Probabilistic Sensitivity Analysis and Value of Information in Cost-Effectiveness Models

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Summary

- One step parameter estimation and cost-effectiveness model
  - Set up a deterministic health economic model
  - Estimate parameters and “Push through” the uncertainty in the parameters underpinning this model by Monte Carlo simulation
- This generates the distribution of the population mean effectiveness and population mean cost in each arm
  - $\mathbb{E}[f(\theta)] \neq f(\mathbb{E}[\theta])$
- We use these distributions to find
  - Incremental cost-effectiveness ratio
  - Incremental net benefit
  - Cost effectiveness acceptability curves
- We calculate the value of reducing the uncertainty in the parameters
  - Expected value of perfect information
  - Expected value of perfect partial information

New chemotherapy drug

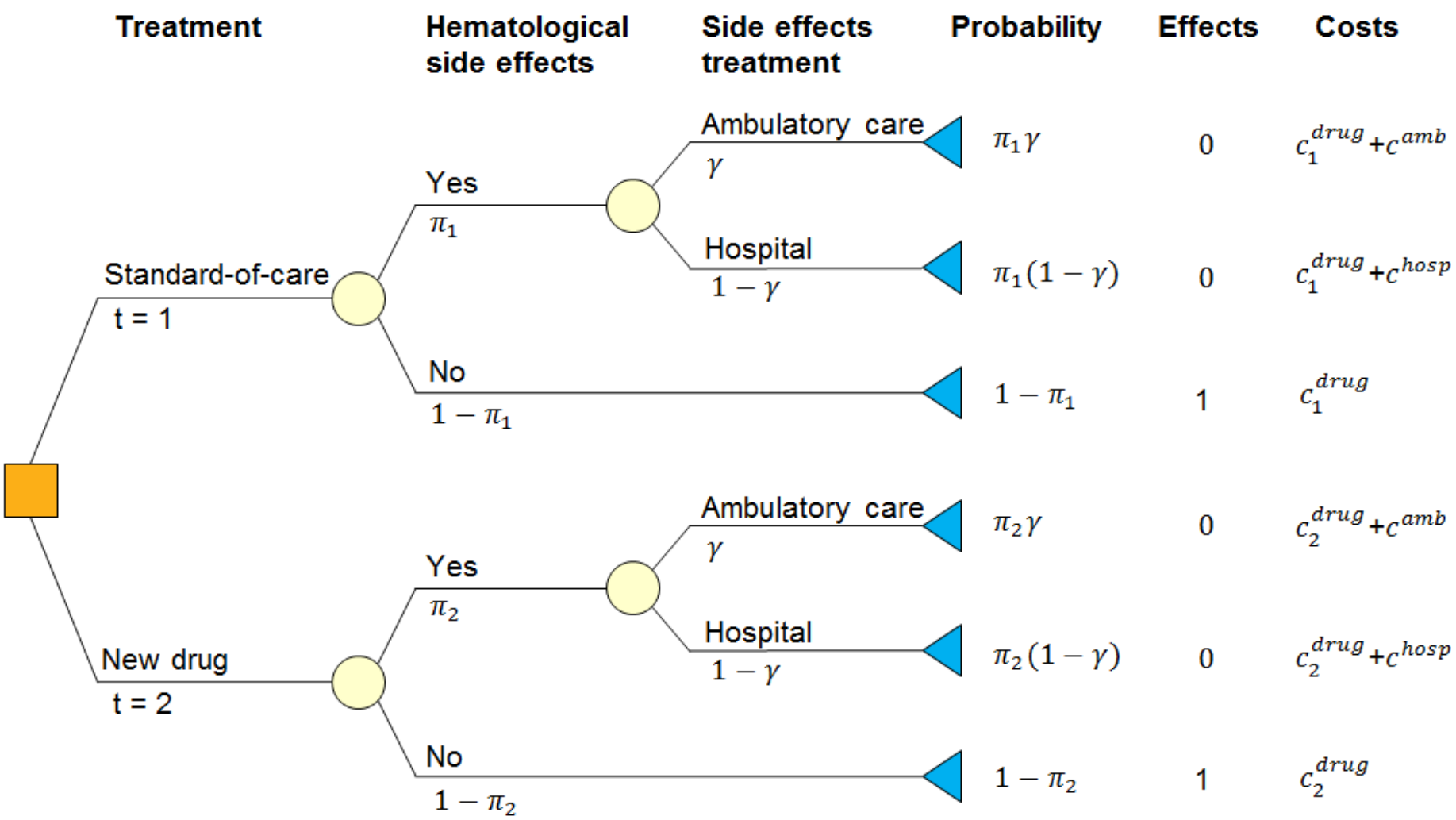
- Evaluate a new chemotherapy drug against the standard of care
- Following treatment, a patient may experience haematological side effects
- If this does happen, depending on the severity, the patient either needs ambulatory care, or is admitted to hospital
- Costs to include: Drug costs, cost of ambulatory care, cost of hospital
- Effect: Being free of side effects

Components of Decision Quality[1]

- What we can do?
  - t is the set of interventions
  - Decide to use standard-or-care or new treatment ($t = 1, 2$)
- What we know?
  - Statistically these are the random variables
  - θ: parameters describing disease model, costs and effects
  - e and c are the observable outcomes
  - $\mu_t^e = \mathbb{E}[e|\theta, t]$ and $\mu_t^c = \mathbb{E}[c|\theta, t]$ are population mean cost and effect given intervention t.
- What we want?
  - The value of the outcomes measured by utility
  - We chose the net (monetary) benefit
    $u(e, c; t) = ke - c$
    k is the willingness-to-pay for one unit of effectivness.
  - Chose intervention t with the highest expected net benefit
    $\mathbb{E}\left[\mathbb{E}[u(e, c; t)]\right] = \mathbb{E}\left[k\mu_t^e - \mu_t^c\right]$

[1] Ron Howard. The Foundations of Decision Analysis Revisited, in Advances in Decision Analysis 2007.

Decision tree model



Disease model data

We have data from a clinical study

Parameter	Value	Description
N^{pat}	111	Number of patients in observed data
N^{se}	27	Number of patients with side effects, given standard-of-care
N^{amb}	17	Number of patient with ambulatory care following side effect, given standard-or-care
μ_ρ	0.8	Mean probability of side effect given new treatment compared to standard-of-care
σ_ρ	0.2	SE of probability of side effect given new treatment compared to standard-of-care

Disease model analysis

Probability of side effects

N^{se}	$\sim$	$\text{Binomial}(\pi_1, N^{pat})$	sampling distribution
π_1	$\sim$	$\text{Beta}(1, 1)$	prior distribution
ρ	$\sim$	$\text{Normal}(\mu_\rho, \sigma^2_\rho)$	Reduction in the occurence of side effects
π_2	$=$	$\rho\pi_1$	

Treatment of side effects

N^{amb}	$\sim$	$\text{Binomial}(\gamma, N^{se})$	sampling distribution
γ	$\sim$	$\text{Beta}(1, 1)$	prior distribution

```
num.se ~ dbin(pi[1], num.pat)
pi[1] ~ dbeta(1, 1)

rho ~ dnorm(m.rho, tau.rho)
pi[2] <- rho * pi[1]

num.amb ~ dbin(gamma, num.se)
gamma ~ dbeta(1, 1)
```

Cost Data

Parameter	Distribution	Description	Mean cost
c^{amb}	logNormal(4.77, 0.17)	Ambulatory care	120
c^{hosp}	logNormal(8.60, 0.18)	Hospital	5483
c_1^{drug}	110	Cost of standard-of-care	
c_2^{drug}	520	Cost of new drug	

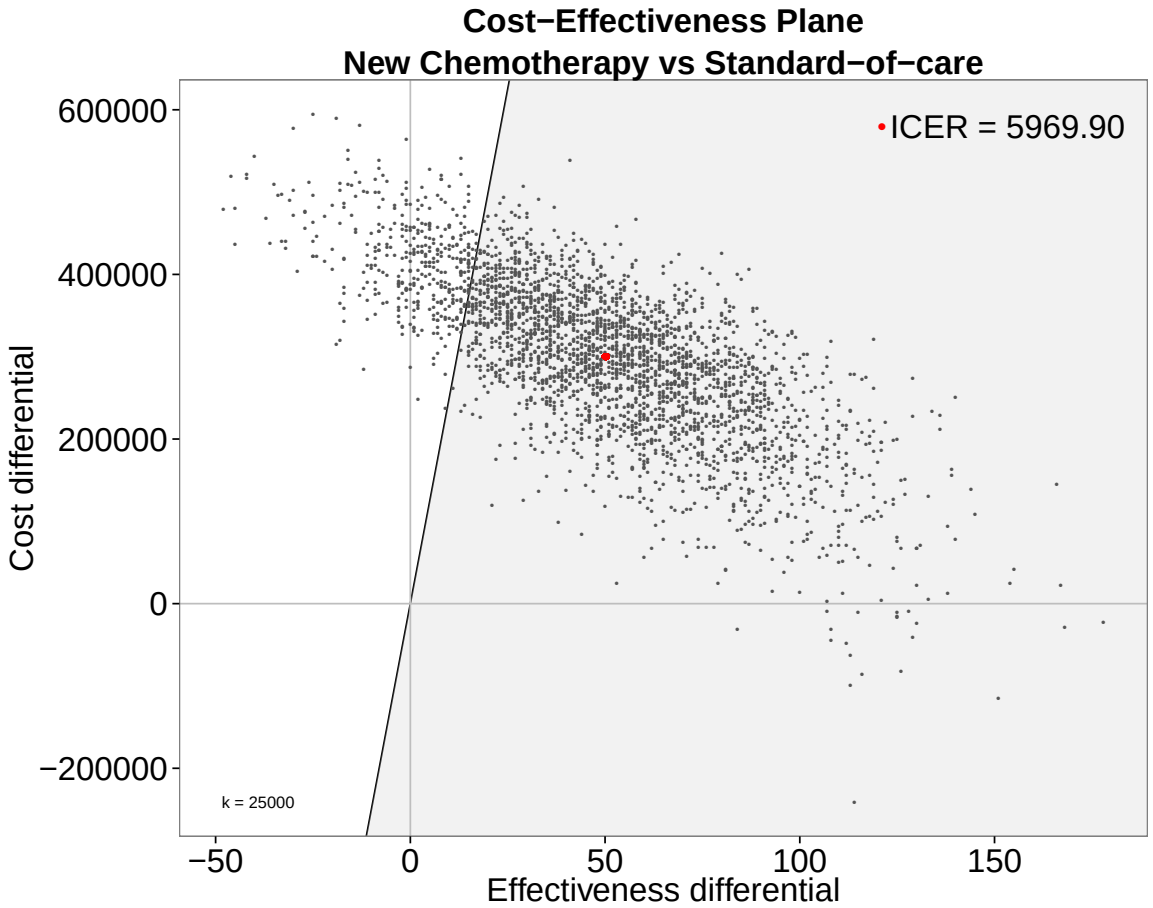
```
c.amb ~ dlnorm(m.amb, tau.amb)      # Cost of ambulatory care
c.hosp ~ dlnorm(m.hosp, tau.hosp)   # Cost of hospitalization

# The drug costs are part of the data set
list(c.drug = c(110, 520))
```

The predictive distributions and total costs and effects

N	$=$	Number of patients in the population to model	
SE_t	$\sim$	$\text{Binomial}(\pi_t, N)$	Expected # with side effects
A_t	$\sim$	$\text{Binomial}(\lambda, SE_t)$	Expected # with with ambulatory care
H_t	$=$	$SE_t - A_t$	Expected # with with hospitalization
μ_t^e	$=$	$N^{\text{pat}} - SE_t$	Expected # with no side effects
μ_t^c	$=$	$c_t^{\text{drug}} N^{\text{pat}} + c^{\text{amb}} A_t + c^{\text{hosp}} H_t$	Expected cost

```
for (t in 1:2){
    SE[t] ~ dbin(pi[t], N)
    A[t] ~ dbin(gamma, SE[t])
    H[t] <- SE[t] - A[t]
    mu.e[t] <- N - SE[t]
    mu.c[t] <- c.drug[t] * N + c.amb * A[t] + c.hosp * H[t]
}
```

Cost-effectiveness plane



k is the amount one is willing to pay for one unit of effectiveness

Incremental Cost Effectiveness Ratio (ICER)

The ICER is the mean incremental cost divided by the mean incremental effect

$$\Delta_e = \mu_2^e - \mu_1^e \quad \text{Expected incremental effects}$$
$$\Delta_c = \mu_2^c - \mu_1^c \quad \text{Expected incremental costs}$$

$$\text{ICER} = \frac{\mathbb{E}[\Delta_c]}{\mathbb{E}[\Delta_e]}$$

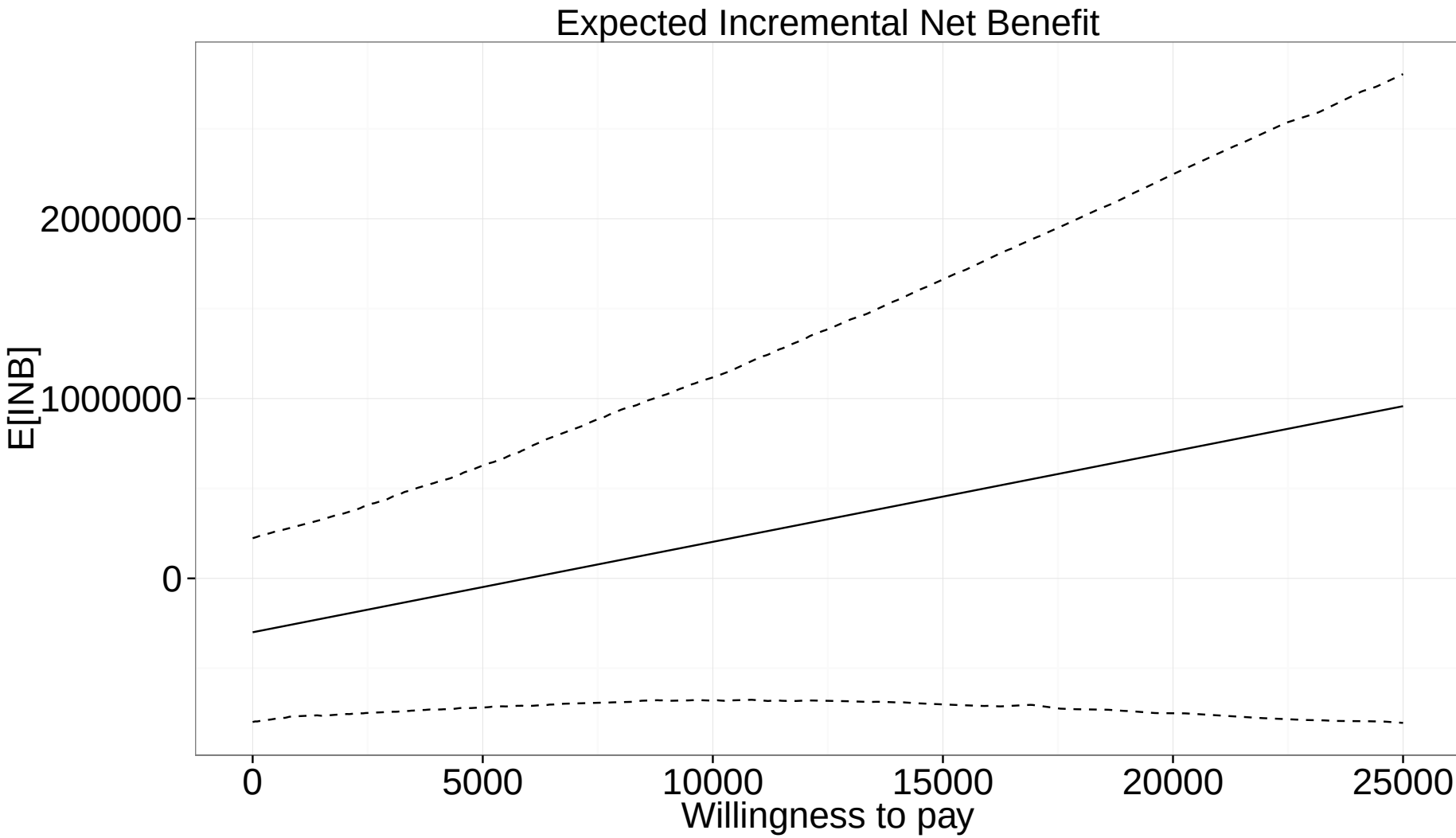
WARNING!

- The ICER cannot be interpreted without knowing the position of Δ_e and Δ_c on the CE plane
- The ICER is not a properly ordered statistic for negative values (e.g. -100/100 is better than -100/50 is better than -50/50 in terms of decision making, but these ratios are -1, -2, -1)

Incremental Net (Monetary) Benefit

- Translate effects onto the cost scale and subtract costs
- INB(θ, k) = k$\Delta_e - \Delta_c$
- k is the amount one is willing to pay for one unit of effectiveness
- If INB(θ, k)$>$0 then the new treatment is cost effective
- We can plot the expected INB and its 95% CI for different values of K
- The break-even point occurs at $\mathbb{E}[\Delta_c]/\mathbb{E}[\Delta_e]$. (Although it is possible the INB is always positive or negative)

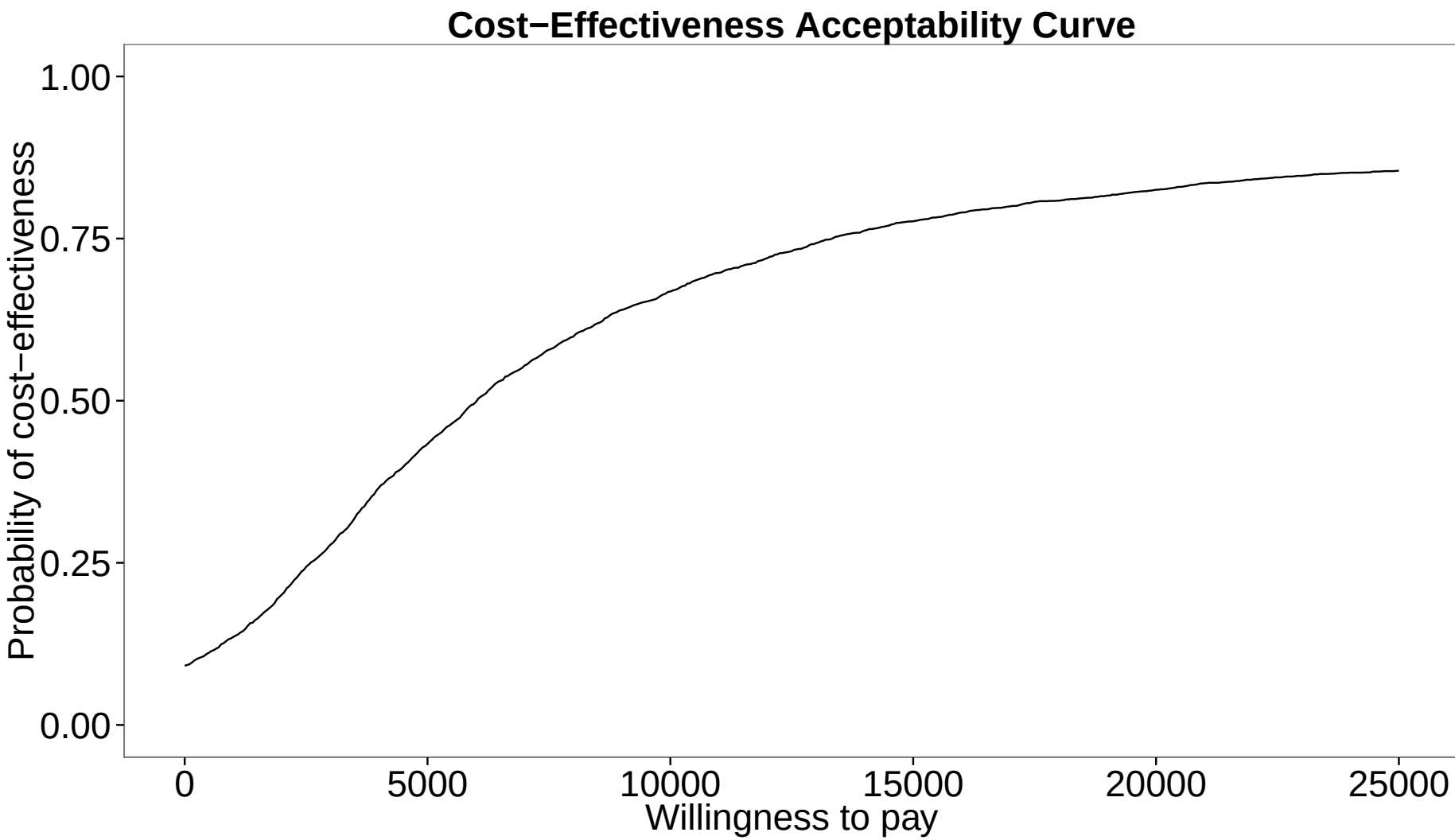
Incremental Net (Monetary) Benefit



Cost Effectiveness Acceptability Curve

- To quantify decision uncertainty consider the probability that INB(K) is positive
- Q(k) = P(INB(k)$>$0)=P(kΔ_e - Δ_c $>$0)
- This is the cost-effectiveness acceptability curve (CEAC)
- Imagine a line on the cost-effectiveness plane going thought the origin and with gradient k. The value of Q(k) is the area under the line.
- (Actually Q(k) is the volume to one side of a plane bisecting the probability density function of costs and effects)

Cost Effectiveness Acceptability Curve



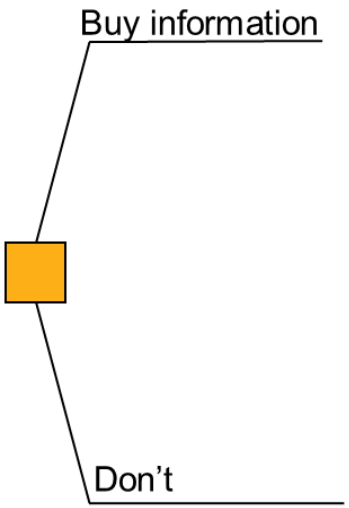
Coding this in BUGS

```
## incremental cost/effectiveness ratio
delta.e <- mu.e[2] - mu.e[1]
delta.c <- mu.c[2] - mu.c[1]

##  CEAC curves
k.space <- 5000
for(j in 1:11){
    k[j]<- (j-1) * k.space
    INB[j] <- K[j] * delta.e - delta.c
    Q[j] <- step( INB[j] )
}
```

Value of perfect information (VPI)

- Consider a simpler model where:
  - The only uncertain parameter is the probability of side effects π given SoC
  - We have a discrete distribution for this
    $P(\pi = 0.25) = 0.5$
    $P(\pi = 0.35) = 0.5$
  - All patients with a side effect are treated the same way, and this costs 2000
- The new treatment has the highest expected net benefit (when WTP = 5000)
  - $\max_t \mathbb{E}[NB(\pi; t)] = 2800$
- Suppose that we know that $\pi = 0.25$
- Now the SoC has the highest net benefit
  - $\max_t NB(\pi, t) = 3140$
- The value of knowing π exactly is the difference between these

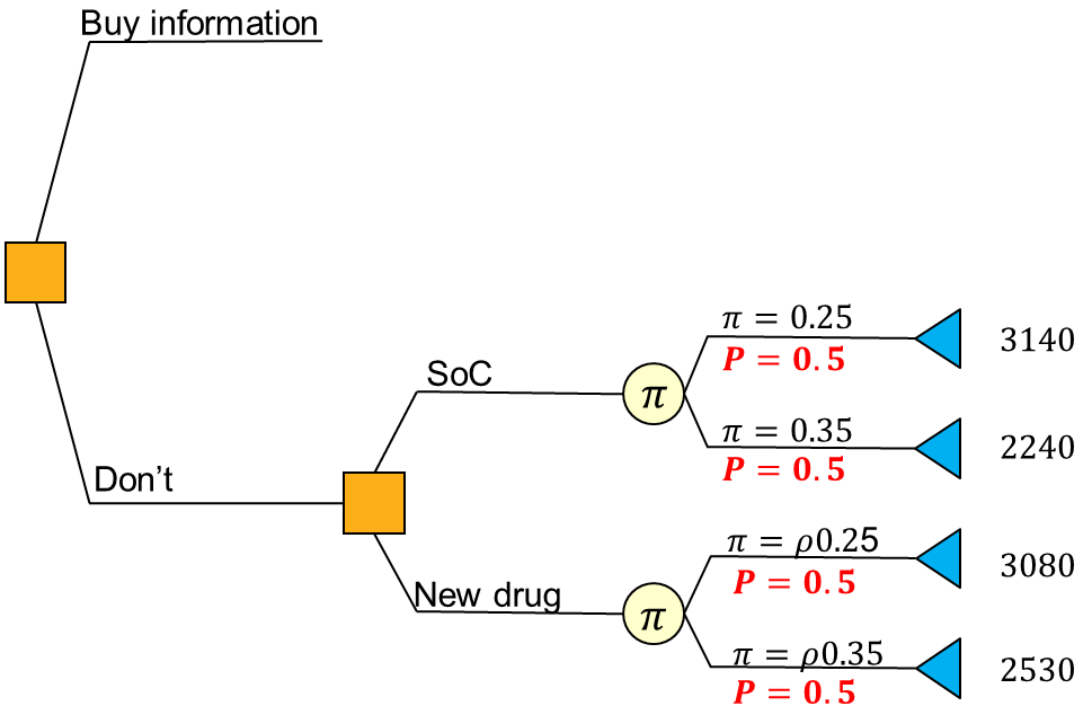
Value of perfect information (VPI)



Value of perfect information (VPI)

NB

$$(1 - \pi_t)k - (c^{drug} + \pi_t c^{amb})$$



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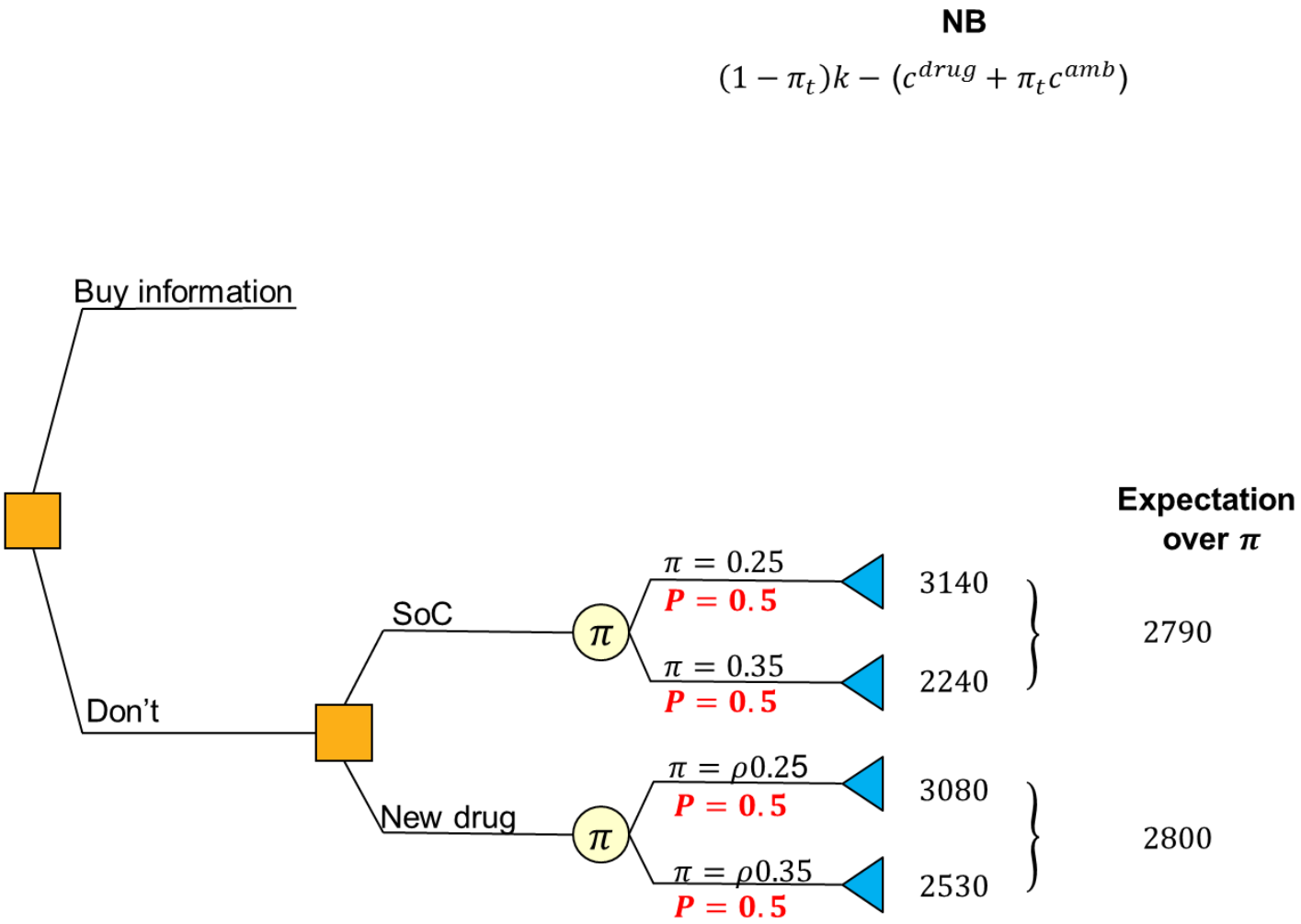

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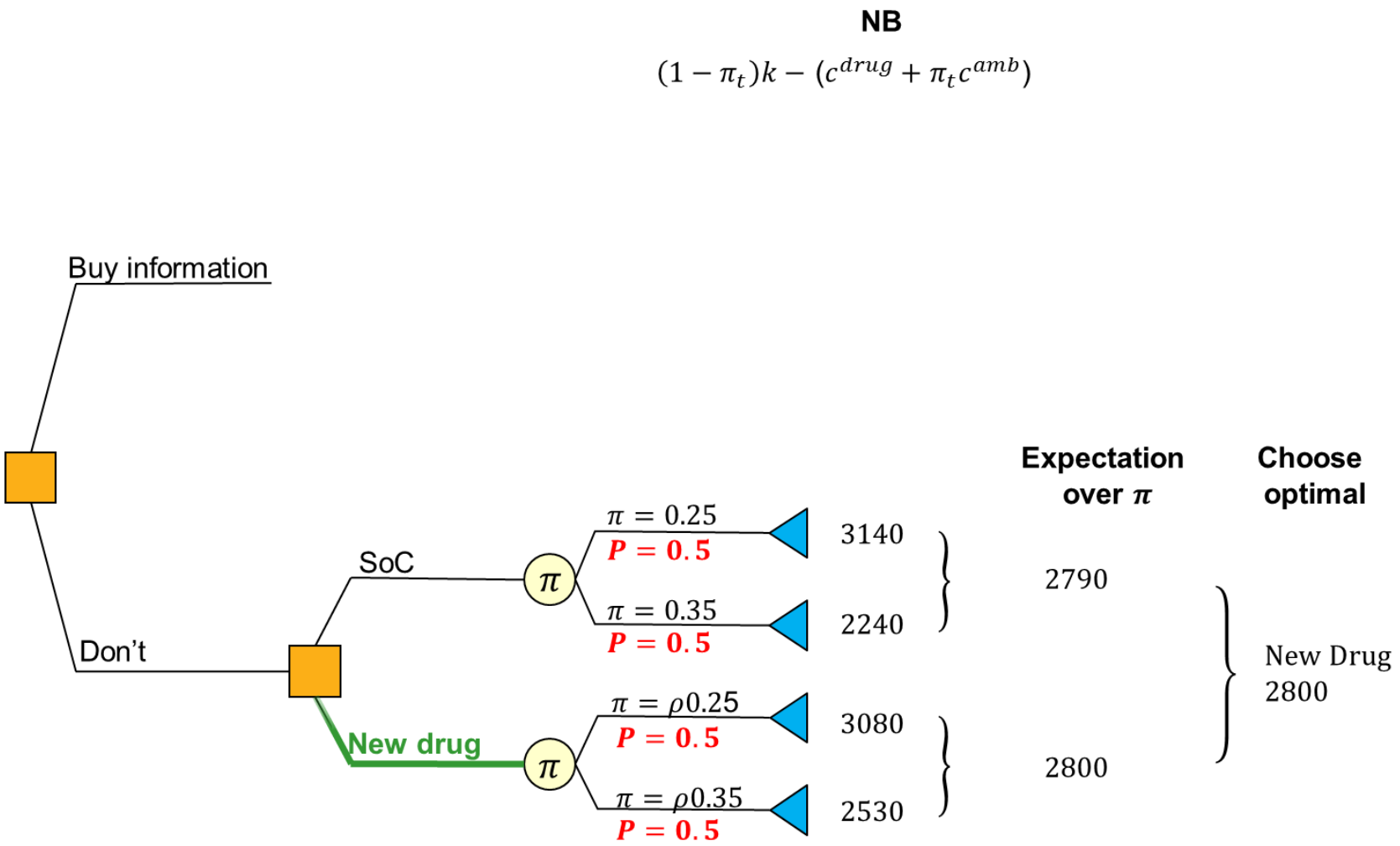

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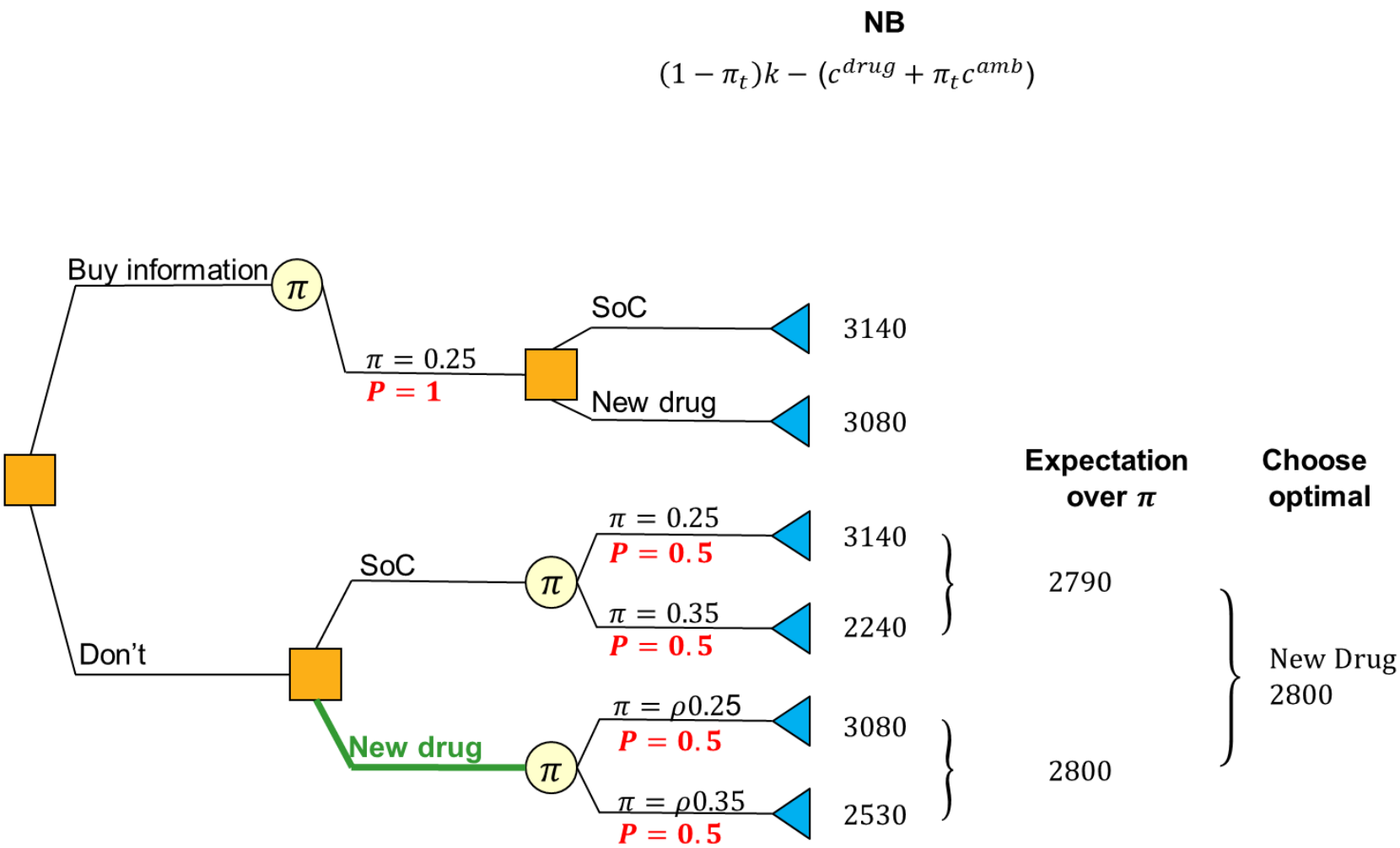
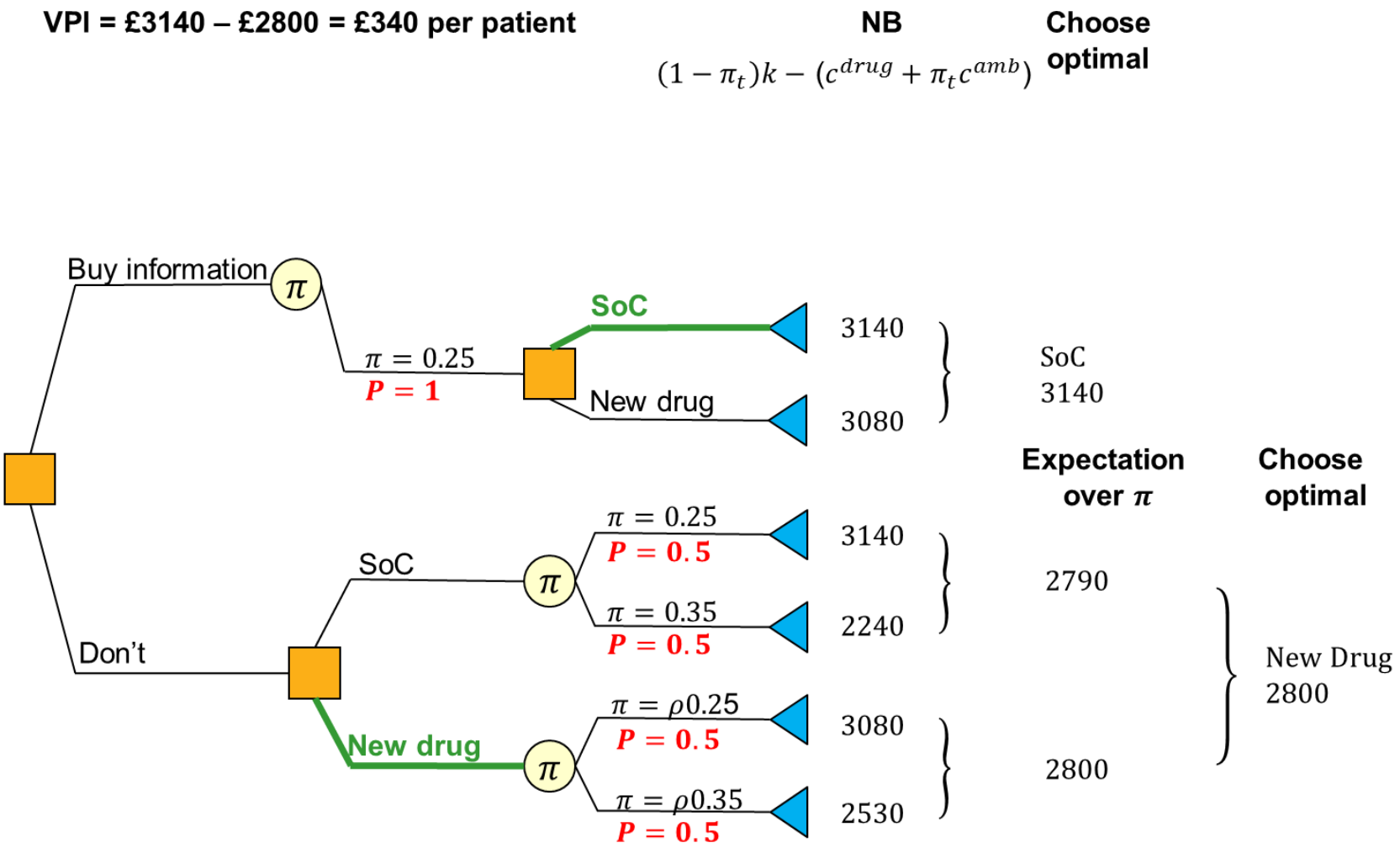


Value of perfect information (VPI)

VPI = £3140 – £2800 = £340 per patient



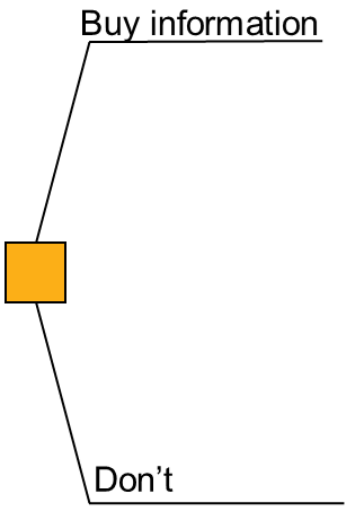
Expected value of perfect information (EVPI)

- Perfect information is a hypothetical concept as we don't know the parameter value when deciding to buy it.
- Instead we find the expected NB, averaging over the possible values of π
  - $\mathbb{E}_\pi[\max_t NB(\pi, t)]$
- The expected value of knowing this infomation is $\mathbb{E}_\pi[\max_t NB(\pi; t)] - \max_t \mathbb{E}_\pi(NB(\pi; t)]$
- This is called the Expected Value of Perfect Information (EVPI)
- Note that, if for every value of π we don't change the treatment decisison, then the EVPI is zero

Golden rule of Value of Information

Information only has value if it changes your decision

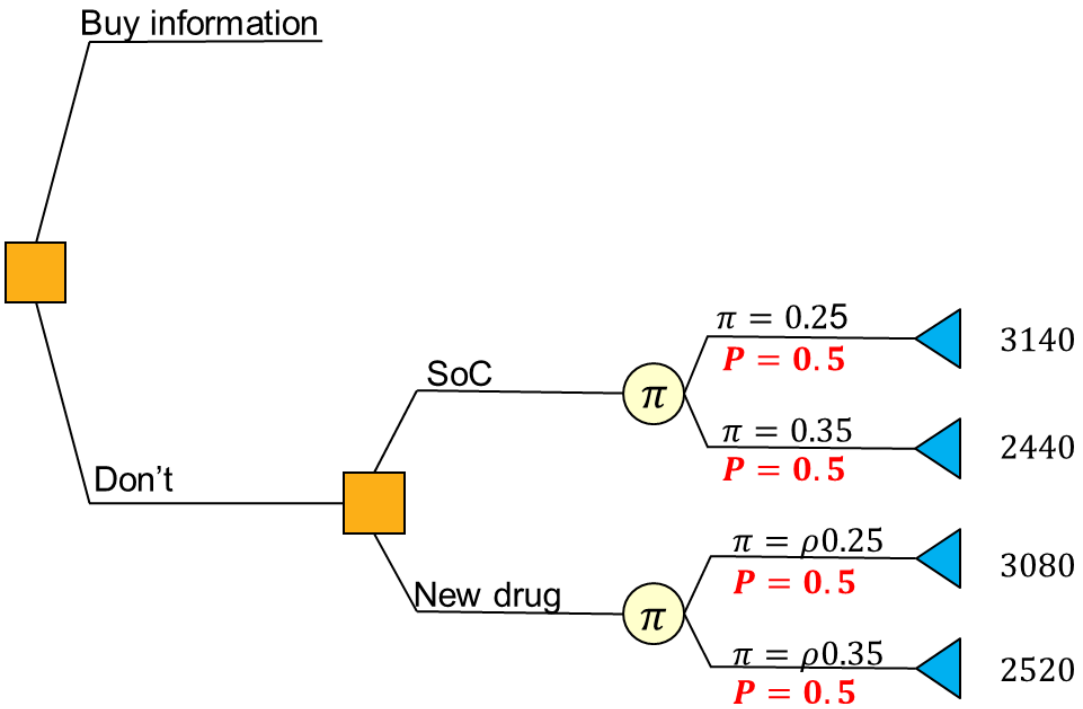
Expected value of perfect information (EVPI)



Expected value of perfect information (EVPI)

NB

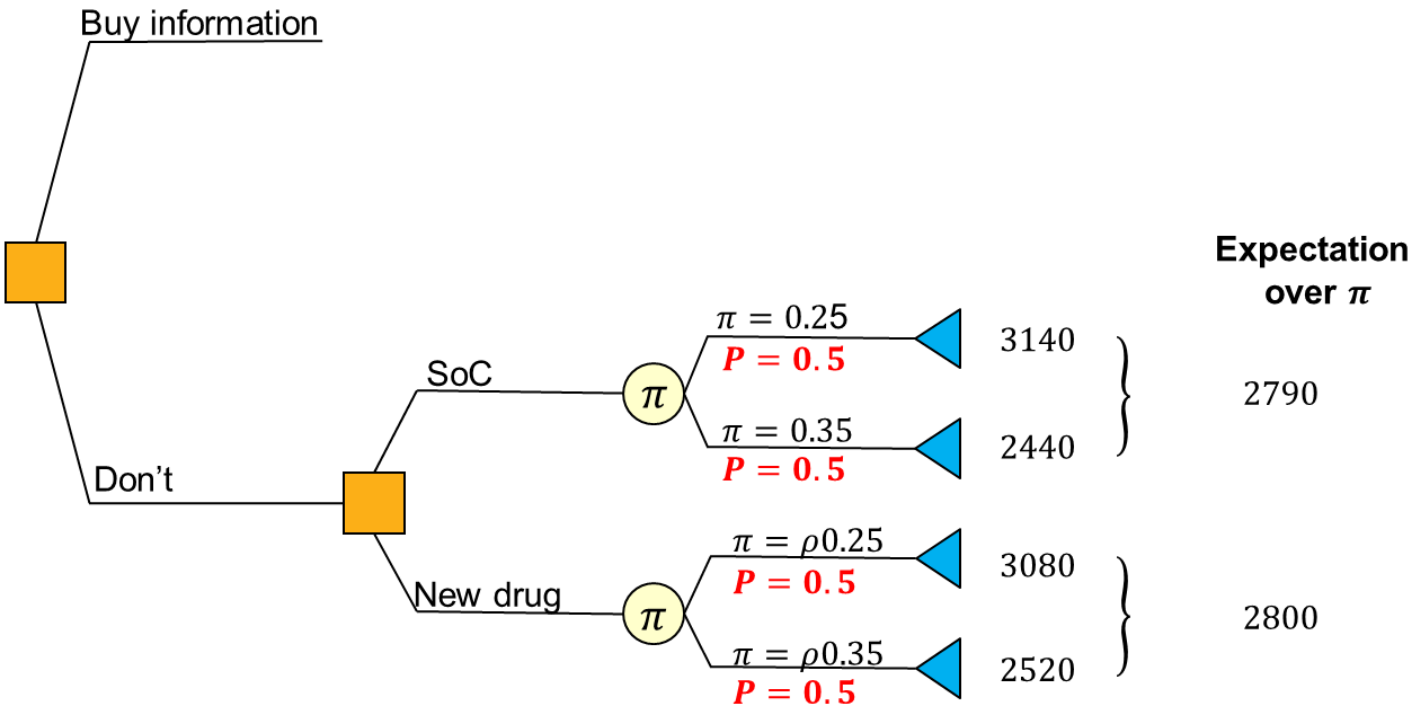
$$(1-\pi_t)k-(c^{drug}+\pi_t c^{amb})$$



Expected value of perfect information (EVPI)

NB

$$(1 - \pi_t)k - (c^{drug} + \pi_t c^{amb})$$



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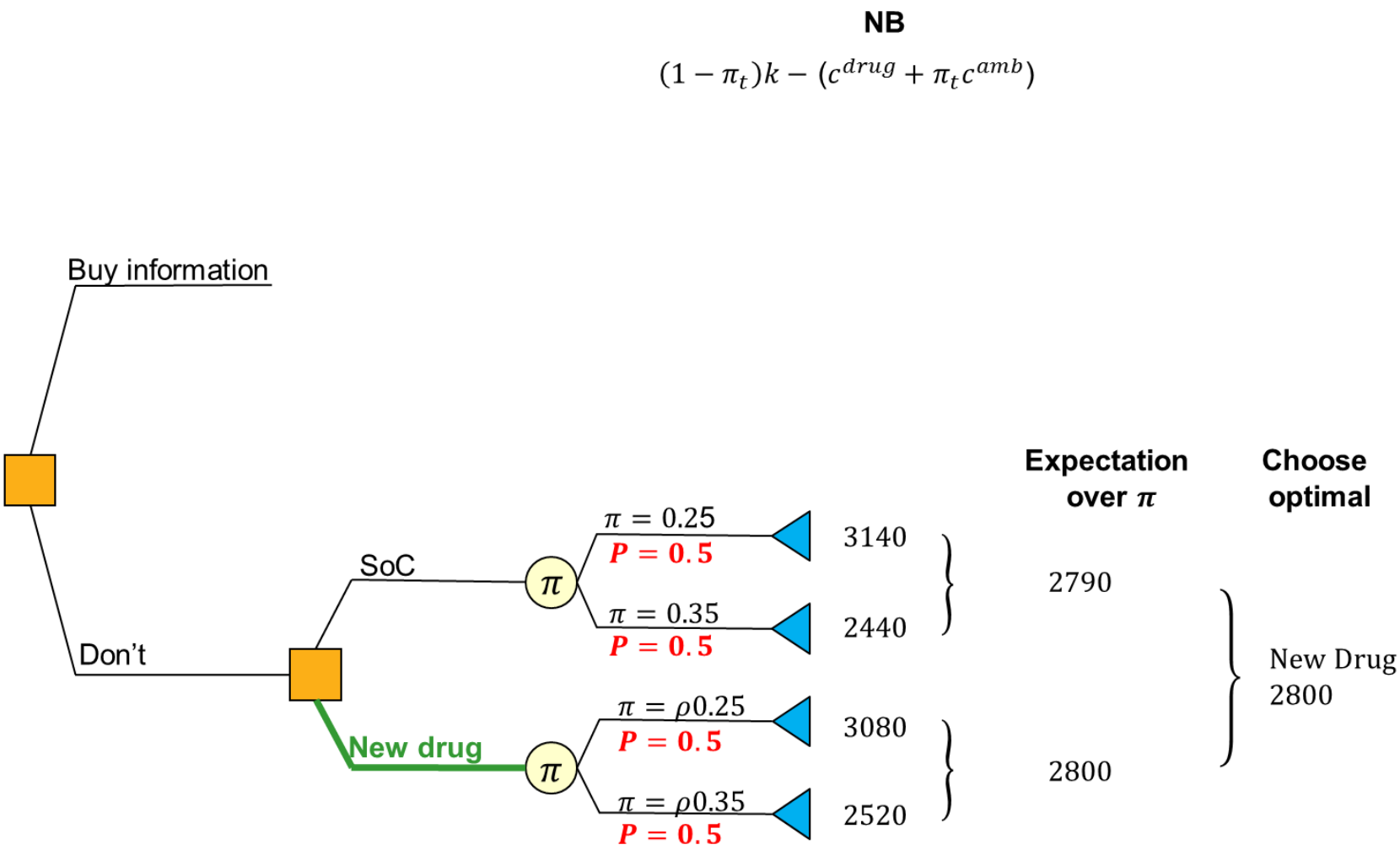

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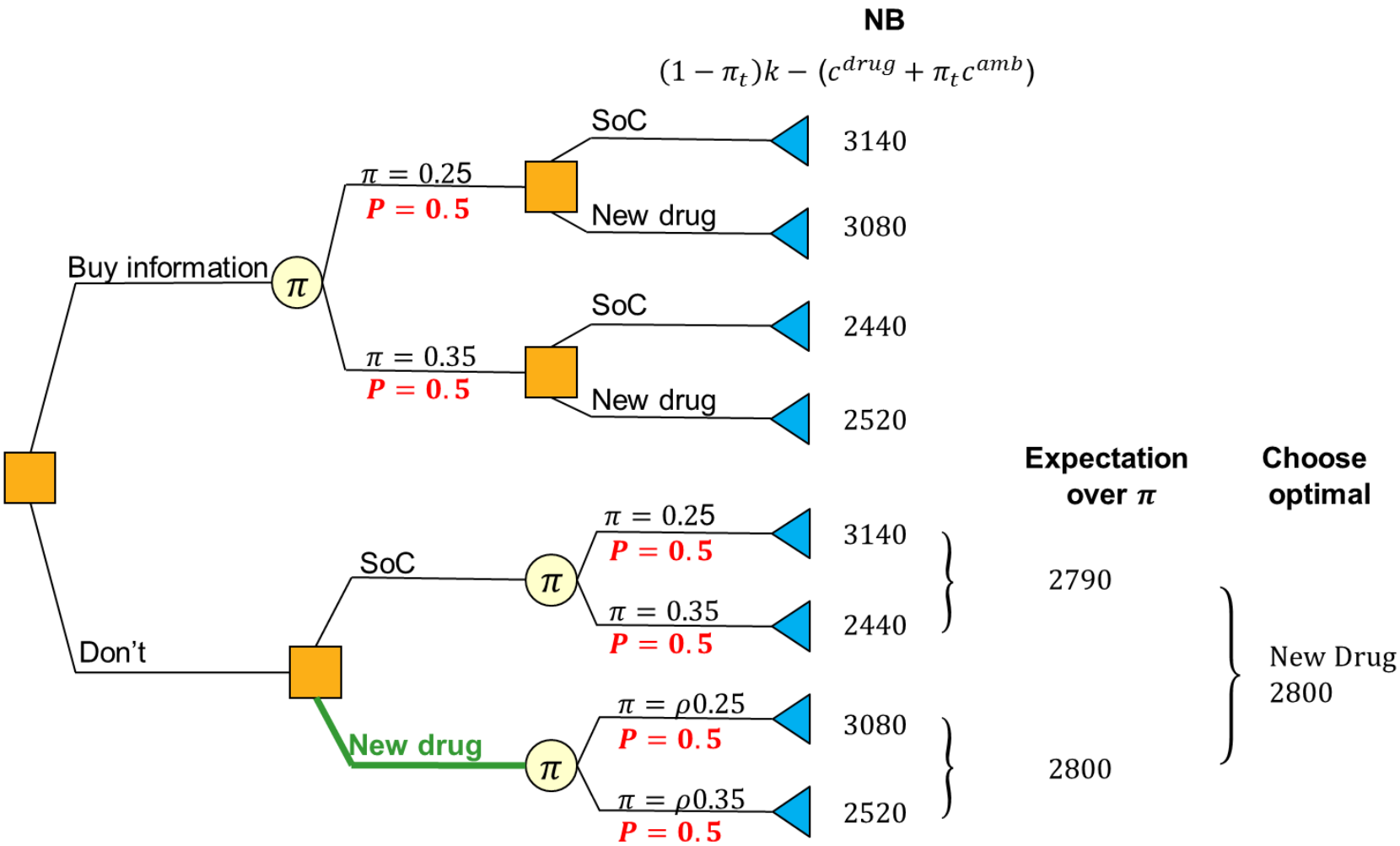

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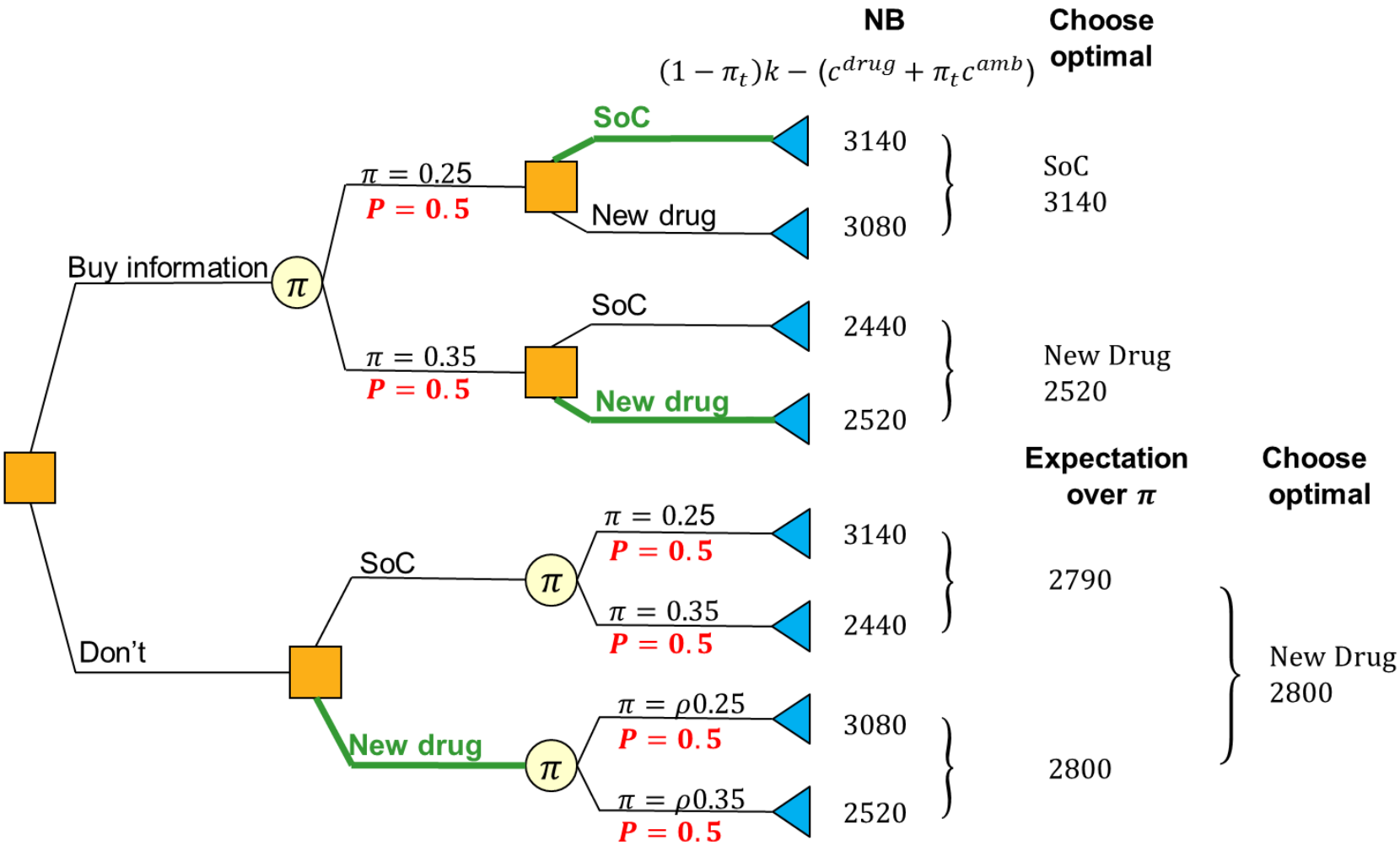

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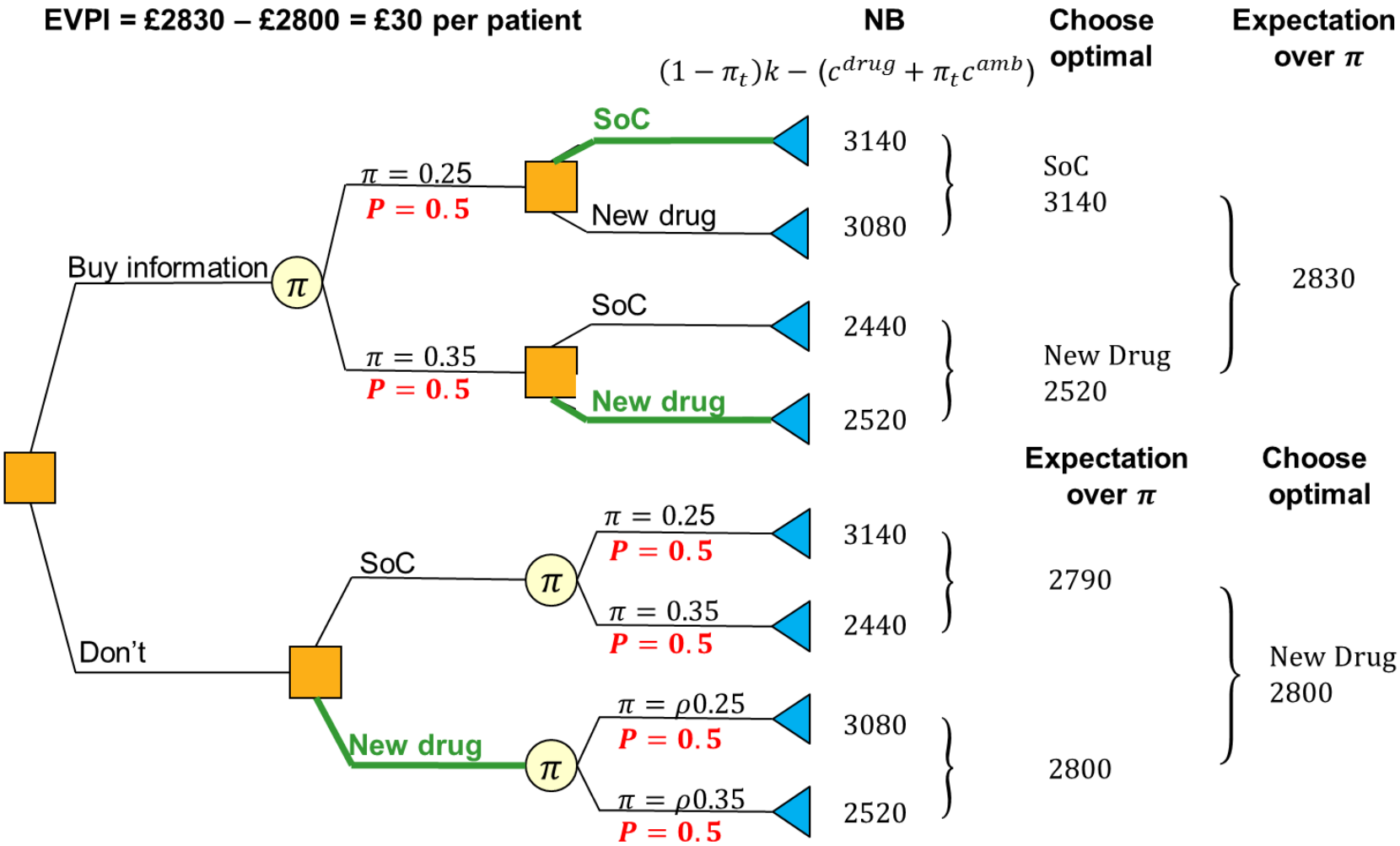

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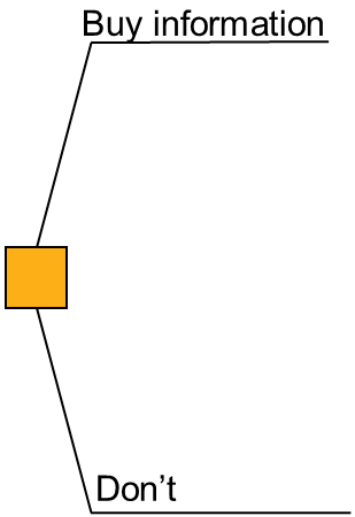

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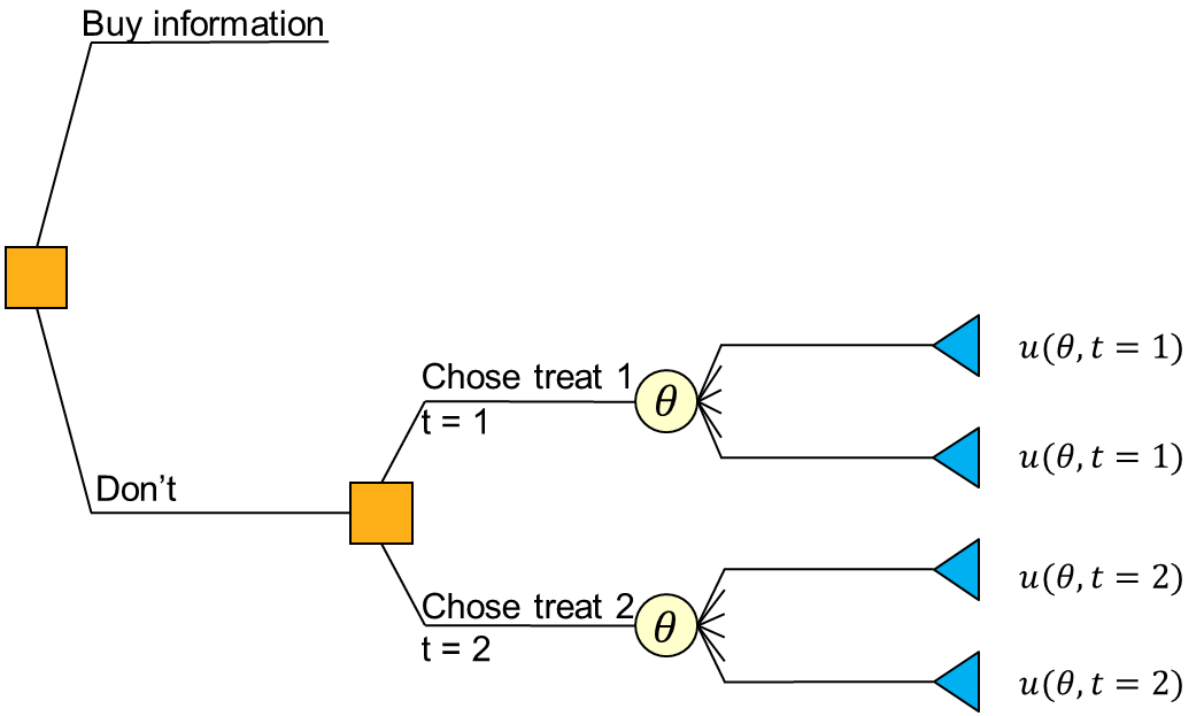

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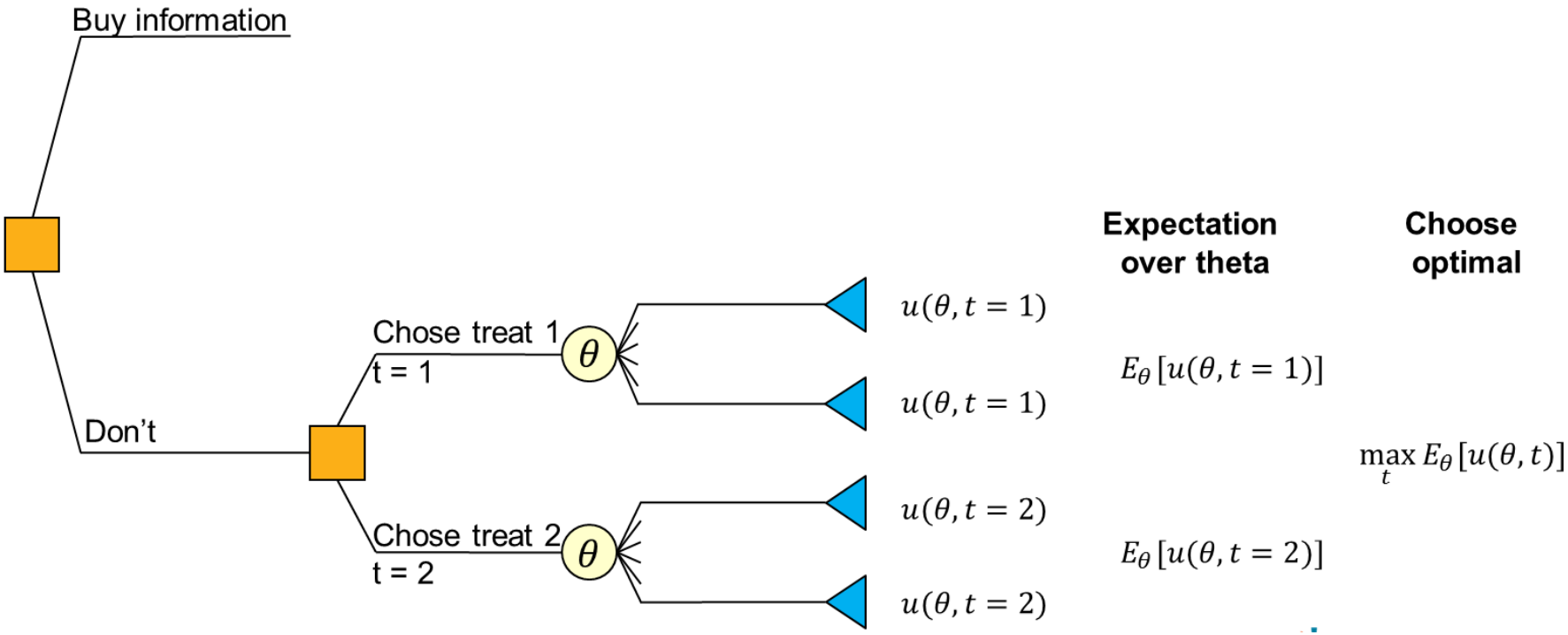

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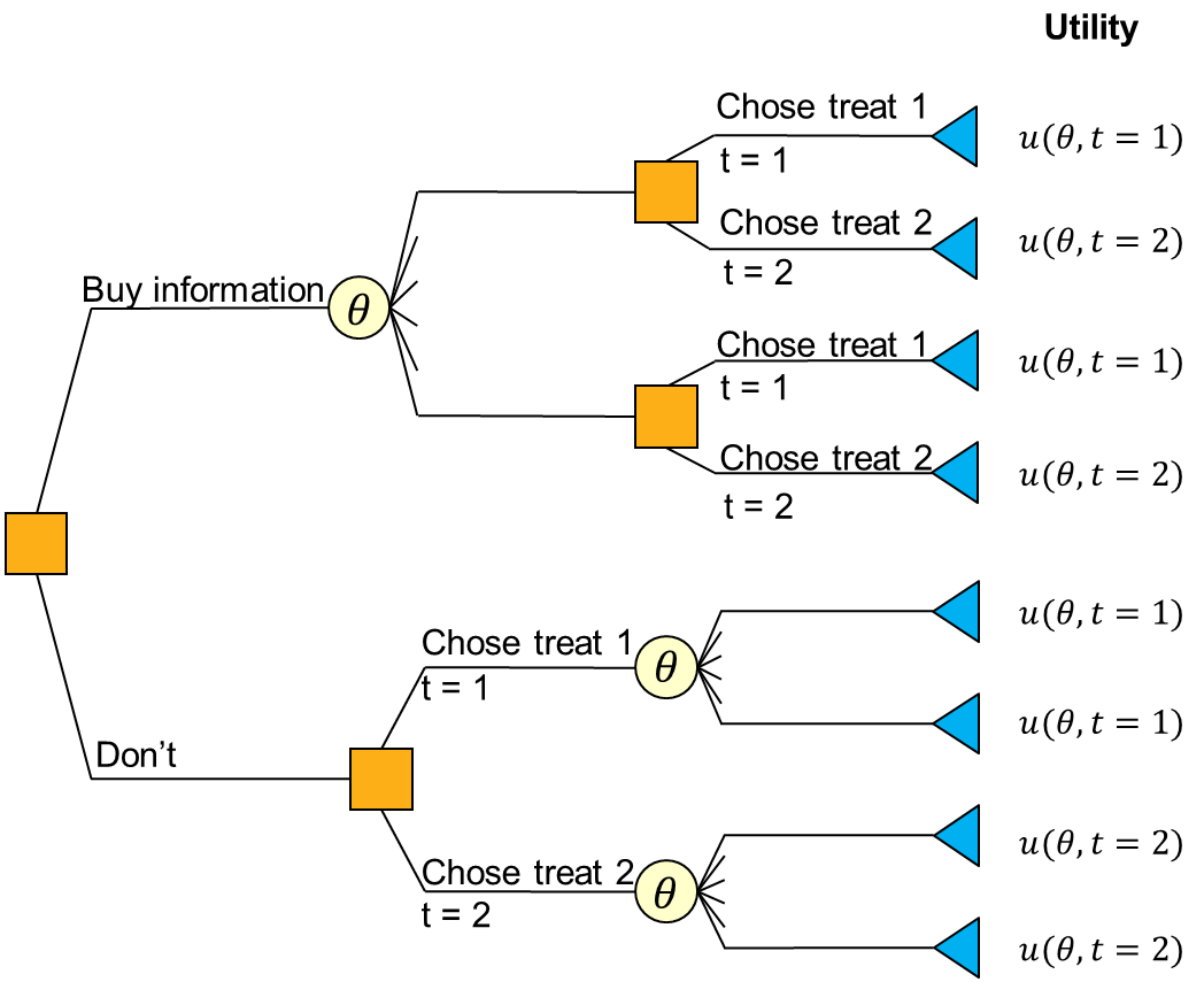
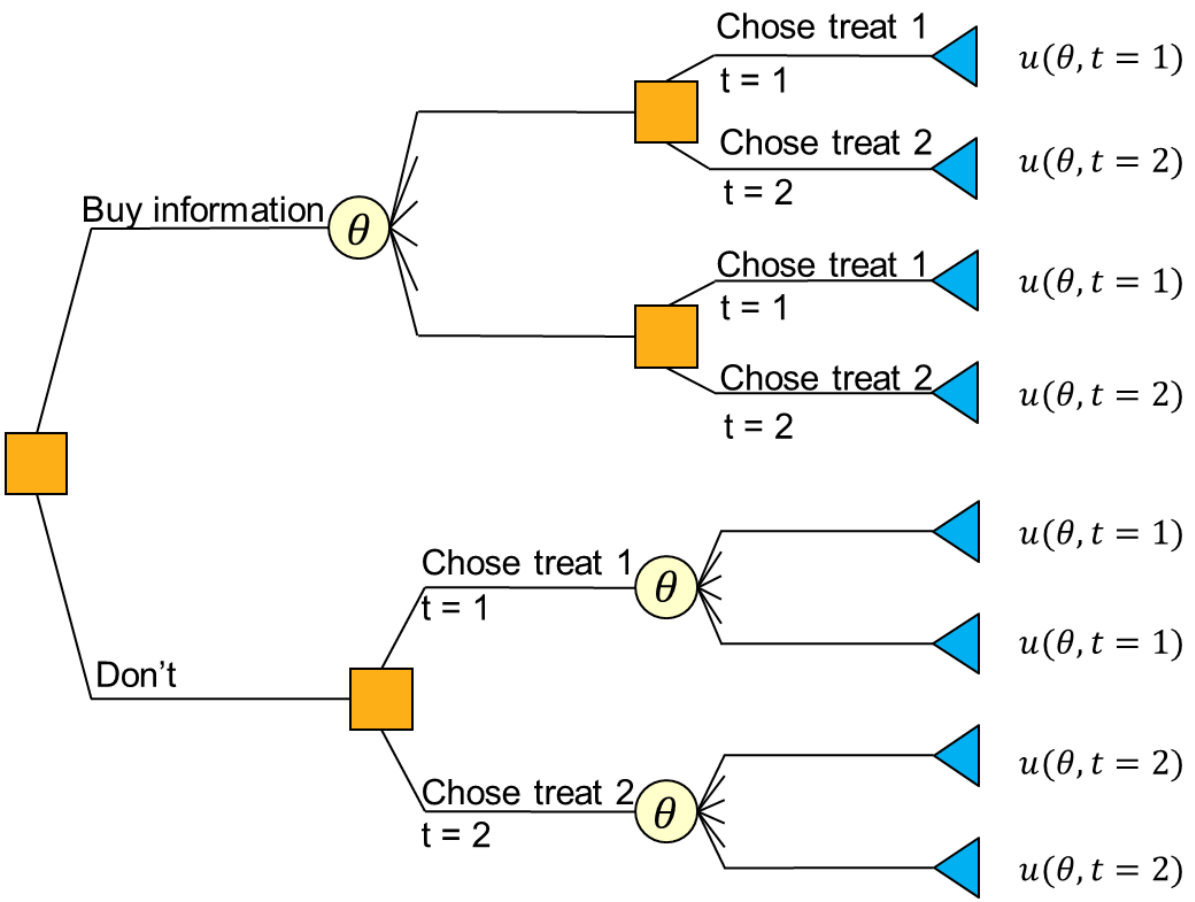


Expected value of perfect information (EVPI)

$$\text{EVPI} = E_\theta\left[\max_t u(\theta, t)\right] - \max_t E[u(\theta, t)]$$



Utility

Choose optimal

$\max_t u(\theta, t)$

$\max_t u(\theta, t)$

Expectation over theta

$E_\theta\left[\max_t u(\theta, t)\right]$

Expectation over theta

$E_\theta[u(\theta, t = 1)]$

$E_\theta[u(\theta, t = 2)]$

Choose optimal

$\max_t E_\theta[u(\theta, t)]$

How to estimate EVPI by simulation

Decide to not buy information
1) Simulate a set of parameters $\theta = \theta_1, \ldots, \theta_I$
2) For each treatment $t_k = t_1, \ldots, t_K$
   a) Find utility of treatment t_k for each θ_i. $u(\theta_i, t_k)$
   b) Estimate $\mathbb{E}_\theta [u(\theta, t_k)]$ by the mean over i of $u(\theta_i, t_k)$
3) The value of the decision is $\max_t \mathbb{E}_\theta [u(\theta, t)]$

Decision to buy information
1) Simulate a set of parameters $\theta = \theta_1, \ldots, \theta_I$
2) For each parameter θ_i
   a) Find utility of θ_i for each treatment $t_k = t_1, \ldots, t_K$. $u(\theta_i, t_k)$
   b) Choose treatment t^* that is $\max_t u(\theta_i, t_k)$
3) Value of decision is $\mathbb{E}_\theta [\max_t u(\theta, t)]$ which is estimated by the mean over i of $\max_t u(\theta_i, t^*)$

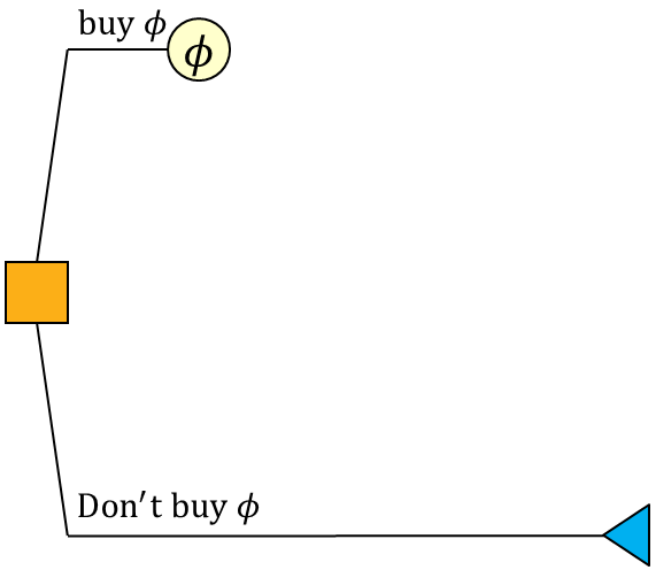
$$EVPI = \mathbb{E}_\theta \left[\max_t u(\theta; t) \right] - \max_t \mathbb{E}_\theta [u(\theta; t)]$$

Expected value of perfect partial information (EVPPI)

- Generally we don't want to know the value of knowing all the parameters exactly, but the value of knowing each parameter (or a group of parameters), exactly.
- Partition the parameters into two groups
  - $\theta = (\phi, \psi)$
- We want to know the value of knowing ϕ perfectly, whilst remaining uncertain about ψ

Expected value of perfect partial information (EVPPI)

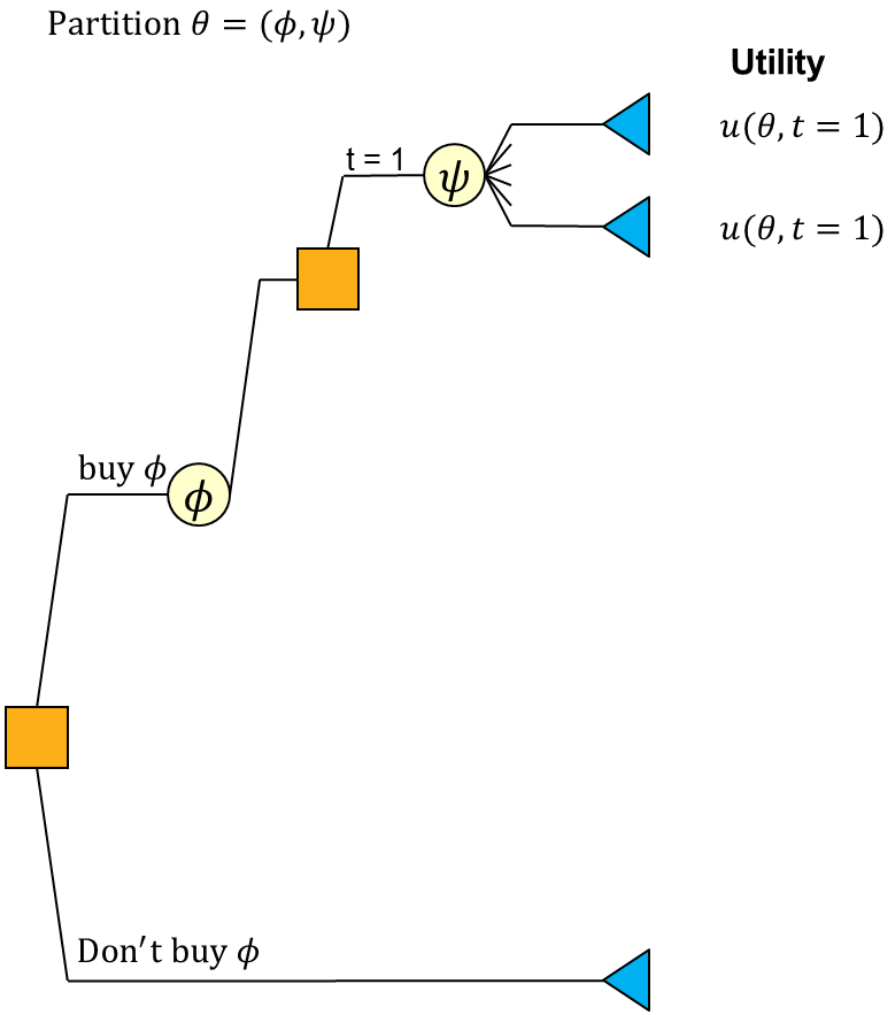
Partition $\theta = (\phi, \psi)$



Current value

$$\max_t E_\theta[u(\theta, t)]$$

Expected value of perfect partial information (EVPPI)



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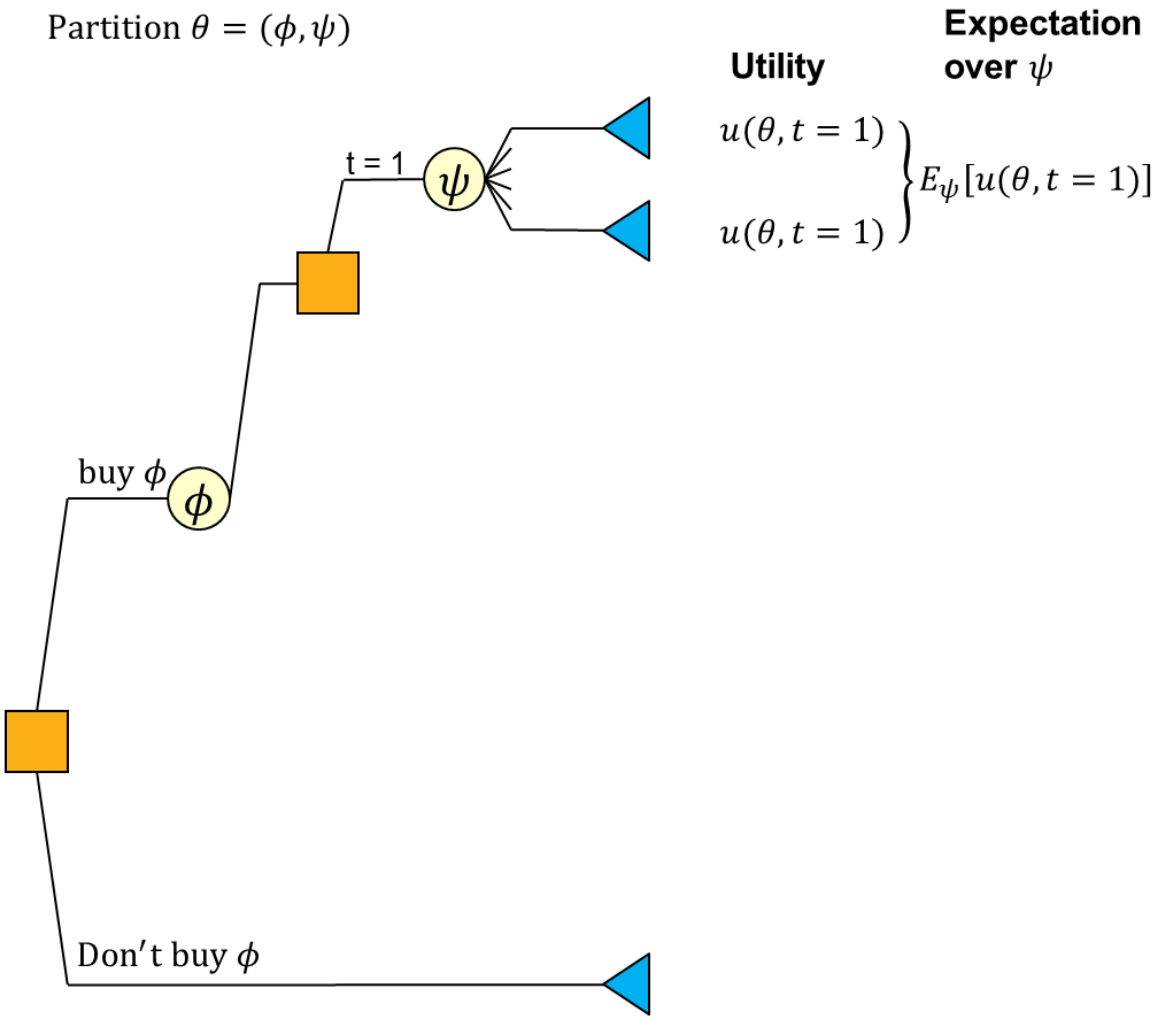

Current value

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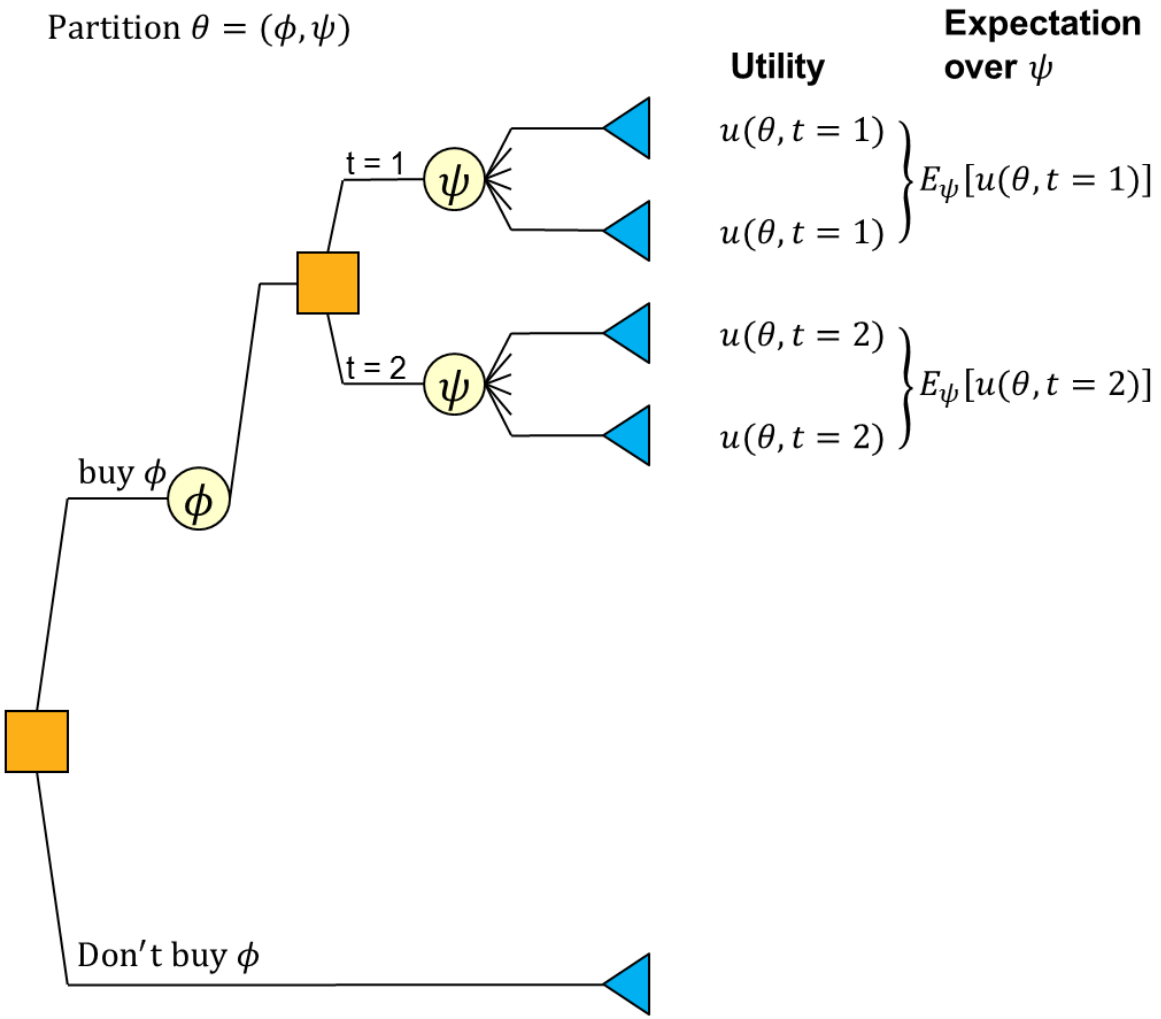

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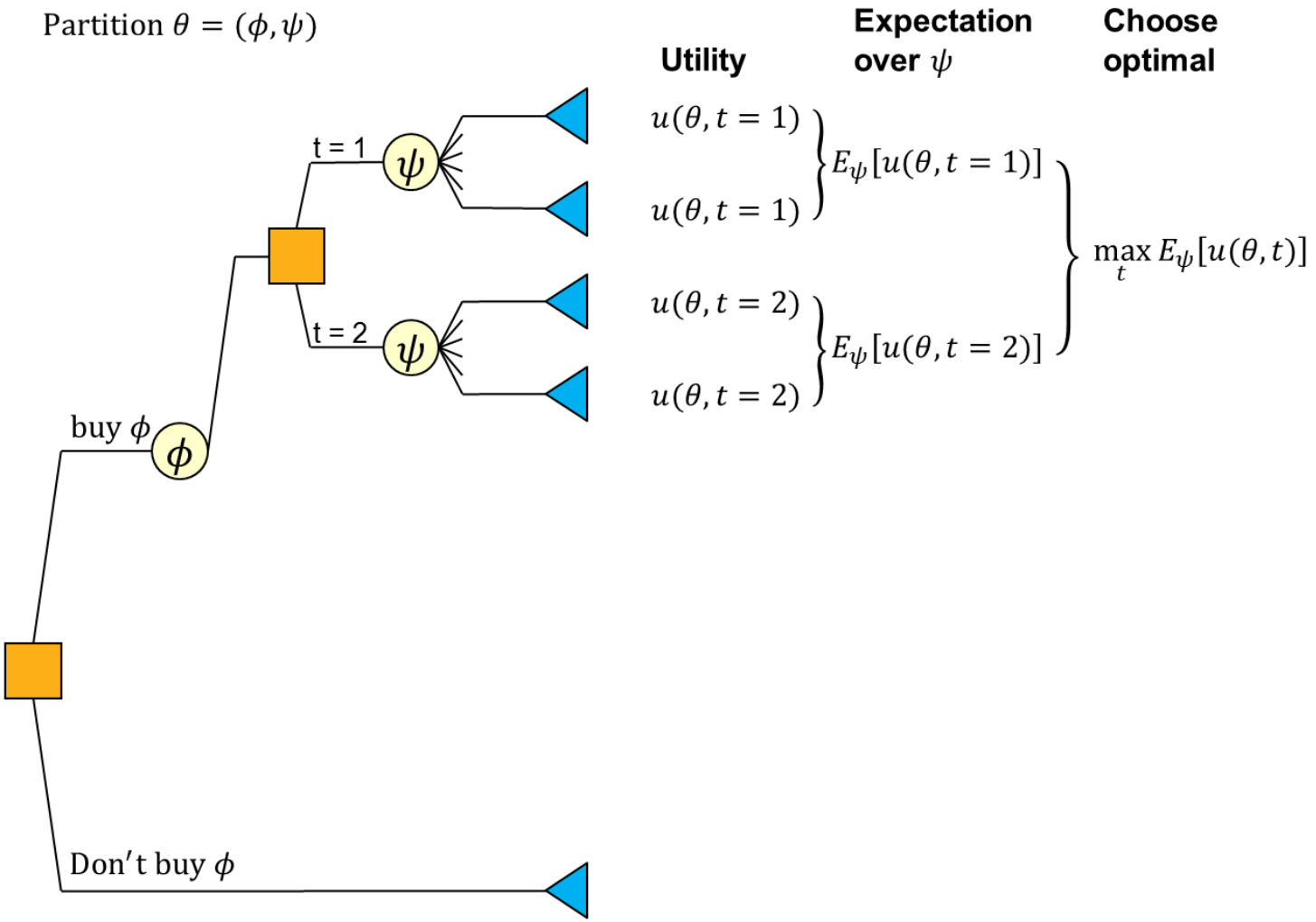

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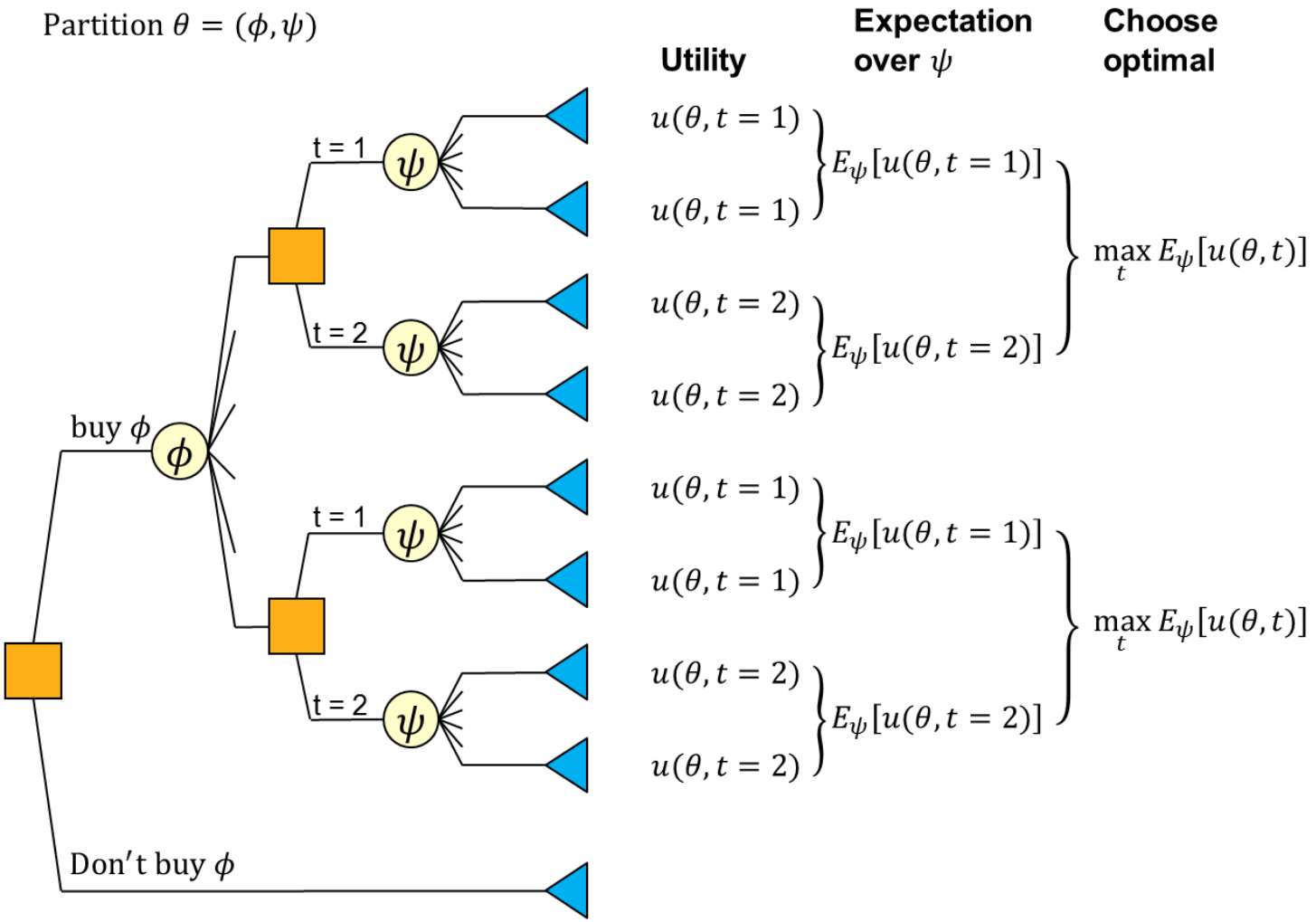

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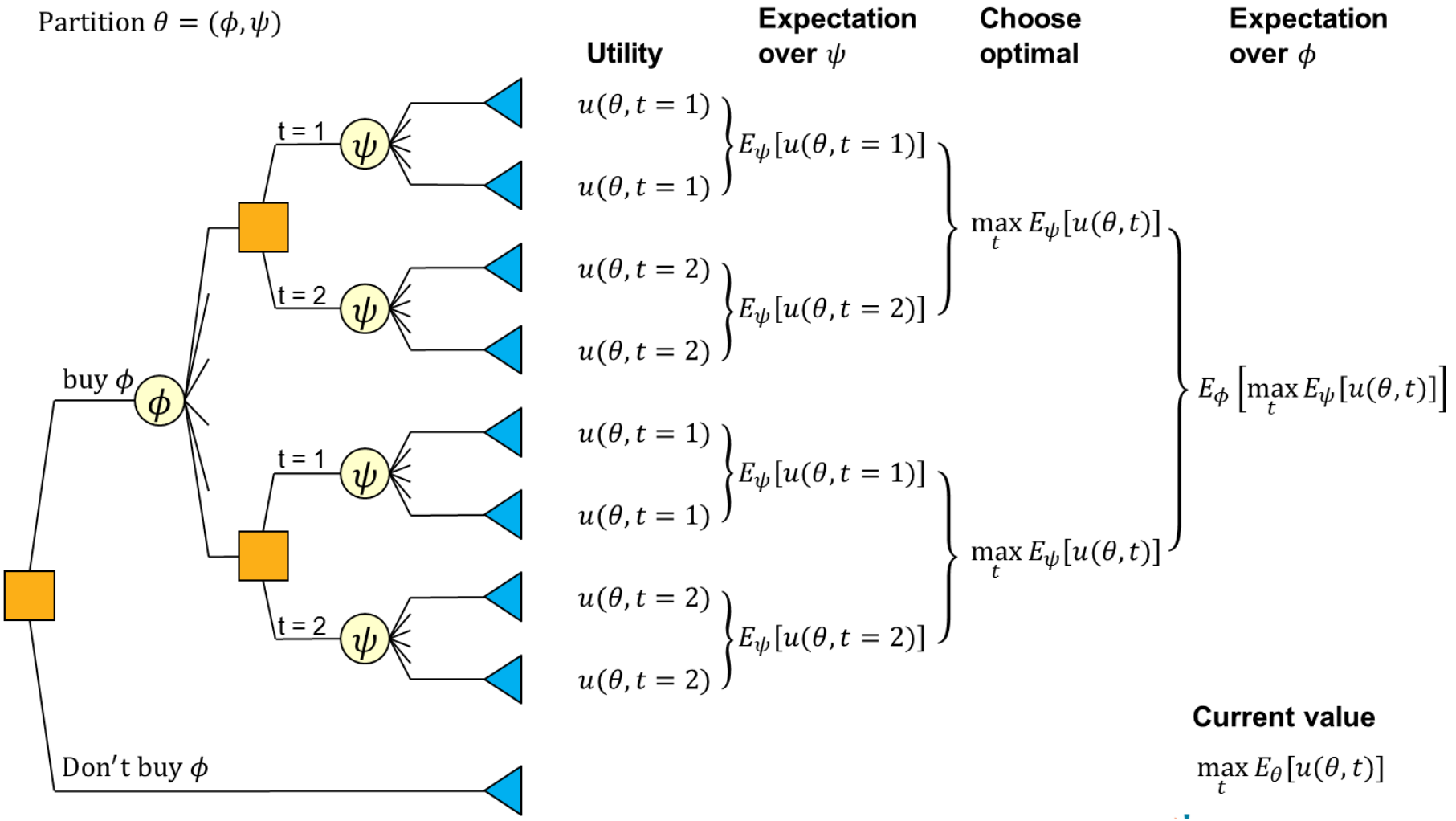


How to estimate EVPPI by simulation

θ is partitioned into (ϕ, ψ)
Decision to buy information on ϕ
1) Simulate a set of parameters $\phi = \phi_1, \ldots, \phi_I$
2) For each parameter ϕ_i
    a) Simulate a set of parameters $\psi = \psi_1, \ldots, \psi_J$
    b) For each treatment $t_k = t_1, \ldots, t_K$
        i) Find utility of treatment t_k for each ψ_j. $u(\phi_i, \psi_j, t_k)$
        ii) Estimate $\mathbb{E}_\psi [u(\phi_i, \psi, t_k)]$ by the mean over j of $u(\phi_i, \psi_j, t_k)$
    c) Choose treatment t^* that is $max_t \mathbb{E}_\psi [u(\phi_i, \psi, t_k)]$
3) Value of decision is $\mathbb{E}_\phi [\max_t \mathbb{E}_\psi [u(\phi, \psi, t)]]$ which is estimated by the mean over i of $\mathbb{E}_\psi [u(\phi_i, \psi, t^*)]$

$$EVPPI = \mathbb{E}_\phi \left[\max_t \mathbb{E}_\psi [u(\phi, \psi; t)] \right] - \max_t \mathbb{E}_\theta [u(\theta; t)]$$

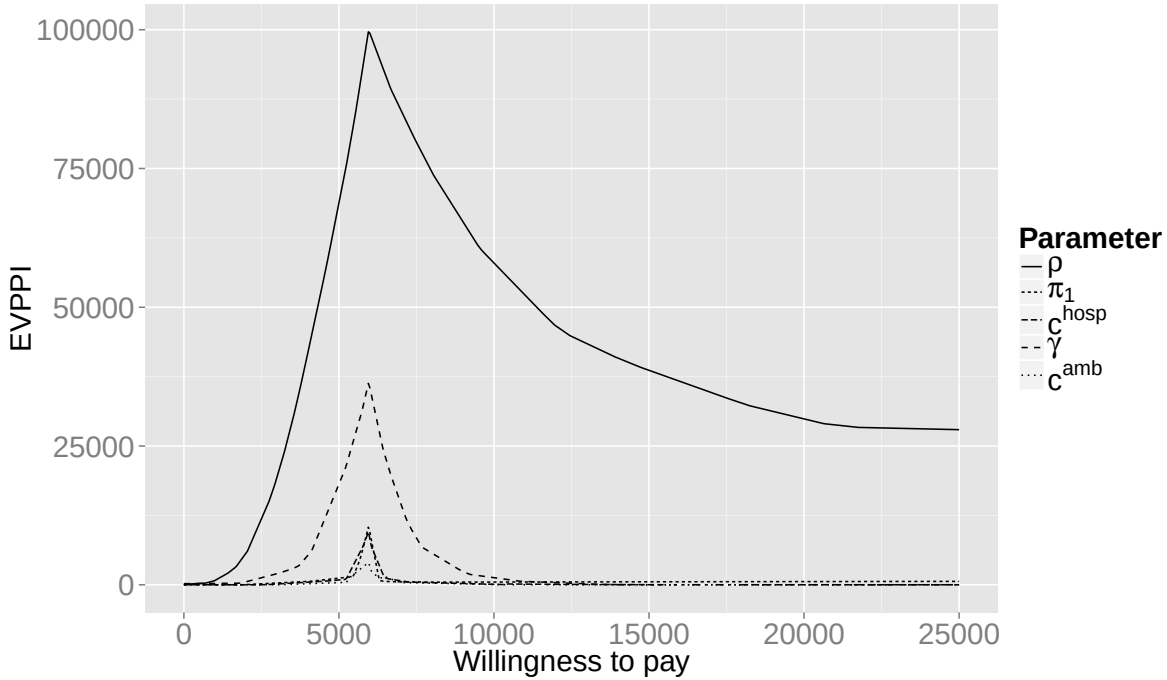
How to estimate EVPPI by simulation

- This algorithm is extremely computationally intensive
- For every simulated value of ϕ, we have to simulate a set of ψ's
- And then repeat this for every parameter, and every WTP threshold
- This means this algorithm is practically infeasible, so approximations have been developed[2]
- These algorithms only need a single set of parameter values, and the corresponding utility values for each treatment
- This is exactly what we get when simulating the expected NB for each treatment in BUGS

Simulation	π_1	ρ	γ	c^{amb}	c^{hosp}	NB_1	NB_2
1	0.15	0.73	0.62	106	5 410	3 654 900	4 049 100
2	0.23	0.78	0.57	146	4 705	3 259 200	3 134 300
3	0.28	0.72	0.65	113	5 858	3 095 200	3 041 100
4	0.27	0.74	0.62	99	6 448	2 588 300	2 755 000
5	0.24	0.89	0.44	107	5 225	2 968 300	2 778 000

[2] Strong and Oakley (2013). Sadatsafavi et al. (2013).

EVPPI plot



- The greatest value in reducing parameter uncertainty are from the parameters
  - ρ Probability of side effect given new treatment compared to SoC
  - π_1 Probability of side effect given SoC
- There is relatively little value in reducing the uncertainty in the other parameters

Appling value of information in a pharmaceutical contex

- From a public policy perspective total Net benefit in the population is an appropiate utility measure.
  - Net benefit = population size x (QALY x WTP - Cost)
- From an industry perspective it is an investment decision so eNPV is an appropiate utility measure.
  - eNPV = NPV | reimbursed x p(reimbursed)
  - p(reimbursed) = p(registered) x p(reimbursed | registered)
  - p(reimbursed | registered) = p(INB $>$ 0)
- Sum over all countries with value based pricing.
- This will also give the value of information for parameters in the market model needed to estimate the NPV.