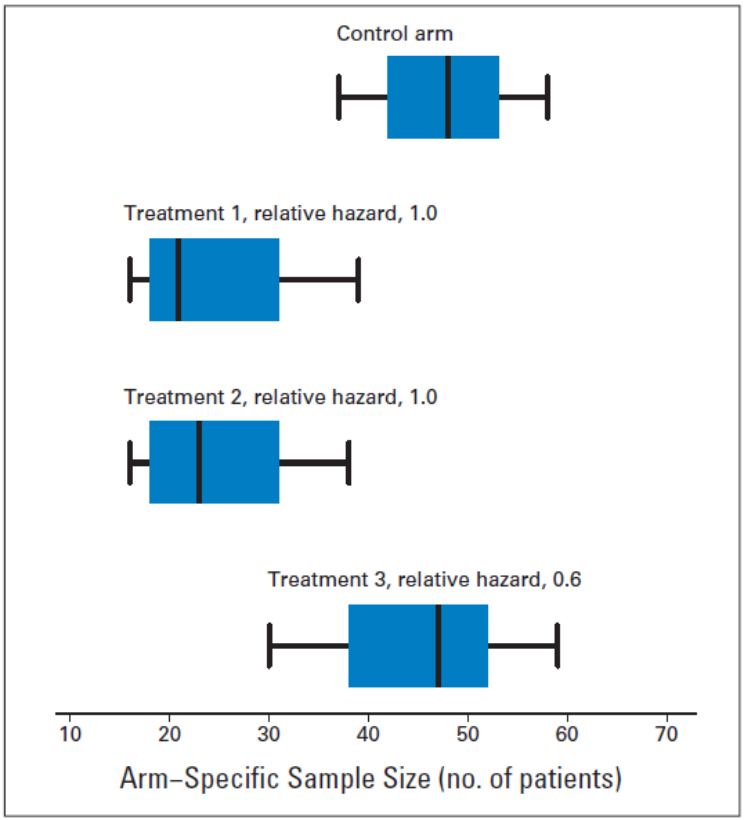
$$\pi_i^k \propto \begin{cases} \dfrac{p(\theta_k < 1 \text{ conditionally on available data})^{\gamma(i)}}{\sum_{j-1}^{3} p(\theta_j < 1 \text{ conditionally on available data})^{\gamma(i)}} & \text{if} \quad k = 1,2,3, \\ \dfrac{1}{3}\exp\left(\max(n_{i,1}, n_{i,2}, n_{i,3}) - n_{i,0}\right)^{\eta(i)} & \text{if} \quad k = 0, \end{cases}$$

Trippa et al. *J Clin Oncol* 2010

Bayesian adaptive randomization: The movie







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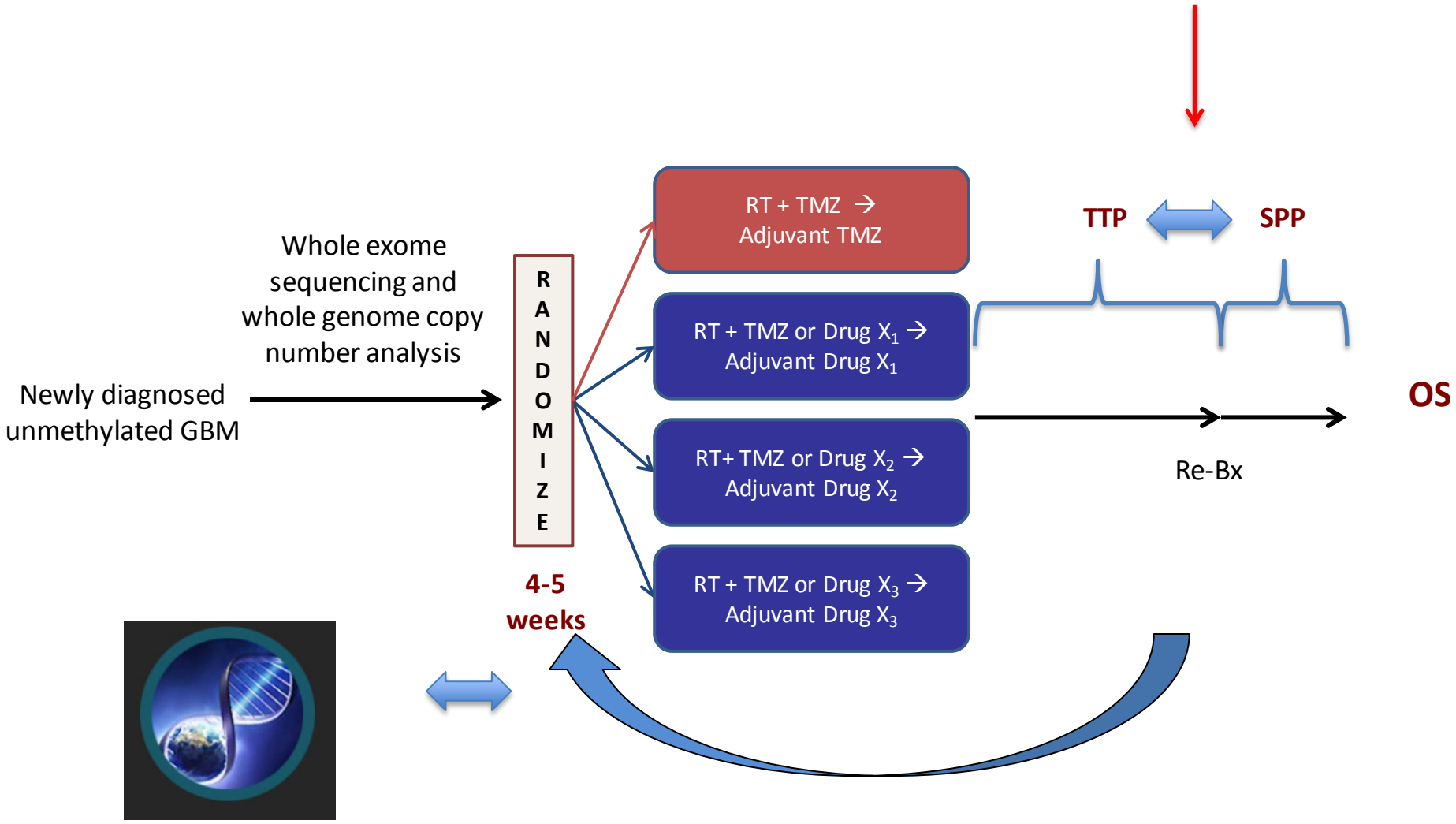
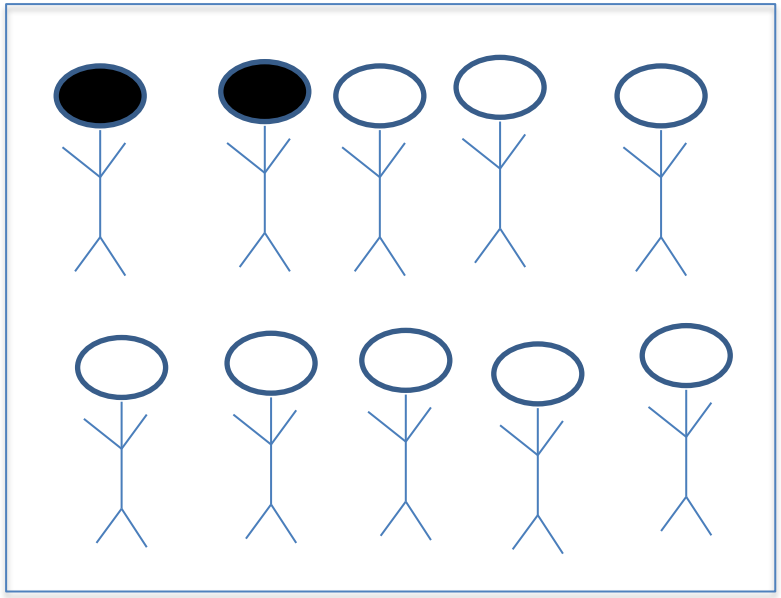


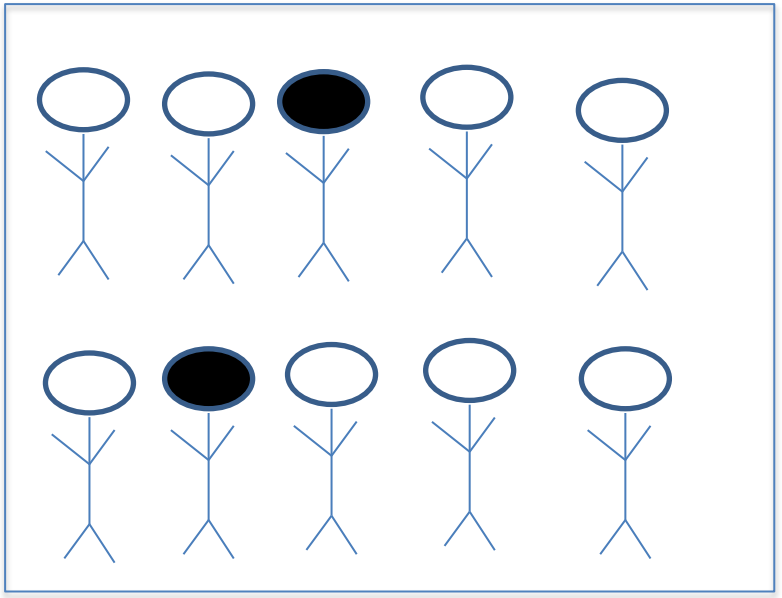
Burroughs Wellcome Fund Innovations in Regulatory Science Award!

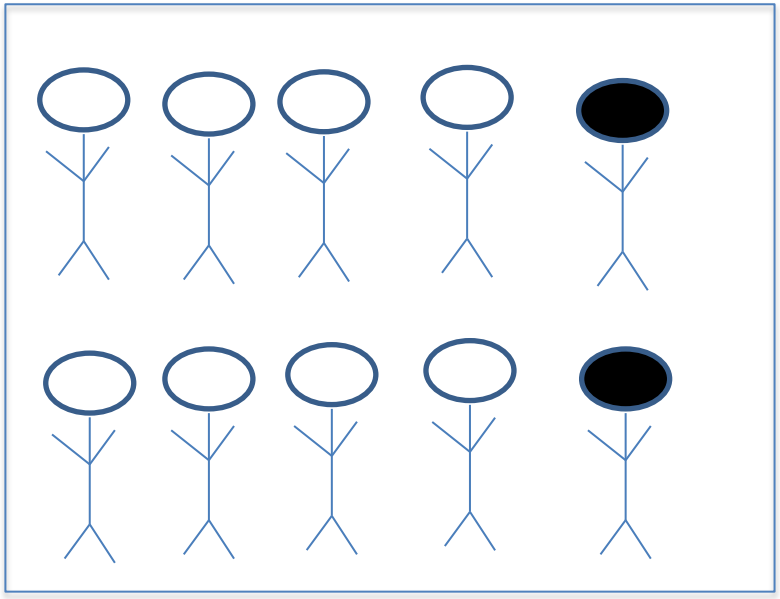
Individualized Screening trial of Innovative GBM therapy (INSIGhT)

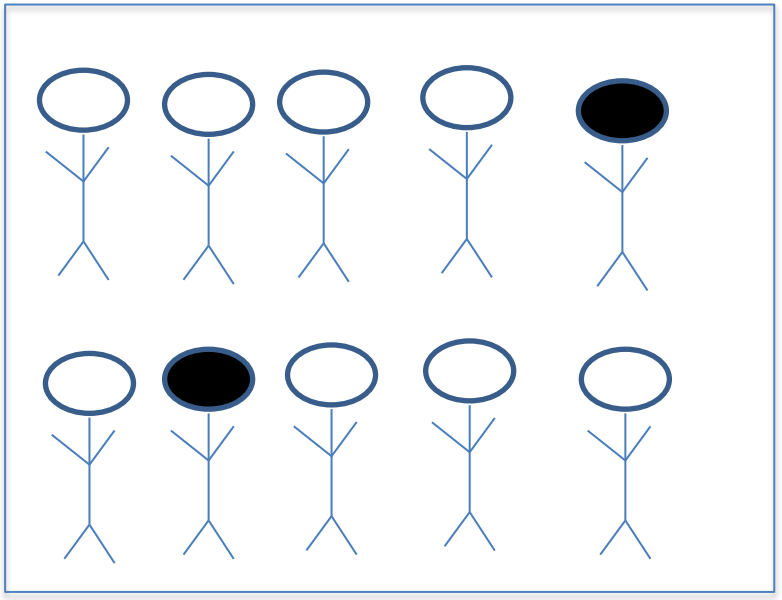
Longitudinal model

- To adaptively randomize, we have to decide which arms to preferentially enroll patients to
- Which arm is doing best?

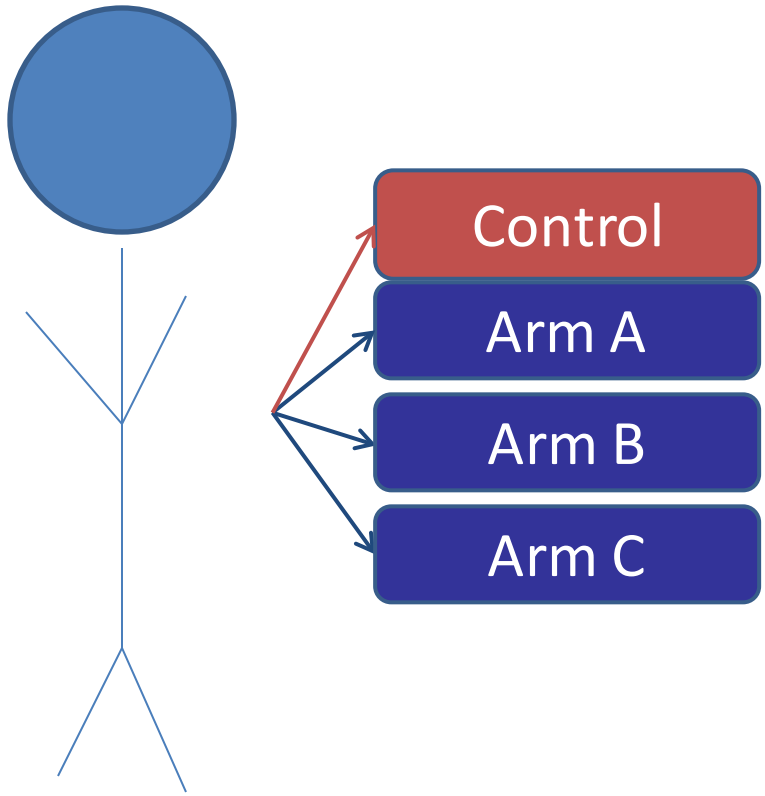




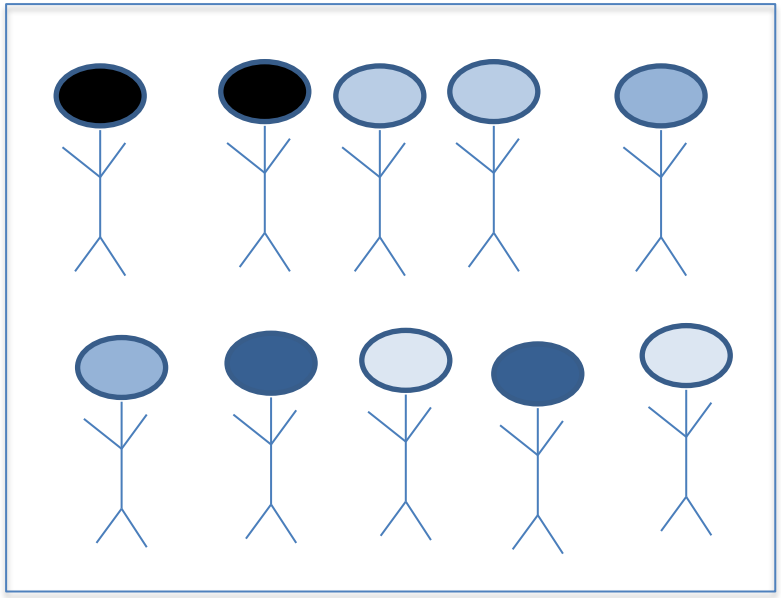


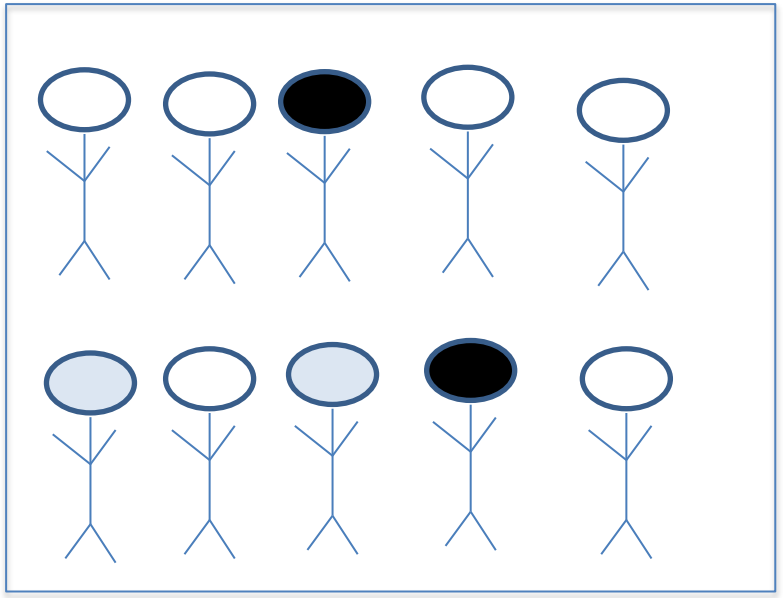


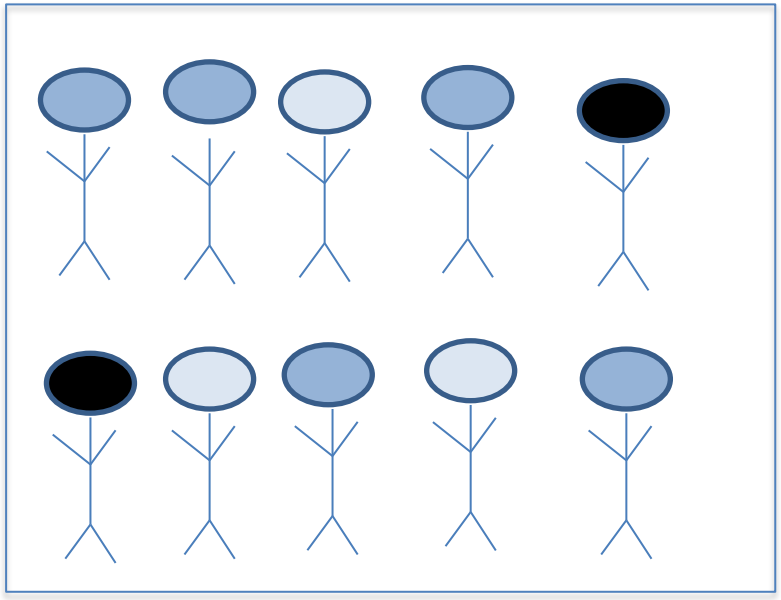
Which to choose?

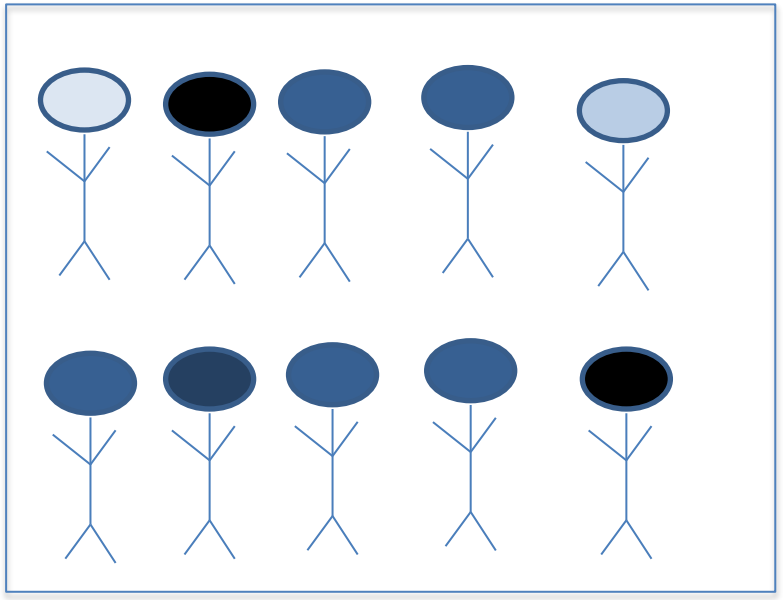


- Death is binary, but *probability* of dying is not
- Factors associated with probability of dying
  - Performance status?
  - Progression?
  - Other response biomarkers?

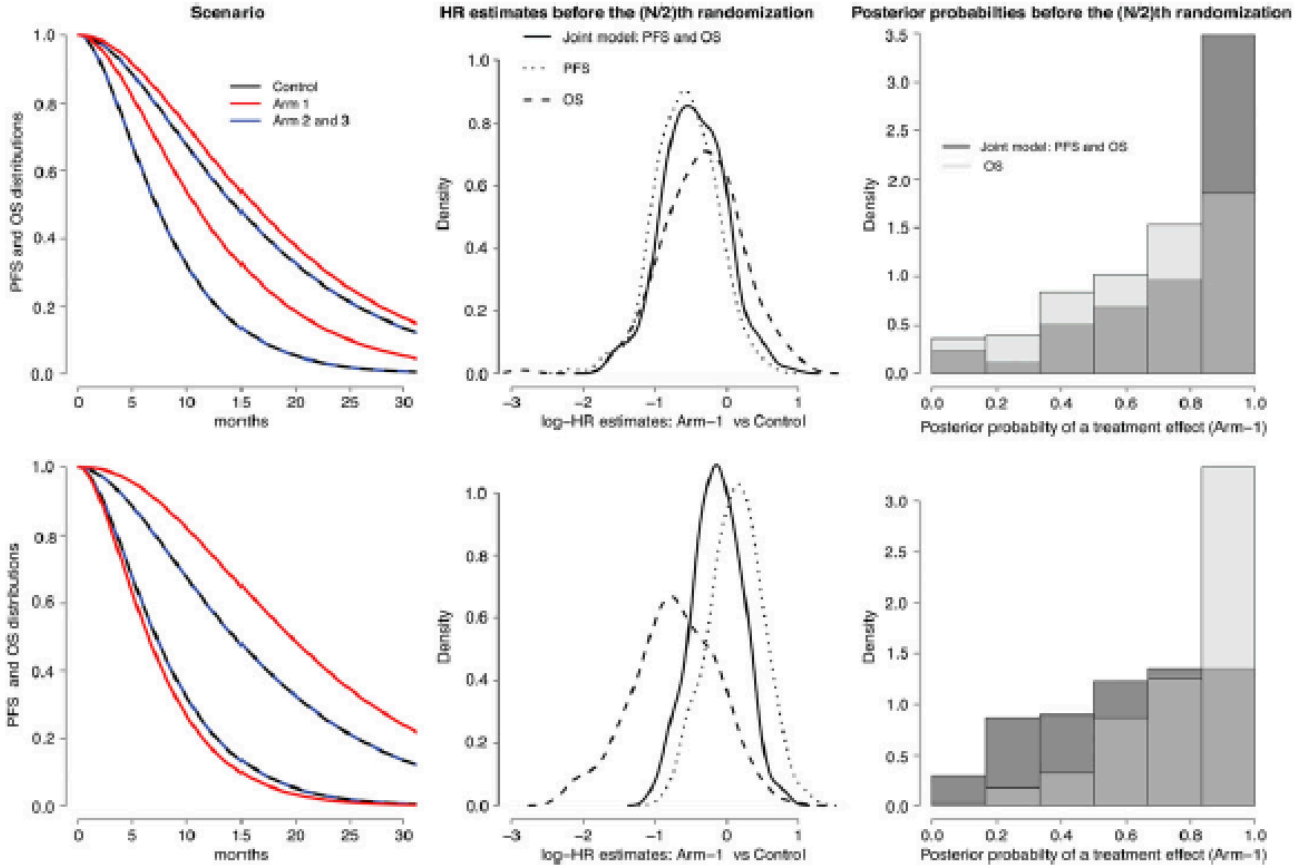




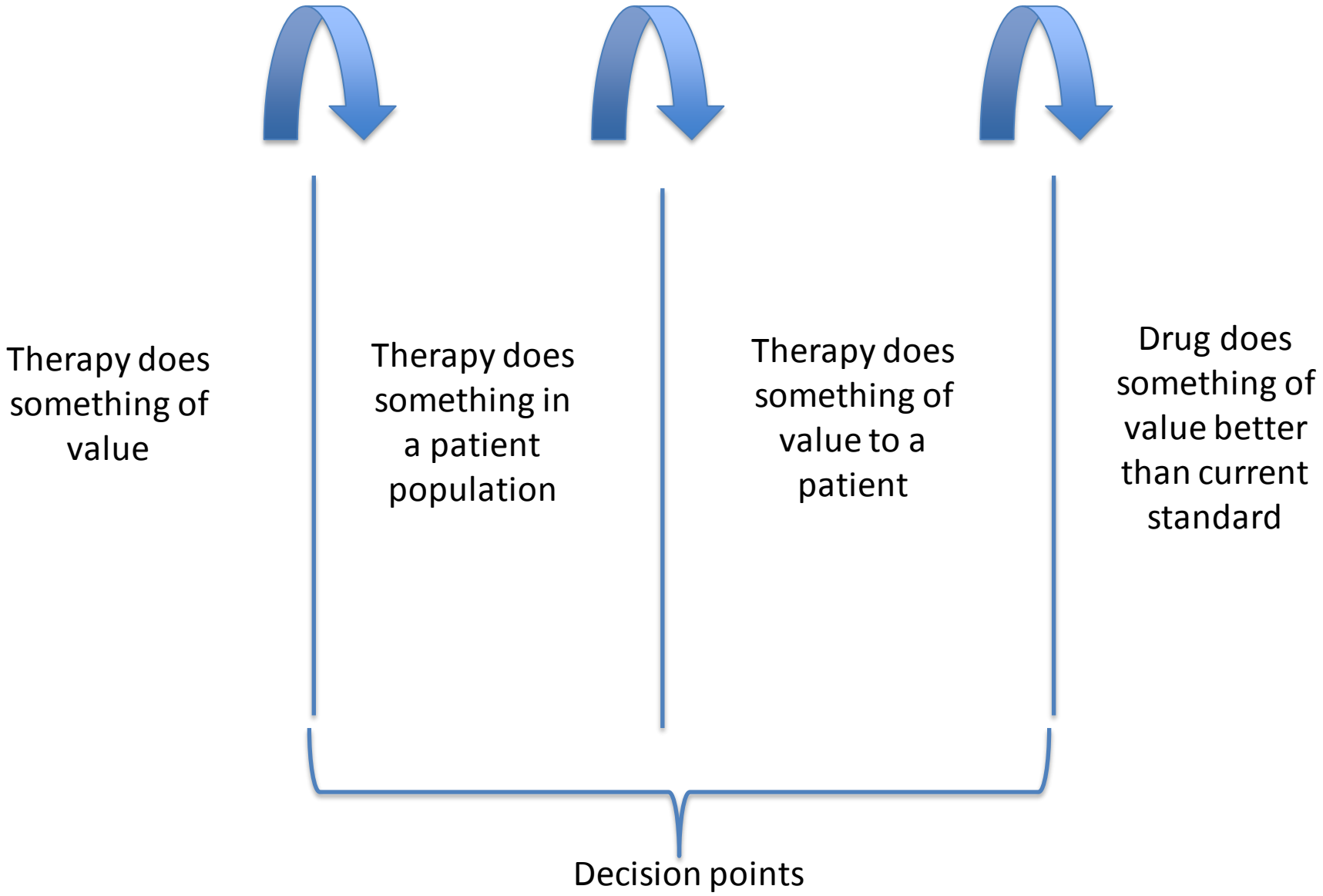




Longitudinal model with PFS



Trippa et al. *Neuro Oncol* 2015


Therapy does something of value
Therapy does something in a patient population
Therapy does something of value to a patient
Drug does something of value better than current standard
Decision points

THANK YOU