Case Study: Decision Analysis for New Atherosclerosis Drug

Assessing Consistent Probabilities of Success for Drug Development Decision Analysis

2010 DAAG Conference
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Case Study: New drug development strategy for atherosclerosis

- Atherosclerosis continues to cause significant morbidity and mortality despite availability of statins
- Sales potential for an effective new drug could easy be several billion dollars, but . . .
- Atherosclerosis presents many challenges for drug development, especially drugs with novel mechanisms
  - Final stage of development requires expensive (>$500M) and time consuming mortality and morbidity studies
  - Lack of predictive and inexpensive biomarkers or imaging technologies to significantly buy-down risk prior to M&M study
  - Overall probability of success is 3-5% starting from first in human testing, much lower than other disease areas

Case study background

- Novel drug in development for atherosclerosis was poised to begin first studies in patients (PIIA) in about 12 months
- Team was challenged to find creative development alternatives that manage cost and risk while optimizing value
- Team identified three broad development themes
  - "Fast to M&M"
  - "Plaque Regression" PIIB (imaging endpoint)
  - "Multiple novel biomarkers" in PIIA

1) “Fast to M&M”

- Do minimum development (establish safety profile) prior to starting M&M study

Pros

- Minimizes cost of PII
- Results in earliest launch
- Minimizes probability of false negative in PII

Cons

- High probability of failure of expensive M&M study

2) “Plaque Regression” PIIB

- Use large imagining studies to show in PIIB that drug reduces and/or stabilizes plaque

Pros

- Reduces risk of expensive M&M study failure
- Approach was used for development of many statins

Cons

- Imaging PII cost makes this the most expensive option
- Latest launch date due to duration of study (by 2 or 3 years)
- Imaging not particularly strong predictor of M&M success, especially for drug’s with novel mechanisms

This option was management’s “momentum plan”

3) “Multiple Biomarkers” PIIA

- Use several biomarker based PII studies to buy down some risk prior to M&M study

Pros

- Demonstrates drug reaches desired biologic targets prior to PIII
  - Not reaching target would be strong “No Go”
- Low incremental cost on top of “Fast to M&M”
- Approximately same launch date as “Fast to M&M” strategy

Cons

- Could increase risk of false negative in PII
- Risk of M&M failure will still be high

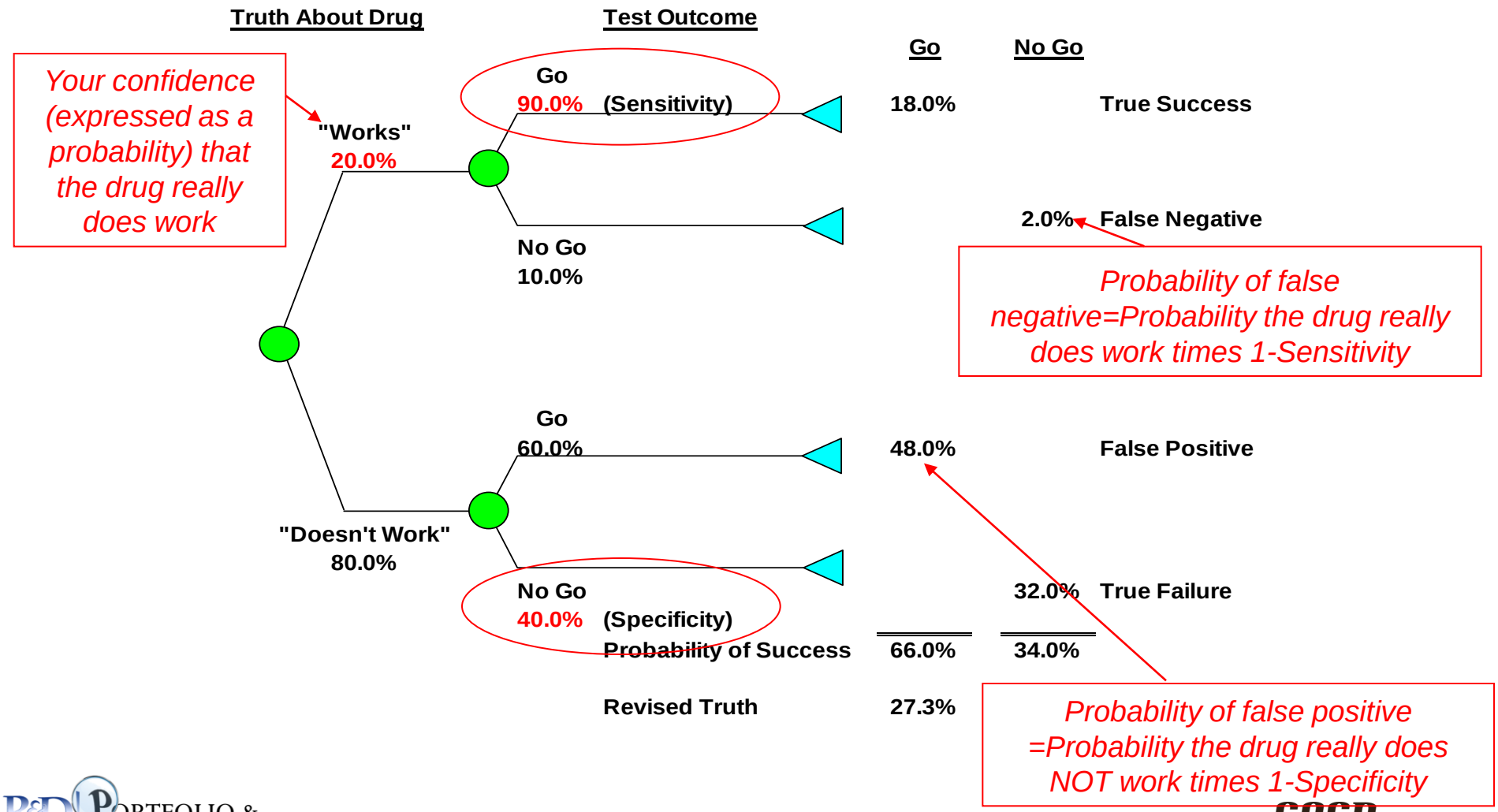
Probability of success assessment is key to valid evaluation of development alternatives

- Small differences in probability assessments have a large impact on valuation because of high commercial value and high development costs
- Critical to have logical, scientific based approach to assessments in order to obtain valid assessments and team buy-in
- Traditional approaches to probability assessment do not meet these criteria

Approach to assessing internally consistent probabilities for drug development analyses

1. **Assess the probability the drug truly works (safe and efficacious)**
   - **Assumption is same for all development alternatives**
2. **Assess sensitivity and specificity of each study after discussion of the study designs and "go/no go" criteria**
   - **Sensitivity is the probability study with give "Go" result when the drug does work**
   - **Specificity is the probability study will give "No Go" result when the drug does not work**
   - **Sensitivity and specificity are functions of statistical designs, the level of "surrogacy" of the endpoints used, and the nature of the drug**
3. **Calculate probabilities of success**
4. **Layer on additional safety risk based on total patient exposures by phase and apply regulatory approval risk**

Example of sensitivity and specificity are used to calculate probabilities of success



After some initial team training, team responded well to assessment approach

- Needed to spend about hour total explaining the assessment methodology using examples
- Helpful to have statistician on team to help calibrate team on the sensitivity and specificity of various study designs and endpoints
- Team was not certain about precise values for each option, but felt the values were correct relative to one another
- Sensitivity analysis was use to show team how much their assessments could change without changing the recommended strategy
- Team preferred approach over the traditional approach because
  - Scientist have some intuition about sensitivity and specificity and
  - They do not feel like they are guessing

So let's look at the assessments made by the team*

		1) Fast to M&M	2A) Plaque Regression	2B) Plaque Progression	3) BM PIIA
PIIA	Sensitivity	95%	95%	95%	80%
	Specificity	40%	40%	40%	65%
PIIB	Sensitivity	95%	50%	85%	95%
	Specificity	30%	85%	50%	30%
PIII	Sensitivity	65%	80%	80%	65%
	Specificity	100%	100%	100%	100%

- PIII sensitivity for Options 1 and 3 are low because PIIB does not inform dose so risk is higher in PIII because we might choose the wrong dose
- PIIB for Options 2A and 2B reflect differences in go/no go criteria for imaging results
- PIIA for Option 3 has relatively high specificity and low sensitivity because of use of biomarkers in this phase
- Overall true probability of success assessed at approximately 20%
- Does not include overlay of "standard" safety risk by phase

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* Values changed to protect confidential information

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Resulting calculated probabilities of success*

Option	Probabilities of Success					
	P I	P IIa	P IIb	P III	Reg.	Overall
1) "Fast to M&M"	75%	61%	70%	20%	80%	5.2%
2A) "Plaque Regression" PII	75%	61%	22%	41%	80%	3.4%
2B) "Reduced Progression" PII	75%	61%	52%	30%	80%	5.7%
3) "Multiple Biomarker PII"	75%	41%	72%	26%	80%	4.5%

- **"Fast to M&M" has very low probability of PIII success (20%) because little risk was discharged in the PII studies**
  - **However, overall probability of success is high because there is less of a chance of a false negative in PII**
- **Setting the "Go" for PIIB high for Plaque Regression lowers PIIB probability, increases PIII probability of success, and lowers overall probability of success significantly**
- **Setting the "Go" for PIIB much lower Reduced progression raises PIIB probability, decreases PIII probability and lowers probability of false negative**
- **"Multiple Biomarker PIIA" strategy attempts to buy down risk prior to PIIB**
  - **Lowers PIIA probability of success and PIIB and PIII increased slightly as a result**

* Values changed to protect confidential information

Overall results suggest not pursuing "Plaque Reduction" PIIB strategy and using "Multiple BM" PIIA*

Option	Probabilities of Success						Costs ($M)						Launch	eNPV ($M)
	P I	P IIa	P IIb	P III	Reg.	Overall	P I	P IIa	P IIb	P III	Reg.	Expected		
1) "Fast to M&M"	75%	61%	70%	20%	80%	5.2%	15	30	25	600	65	585	1H2019	75
2A) "Plaque Regression" PII	75%	61%	22%	41%	80%	3.4%	15	30	125	600	65	675	1H2022	-
2B) "Reduced Progression" PII	75%	61%	52%	30%	80%	5.7%	15	30	125	600	65	685	1H2022	25
3) "Multiple Biomarker PII"	75%	41%	72%	26%	80%	4.5%	15	37	25	600	65	590	1H2019	70

- **Despite significantly lowering PIII risk, both "Plaque Reduction PIIB" strategies have the lowest value largely due to the high cost of PIIB and the launch delay**
- **"Multiple BM" PIIA has equivalent expected value but has a superior risk profile**

- **Team recommended "Multiple BM" PIIA strategy**
- **Team resigned to reality atherosclerosis drug development is "risky"**

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Conclusions

- When evaluating alternative development plans, it is important to have internally consistent probabilities of success assessments
- Assessing probabilities utilizing sensitivity and specificity by phase can be an effective technique for obtain consistent probabilities