Optimizing Phase II:

Setting The Stage For Phase III Success

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Outline

- **Background**
- **Trial-level optimization**
  - **Missing Data**
  - **Placebo Response**
- **Compound-level optimization**
  - **3 Pillars**
  - **Design archetypes**
  - **Active comparators**
- **Portfolio-level optimization**
  - **Trial size, power, type I error**

Motivation for Hierarchy

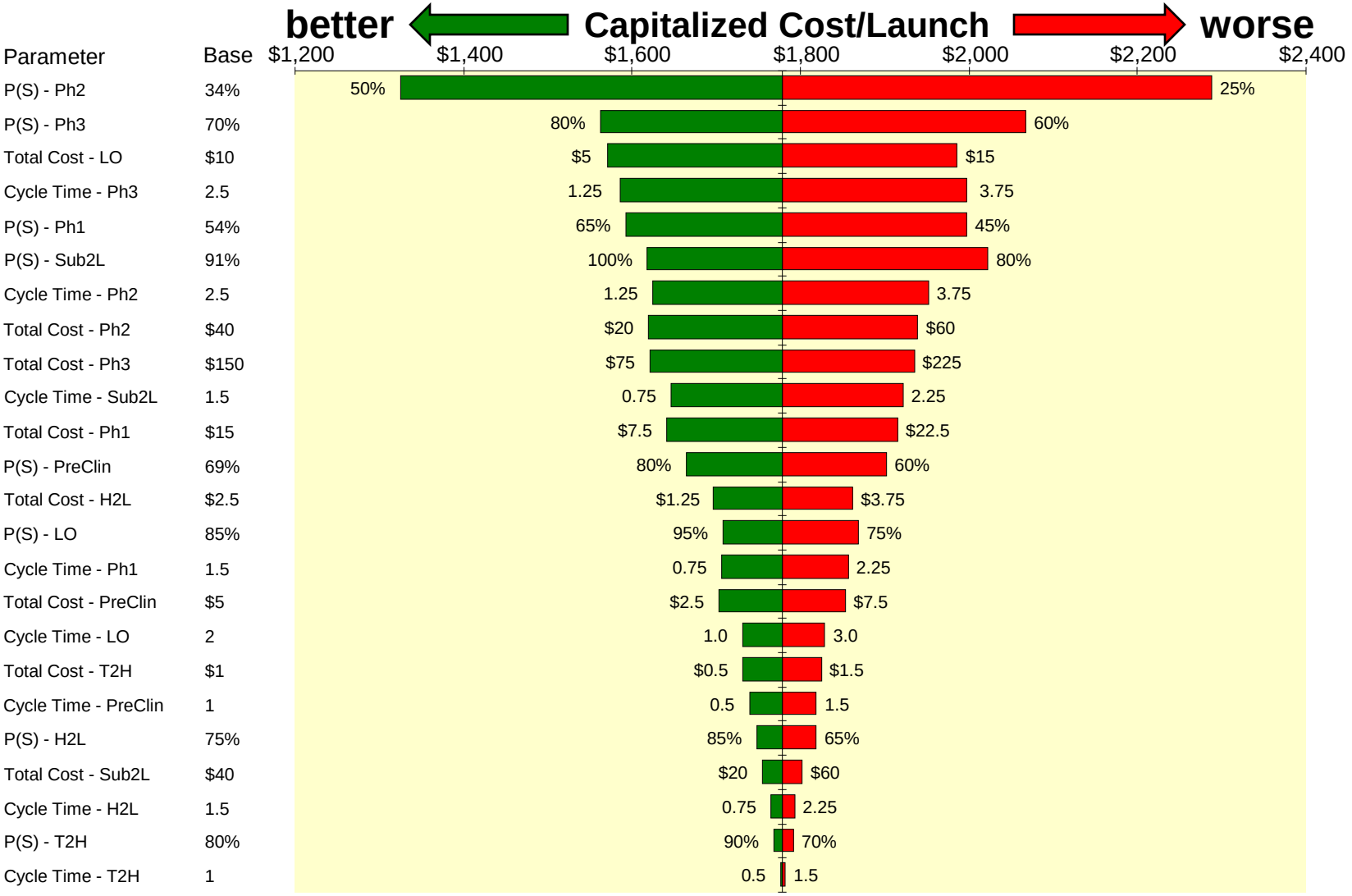
- **Optimizing each trial in a series does not optimize the series. Need clinical plan optimization**
- **Optimizing each compound in a portfolio does not optimize the portfolio**
- **To optimize a Phase II trial need to consider the following hierarchy:**

  Trial - Compound - Portfolio

J. Biopharm Statistics. 2012. 22: 596–607.

R & D Productivity

Nature Reviews Drug Discovery (Paul et. al.; 2009)



Begin With The End In Mind

- **Define what is needed for a Phase III go**
- **How sure do we need to be before committing to the large phase III investment**

Assessing Uncertainty

- **A diagnostic test has 99% sensitivity, 99% specificity**
- Sensitivity = probability person with disease tests positive
- Specificity = probability person without disease tests negative
- **The disease has 0.5% prevalence**
- **A patient tests positive**
- **Probability patient has the disease =**
- **33%**

Consequences

- **For novel mechanisms, a single phase II study can get you to pS ≥ .7 only if it is very large – requiring considerable spend at risk – and/or very positive**
- **Separate phase 2a and 2b studies can provide greater assurrance, but can be slow and inefficient**

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Are We Ready To Test Efficacy?

- 3 pillars of Phase II success
  - Exposure at the target
  - Binding to the target
  - Pharmacological activity commensurate with target exposure and binding
- With 3 pillars in place 8/14 advanced to ph 3
- Without 3 pillars 2/30 advanced to ph 3
- Without 3 pillars, may not be testing H_0

Morgan et al. Drug Discovery Today, 2012

Phase II Goals

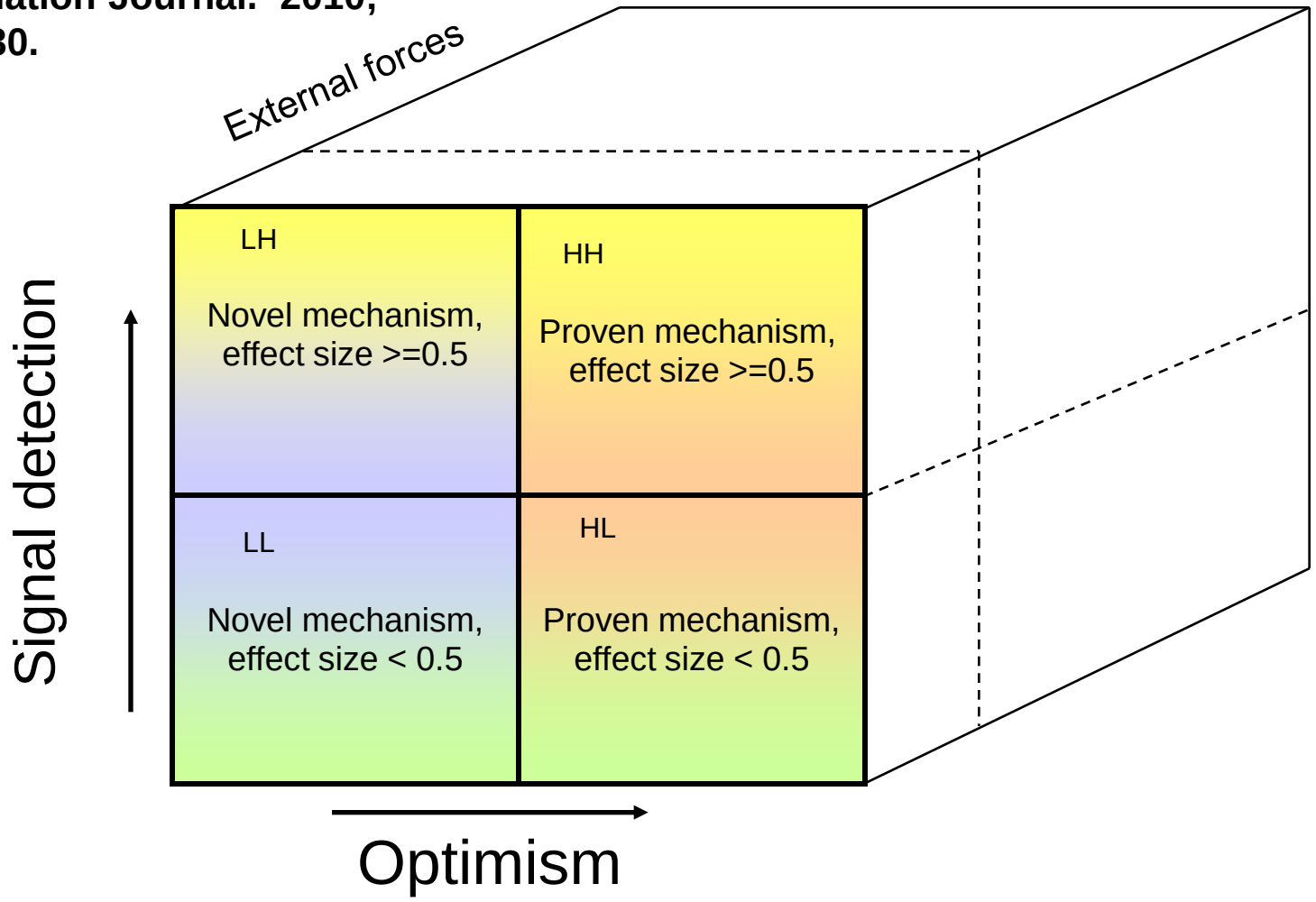
- **Determine if drug has benefit – PoC**
- **Learn “something” about dose-response**
- **Ascertain “value” of drug vs. SoC**

Comparing Phase II Plans

- Single dose-response study in phase II
  - Fast efficient win if drug works
  - Expensive kill if it doesn’t
- Small phase 2a for PoC followed by phase 2b dose response
  - Fast, efficient kill if drug doesn’t work
  - Slow, inefficient win if drug works

Axes of Development: Framework for choosing a plan

Drug Information Journal. 2010; 44(4):421-430.



Primary Archetypes

- **Efficient to PoC – 2a followed by 2b**
  - **Focus on quick kill if optimism low or Δ small**
  - **Defer dose-response until after PoC**
- **Fast to registration – dose response only**
  - **Focus on quick win if optimism is high**
  - **Find dose-response ASAP if showing it is possible – e.g., when Δ is large**

Seamless, Adaptive 2a/2b Can Mitigate Trade-offs

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		Average Sample Size					
Dose Response	**Design**	**Total**	**Placebo**	**Low Dose**	**Mid Dose**	**High Dose**	**% Success**
High Dose Effective	A	204.4	83.1	28.0	31.7	61.6	84.50%
	B	205.9	83.6	21.2	26.2	74.9	87.10%
	C	205.0	83.3	19.8	20.1	81.8	89.30%
	D	323.1	131.0	40.1	41.0	111.0	87.20%
No Dose Effective	A	157.0	67.3	30.8	29.8	29.0	7.90%
	B	161.7	69.0	25.0	26.1	41.7	8.40%
	C	139.6	61.5	13.4	11.6	53.1	6.10%
	D	149.5	73.2	2.1	2.1	72.1	4.50%

A: Stage 1 allocation of **(45, 15, 15, 15)** for (Placebo, Low, Mid, High) followed by adaptive allocation, maximum N=210
B: Stage 1 allocation of **(45, 5, 10, 45)** followed by adaptive allocation, maximum N= 210
C: Stage 1 allocation of **(45, 0, 0, 45)** followed by adaptive allocation, maximum N= 210
D: PoC trial allocated **(70, 0, 0, 70)**, if successful, fixed dose ranging trial with N=210 allocated (70, 46, 47, 47)

Uses of Active Arm in Placebo-controlled PoC Studies

- **Compare vs. SoC**
  - **Beating placebo does not ensure a drug is worth developing in areas with well-established SoC**

Drug Information Journal. 2010; 44(4):431-441.

- **Positive Control**
  - **Assess assay sensitivity and improve decision-making**

Drug Information Journal. 2010; 44(4):443-452

Operational Characteristics of SoC Contrasts

Power and sample size assuming test drug is better than Soc by an effect size of 0.20

Power

N/arm	α = .05	α = .10	α = .20	α = .40
100	29%	40%	55%	71%
200	51%	63%	76%	87%
500	88%	95%	96%	98%

Indirect Comparisons Using Historical Data

- **Use of historical vs. concurrent control is a trade–off between bias and precision**
  - **Concurrent control is not precise when using feasible sample sizes for a 2b trial**
  - **Historical control is probably not unbiased**
- **In MDD, many trials of SSRI. Extract "similar" trials to minimize bias, estimate of SoC still based on large N**
- **For *non-confirmatory* purposes, such as an early benchmarking of a drug's effects**

Result Probabilities In Trials with Positive Controls: Test Drug Effective

Power = 80% for Test drug & PC

Test Drug Significant	PC Significant: Yes	PC Significant: No
Yes	.8 x .8 = .64 (.687)	.8 x .2 = .16 (.113)
No	.2 x .8 = .16 (.113)	.2 x .2 = .04 (.087)

Considerations for Positive Controls

- **Failure of the PC to separate due to chance alone does not mean the study lacked assay sensitivity - we planned for it to happen at a rate = 1 – power**
- **Power for PC must be high (>=90%) so that when PC fails to separate it is because the experiment did not work as expected**
- **PC more useful as p(E) gets lower, power for PC vs. placebo increases, and reasons for failure are less clear**

Considerations for Positive Controls

- PCs may reduce assay sensitivity
  - MDD studies with > 1 drug had higher placebo response rate (44% vs. 34%)
- % on Placebo influences signal detection
- Use unequal allocation to ensure adequate % on placebo
- Study with PC may require 2N patients to achieve same characteristics as N patients randomized 1:1 drug-placebo

Considerations for Positive Controls

- **Rates of missing data and placebo response can be used to assess assay sensitivity**
- **Savings from not having PC to *assess* assay sensitivity may be used on design and conduct features to *improve* assay sensitivity**

Dose ranging / dose selection

- Operating characteristics when comparing doses is similar to comparisons vs. SoC
- Model-based methods can be more efficient than pairwise comparisons
- Consider whether goal is to ID “best” dose / doses for phase III vs. eliminating doses from future consideration
- With small Δ, often best we can do is take a range “off the table”
  - Another opportunity for adaptive allocation

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Ph II Choices Drive Ph III Outcomes

- ***Power*** **in phase II drives # of ph III successes. More important as p(E) increases: need more protection against false negatives as likelihood drugs are effective increases**

- ***False positive rate*** **in Phase II drives rate of ph III success. More important as p(E) decreases: need more protection against false positives as likelihood drugs are not effective increases**

- ***Quality of the candidate [p(E)]*** **drives both # and rate of ph III success**

J Biopharmaceutical Statistics. 2012. 22: 596–607.

Principles of Portfolio Optimization

- **Optimum approach situation dependent**
- **What is best for the compound may not be what is best for the portfolio**
- **Trade-offs**
  - **Larger Phase II can increase Phase III success**
  - **Smaller phase II can reduce cost and fund compounds that would not have been developed**
  - **As fixed cost of Phase II increases, benefit from smaller studies decreases**

Principles of Portfolio Optimization

- **In simulation scenarios patterned after an "average" drug company optimum phase II power > 90% and optimum type 1 error near 10%**
- **When basing phase III go/no go on success from both a 2a and 2b study the optimum power for each study > 95% and optimum type I error near 30%**
- **No universally best choice. Must evaluate**
  - **Portfolio constraints vs. opportunities**

Alzheimer's Example

- **Compare 3 plans**
  - **1) Small clinical endpoints Phase 2 followed by two Phase 3 studies**
  - **2) Biomarker / safety phase 2 followed by two Phase 3**
  - **3) Seamless 2/3 w \ clinical endpoints with one phase 3 commencing when a positive signal is seen in the seamless 2/3**

	Phase 2			Phase III			Total		
	Cost	CT	pTS	Cost	CT	pTS	Cost	CT	pTS
1									
2									
3									

Discussion

- **Optimizing Phase II is critical**
  - **Consider the overall development plan**
  - **Consider the portfolio**
- **Favor compounds / platforms for which the 3 pillars can be established in phase I**
- **Emphasize design and conduct features to limit placebo response and dropout**
- **Use axes of development for guidance**
- **Set control of false + and false - decisions at rates commensurate with portfolio constraints**


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