Evaluating Probability of Success in Oncology Clinical Trials

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Global Pharmaceutical R&D
Abbott
Outline

• What is “success”?
• Probability of success vs. Power
• How does phase 2 affect the probability of success in phase 3?
• P(success) for binary data
• P(success) for time-to-event data
• Examples
Defining success

• Some possible definitions of success
  – P-value <0.05 vs. placebo
  – P-value <0.05 vs. placebo with efficacy $\geq$ competing drug
  – P-value <0.05 vs. placebo with efficacy $\geq$ competing drug and better safety, tolerability, and convenience
Probability of Success vs. Power
(From protocol) Determination of Sample Size

Assuming a significance level of 0.05 and an effect size of 0.30, the planned sample size of 176 subjects per group provides 80% power to detect a difference between drug and placebo.

Voicemail from clinical team: “We need a trial with 90% power, but we can’t afford to increase the sample size.”
Typical phase 3 trial?

(From protocol) Determination of Sample Size

Assuming a significance level of 0.05 and an effect size of 0.30, the planned sample size of 176 subjects per group provides 80% power to detect a difference between drug and placebo.

(From protocol) Determination of Sample Size

Assuming a significance level of 0.05 and an effect size of 0.35, the planned sample size of 176 subjects per group provides 90% power to detect a difference between drug and placebo.

But what is truly the probability of a successful trial?
Power vs. $P(\text{Success})$

- Power is a **conditional** value
  - Choose an effect size
  - Power is the probability of statistical significance *if that is the true effect size*

- The probability of success is an **unconditional** value
  - $P(\text{success})$ is the weighted average of the power *across the range of possible effect sizes*
    - Expected value of power

How do we calculate the probability of success?

• Phase 2 trial – continuous endpoint
  – Drug vs. placebo, 20 subjects per arm
  – Mean difference is 0.3, SD is 1.0
  – Effect size = 0.3/1 = 0.3

• Naive approach to phase 3:
  – Effect size = 0.3
    • 176 subjects per group for 80% power
    • 235 subjects per group for 90% power

• But is 0.3 the right effect size?
What do we know about the effect size?

• The phase 2 study implies a distribution of possible treatment differences

• (Of note, this is the posterior distribution of the true treatment difference, given the phase 2 study results and a uniform prior)
The central problem

- The power curve is asymmetric
The central problem

- The power curve is asymmetric
Calculating $P(\text{success}) = \text{expected power}$

- \( E(\text{power}) = \int P(\text{success}|\text{true diff}) \, P(\text{true diff}|\text{Ph2 diff}) \, d(\text{true diff}) \)

- Crude numerical integration:
  - \( \approx 17\% \) chance of \( \approx 0\% \) power
  - \( \approx 36\% \) chance of \( \approx 100\% \) power
  - \( \approx 47\% \) chance of \( \approx 50\% \) power
  - \( 17\%(0) + 36\%(1) + 47\%(0.5) = 59.5\% \)

- Exact answer
  - \( 60.8\% \)
Probability of success

\[ d = \text{observed difference in phase 2 study} \]
\[ s = \text{observed standard deviation in phase 2 study} \]
\[ n_2 = \text{number of subjects per group in phase 2 study} \]
\[ n_3 = \text{planned number of subjects per group in phase 3 study} \]

Probability of success = \[ \Phi \left( \frac{d - 1.96s \sqrt{\frac{2}{n_3}}}{s \sqrt{\frac{2}{n_2} + \frac{2}{n_3}}} \right) \]

(1-sided significance test at \( \alpha = 0.025 \))
How does Phase 2 impact Probability of Success in Phase 3?
Improving the probability of success

- So we should add more subjects, right?

![Graph showing the probability of success with treatment difference and power with n=176 per arm. The graph indicates a probability of success of 60.7%.]
Improving the probability of success

- So we should add more subjects, right?

<table>
<thead>
<tr>
<th>Phase 3 n per arm</th>
<th>Power if true difference is 0.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>176</td>
<td>80%</td>
</tr>
<tr>
<td>235</td>
<td>90%</td>
</tr>
<tr>
<td>500</td>
<td>99.7%</td>
</tr>
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</table>

-0.6 -0.3 0 0.3 0.6 0.9 1.2
Treatment difference
Improving the probability of success

- So we should add more subjects, right?

<table>
<thead>
<tr>
<th>Phase 3</th>
<th>Power if true difference is 0.3</th>
<th>P(success)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n per arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>176</td>
<td>80%</td>
<td>60.8%</td>
</tr>
<tr>
<td>235</td>
<td>90%</td>
<td>64.1%</td>
</tr>
<tr>
<td>500</td>
<td>99.7%</td>
<td>70.7%</td>
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Improving the probability of success

• So we should add more subjects, right?

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<tr>
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<td>99.7%</td>
<td>70.7%</td>
</tr>
</tbody>
</table>

• The problem is not the power curves!
  – Too much blue curve at small or negative values
Improving the probability of success

- How do we move the blue curve?

  Get a better drug: effect size of 0.6 instead of 0.3.
  With only \( n=88 \)/arm in phase 3, \( P(\text{success}) \) is 81%

- More feasible: get a tighter estimate from Phase 2
Improving the probability of success

- SD of treatment-difference curve is based on phase 2 sample size
  - ↑ phase 2 sample size → tighter estimate of effect size
Improving the probability of success

- SD of treatment-difference curve is based on phase 2 sample size
  - → phase 2 sample size → tighter estimate of effect size

![Graph showing treatment difference distribution with phase 2 sample sizes of 20 and 50](image-url)
Improving the probability of success

- SD of treatment-difference curve is based on phase 2 sample size
  - $\uparrow$ phase 2 sample size $\rightarrow$ tighter estimate of effect size

<table>
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<tr>
<th>Phase 2 n per arm</th>
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<th>P(success)</th>
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<tbody>
<tr>
<td>20</td>
<td>80%</td>
<td>60.8%</td>
</tr>
<tr>
<td>50</td>
<td>80%</td>
<td>65.6%</td>
</tr>
<tr>
<td>80</td>
<td>80%</td>
<td>68.4%</td>
</tr>
</tbody>
</table>

Phase 3: n=176 per arm

<table>
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<tr>
<th>Phase 2 n per arm</th>
<th>Power if true difference is 0.3</th>
<th>P(success)</th>
</tr>
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<tbody>
<tr>
<td>20</td>
<td>90%</td>
<td>64.1%</td>
</tr>
<tr>
<td>50</td>
<td>90%</td>
<td>70.6%</td>
</tr>
<tr>
<td>80</td>
<td>90%</td>
<td>74.3%</td>
</tr>
</tbody>
</table>
Probability of success for binary data
Binary data example: tumor response rate

- Phase 2 study with 20 subjects per group
- Endpoint: Tumor response
- Results: Control 20%, Experimental drug 40%

- Naive phase 3 power calculation
  - Assume underlying response rates of 20% vs. 40%, 2-sided $\alpha=0.05$
  - N=120/group provides 90% power
  - Does not account for uncertainty of response estimates
Complication with binary data

- Based on randomized trial, possible to construct posterior distribution for treatment difference
  - n=20 per arm, 20% vs. 40% response rate
- But problems arise computing expected value of power
Complication with binary data

• To do the numerical integration, need to calculate power at each point across the distribution
  – Consider a specific point on the curve (difference of 10%, e.g.)
  – Since SD varies with specific rates, not possible to calculate power knowing only the difference in response rates
    • For a given sample size, power for 20% vs. 10% is higher than for 50% vs. 40%
Uncertainty of response rate estimates

• How do we account for uncertainty of response rate estimates?

  – Consider Beta distribution to approximate the binomial for each group: Beta(\(\alpha, \beta\)), where
    • \(\alpha\) = # of responders
    • \(\beta\) = # non-responders
  – Control group (4 responders out of 20): Beta(4, 16)
  – Experimental group (8 responders out of 20): Beta(8, 12)
Evaluating probability of success in oncology clinical trials

Control group (4/20 responders)

Experimental group (8/20 responders)

Beta distribution vs. normal approximation

- Normal approximation
- Beta(4,16)
- Beta(8,12)
Simulations to compute $P(\text{success})$ for phase 3

- $P(\text{success}) = P(\text{p-value} \leq 0.05) = E(\text{Power})$
  1. Select response rate at random from each Beta distribution
  2. Calculate power based on selected response rates
  3. Repeat 1000 times (or 10,000, or 100,000)
  4. Compute average power across simulation runs

![Beta distributions](image)
Simulation results

- Based on Phase 3 sample size of 120/group, $P(\text{success}) = 66\%$
- Recall N=120/group provides 90% power in naive calculation that does not account for uncertainty in 20% vs. 40% response rates
Probability of success for time-to-event data
Phase 2 Study with time-to-event endpoint: Example

Control
Experimental

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>60</td>
<td>44</td>
</tr>
<tr>
<td>Experimental</td>
<td>60</td>
<td>36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Total follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6.9</td>
<td>438</td>
</tr>
<tr>
<td>Experimental</td>
<td>10.8</td>
<td>547</td>
</tr>
</tbody>
</table>

P-values
Log-rank         0.06
Cox PH           0.061

Hazard Ratio (95% CI)
0.656 (0.42, 1.02)
Probability of success for time-to-event data

- Simple implementation of probability of success – make use of the normal approximation for the log-hazard ratio

\[
\log(hr) \sim N(\log(hr_2), \frac{4}{n_{e2}})
\]

- Where

\[
hr_2 = \text{observed hazard ratio in phase 2 study}
\]
\[
n_{e2} = \text{number of events in phase 2 study}
\]
Probability of success for time-to-event data

Then the probability of success of the phase 3 trial (one-sided test at $\alpha = 0.025$) is

$$P(success) = P\left( \log(\hat{hr}) < -\sqrt{4/n_{e3} \cdot 1.96} \right) = \Phi \left( \frac{-\sqrt{4/n_{e3} \cdot 1.96} - \log(hr_2)}{\sqrt{4/n_{e3} + 4/n_{e2}}} \right)$$

Where

- $hr_2 = \text{observed hazard ratio in phase 2 study}$
- $n_{e2} = \text{number of events in phase 2 study}$
- $n_{e3} = \text{planned number of events in phase 3 study}$
Example – Phase 3 time-to-event study

• Naive power estimate: If the true hazard ratio is 0.656, then 236 events provides 90% power

• Probability of success:

\[ hr_2 = 0.656 \quad \text{= observed hazard ratio in phase 2 study} \]
\[ n_{e2} = 80 \quad \text{= number of events in phase 2 study} \]
\[ n_{e3} = 236 \quad \text{= planned number of events in phase 3 study} \]

\[
P(\text{success}) = \Phi \left( \frac{-\sqrt{4/236} \cdot 1.96 - \log(0.656)}{\sqrt{4/236 + 4/80}} \right) = 74.0\%
\]
Probability of success for time-to-event data: a more general formulation

• Problem: may not always have a direct estimate of the hazard ratio
  – Single-arm phase 2 study
  – Historical data for phase 3 control arm

• Solution: Exponential – Inverse Gamma Model:
  – For exponential survival with parameter $\lambda$, let

\[
\lambda \sim \text{Inverse-gamma}(a, b)
\]

  – where $a = \text{number of events}$ and $b = \text{total follow-up time}$. 
Inverse gamma

- Then for the two arms in the phase 2 study
  - \( \lambda_{control} = IG(44, 438) \)
    Mean survival = \( 438/44 = 9.95 \)
    Median = \( 9.95 \times \log(2) = 6.9 \)
  - \( \lambda_{experimental} = IG(36/547) \)
    Mean survival = \( 547/36 = 15.2 \)
    Median = \( 15.2 \times \log(2) = 10.5 \)
Calculating \( P(\text{success}) \) from inverse-gamma model: Simulation Algorithm

1. Randomly draw a mean survival time from each inverse-gamma distribution.

2. “Enroll” patients into the study according to a certain accrual rate and randomize to experimental or control arm.

3. Draw event times randomly from the corresponding exponential distributions. Censor patients without events at the end of the study.

4. Compare survival curves of experimental vs. control arms after the planned number of events is obtained.

5. Repeat steps 1 - 4 for a large number of replications \( K \). Probability of success is calculated as number of times the trial results in a successful outcome divided by total number of replications \( K \).
Summary of time-to-event data

• Time-to-event data have additional features and complexities compared to continuous (uncensored) data

• But the approach to assess the probability of success with time-to-event data is conceptually similar to that with other types of data

• The Bayesian framework used here can easily incorporate additional success criteria beyond the requirement of a p-value <0.05
Examples
Example 1
Using P(success) to decide when to begin Phase 3

• 2\textsuperscript{nd}-line or later treatment for a particular tumor type
• Uncontrolled Phase 2 study of experimental drug
• Endpoint: Response rate
• Standard of care: 9\% response rate in prior uncontrolled trial of 90 subjects (8/90 subjects with partial response)
• Sample size: N=40
• Goal: determine whether to run a phase 3 study vs. the standard of care
  – Two phase 3 sample sizes considered: N=40/group or N=200/group
Standard of care treatment – historical data

• Standard of care: 9% response rate in prior uncontrolled trial of 90 subjects (8/90 subjects with partial response)

• Suggests a Beta(8, 82) distribution to characterize control arm
  – 8 responders
  – 82 non-responders
Establishing beliefs about response rate for experimental drug

- Suppose 2 responders in first 5 subjects

![Graph showing probability density for response rates in experimental and standard care arms with Beta distributions Beta(8, 82) for experimental arm and Beta(2, 3) for standard of care.](chart.png)
What do we know after 2/5 responses?

• Naive power calculation
  – N=40/arm in phase 3 study provides 86% power if the true rates are 9% (control) vs. 40% (experimental)

• To get probability of success (p<0.05 in phase 3 study), simulate:
  – Select response rates from Beta(8,82) and Beta(2,3) distributions
  – Compute power based on N=40/group
  – Repeat a large number of times calculate average power

• With N=40/arm, P(success) = 68%
• With N=200/arm, P(success) = 99%
P(success) of phase 3 study after 5 subjects in phase 2 study

- P(success)
  - Select response rate at random from each Beta distribution
  - Calculate power based on selected response rates
  - Repeat 1000 times (or 10,000, or 100,000)
  - Compute average power across simulation runs

<table>
<thead>
<tr>
<th>Phase 2 outcome (# of responses out of 5 subjects)</th>
<th>P(superiority) in phase 3 study at n=40/arm</th>
<th>P(superiority) in phase 3 study at n=200/arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (20%)</td>
<td>0.28</td>
<td>0.49</td>
</tr>
<tr>
<td>2 (40%)</td>
<td>0.68</td>
<td>0.87</td>
</tr>
<tr>
<td>3 (60%)</td>
<td>0.91</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Strength of evidence vs. sample size

- Our beliefs about the true response rate for the experimental drug get stronger with more subjects
  - 40% response rate based on 5, 10, and 20 subjects →
P(success) of phase 3 study after 10 subjects in phase 2 study

<table>
<thead>
<tr>
<th>Phase 2 outcome (# of responses out of 10 subjects)</th>
<th>P(superiority) in phase 3 study at n=40/arm</th>
<th>P(superiority) in phase 3 study at n=200/arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (10%)</td>
<td>0.10</td>
<td>0.27</td>
</tr>
<tr>
<td>2 (20%)</td>
<td>0.28</td>
<td>0.57</td>
</tr>
<tr>
<td>3 (30%)</td>
<td>0.51</td>
<td>0.81</td>
</tr>
<tr>
<td>4 (40%)</td>
<td>0.74</td>
<td>0.94</td>
</tr>
<tr>
<td>5 (50%)</td>
<td>0.88</td>
<td>0.98</td>
</tr>
<tr>
<td>6 (60%)</td>
<td>0.96</td>
<td>0.99</td>
</tr>
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</table>
P(success) of phase 3 study after 20 subjects in phase 2 study

<table>
<thead>
<tr>
<th>Phase 2 outcome (# of responses out of 20 subjects)</th>
<th>P(superiority) in phase 3 study at n=40/arm</th>
<th>P(superiority) in phase 3 study at n=200/arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (10%)</td>
<td>0.08</td>
<td>0.24</td>
</tr>
<tr>
<td>3 (15%)</td>
<td>0.16</td>
<td>0.43</td>
</tr>
<tr>
<td>4 (20%)</td>
<td>0.27</td>
<td>0.64</td>
</tr>
<tr>
<td>5 (25%)</td>
<td>0.41</td>
<td>0.79</td>
</tr>
<tr>
<td>6 (30%)</td>
<td>0.55</td>
<td>0.90</td>
</tr>
<tr>
<td>7 (35%)</td>
<td>0.67</td>
<td>0.95</td>
</tr>
<tr>
<td>8 (40%)</td>
<td>0.77</td>
<td>0.98</td>
</tr>
<tr>
<td>9 (45%)</td>
<td>0.86</td>
<td>0.99</td>
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Evaluating probability of success in oncology clinical trials

P(success) in Phase 3 by Phase 2 response rate

n=40/arm in Phase 3

n=200/arm in Phase 3

Observed response rate

P(success) in subsequent trial

5 subjects
10 subjects
20 subjects

Observed response rate
Example 2
Using $P(\text{success})$ to evaluate a development plan

- Randomized phase 2 study is about to start
  - Primary endpoint: overall survival, 30% improvement considered clinically meaningful
  - Number of events in phase 2 study: 40 vs. 60 vs. 80 vs. 100?
  - Company willing to run a 460-event phase 3 study (80% power for a true improvement of 30%) if $P(\text{success})$ is high enough

  - What is a “high enough” probability of success?
### Possible outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Win in phase 2</td>
<td>Probability, date of approval</td>
</tr>
<tr>
<td>Lose in phase 2 (stop development)</td>
<td>Probability, study cost, P(type II error) (stopping development if drug actually works)</td>
</tr>
<tr>
<td>Continue to phase 3 and win</td>
<td>Probability, date of approval</td>
</tr>
<tr>
<td>Continue to phase 3 and lose</td>
<td>Probability, study cost</td>
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</table>
P(success) for the phase 3 study based on phase 2 results

• Based on 460-event phase 3 trial:

<table>
<thead>
<tr>
<th>Observed % improvement</th>
<th>Observed HR</th>
<th>P(success) in Phase 3 for given observed % improvement and given # of events in Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>25.0%</td>
<td>0.8000</td>
<td>0.535</td>
</tr>
<tr>
<td>30.0%</td>
<td>0.7692</td>
<td>0.569</td>
</tr>
<tr>
<td>35.0%</td>
<td>0.7407</td>
<td>0.601</td>
</tr>
<tr>
<td>40.0%</td>
<td>0.7143</td>
<td>0.632</td>
</tr>
<tr>
<td>45.0%</td>
<td>0.6897</td>
<td>0.660</td>
</tr>
<tr>
<td>50.0%</td>
<td>0.6667</td>
<td>0.687</td>
</tr>
</tbody>
</table>

• What should the rule be to move into phase 3?
  – P(success) >80%?
  – P(success) >75%?
  – P(success) >60%?
Probability of each outcome in phase 2 or phase 3

• Assumptions
  – Conduct phase 3 study if \( P(\text{success}) \) is at least 75%
  – true HR is 0.7692 (30% improvement)
  – 40-event phase 2 study
  – 460-event phase 3 study

\[
\begin{align*}
P(\text{win in Phase 2}) &= P(\text{observed HR} < 0.536) = 0.13 \\
P(\text{stop after Phase 2}) &= P(\text{observed HR} \geq 0.667) = 0.67 \\
P(\text{continue to Phase 3 and win}) &= 80\% \times (1 - 0.13 - 0.67) = 0.16 \\
P(\text{continue to Phase 3 and lose}) &= 20\% \times (1 - 0.13 - 0.67) = 0.04
\end{align*}
\]
Evaluating probability of success in oncology clinical trials

• Phase 2 design: 40-event study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Run phase 3 if P(success) is &gt;75%</th>
<th>Run phase 3 if P(success) is &gt;60%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>True HR</td>
<td>True HR</td>
</tr>
<tr>
<td></td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>0.769</td>
<td>0.769</td>
</tr>
<tr>
<td></td>
<td>0.667</td>
<td>0.667</td>
</tr>
<tr>
<td>Win in phase 2</td>
<td>0.025</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Stop after phase 2</td>
<td>0.90</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>0.67</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.33</td>
</tr>
<tr>
<td>Win in phase 3</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0.16</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.42</td>
</tr>
<tr>
<td>Lose in phase 3</td>
<td>0.07</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>0.04</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Probability of each outcome by phase 3 decision rule and true underlying hazard ratio

- Phase 2 design: 100-event study

<table>
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<tr>
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<th>Run phase 3 if P(success) is &gt;75%</th>
<th>Run phase 3 if P(success) is &gt;60%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>True HR</td>
<td>True HR</td>
</tr>
<tr>
<td></td>
<td>1.000 0.769 0.667</td>
<td>1.000 0.769 0.667</td>
</tr>
<tr>
<td>Win in phase 2</td>
<td>0.025 0.26 0.53</td>
<td>0.025 0.26 0.53</td>
</tr>
<tr>
<td>Stop after phase 2</td>
<td>0.95 0.64 0.36</td>
<td>0.88 0.45 0.20</td>
</tr>
<tr>
<td>Win in phase 3</td>
<td>0.00 0.09 0.12</td>
<td>0.00 0.23 0.27</td>
</tr>
<tr>
<td>Lose in phase 3</td>
<td>0.02 0.02 0.00</td>
<td>0.09 0.06 0.00</td>
</tr>
</tbody>
</table>
Assigning value to each outcome

• Model inputs
  – 40-event phase 2 study
  – true HR = 0.7692 (30% improvement)

• Model output

<table>
<thead>
<tr>
<th>Outcome</th>
<th>P(outcome) (60% rule)</th>
<th>P(outcome) (75% rule)</th>
<th>Timing of outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Win in phase 2</td>
<td>0.13</td>
<td>0.13</td>
<td>Approval in 2Q2014</td>
<td>XXX MM</td>
</tr>
<tr>
<td>Stop after phase 2</td>
<td>0.51</td>
<td>0.67</td>
<td>Study ends in 2Q2013</td>
<td>−4 MM</td>
</tr>
<tr>
<td>Win in phase 3</td>
<td>0.29</td>
<td>0.16</td>
<td>Approval 2Q2018</td>
<td>YYY MM</td>
</tr>
<tr>
<td>Lose in phase 3</td>
<td>0.07</td>
<td>0.04</td>
<td>Study ends 1Q2017</td>
<td>−54 MM</td>
</tr>
</tbody>
</table>

Expected value (60% rule) = 0.13(XXX) + 0.51(−4) + 0.29(YYY) + 0.07(−54)
Expected value (75% rule) = 0.13(XXX) + 0.67(−4) + 0.16(YYY) + 0.04(−54)

• Study cost assumptions:
  – 40-event study = 4 MM
  – 100-event study = 10 MM
  – Phase 3 study = 50 MM
Extensions

• How do different beliefs about the drug’s efficacy affect expected value?
  – Individual 1 believes there’s 50% chance the drug has no efficacy (HR=1.0) and a 50% chance the drug gives a 30% improvement (HR=0.769)
  – Individual 2 believes there’s 75% chance the drug has no efficacy (HR=1.0) and a 25% chance the drug gives a 30% improvement (HR=0.769)

• Calculate weighted average of the expected values for HR=1.00 and HR=0.769 and compare between individuals
Closing remarks
Complications

• Phase 3 is just like phase 2, except
  – Different year
  – Different sites
  – Different dose?
  – Different design
  – Different endpoint
  – Different formulation
  – Different inclusion criteria
  – Different statistical analysis

• Furthermore, development programs rarely consist of a single phase 2 study and a single phase 3 study
Conclusions

• Remember that
  – Power is a conditional value (more importantly, remind your clinical team)
  – The foundation for success in phase 3 is built in phase 2
  – The optimal probability of success may or may not be the familiar 80% or 90%
References
