Presenting:

Are You Sure Your Proof of Concept Studies Add Value?

by David Swank and Lee Hodge

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Are You Sure Your Proof of Concept Studies Add Value?

David Swank and Lee Hodge
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Over the past decade, Proof of Concept (PoC) studies have become an important tool in drug development

- In my presentation today, I will
  - Review where PoC fits in drug development
  - Share with you the process we use to ensure that our PoC studies add value
  - Illustrate our process with a real example

Traditional drug development milestones

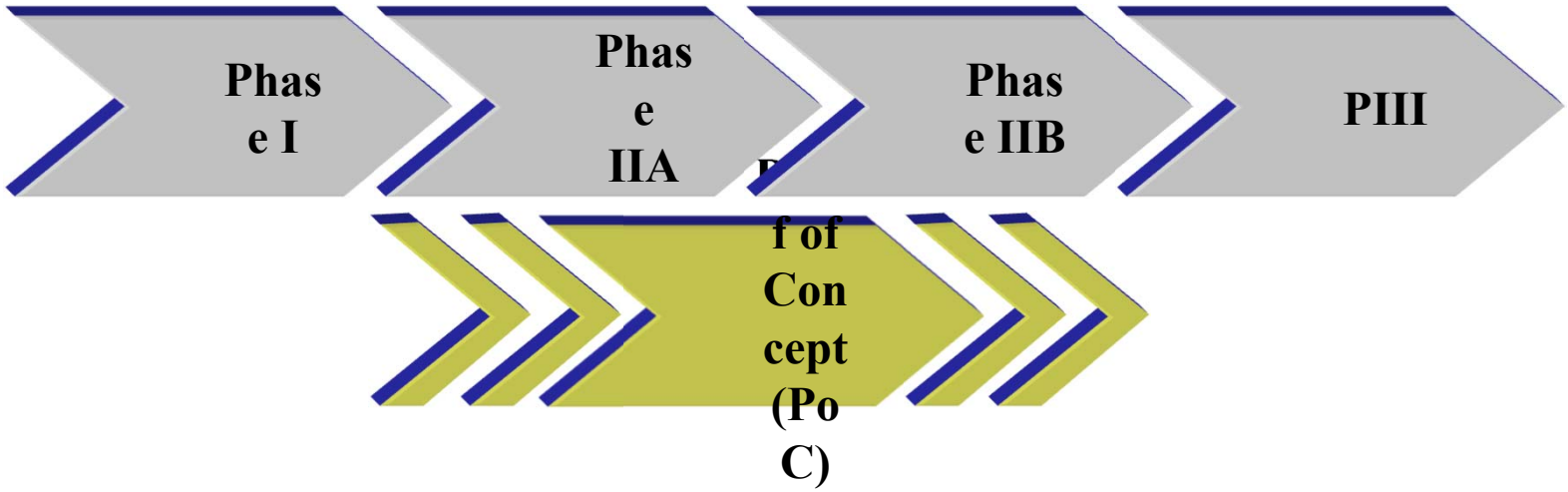
Approach designed to ensure adequate safety data available before progressing to the next phase of development

- Phase I-studies in healthy volunteers
- Phase IIA-limited safety studies in patients with actual disease to be treated
- Phase IIB-determine safe and efficacious dose regiment to use in Phase III
- Phase III-large, expensive, randomized clinical trials to prove efficacy and safety

Significant efficacy risk carried into Phase III with traditional approach

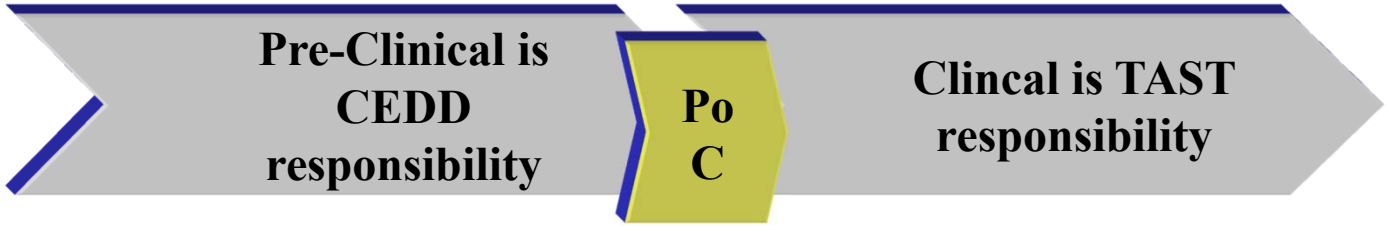
- Much of the risk of inadequate efficacy remains prior to the start of the expensive Phase III studies
- Asset value could be increased if we could find a way to remove more of the efficacy risk prior to Phase III

In 1990's drug companies started adding a new decision point called Proof of Concept or Proof of Principle



- May be considered as Phase IIA or IIB or can occur sometime between Phase IIA and Phase IIB
- Decision based on studies specifically chosen to demonstrate or "prove" the drug will be efficacious and safe in Phase III

At GSK, PoC also marks an important organization transition



- Centers for Excellence in Drug Discovery (CEDDs) are responsible for compounds from Discovery through PoC
- Therapeutic Area Strategy Teams (TASTs) are responsible for compounds from PoC to product launch
- Each organization has different objectives that result in a healthy, though sometimes contentious, negotiation on what will constitute Proof of Concept

In 2001, Management asked us to help create a process to help project teams create their PoC development plan

- Based on a value of imperfect information methodology
- Piloted process in early 2002 on three projects and
- Now used on “difficult” projects within GSK on an as needed basis

Backbone of process is real-time creation and analysis of options

- Analysis occurs over several half day facilitated meetings with key members of the project team including
  - Project management,
  - Clinical,
  - Clinical Operations,
  - Commercial, and
  - Statistics
- Team gets real time feedback to enhance creativity
- Time between meetings allows for data validation, options generation, and “reality checks” with key stakeholders
- Options documented for clarity and future reference

Easiest to illustrate how the process works with a real example of Disease X

- Disease X treatment
- Relatively low value indication
- Disease X treatment is a serious unmet medical need
- Many drugs have been studied for Disease X treatment but there is currently only one approved therapy
- Team's original development plan was a traditional one without a true PoC study
- The plan was rejected by management
- Team was told to consider adding a PoC study based on imaging measurements

Commercial value data were assessed prior to facilitated project team meetings

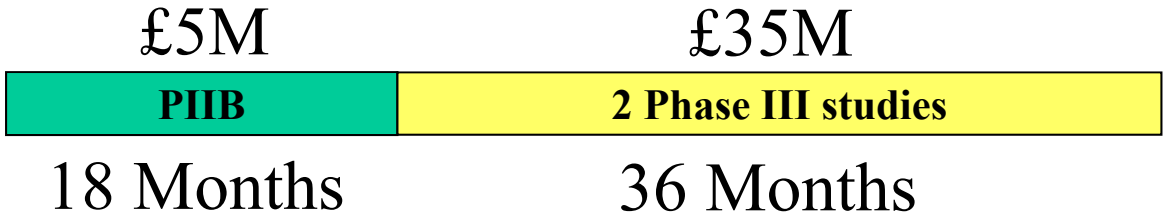
- For this product, Commercial estimated that the
  - NPV of the product without development costs was £300M if we launched on time
  - Asset estimated to lose about 15% of its value per year of delay
- The commercial value for other launch dates were estimated from these two parameters

The team then created their development plans

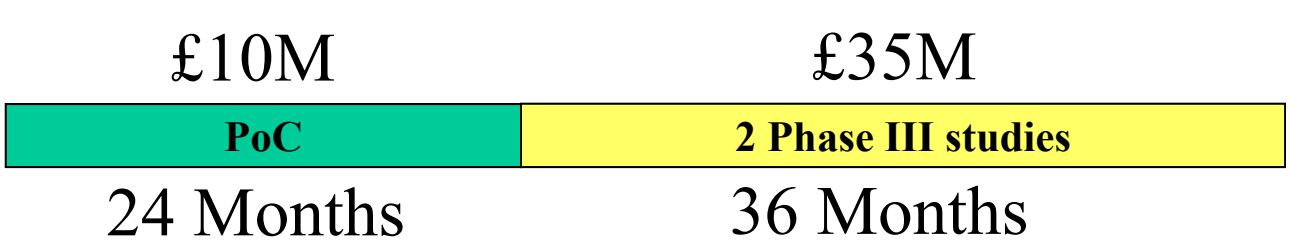
- Carefully define
  - Objectives of study (Target Product Profile (TPP), Indication, etc.)
  - Number of patients and patient population
  - End points
  - Go/No Go criteria
  - Inclusion/Exclusion criteria
  - Enrollment rates, follow-up time, data review time, etc.
- These values were translated into study costs and duration

Options

1. “Traditional” Development Plan



2. “Imaging” PoC Development Plan



- “Imaging” costs £5M more and
- Increased time to launch reduces commercial value by £22M

In order to add value, the Imaging PoC must provide information worth more than the cost of the study

- To determine the value of the information added by the Imaging PoC, we need determine what information will be obtained from the studies
- Team asked to provide probability of success information for non-clinical risk items that are common to both options
  - Toxicology
  - Manufacturing
  - Regulatory
- For this presentation we will assume these risks can be ignored (they normally can not be ignored!)

Assessment of Clinical Risks

- For the clinical risks, we ask the team for their confidence the drug really will be safe and efficacious based on what they know today
- Then we ask for the team to assess the probability that the study or studies will
  - Correctly indicate success when the drug works (sensitivity), and
  - Correctly indicate failure when the drug does not work (specificity)

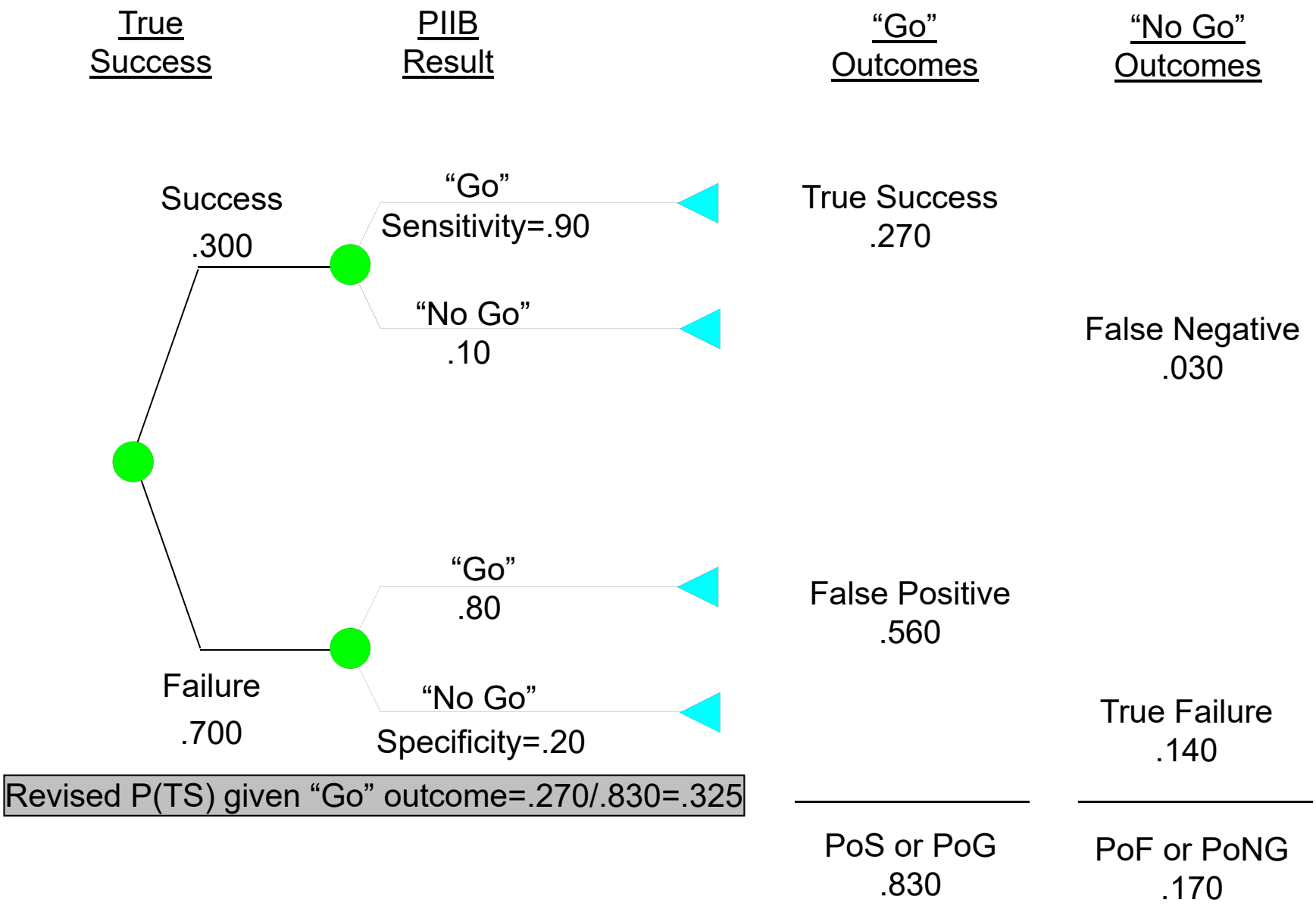
It takes practice to do these probability assessments well

- Statistician on project team can help team understand how well the studies will distinguish between drugs that work and those that do not
  - If the study is measuring the actual PIII outcome, but on fewer patients, you can easily calculate the sensitivities and specificities using statistical models
  - If the study is measuring a surrogate for the actual PIII outcome, you have to factor in how well the surrogate correlates with the actual PIII outcome

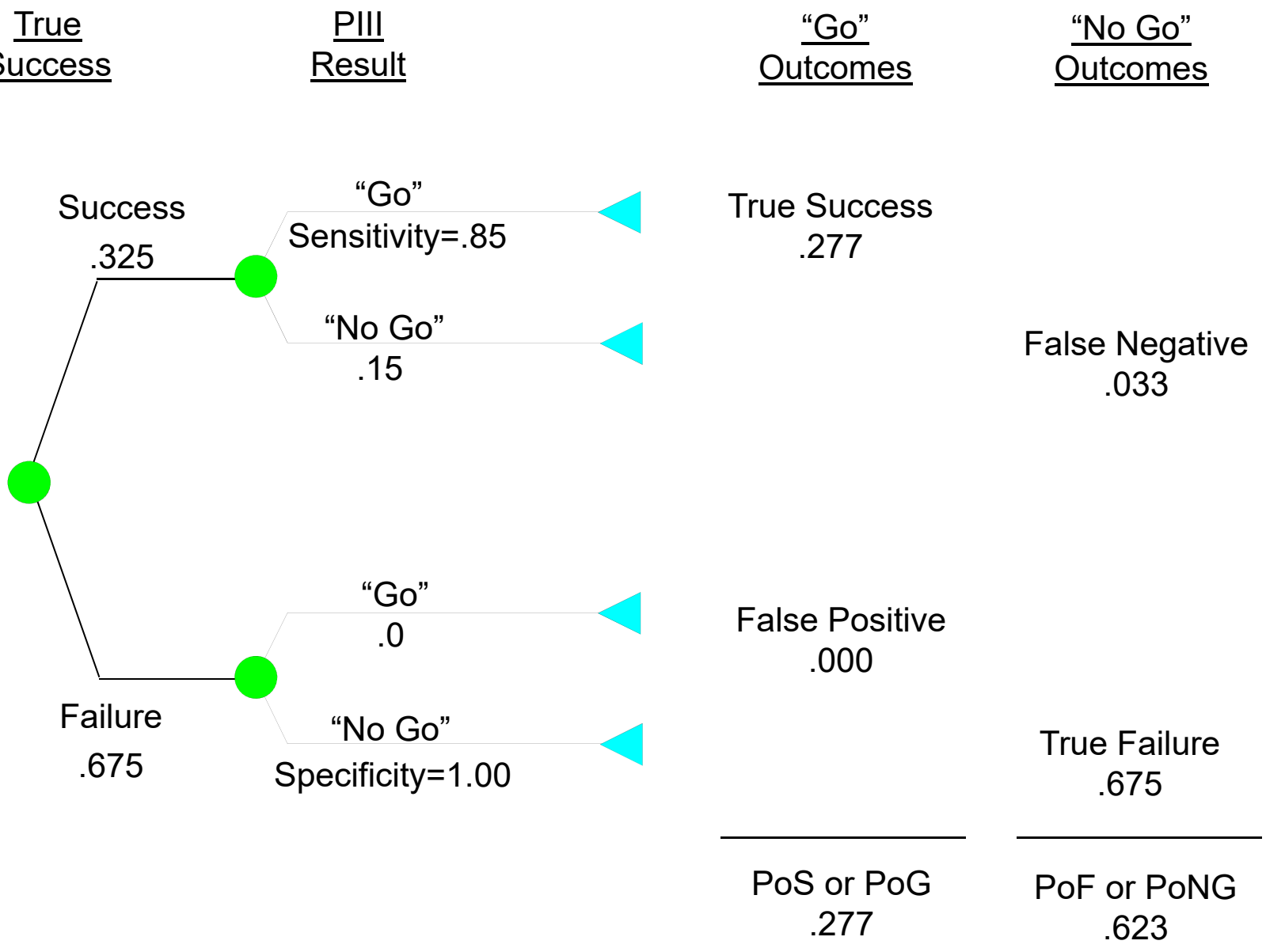
In our example, the statistician reviewed the available literature to assess the imaging study

- The analysis indicated that imaging results correlate poorly with actual Disease X patient outcomes
- In order to reduce PIII risk, the go/no go criteria was set high
- With this high go/no go criteria the
  - Sensitivity was assessed at 0.50 (probability of a “go” given the drug works)
  - Specificity was assessed at 0.90 (probability of a “no go” given the drug does not work)

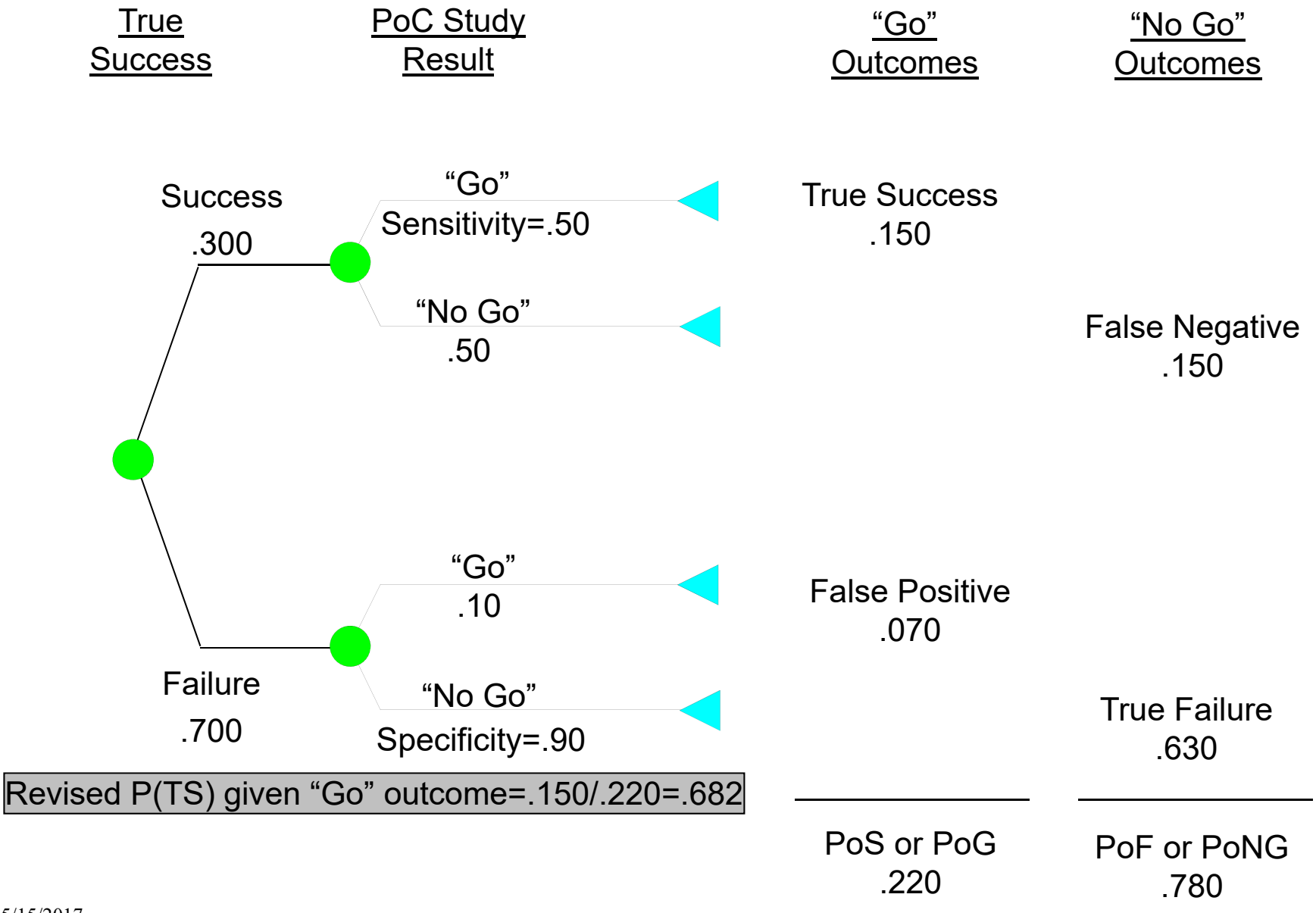
Probability Assessments-Traditional PIIB



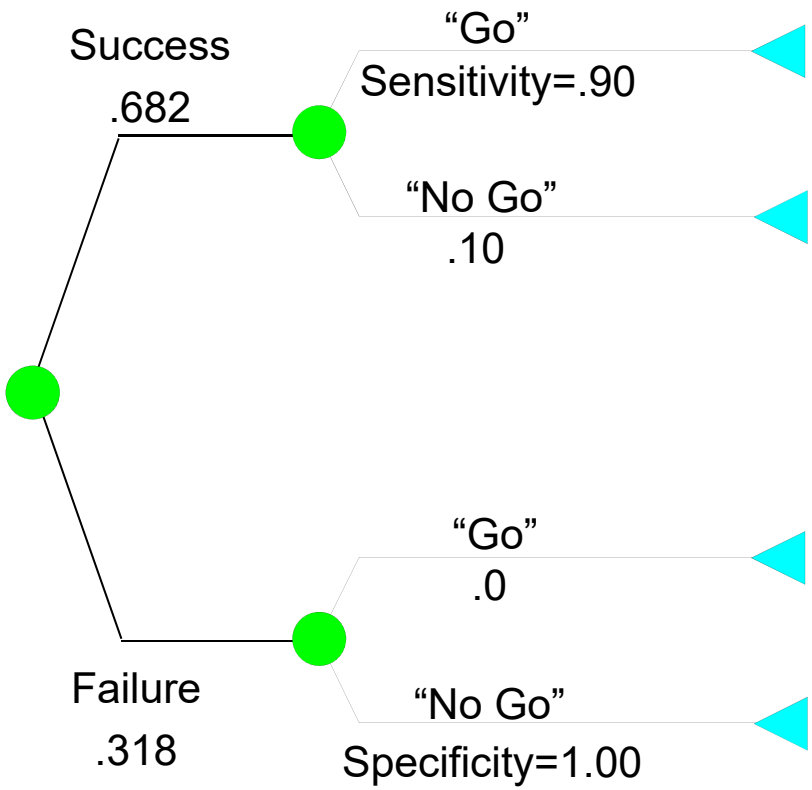
Probability Assessments-Traditional PIII



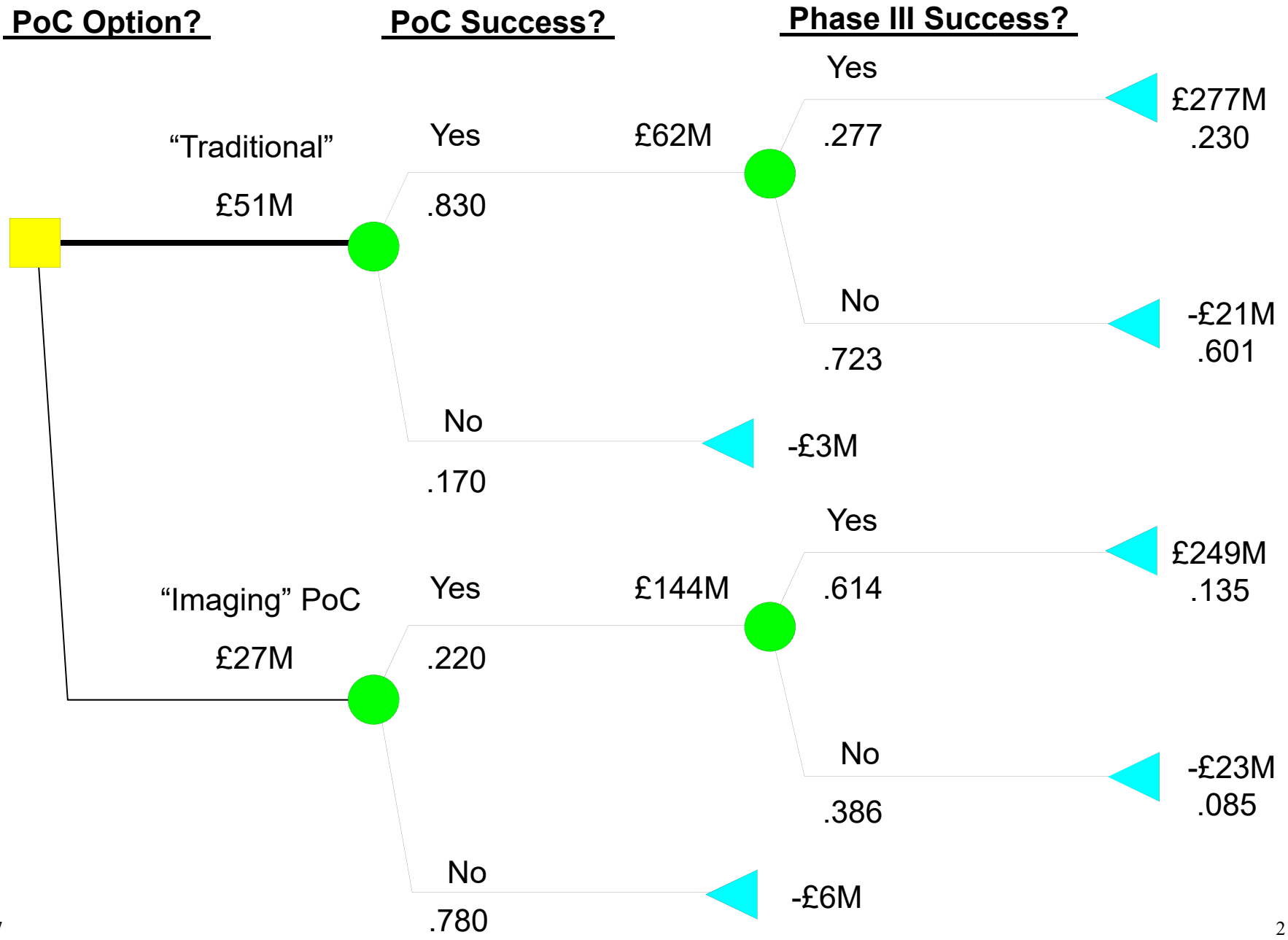
Probability Assessments-Imaging PoC



Probability Assessments-Imaging Plan's PIII



The Traditional Option was preferred



The Imaging PoC destroyed value!

- The cost of the study (cost and impact of delay) lowered the eNPV by £7M
- The value of imperfect information actually lowered the eNPV by an additional £16M!

The team dropped the imaging PoC idea and focused on alternative study designs

- Ultimately, they increased the value of the project significantly by staging their PIII studies and utilizing an adaptive PIIB/PIII study, which became their PoC study

Conclusions

- PoC studies can increase the value of an asset but it is not automatic--you have to be careful, insightful, and clever!