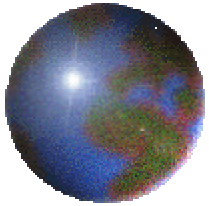
Decision Analysis To Evaluate Clinical Proof-of-Principle (PoP) Trial Design For A New Drug:

Value of Information In A Complex Drug Trial Using A Bayesian Approach



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Outline

- Significance of the problem
- The decision frame

- PoP strategy alternatives
- Decision analysis to select the best alternative
- Decision to conduct PoP
- Implications of comparator drug arm

- Actions taken & value added to decision
- Conclusions and wrap-up

Project in a nutshell

- **Problem:**
  - **Which of the 4 alternatives is the best PoP trial design?**

- **Solution:**
  - **Generated an approach to compare strategic alternatives**
  - **Expanded the decision frame to include all relevant decisions**
  - **Performed risk assessment and decision analysis to pick the best design**

- **Value Added:**
  - **Enabled the team to pick the best trial design. The team followed our recommendation**
  - **Projected savings of $8-9MM (comparison to next best design)**

Significance of the Project

Importance

- **Millions of dollars were at stake in the decision regarding a PoP trial and the choice of its design**
- **The costs of wrong decisions are high**
  - **Downstream investments in the wrong project**
  - **Opportunity costs of not investing in a highly profitable drug**

Innovative Aspect

- **Translating the perceived risk, costs, and biostatistical issues of a trial design problem into a logically consistent Decision Analysis framework with an appropriate Bayesian Inference process embedded into it**

Value Added

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- **Projected savings of $8-9MM (comparison to next best design)**

Given

- Drug candidate
- Therapeutic fit
- Conduct PoP
- Use drug comparator

Decisions Made Now

PoP trial design

- # of trial arms
- Sample size
- # of trials

Decisions Made Later

- When to repeat PoP
- Full development "Go – No Go"
- Details of full development program

Given

- Drug candidate
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PoP trial design

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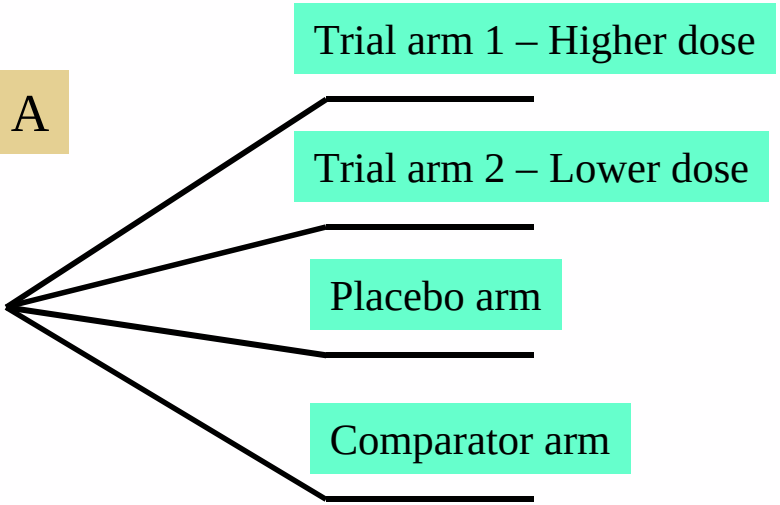
Decisions Made Later

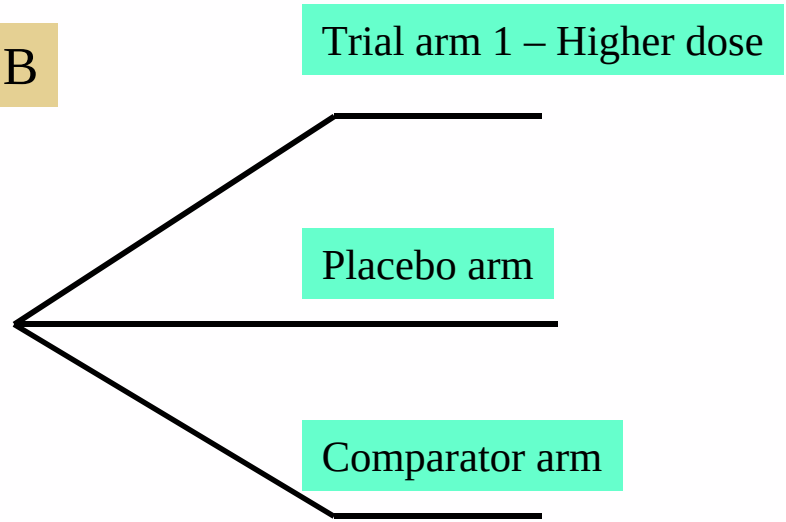
- Details of full development program

Clinical trial alternatives

Design A



Design B



Design C

Conduct Design B twice

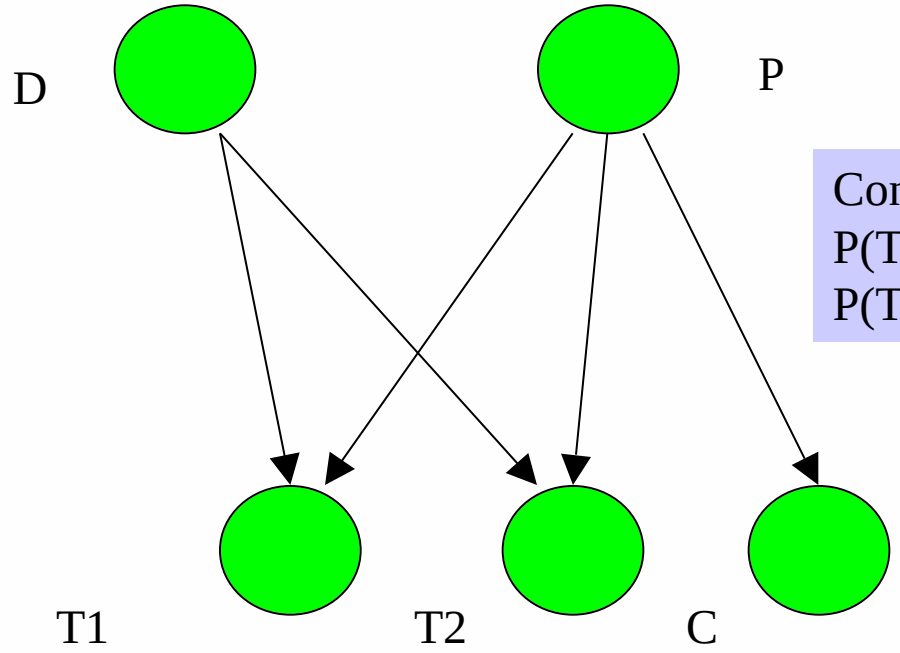
Design D

Higher sample sizes
for all arms

Influence Diagram for trial Design A

Drug efficacy – states of nature
- **"Effective at both doses,"**
- **"Effective at lower dose only,"**
- **"Effective at higher dose only,"**
- **"Not effective,"**

Placebo response – states of nature
- **Strong response**
- **Typical response**
- **Weak response**

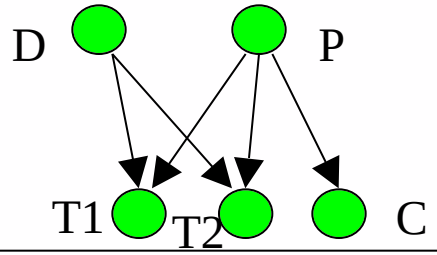
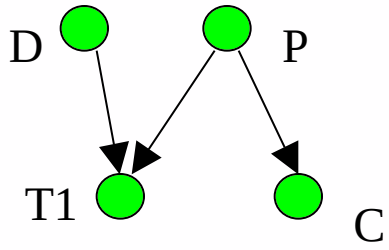
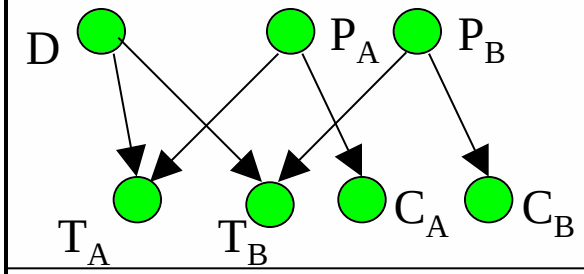


Conditional Independence →
P(T1,T2|D,P) =
P(T1,|D,P).P(T2|D,P)

D – Underlying drug efficacy
P – Placebo response
T1 – High dose trial arm outcome
T2 – Low dose trial arm outcome
C – Comparator arm outcome

The active comparator is used for internal validation of the trial and provides imperfect information about the placebo response:
- **Positive**
- **Negative**

Pros & Cons of alternative trial designs

	INFLUENCE DIAGRAM	PROS	CONS
Design A		Two different dose arms enable higher success in proving efficacy	More number arms → lower chance of being on placebo → increased placebo response and patient variability
Design B		Smaller number of patients and higher chance of being on placebo → lower placebo response and patient variability	Only one dose level and hence chance of proving efficacy reduced correspondingly
Design C II X 2		More than one chance to show success	Double the number of patients will need to be recruited → patient variability → lower sensitivity and higher variability
Design D	II with higher sample size	Increased power	Same issues in controlling quality of the sample and hence higher variability

Design A – prior & conditional probabilities

Prior Probabilities

Efficacy	
both	0.11
at High	0.14
at Low	0.20
None	0.55
	1.0

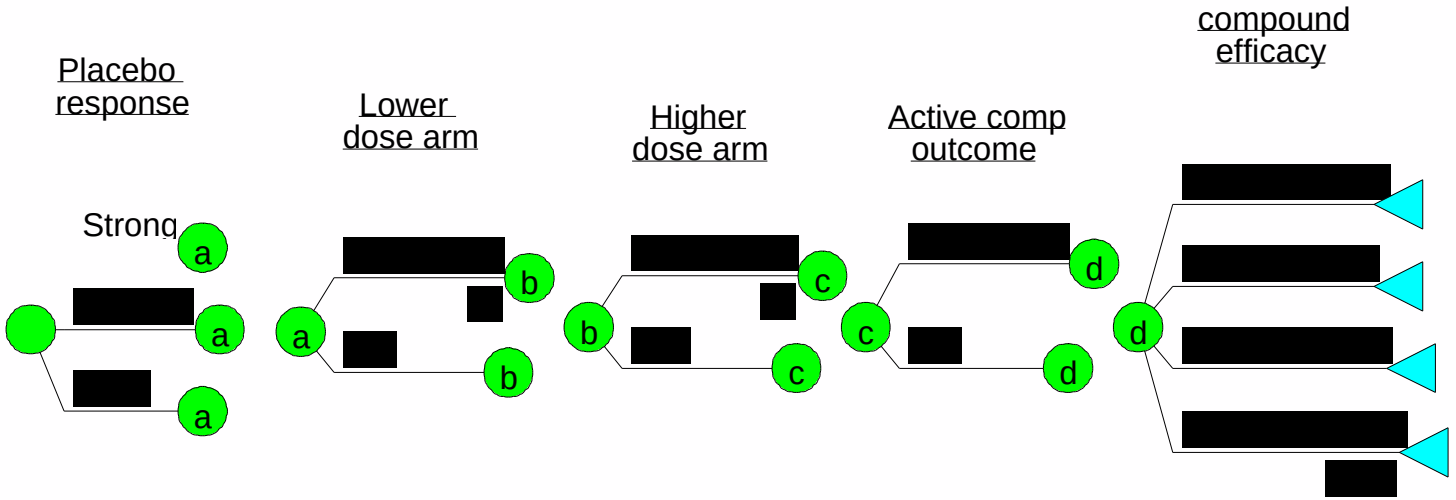
Placebo Response	
Strong	0.25
Typical	0.50
Weak	0.25
	1.00

Conditional Probabilities

Efficacy	Placebo	joint	Low dose arm	High dose arm	comparator
Both	Strong	0.03	0.10	0.10	0.10
Both	Typical	0.06	0.35	0.45	0.50
Both	Weak	0.03	0.60	0.65	0.75
at High	Strong	0.03	0.01	0.15	0.10
at High	Typical	0.07	0.07	0.45	0.50
at High	Weak	0.03	0.15	0.70	0.75
at Low	Strong	0.05	0.10	0.05	0.10
at Low	Typical	0.10	0.40	0.15	0.50
at Low	Weak	0.05	0.65	0.35	0.75
None	Strong	0.14	0.00	0.00	0.10
None	Typical	0.28	0.05	0.05	0.50
None	Weak	0.14	0.10	0.10	0.75
		100%			

Numbers Illustrative Only

Estimation of posterior probabilities



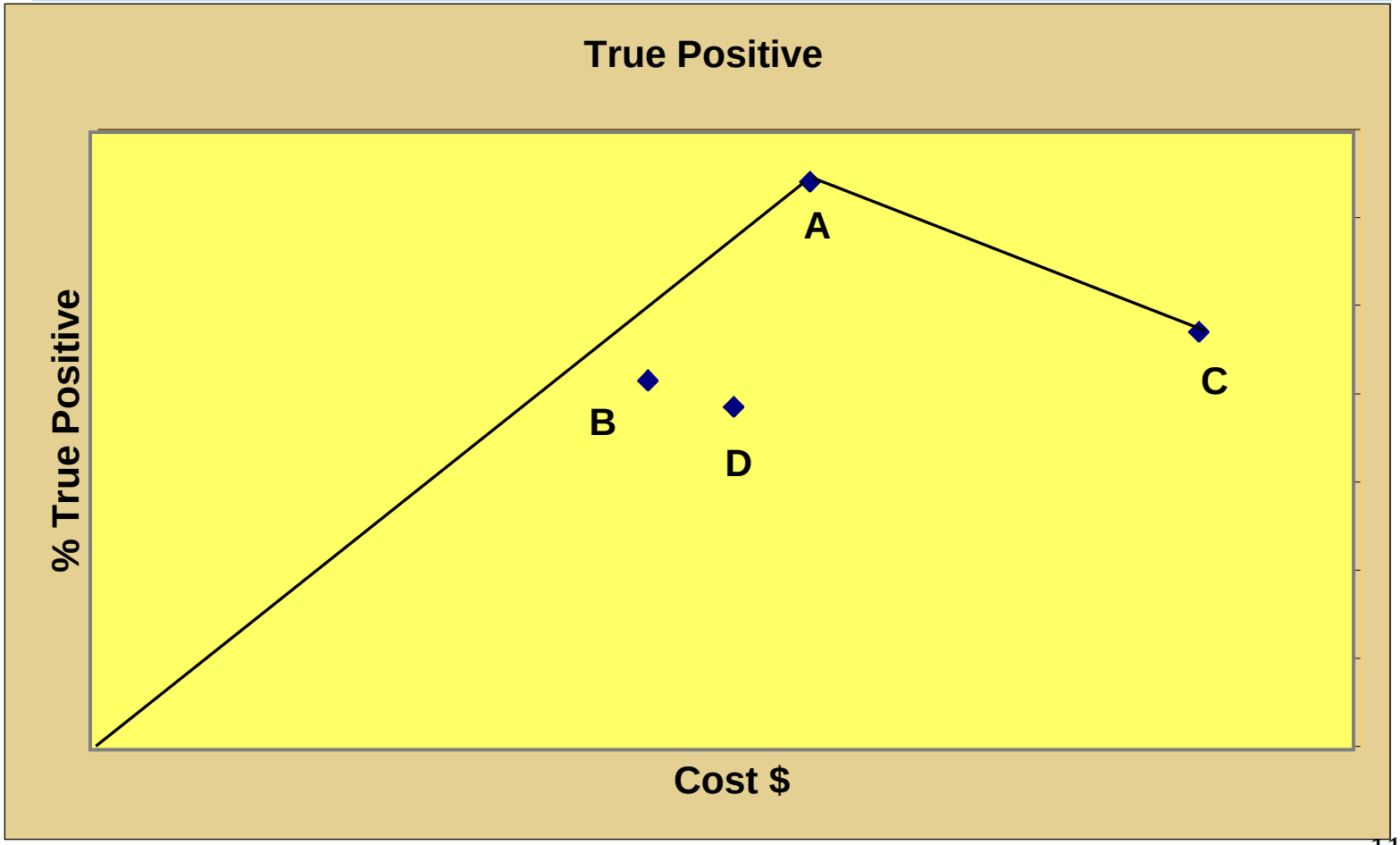
We calculate all the joint probabilities characterized by --
P(T1,T2,P,C,D) = P(D).P(P).P(T1|D,P). P(T2|D,P).P(C|P)

From this we develop the posterior probabilities such as the true positive by summing the appropriate joint probabilities

P(D positive| T1 and/or T2 positive) = **P(D).P(P).P(T1|D,P). P(T2|D,P)**

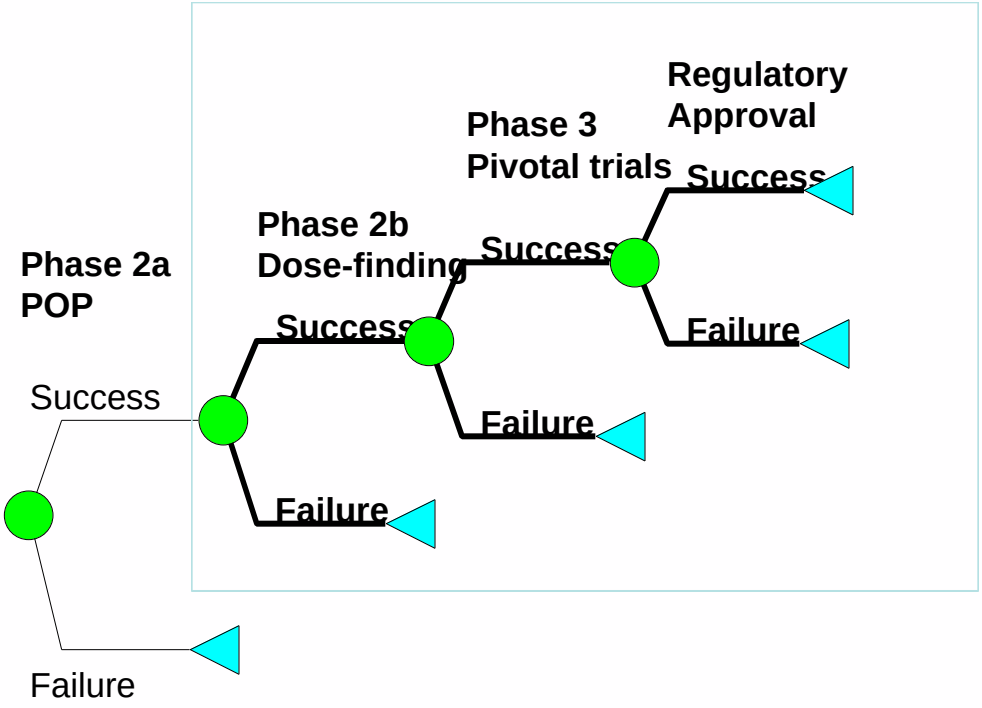
Comparison of true positive rates of designs

Design A is dominant based on a trade-off between cost and % true positive. This is a good preliminary decision since the true positive contributes the most to the eventual expected value of the alternative. A more complete Decision Analysis based on maximizing expected value confirms this.

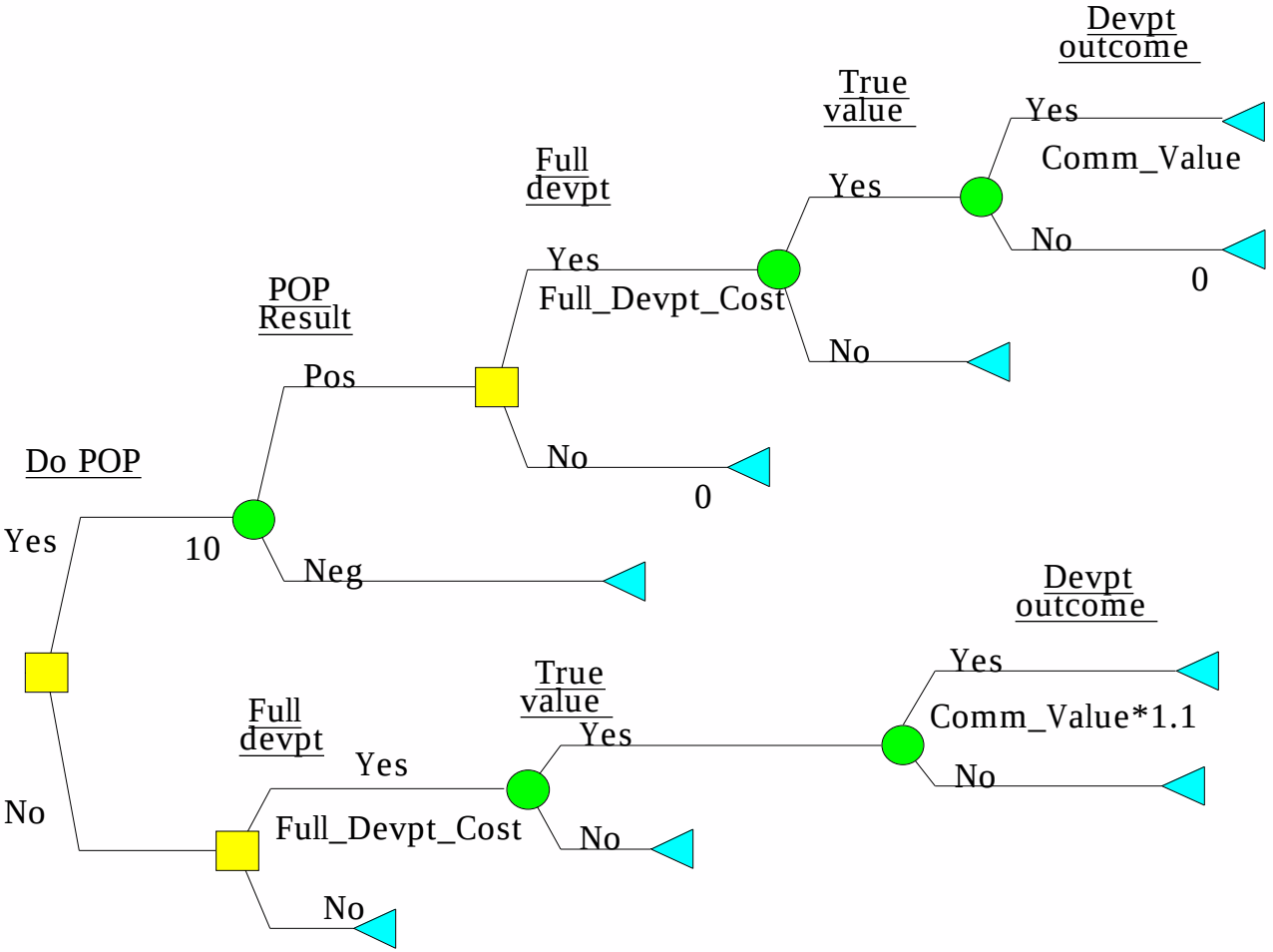


Full clinical development program

Full Development Plan includes one or two additional phases of development as shown below. For the purpose of our analysis, the entire Full Development plan can be summarized into one chance node and value.

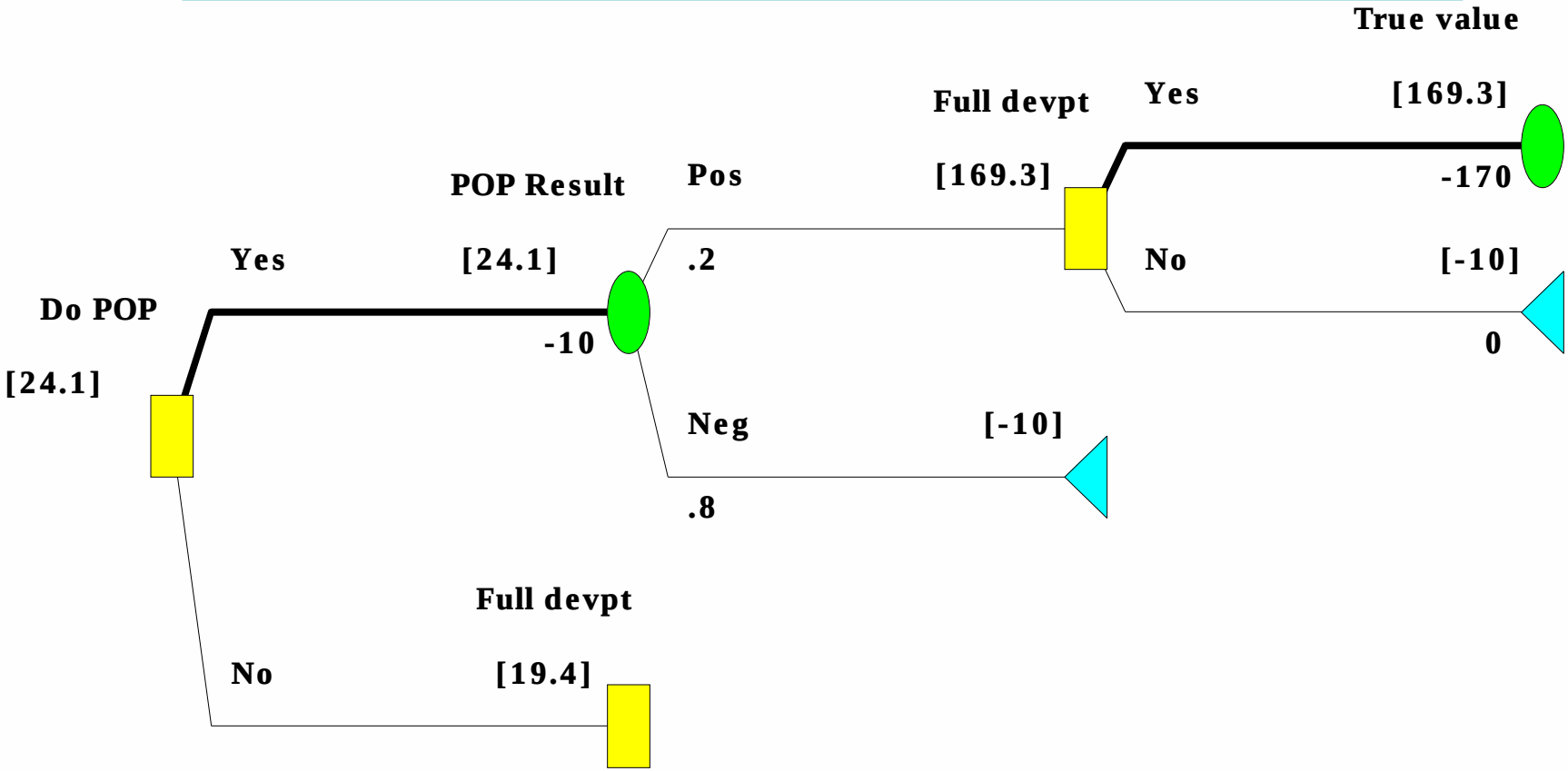


Comparison of PoP designs - EV



Decision Policy and EV of Design A

Doing similar analyses for other designs and comparing the value of information provided by the PoP confirms design A as the best choice.



Details of Full Decision Analysis

First two additional questions are answered here as part of the decision frame seen earlier.

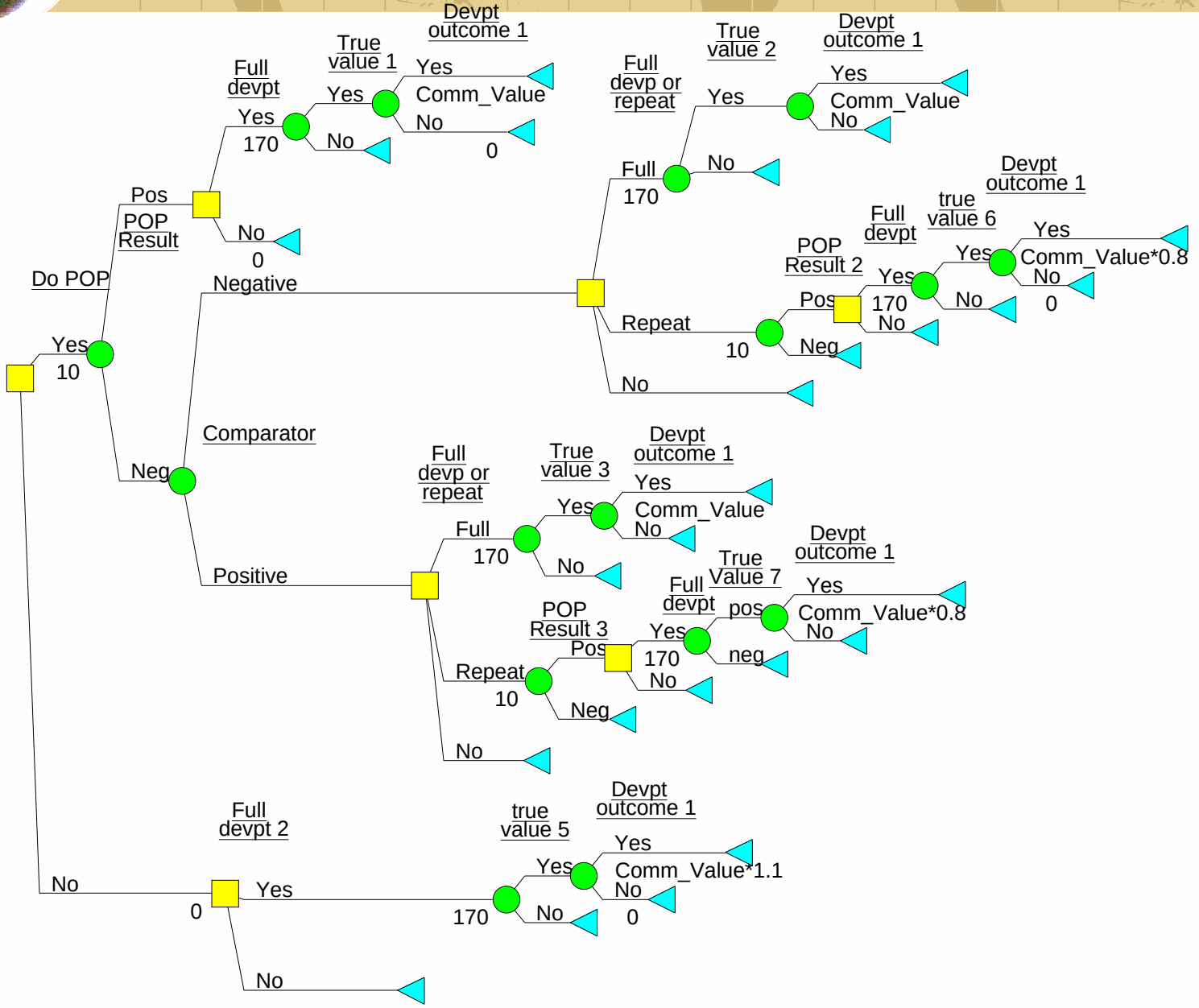
- When is a PoP warranted? We evaluated this in terms of sensitivity with respect to commercial value for the best trial alternative – Design A.
- What does the comparator arm tell us about the true positive when the PoP result is negative? If the comparator arm is negative, should you repeat the trial OR proceed directly to Full Development OR abandon the program altogether?

We also asked the following question:

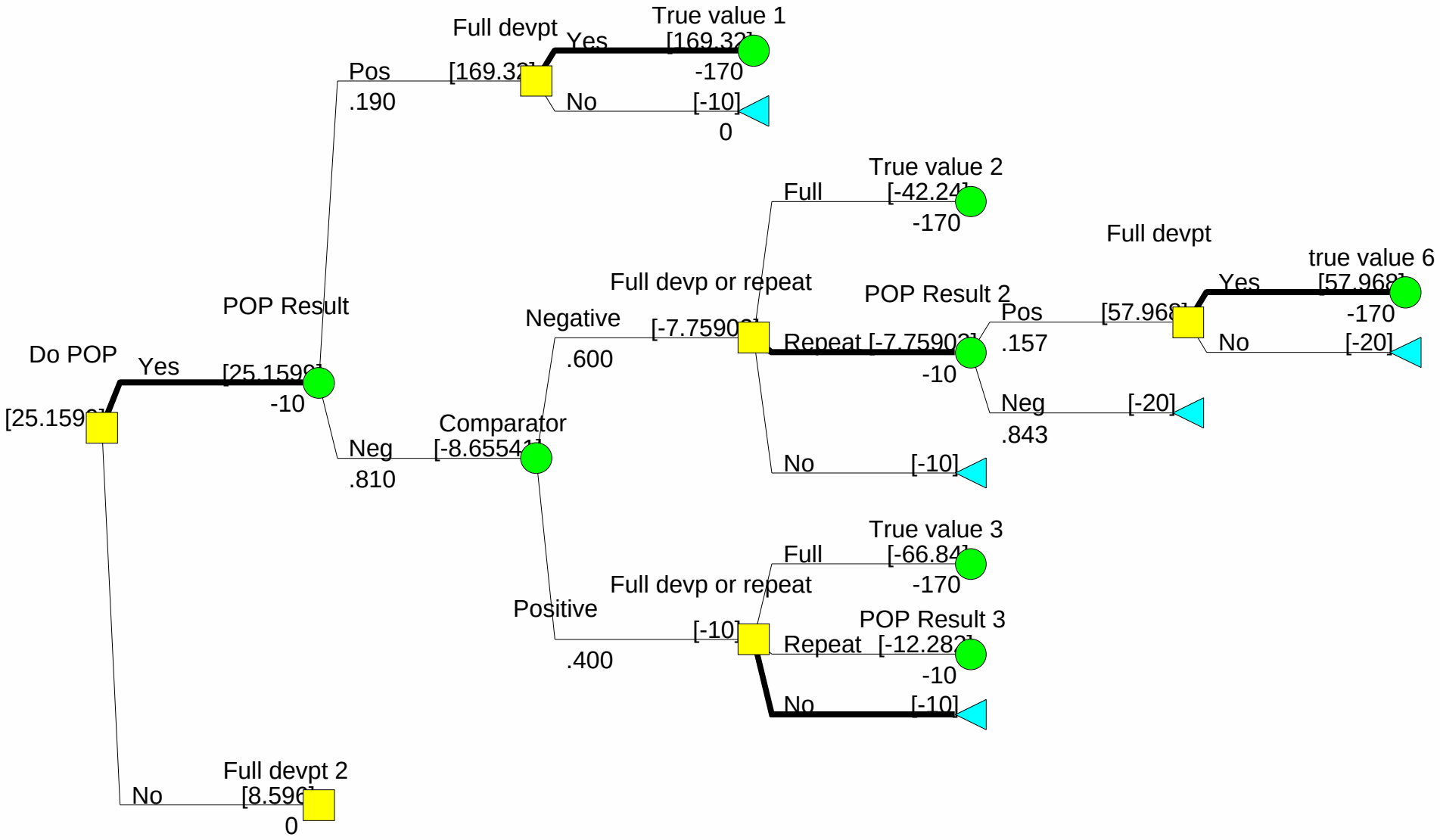
How does an ideal comparator perform? – Insight into "the most informational value that a comparator can contribute"

Also, can the observed placebo results be utilized in conjunction with the comparator arm?

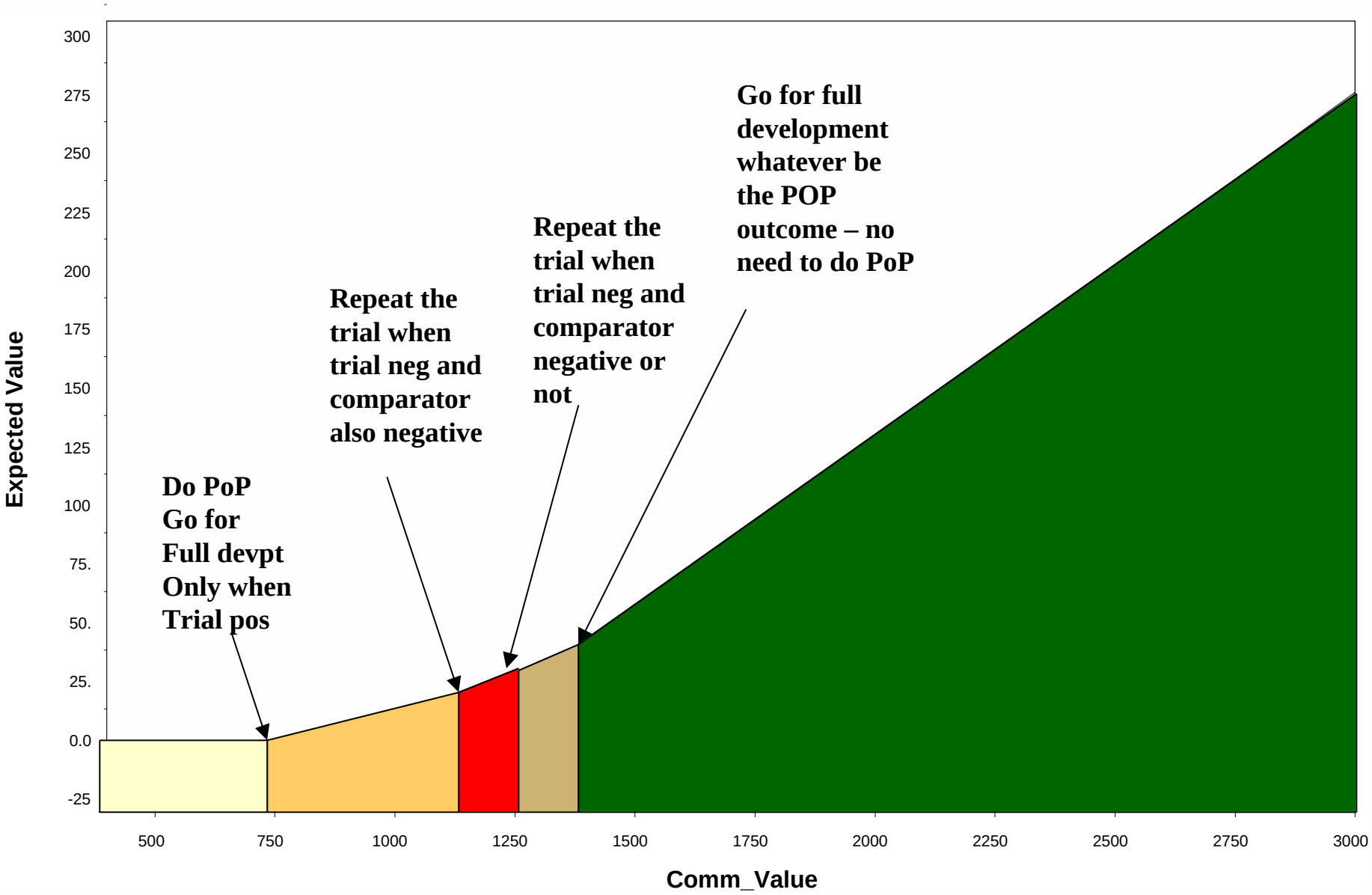
Full sequence of decisions & uncertainties



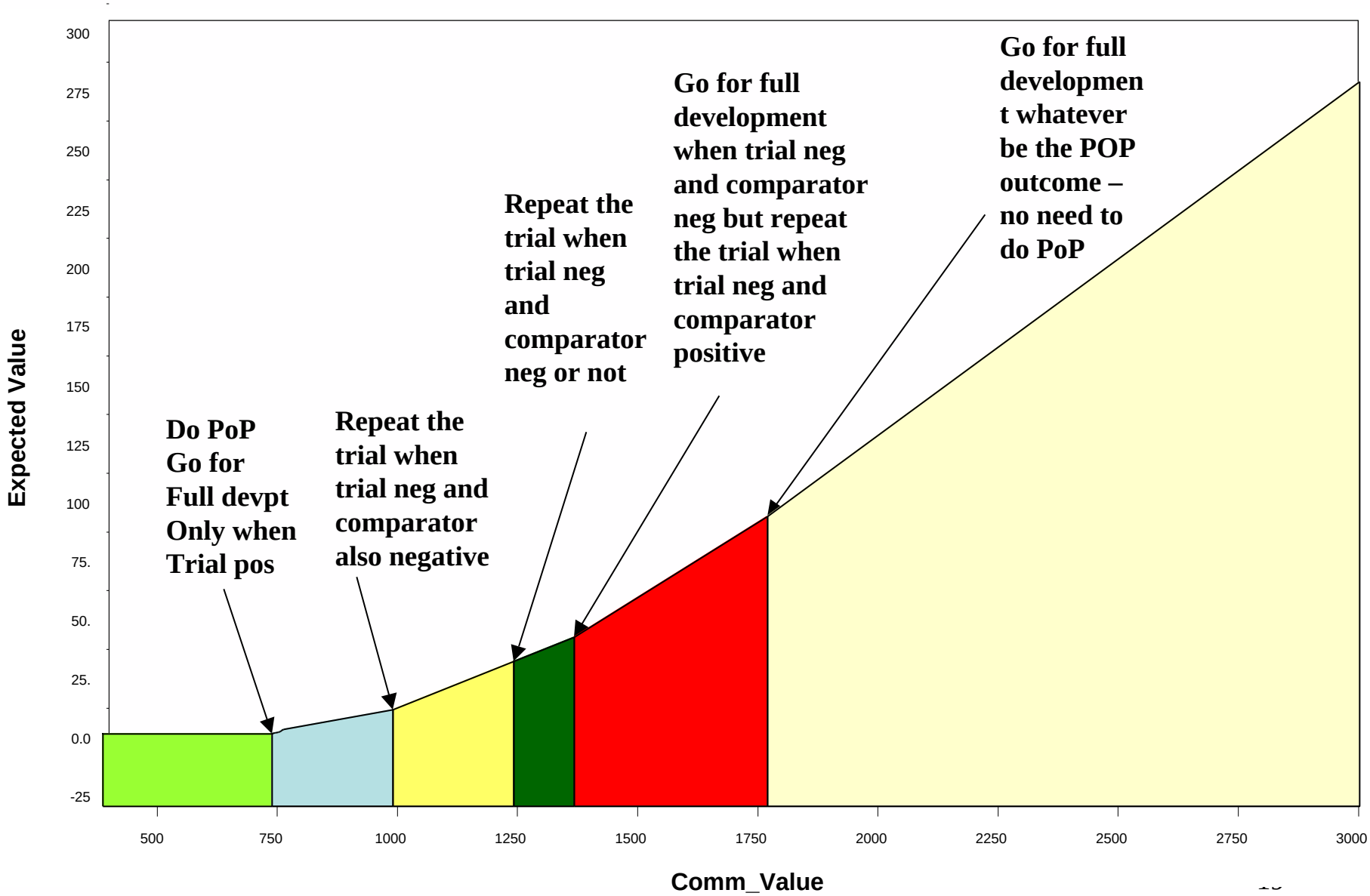
Detailed Policy Tree



Sensitivity of decisions to commercial value
Actual Comparator



Sensitivity of decisions to Commercial Value
Ideal Comparator



Value of Information comparisons

PoP Scenario	Comparator	Expected Value	Incremental Informational value vs. No PoP
No PoP	None	19.4	-
Design A	None	24.1	4.7
Design A	Actual comparator	25.2	5.8
Design A	Ideal comparator	26.5	7.1
Design B	None	15.3	- 4.1*

* While value of information for design B per the standard definition is zero, the incremental value if design B is undertaken is negative, since not using design B is better than using it.

Results and Actions

- **Decision to do a PoP confirmed**
- **Best design for PoP confirmed and implemented**
- **True understanding of the role of the comparator arm and the interpretation of the results for downstream decisions**
- **Formal decision-theoretic criteria for identifying "failed trial" established, and clarity regarding "Go/No-Go-Repeat" policy for the downstream decisions obtained**
- **Created a template for future PoP trial decisions**
- **Generated immediate savings of $8-9 MM in EV – by comparison to next best trial design**

Conclusions

- **Decision on PoP trial depends on a number of factors:**
  - **Predicted true positive rate of the trial**
  - **Cost of the PoP**
  - **Size of the investment in full development**
  - **Size of the commercial opportunity**
- **Bayesian approach can provide a logical framework to PoP trial design decisions – number of arms, sample size, comparator selection**
- **The value of the comparator arm depends on how accurately it can help infer the placebo effect**
- **A number of alternative downstream decisions, such as stopping the development, repeating the PoP, and continuing the development, should be factored into the analysis**
- **The approach helped the development team gain valuable insight into the various strategic implications of their decisions.**