A Case Study

Drug Development has a new step called “Proof of Concept.” Does the PoC actually increase value?

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Note

Although drug, indication, and numbers are fictitious, the process and results reflect an actual D&RA study using the value of imperfect information.

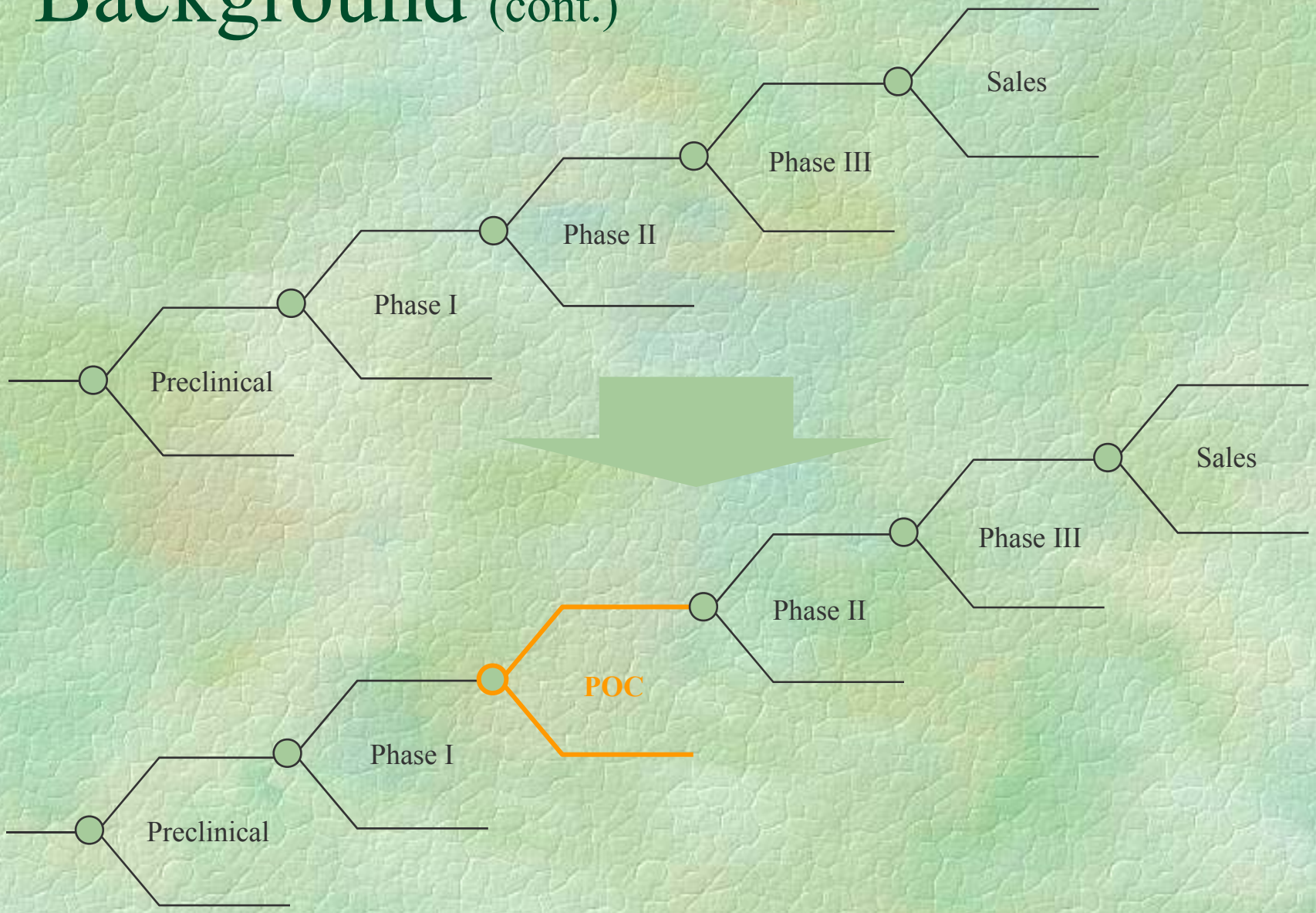
Background

In the past two years, the drug industry has introduced a new step in drug development. At GlaxoWellcome (GW) it is called Proof of Concept (PoC).

The step is an early test of efficacy or potentially problematic properties of a new chemical entity (NCE). The motivation is to learn earlier if a drug is going to work or have problems.

If it won't work or will have critical problems, then hundreds of millions of dollars can be saved. If it appears safe and effective, then extra effort can be focused with greater confidence.

Background (cont.)



Background (cont.)

In 1999, the Decision Sciences Group at GW were asked to question the value of performing a PoC on a specific compound. We treated the PoC as imperfect information and assessed its value. We then compared the value of imperfect information to the costs of additional resources to perform the PoC and the risk-adjusted cost of delay.

The results were surprising!

Project Objective

It was believed that compound XYZ would reduce complications in post operative surgery. The drug was in Phase I safety studies.

What was the value, what were the dangers, and what were the costs of running a small PoC clinical trial prior to Phase II trials?

Assumptions

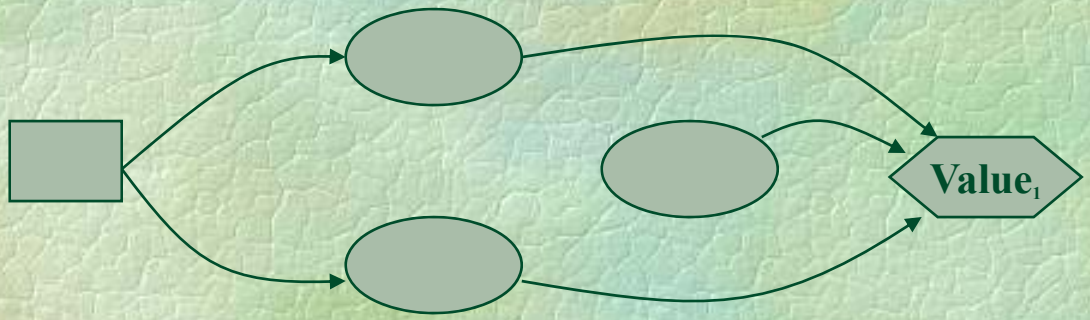
- High variance implied Type I and Type II errors were real possibilities.

  Type I $\Rightarrow$ hang an innocent man = kill a viable treatment
  Type II $\Rightarrow$ free a guilty man = continue with an ineffective compound

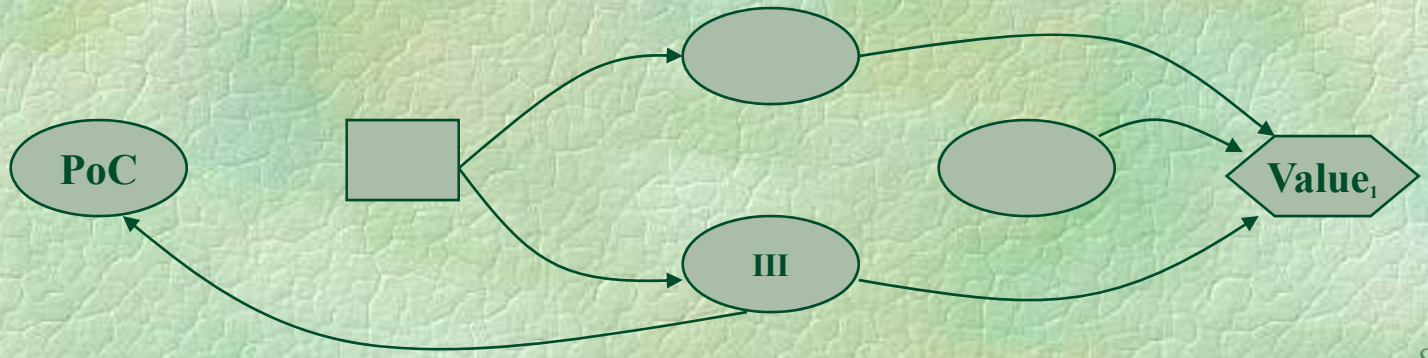
- If effective, XYZ would be first to market with no imminent competition.
- LOS significantly affects value, but not the likelihood of success. (i.e., big potential upside)
- The PoC could possibly replace the Phase II trial and accelerate development.

The Steps

Step 1 - Create a model of uncertainties and calculate value$_1$

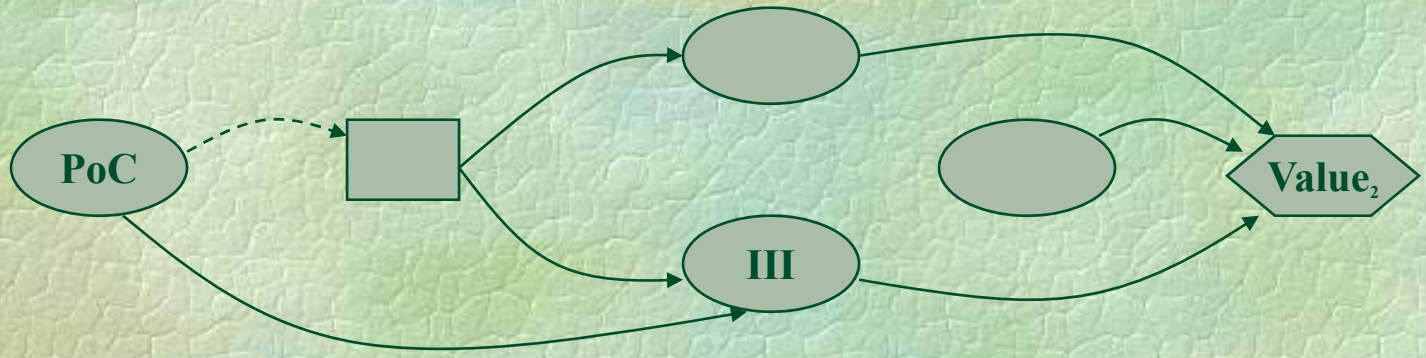


Step 2 - Insert a "sample-based" uncertainty that provides conditional information.



The Steps

Step 3 - Perform a Bayesian Revision and Recalculate $Value_1$.



Step 4 - The Difference in Values is the value of imperfect information. This should be greater than the costs in £s and delay (i.e., lost sales).

Value of Imperfect Information = $Value_2$ - $Value_1$

The XYZ Model

3 Alternative Courses of Action

1. **Base Case** No POC - A minimum Phase II study is performed with 5 arms and 30 patients per arm and no PoC.
2. **Small PoC** A minimum PoC study is performed prior to phase II with 2 arms and 30 patients per arm.
3. **Large PoC** A PoC study is performed with 3 arms and 30 patients per arm. In addition, there is a chance that phase II will be combined with phase III for an overall savings in time and money.

The XYZ Model
Optimal Course of Action

Decision Alternatives	Expected Value (millions)	Value of PoC	Minus PoC Costs	Minus Cost of 6 mo Delay	Net Value of PoC
1. Minimum Phase II study with 30 patient per group and 5 groups	£886.23	--	--	--	--
2. Small PoC with 30 patient per group and 2 groups	£887.11	£.88	-£0.894	-£5.691	-£5.705
3. Large PoC with 30 patient per group and 3 groups	£889.62	£3.39	-£1.904	-£6.469	-£6.983

The XYZ Model

Why is value reduced by the PoC?

Value is gained, if and only if, the small PoC study ***changes our decision*** and significantly ***shifts risk forward*** in the drug development process. Neither is the case:

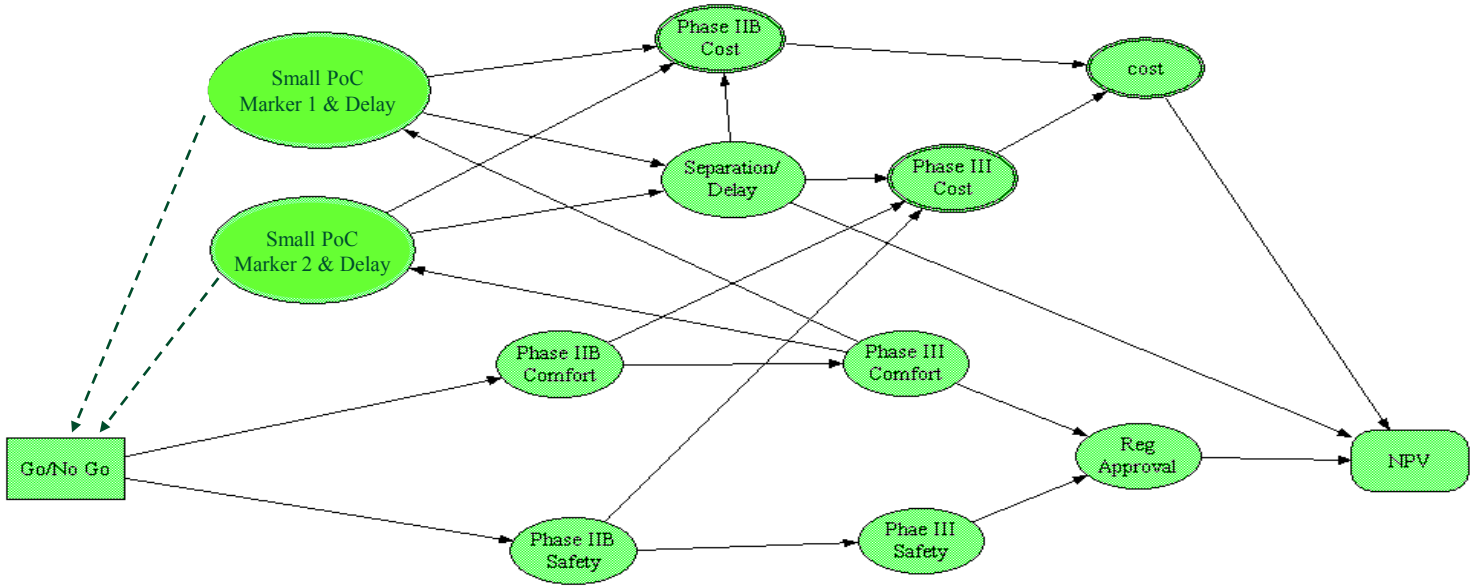
- If the small PoC suggests STOP, the project still has value of £513m because of Type I error (i.e., killing a viable drug). We'd still want to continue.
- The cost to perform a small PoC is almost £900,000 and includes a [risk adjusted] delay or loss of sales which greatly overshadows the value of the PoC.

The XYZ Model

How well does the PoC predict value?

Results of First Marker	Results of Second Marker	Expected Value of XYZ (£millions)
Pos	Pos	£2,839
Pos	Questionable	£2,103
Pos	Neg	£1,242
Neg	Pos	£850
Neg	Questionable	£367
Neg	Neg	£146

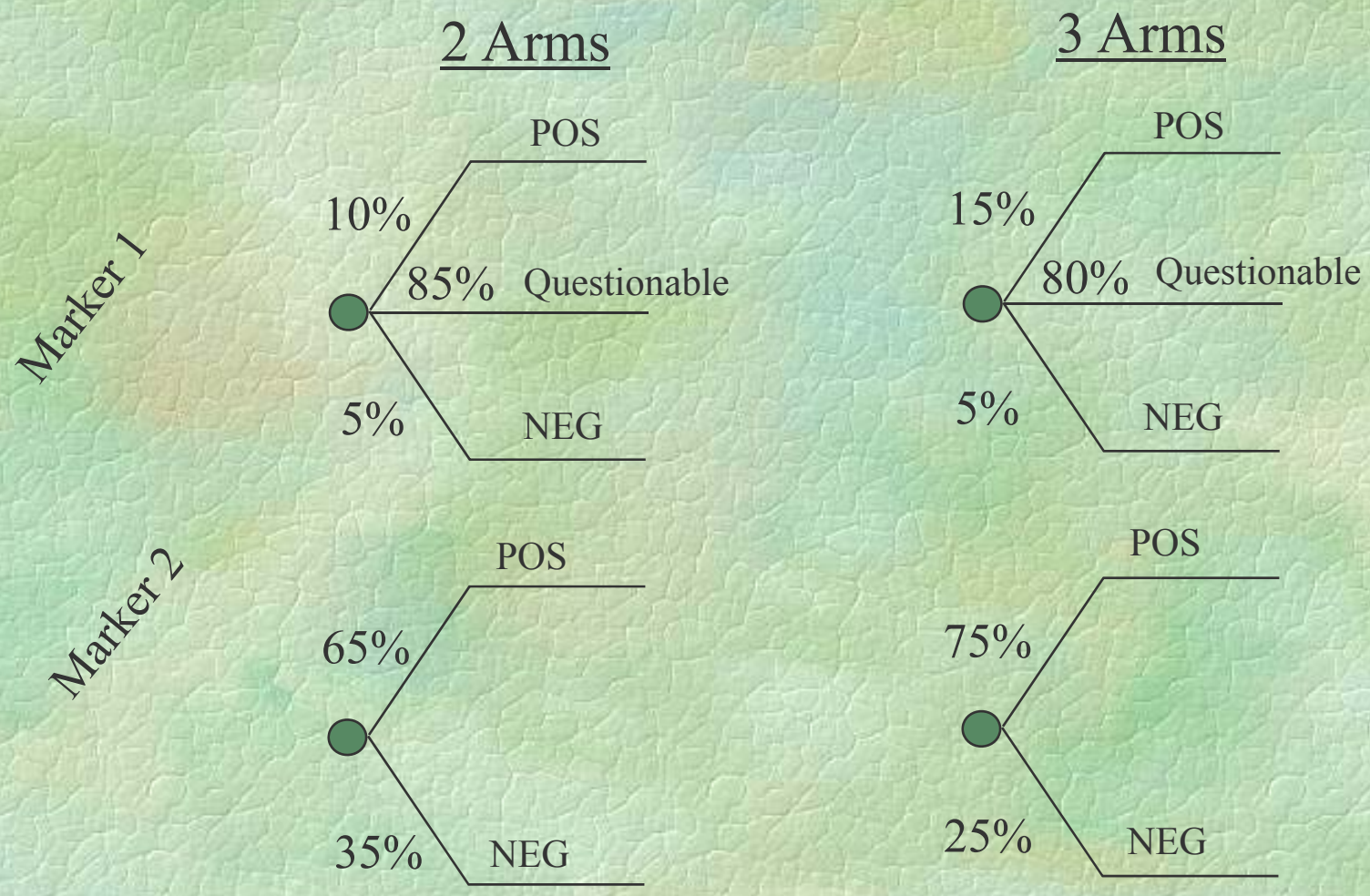
The XYZ Model



Software: CADET for Windows™ by AT&T

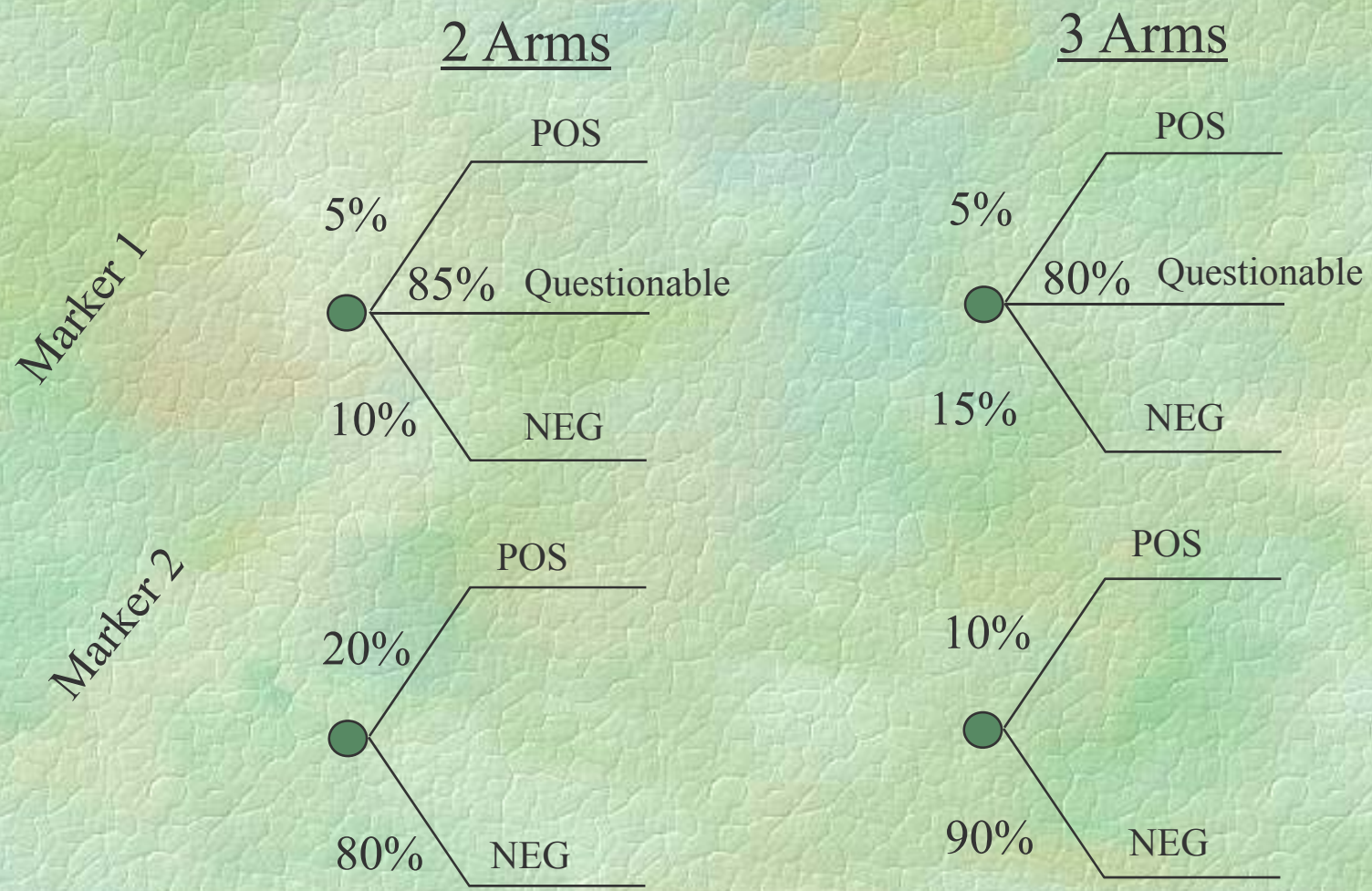
The XYZ Model

Uncertainty Assumptions [if drug works]



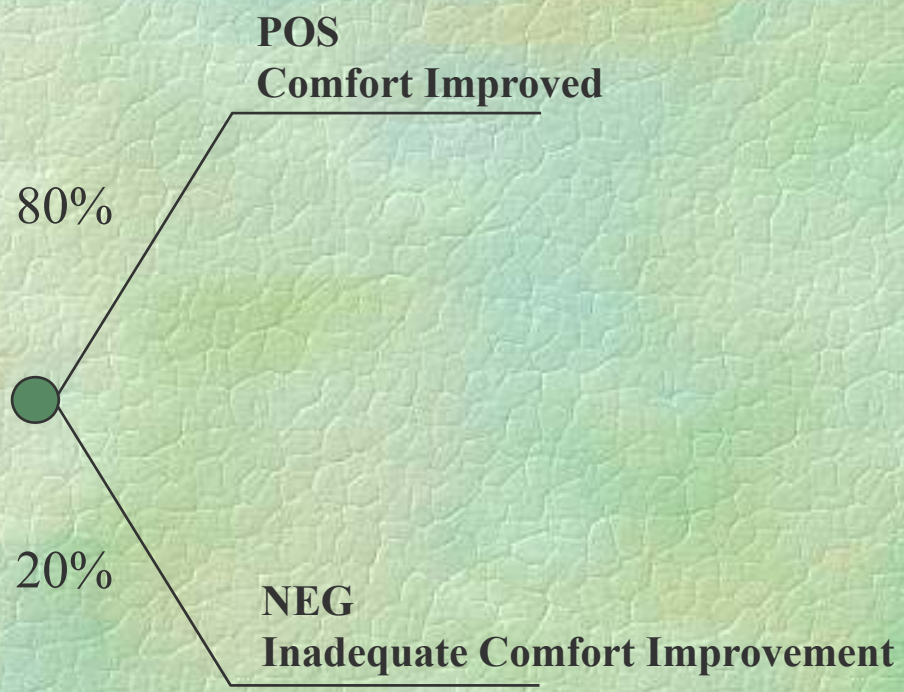
The XYZ Model

Uncertainty Assumptions [if drug doesn't work]



The XYZ Model

Uncertainty Assumptions for Phase II



Conclusion

The small PoC did not provide adequate confidence that the drug worked to compensate for its cost and time (i.e., potential loss of sales). Even if additional value is "squeezed out" by performing streamlined dose ranging studies in Phase III trials, the risk adjusted incremental value remained negative.

Consequently, we recommended to not perform a small PoC, but move directly to Phase II trials. It is important to remember that this may not be true for other compounds. If a PoC is a better predictor of Phase III outcomes and/or there is great risk involved, then the results could have gone in the other direction.