Sensitivity Analyses for Decision Modeling

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Content

- Why sensitivity analyses?

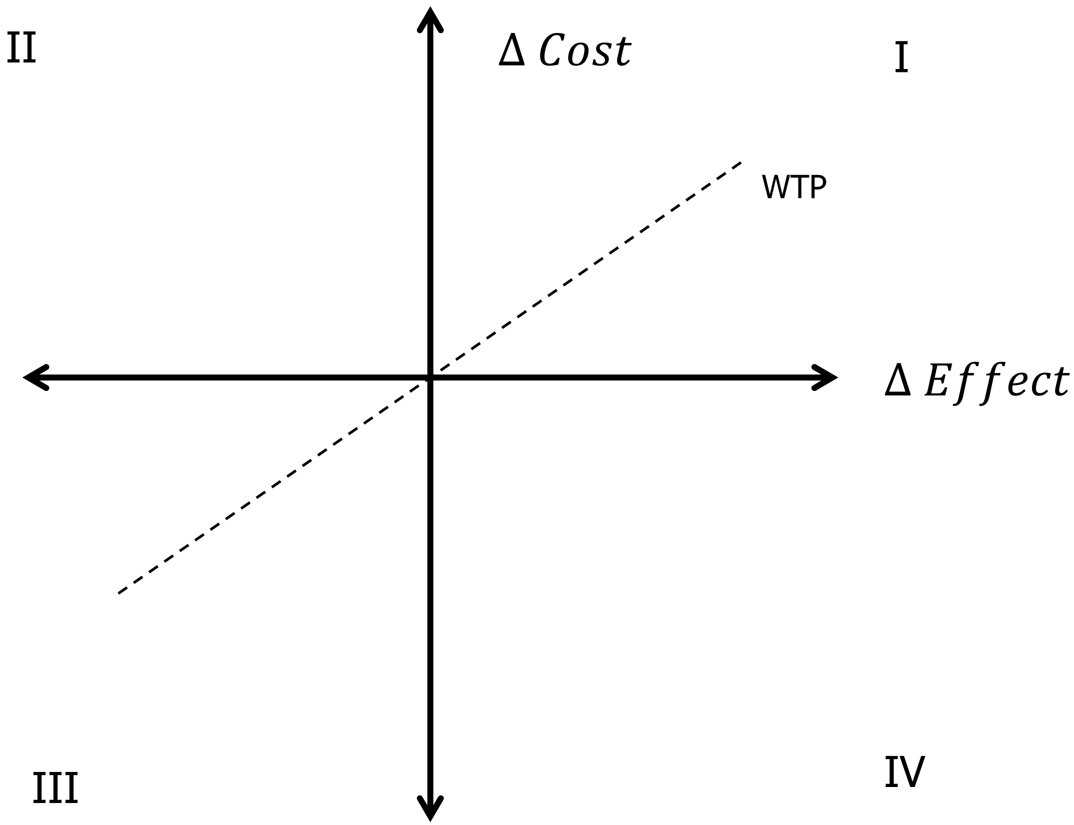
- Types of Sensitivity Analyses
  - One-way sensitivity Analyses
  - Tornado Diagrams
  - Scenario Analyses
  - Probabilistic Sensitivity Analyses

Output of a Decision Model

Type of Model	Output
Budget Impact Model	*Cost per strategy*
Cost Benefit Model	*Net social benefit = Incremental Benefit (cost) – Incremental Costs*
Cost-Effectiveness Model	$ICER = \frac{\Delta\, cost}{\Delta\, health\ effect}$
Cost-utility Model	$ICER = \frac{\Delta\, cost}{\Delta\, QALYs}$

Point Estimates

Cost-effectiveness Model quadrants



Poll: Which quadrant represents a cost-effective strategy?

Cost-effectiveness Model quadrants

Quadrant I:

- More costly and more effective

  (if below WTP)

Quadrant II:

- More costly and less effective

  (No)

Quadrant III:

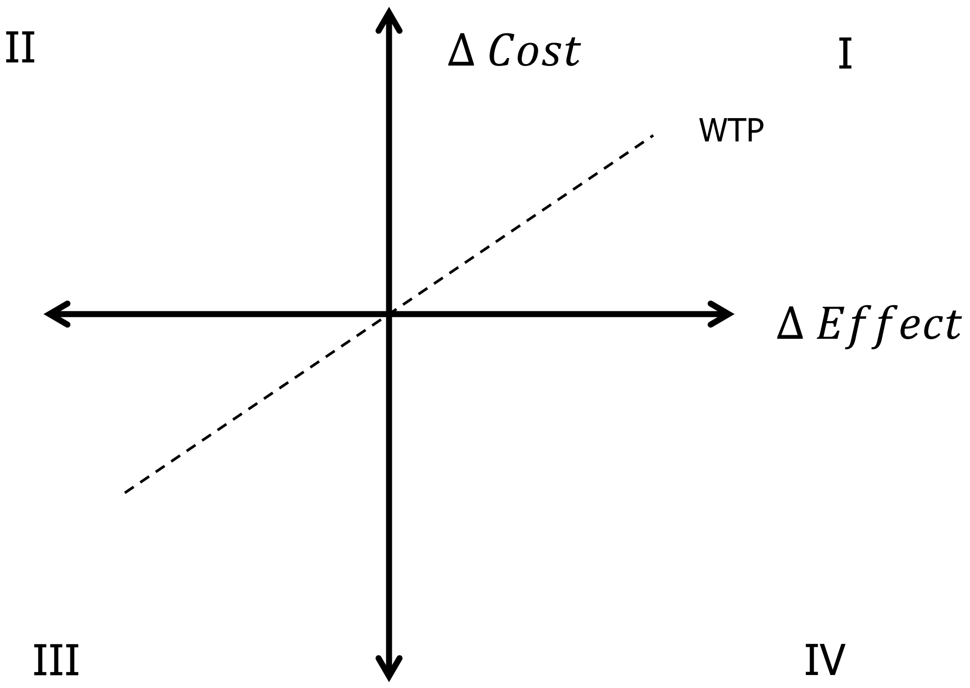
- Less costly and less effective

  (If below WTP)

Quadrant IV:

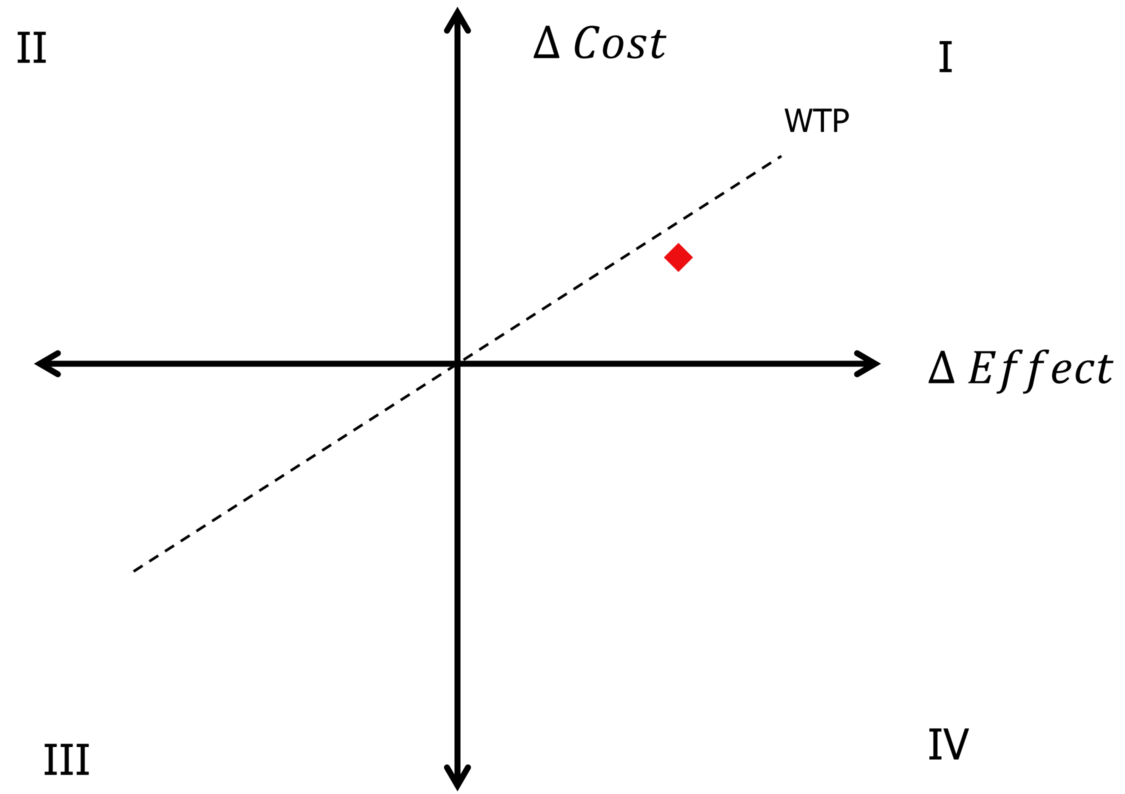
- Less costly and more effective

  (Yes!)

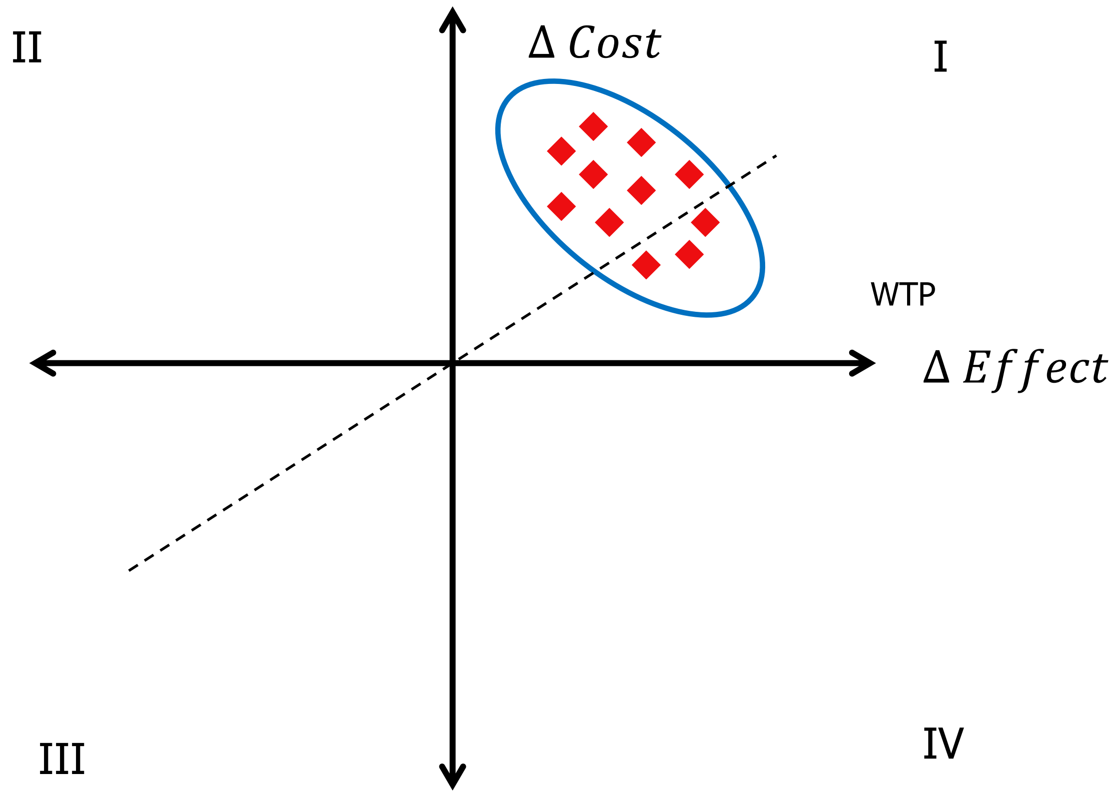


Poll 2

Would you recommend to adopt a new technology, based on this ICER result?



Cost-effectiveness Model output



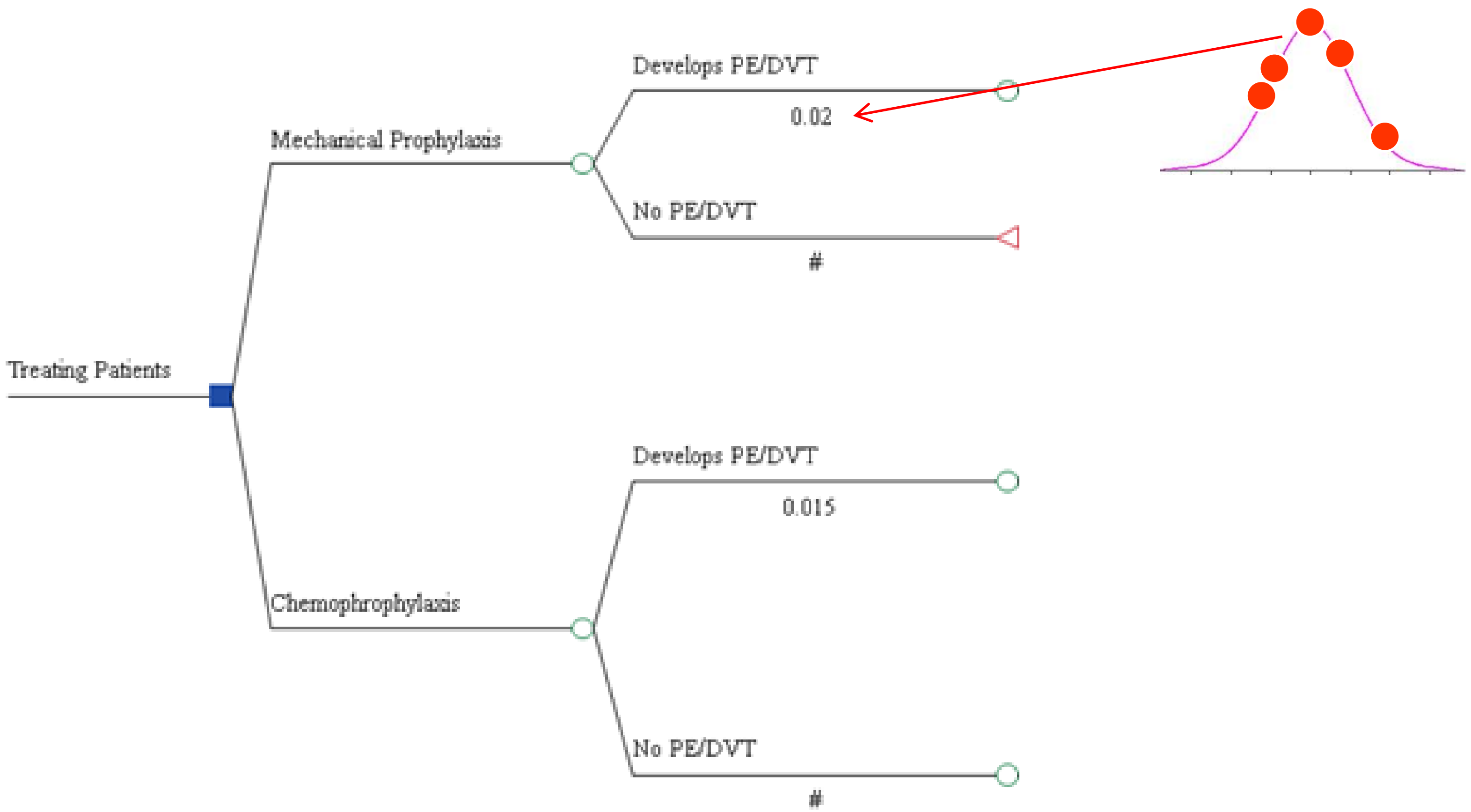
Variation in your ICER may cause your decision to change

Why sensitivity analysis?

- Evaluate how uncertainty in model inputs affects the model outputs
  - Base-case model → ICERs
  - Sensitivity Analyses → Variation in ICER

Statistical Analysis	Cost Effectiveness Analysis
Mean	ICER (Base-Case)
Variation around Mean	Variation around ICER

Varying point estimates
(TreeAge model)



General Approach, Sensitivity Analysis

1. Change model input

2. Recalculate ICER

3. If new ICER is substantially different from old ICER → model is sensitive to that parameter
   - *In this case, it is very important to be accurate about this parameter!*

Types of inputs

- **Cost**

- **Health Effect**
  - Life Years Saved
  - Utilities
  - Cases of Disease Avoided
  - Infections Cured

- **Probabilities**

- **Discount Rate**

Types of Uncertainty

Term
Stochastic Uncertainty
Parameter Uncertainty
Heterogeneity

Briggs et al. 2012 Model Parameter Estimation and Uncertainty:
A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force – 6.
Value in Health, 15: 835-842.

Types of Uncertainty

Term	Models	AKA	Analagous term in regression	Example
Stochastic Uncertainty	Variation between identical patients	- First-order uncertainty - microsimulation	Error term	19% of Medicare beneficiaries readmitted to the hospital within 30 days. Person 1 = readmitted, Persons 2, 3, 4, 5 = not readmitted
Parameter Uncertainty	Uncertainty in estimation of parameter of interest	- Second-order uncertainty - PSA	Standard Error of the estimate	Toss a fair coin 100 times. You get 55 “heads” and 45 “tails”
Heterogeneity	Differences in patient characteristics	- Observed heterogeneity - variability	**B**eta-coefficients/test of sig. amongst different levels of a covariate	Drug is cost-effective for people with moderate disease, but is not cost-effective for people with mild or advanced disease

Briggs et al. 2012 Model Parameter Estimation and Uncertainty:
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Value in Health, 15: 835-842.

Types of Sensitivity Analyses

Types of Sensitivity Analyses

- One-way sensitivity Analyses
- Tornado Diagrams
- Scenario Analyses
- Probabilistic Sensitivity Analyses

} Often Deterministic (first three)

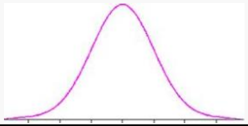
Types of Sensitivity Analyses

- **Deterministic (DSA)**
  - model input is specified as multiple point estimates (sequentially) and varied manually

- **Probabilistic (PSA)**
  - model inputs are specified as a distribution and varied

DSA versus PSA

Example: Cost input, cost of outpatient visit

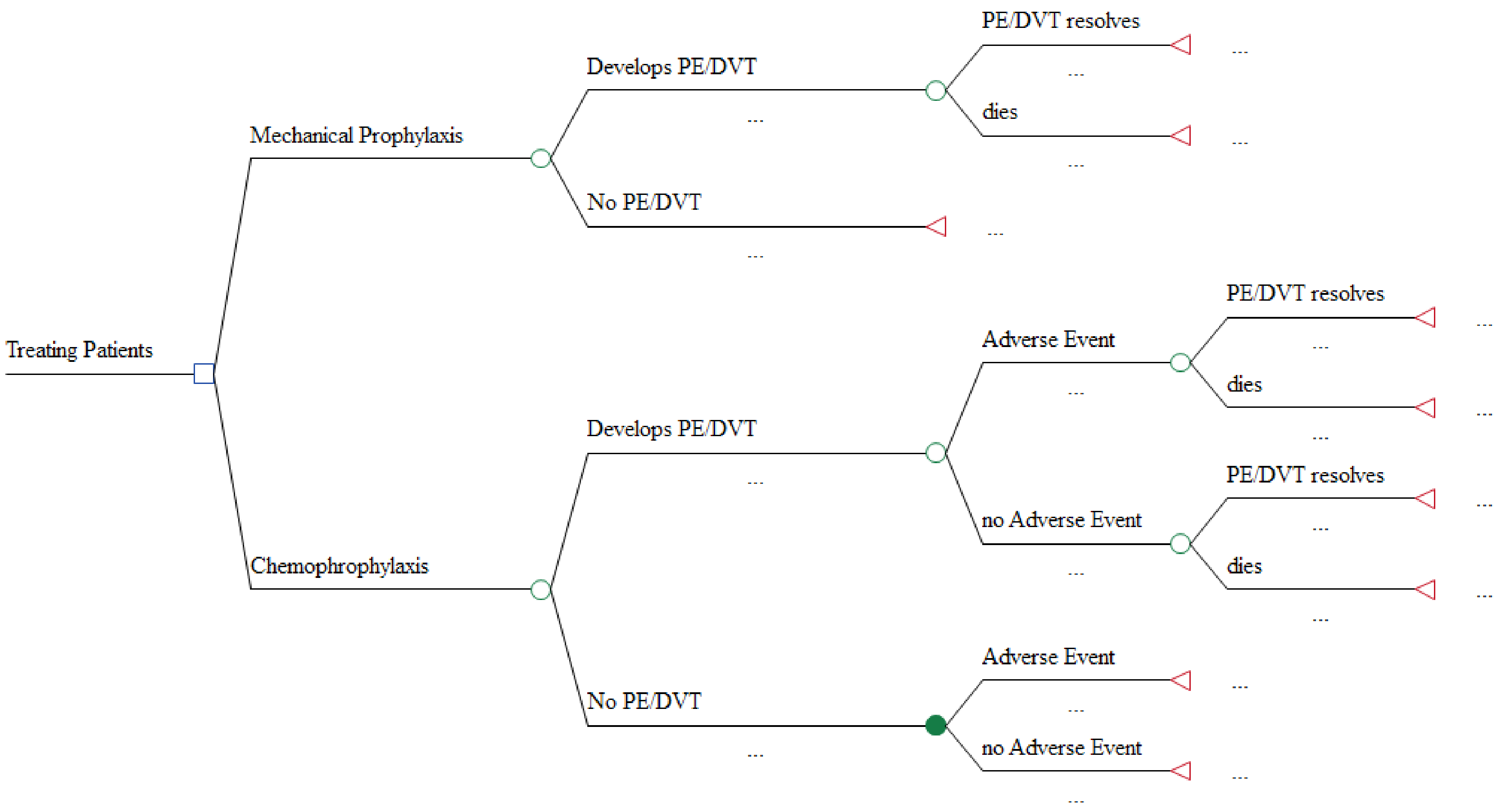
	DSA	PSA
Base case	$100	$100
Input	$80, $90, $110, $120	
Results	ICER A (when cost is $80) ICER B (when cost is $90) ICER C (when cost is $110) ICER D (when cost is $120)	The mean ICER when we vary the base-case using a normal distribution with a mean of $100 and standard deviation of $10 is X, using 1000 iterations

DSA, PSA and Model structure

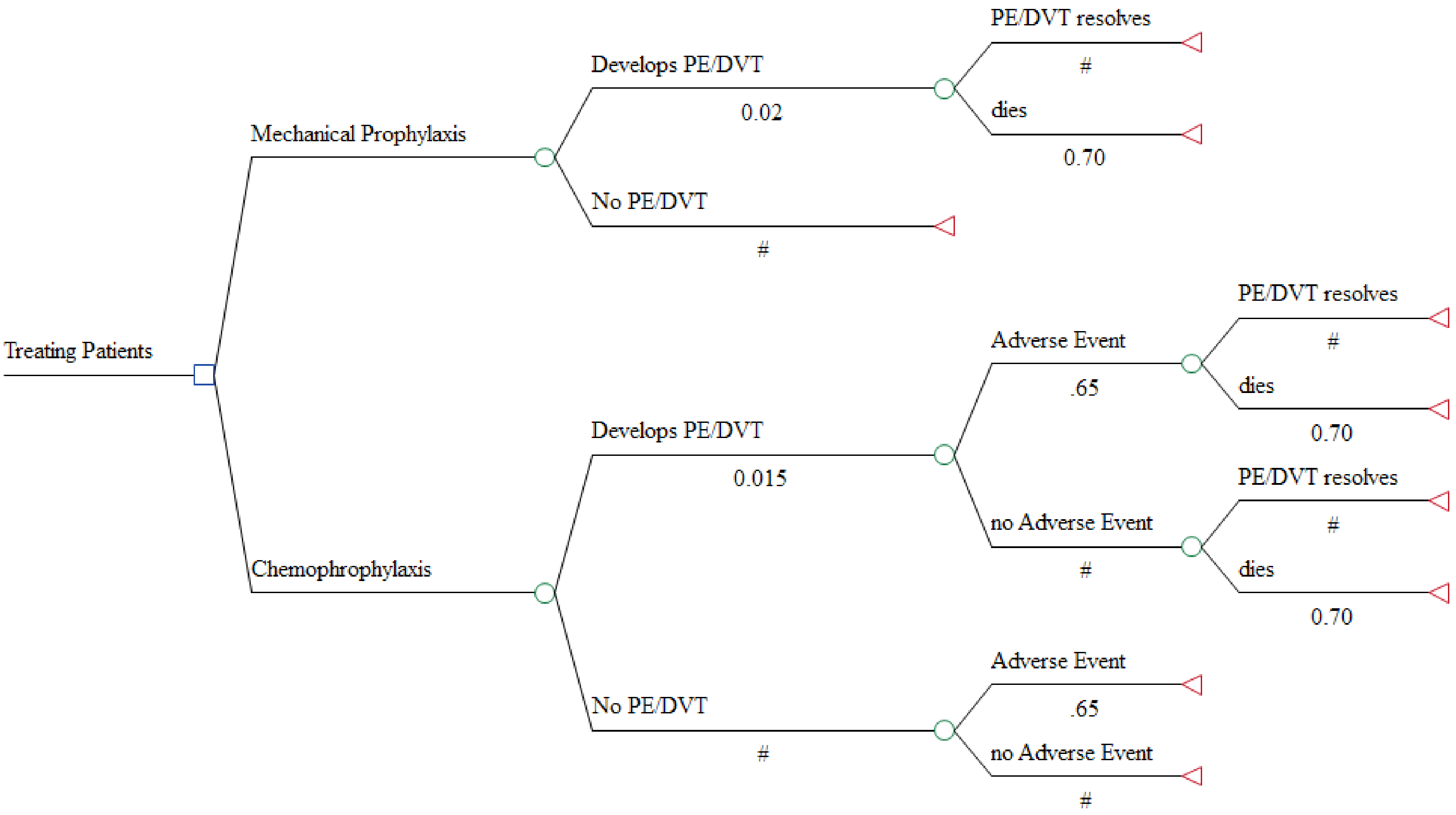
	DSA	PSA
Markov Cohort	X	X
Individual-level Markov Model	X	X
Discrete-Event Simulation	X	X

Sensitivity Analyses in TreeAge

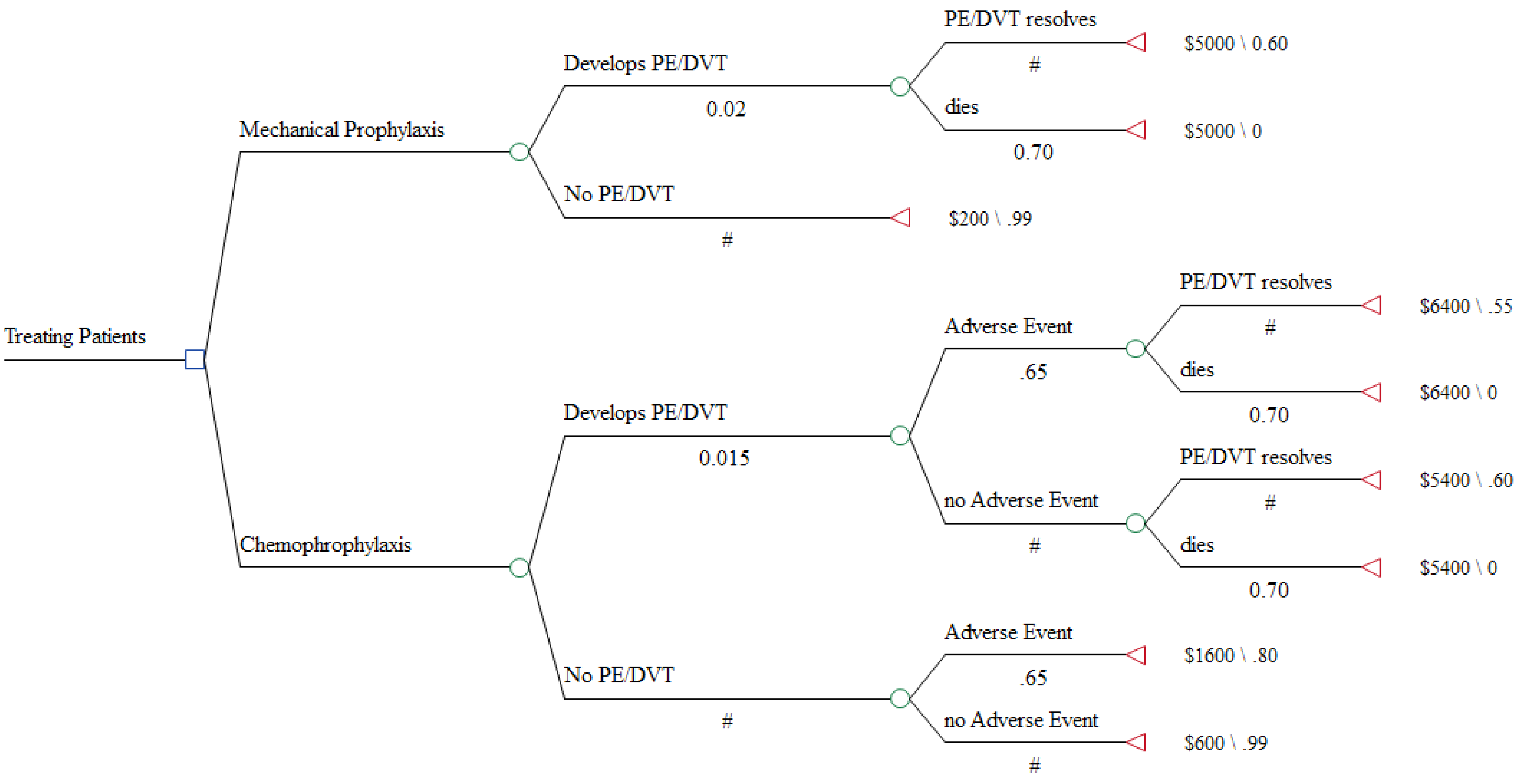
PE/DVT example



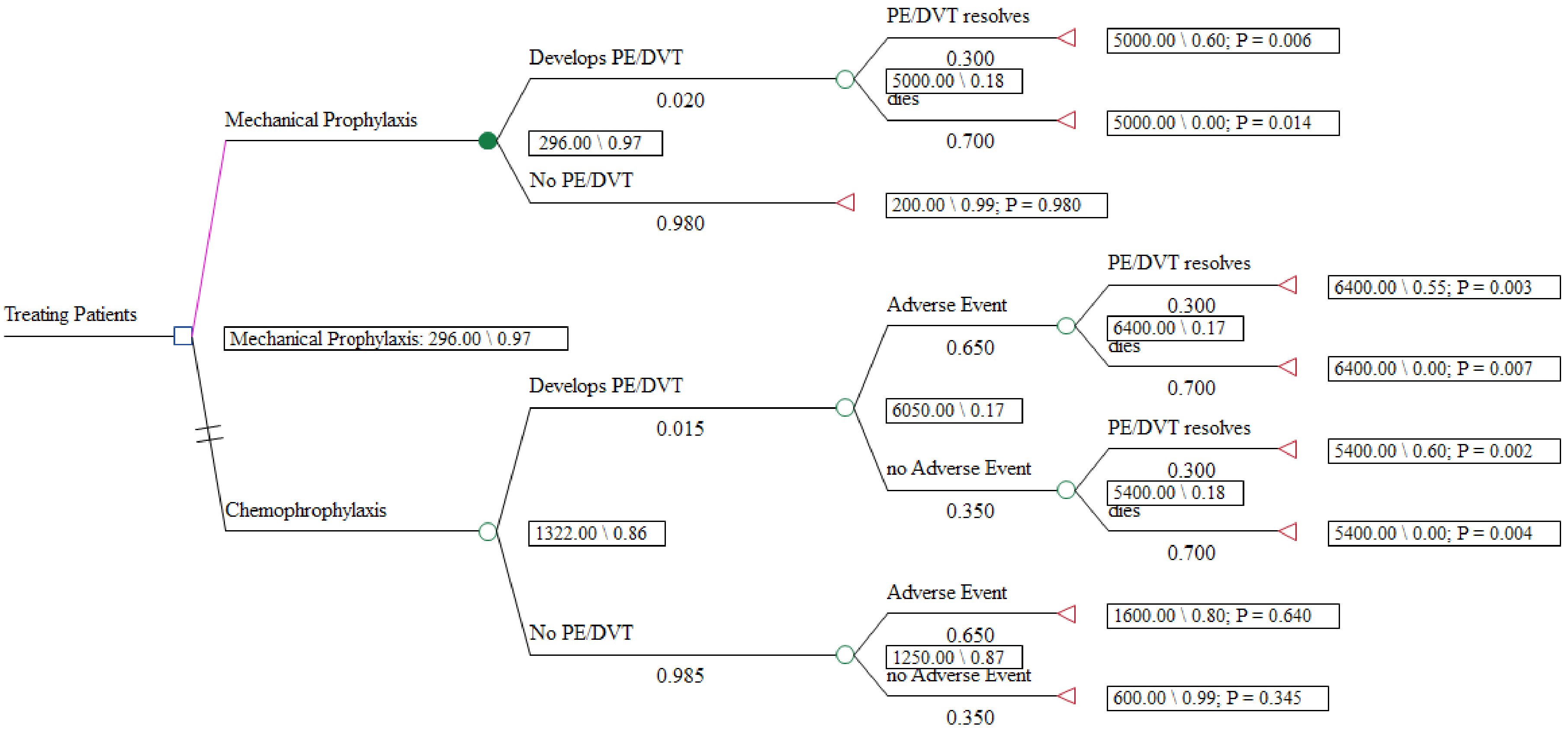
PE/DVT example – Hypothetical Probabilities



PE/DVT example – Hypothetical full inputs



Model results, with point estimates



One-Way Sensitivity Analyses

One-way sensitivity analysis

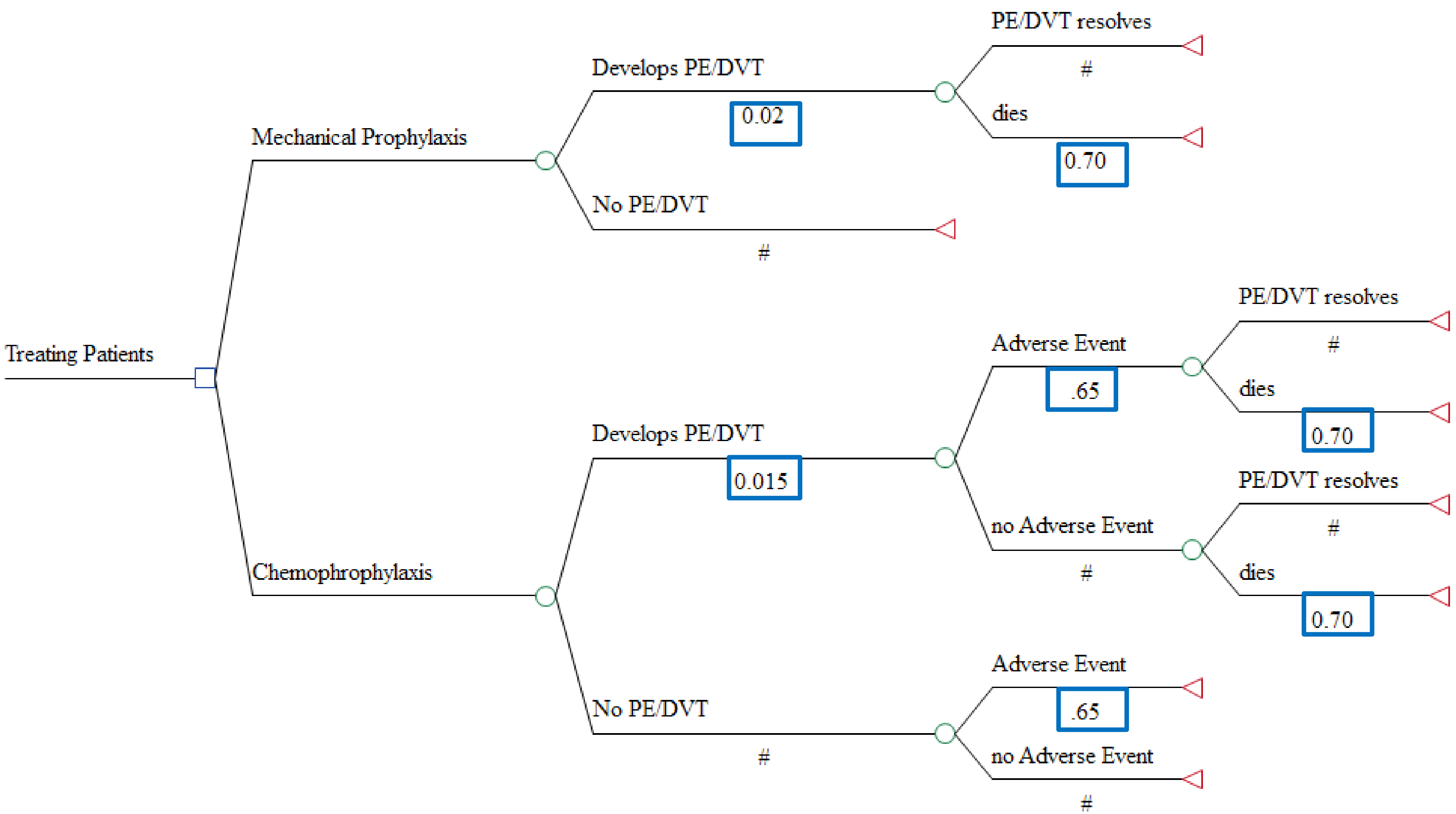
- Vary one input (parameter) at a time, and see how model results are affected
- Deterministic Example: probability of AE_chemo
  - Base-case: 0.02
  - Sensitivity analysis: range from 1-8%
    - Run 8 models, each with the following input: 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08
- Probabilistic Example
  - Base-case: 0.02
  - Sensitivity analysis: insert a *distribution*, each iteration selects a single value from this distribution to be used as the Prob of AE_chemo

Inputting variables to run a sensitivity analysis: best Practices

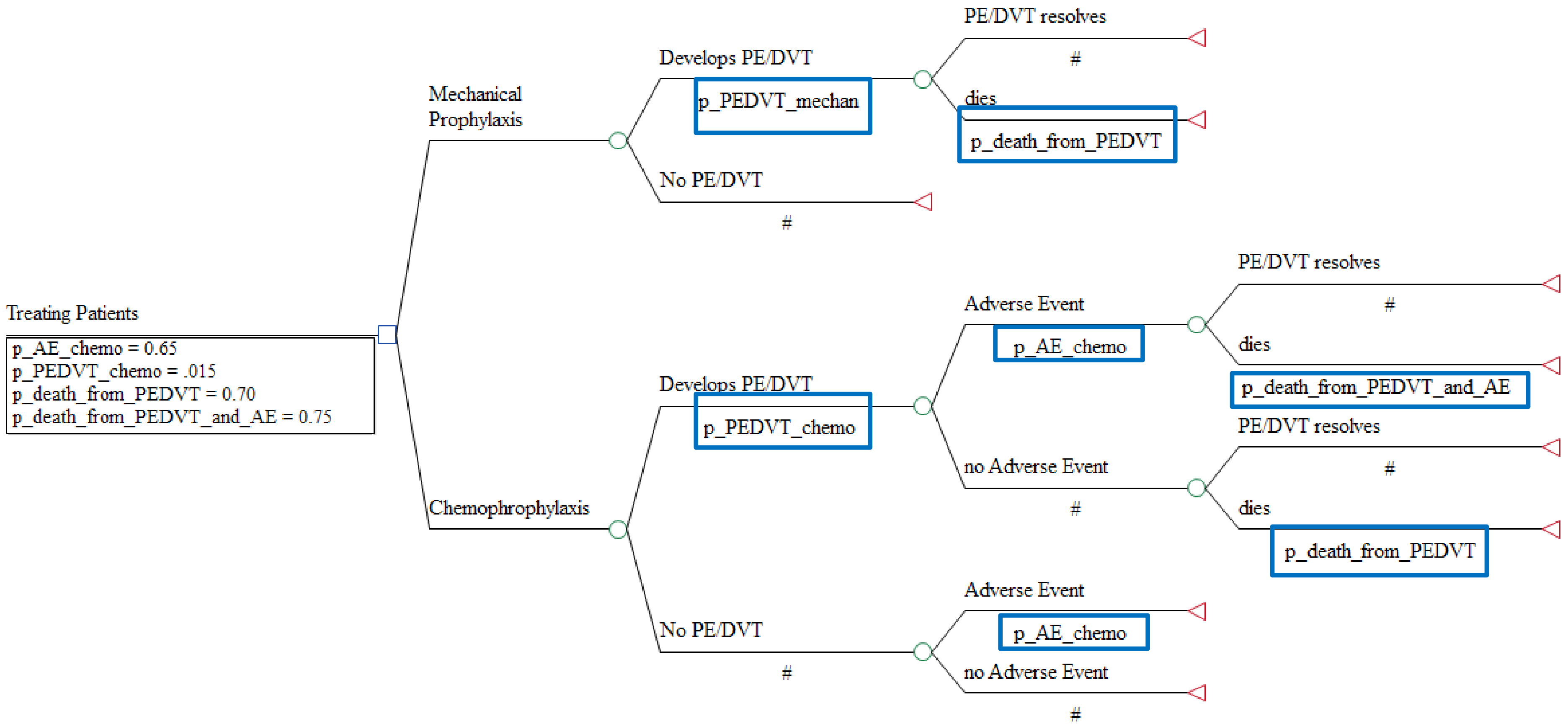
1. **Insert variables, not point estimates**
   - Example: probability of PE, mechanical prophylaxis
     - "0.02" (Point estimate)
     - "p_PEDVT_mechan" (Variable)

2. **Then, define variables** as:
   - Point estimates (DSA) or
   - Distributions (PSA)
   - Example: definition of probability of PE/DVT, mechanical
     - Defining variable as a point estimate: "p_PEDVT_mechan = 0.02"
     - Defining variable as a distribution: "p_PEDVT_mechan = dist_death"

PE/DVT example – Probabilities as Point Estimates



PE/DVT example – Probabilities as Variables and Variables defined as Point Estimates



One-way sensitivity analyses

Define your range

One-Way Sensitivity Analysis Setup

Variable	Low value	High value	Intervals	Definitions	Correlations
p_AE_chemo	0.4	0.8	4	[Treating Patients: 0....	

Output, one-way sensitivity analyses

Sensitivity Cost Effectiveness Analysis

p_AE_chemo	Strategy	Cost	Incr cost	Eff	Incr Eff	C/E	Incr C/E (ICER)	Dominance
0.4								
	Mechanical Prophylaxis	296.00	0.00	0.97	0.00	303.96	0.00	
	Chemophrophylaxis	1072.00	776.00	0.90	-0.07	1187.50	-10919.58	(Dominated)
0.5								
	Mechanical Prophylaxis	296.00	0.00	0.97	0.00	303.96	0.00	
	Chemophrophylaxis	1172.00	876.00	0.88	-0.09	1325.86	-9750.26	(Dominated)
0.6								
	Mechanical Prophylaxis	296.00	0.00	0.97	0.00	303.96	0.00	
	Chemophrophylaxis	1272.00	976.00	0.87	-0.11	1470.22	-8985.25	(Dominated)
0.7								
	Mechanical Prophylaxis	296.00	0.00	0.97	0.00	303.96	0.00	
	Chemophrophylaxis	1372.00	1076.00	0.85	-0.13	1620.99	-8445.76	(Dominated)
0.8								
	Mechanical Prophylaxis	296.00	0.00	0.97	0.00	303.96	0.00	
	Chemophrophylaxis	1472.00	1176.00	0.83	-0.15	1778.59	-8044.88	(Dominated)

Inputs for a one-way sensitivity analysis

- Range from reported 95% Confidence Interval
- Varying a parameter an arbitrary range, such as ± 50% -- not a great practice
  - This will demonstrate model sensitivity, but does not reflect uncertainty
- Expert Opinion

Series of One-way Sensitivity Analyses

1) Vary probability of chemoprophylaxis-related adverse event
   a. Compare these ICERs to base-case ICER
2) Vary cost of treating adverse event
   a. Compare these ICERs to base-case ICER
3) Vary probability of death from PE/DVT
   a. Compare these ICERs to base-case ICER
4) Etc.

Caution

- Generally, a series of one-way sensitivity analyses will underestimate uncertainty in a cost-effectiveness ratio:
  - The ICER is based off of multiple parameters, not just one
  - Here, you are assuming that uncertainty exists only in one parameter
  - Solution: Probabilistic Sensitivity Analyses!

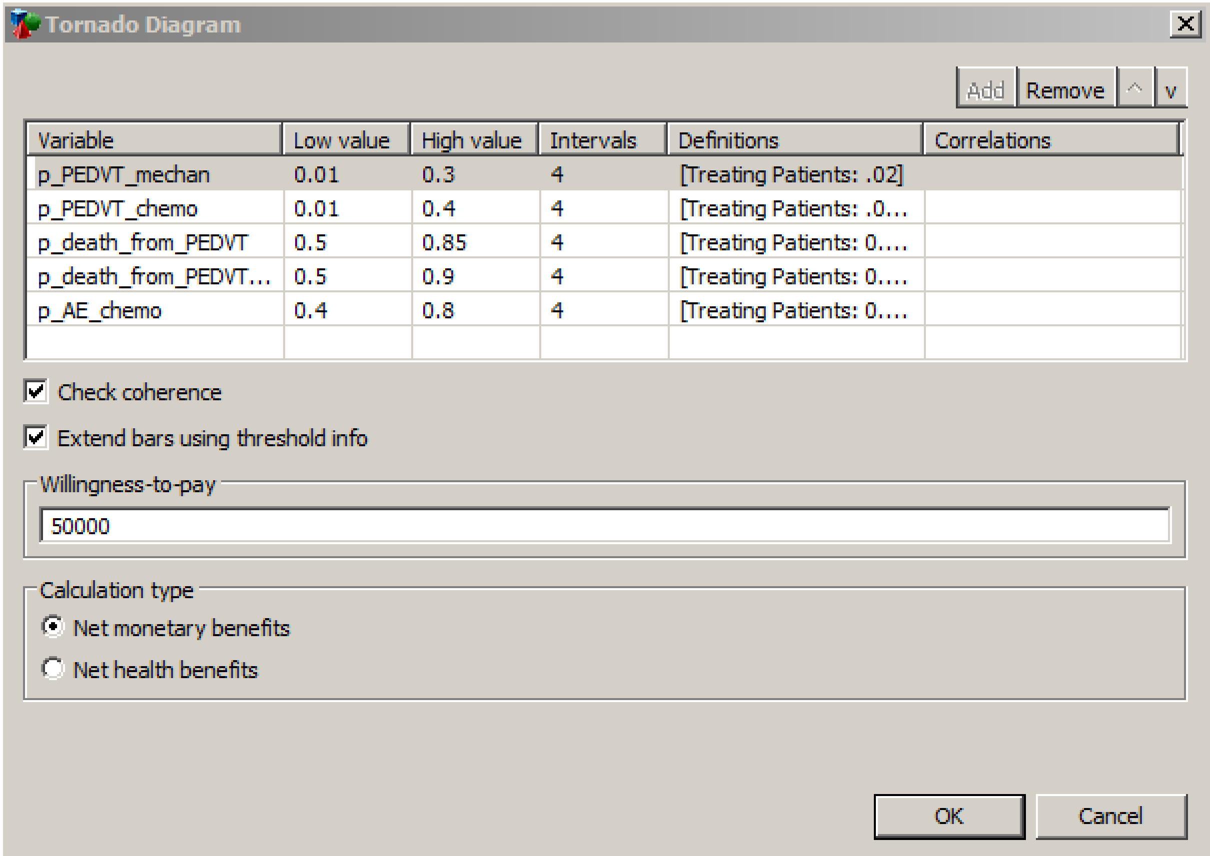
But…

- You should still do one-way sensitivity analyses!
- Easy way to understand which parameters matter

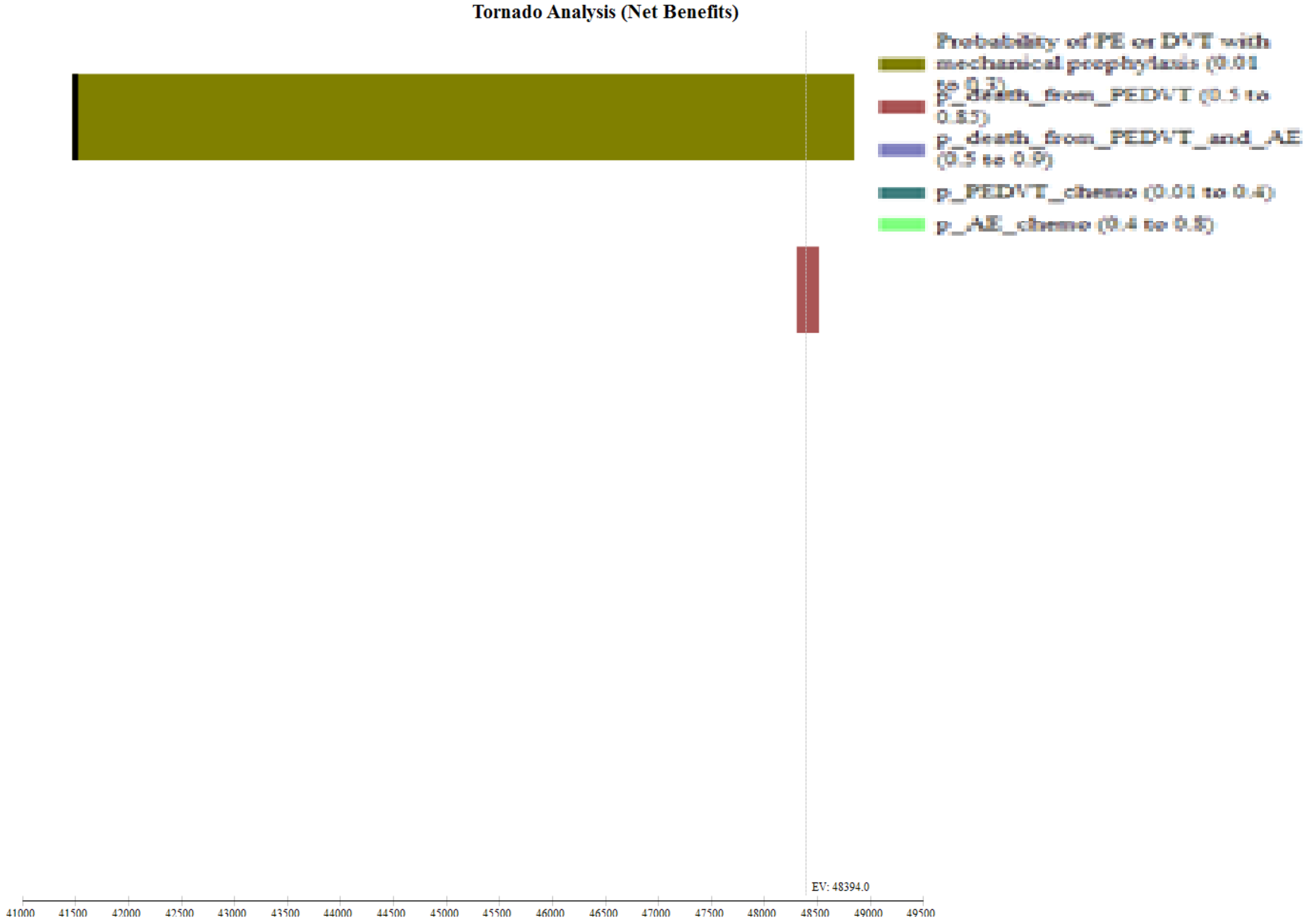
Tornado diagrams

- Tell you which of your one-way sensitivity analyses had the greatest impact on model results
- Bar: a one-way sensitivity analysis
- Width of bar represents impact on model results

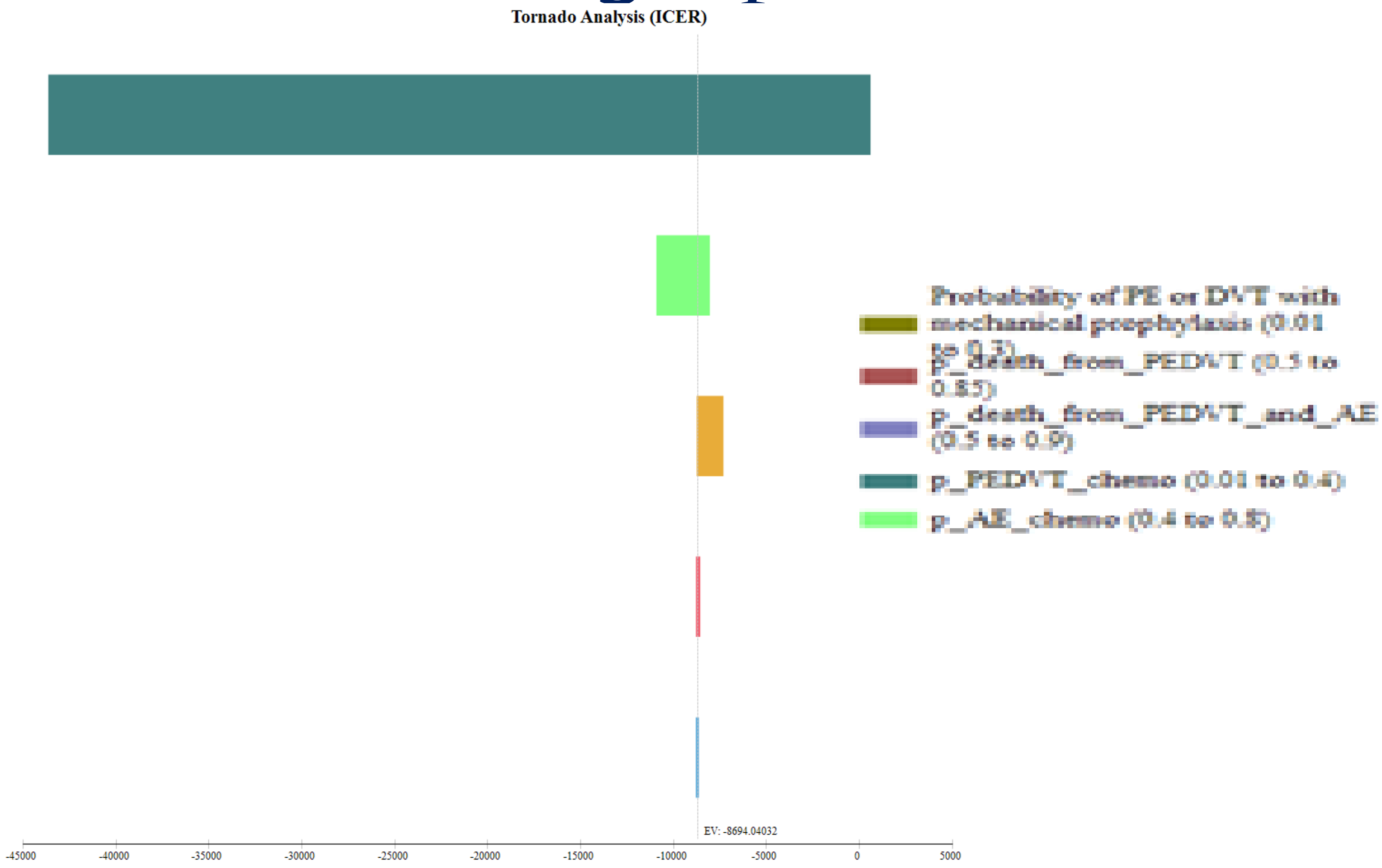
Conducting a tornado diagram



Tornado Diagram (Net Benefits)



Tornado Results (ICER) – *recommended graph to view*



Tornado diagram, text report

Tornado Sensitivity Analysis - ICER Report

VARIABLE_NAME	VARIABLE_RANGE	LOW_VALUE	HIGH_VALUE	SPREAD	SPREAD_SQR	RISK_PCT	CUMUL_PCT
p_PEDVT_mechan	0.01 to 0.3	-43639.51223	599.24346	44238.75569	1957067504.59758	35.90785	35.90785
p_AE_chemo	0.4 to 0.8	-10919.58067	-8044.87618	2874.70449	8263925.87916	0.15162	36.09902
p_PEDVT_chemo	0.01 to 0.4	-8755.5842	-7313.90762	1441.67658	2078431.34776	0.03813	35.94598
p_death_from_PEDVT	0.5 to 0.85	-8792.95107	-8565.56971	227.38136	51702.28401	0.00095	35.94693
p_death_from_PEDVT_and_AE	0.5 to 0.9	-8793.94024	-8635.18248	158.75776	25204.02665	0.00046	35.94739

- The high value for p_PEDVT_mechan results in chemoprophylaxis now being the preferred strategy
- Tells us we need to be more precise with our estimate of PE/DVT associated with mechanical prophylaxis

Limitations of Tornado diagrams

- Just a series of one-way sensitivity analyses, with results presented on top of one another

- There is not just uncertainty in one parameter – there is uncertainty in most, if not all, parameters

Scenario Analyses

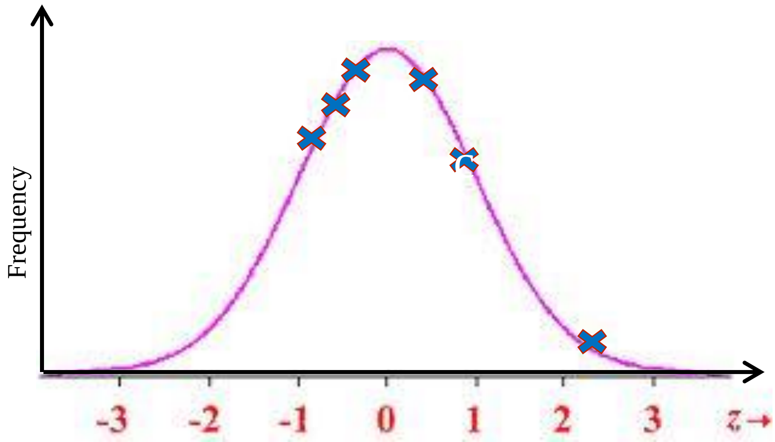
Scenario analyses

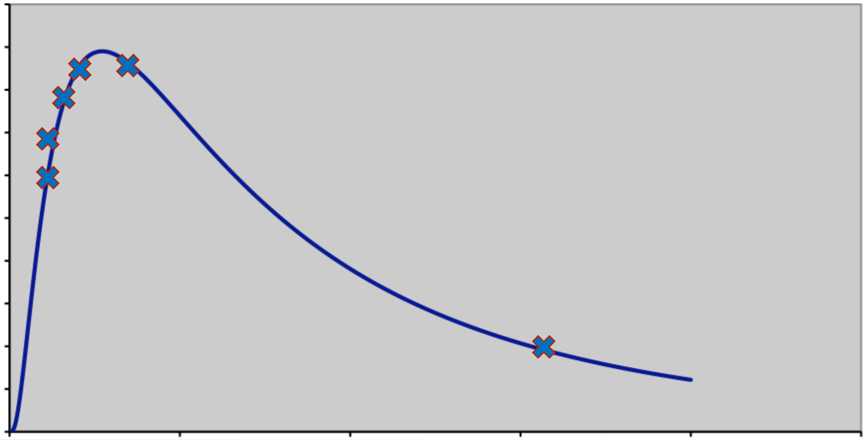
- Interested in subgroups
  - Cost-effectiveness of chemical versus mechanical prophylaxis in 85+ only
    - Change risk of PE/DVT, risk of AE, risk of death from PE/DVT/AE
- Changes the point estimate of multiple parameters
- Do not incorporate uncertainty !

Probabilistic Sensitivity Analyses

Probabilistic sensitivity analysis

- Vary multiple parameters simultaneously
- Each variable comes from a *distribution*
- Model is run many times (1,000, 10,000, etc.)
  - Each model iteration plucks a value from that distribution and uses it as the model input





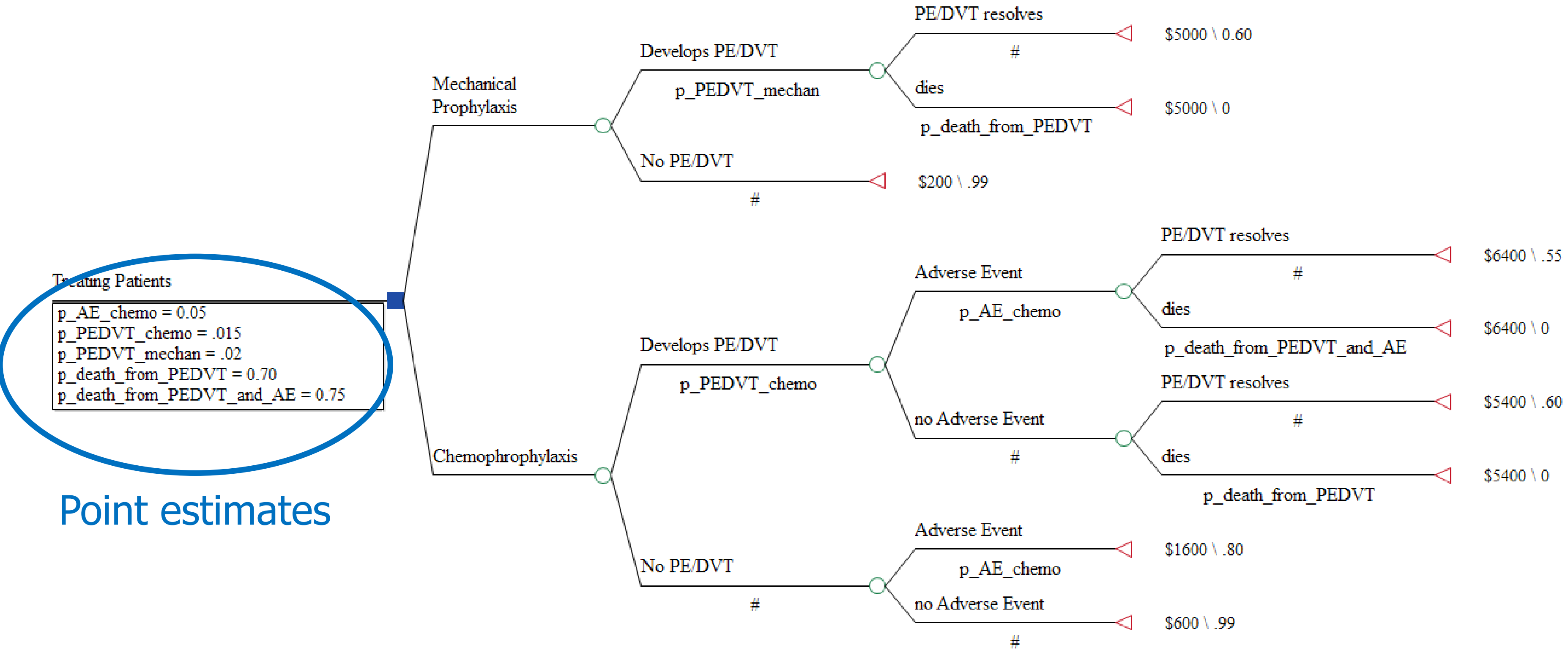
PSA

- Values are sampled with replacement!
- Values sampled based on their likelihood of occurrence
- Results (comparing strategy A to B):
  - Mean $Cost_A$ & variation in $Cost_A$
  - Mean $Cost_B$ & variation in $Cost_B$
  - Mean Health $Effect_A$ & variation in Health $Effect_A$
  - Mean Health $Effect_B$ & variation in Health $Effect_B$

Choosing distributions for your PSA – general guidance

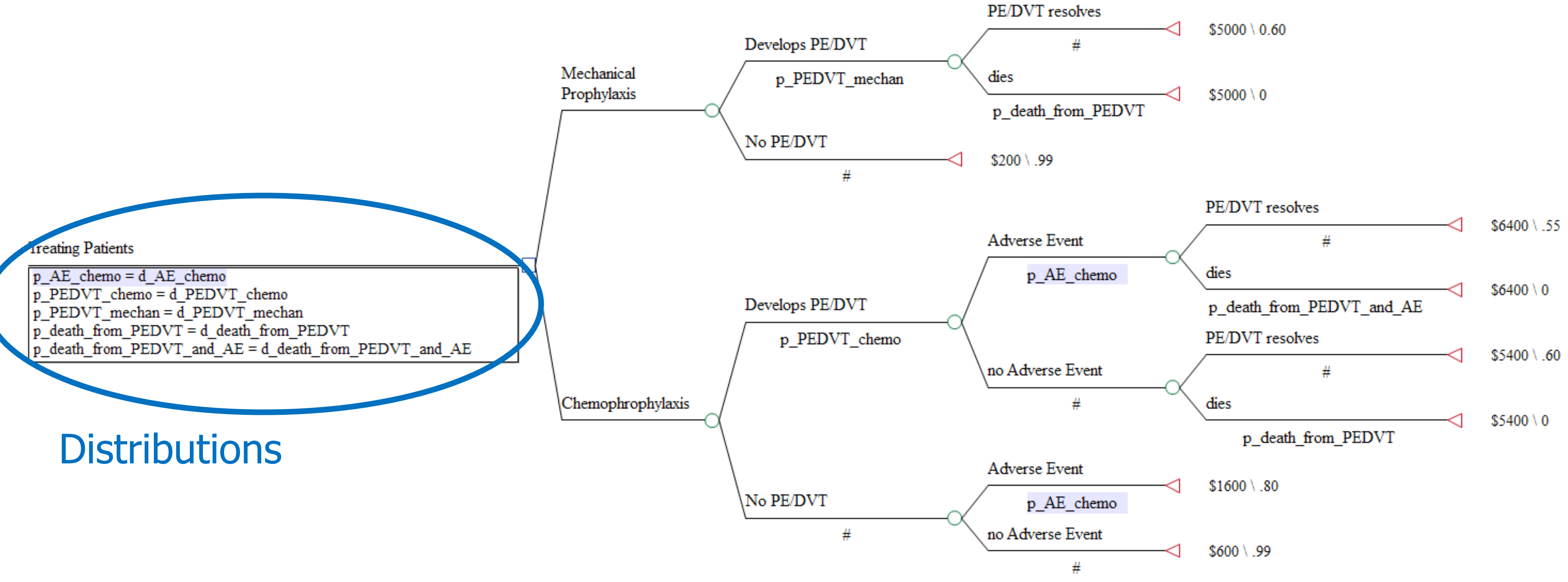
- Costs: log-normal, normal
- Probabilities: beta
- Utilities: beta

Inputting variables into your PSA



- Need to define variables in terms of distributions, rather than point estimates

Defining distributions in a PSA



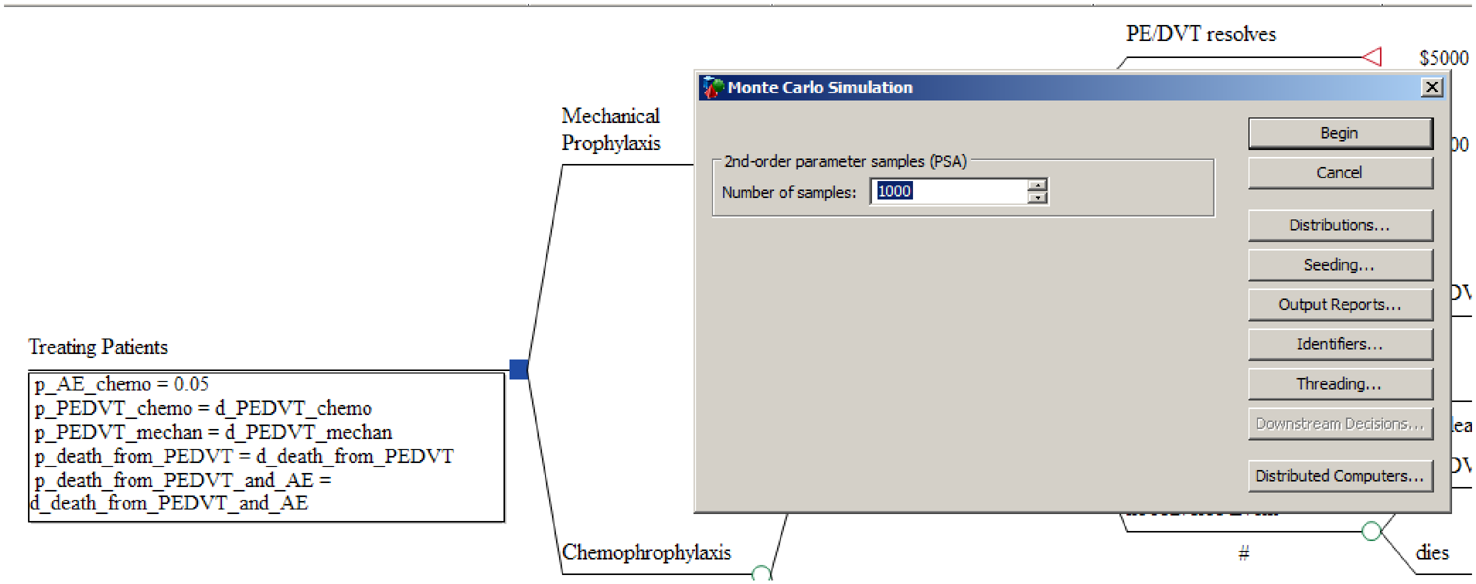
Creating distribution-based definitions

1. **Create the distribution**: d_AE_chemoprophyalxis
   - Define the distribution in terms of its shape
     - normal, beta, etc
   - Define the parameters for that distribution
     - mean/variance, alpha/beta, etc.

2. **Assign the distribution to a variable**:
prob_AE_chemoprophylaxis = d_AE_chemoprophylaxis

Running a PSA

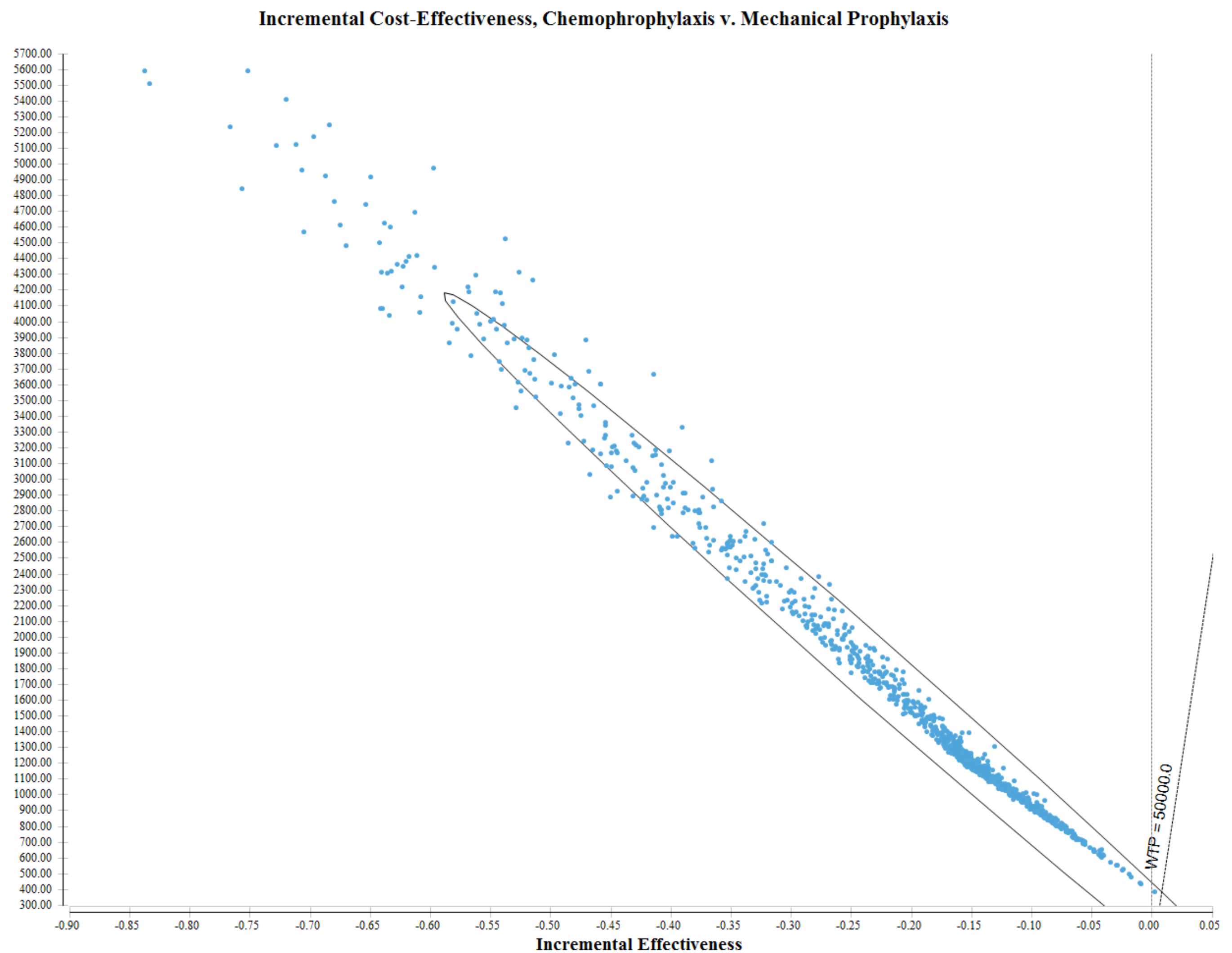
- Define all variables (model inputs) as distributions
- Determine your number of iterations



Ways to show uncertainty in the ICER

- Cost-effectiveness planes (CE scatterplot)
- Cost-effectiveness acceptability curve
- Net benefits

CE Scatter Plot



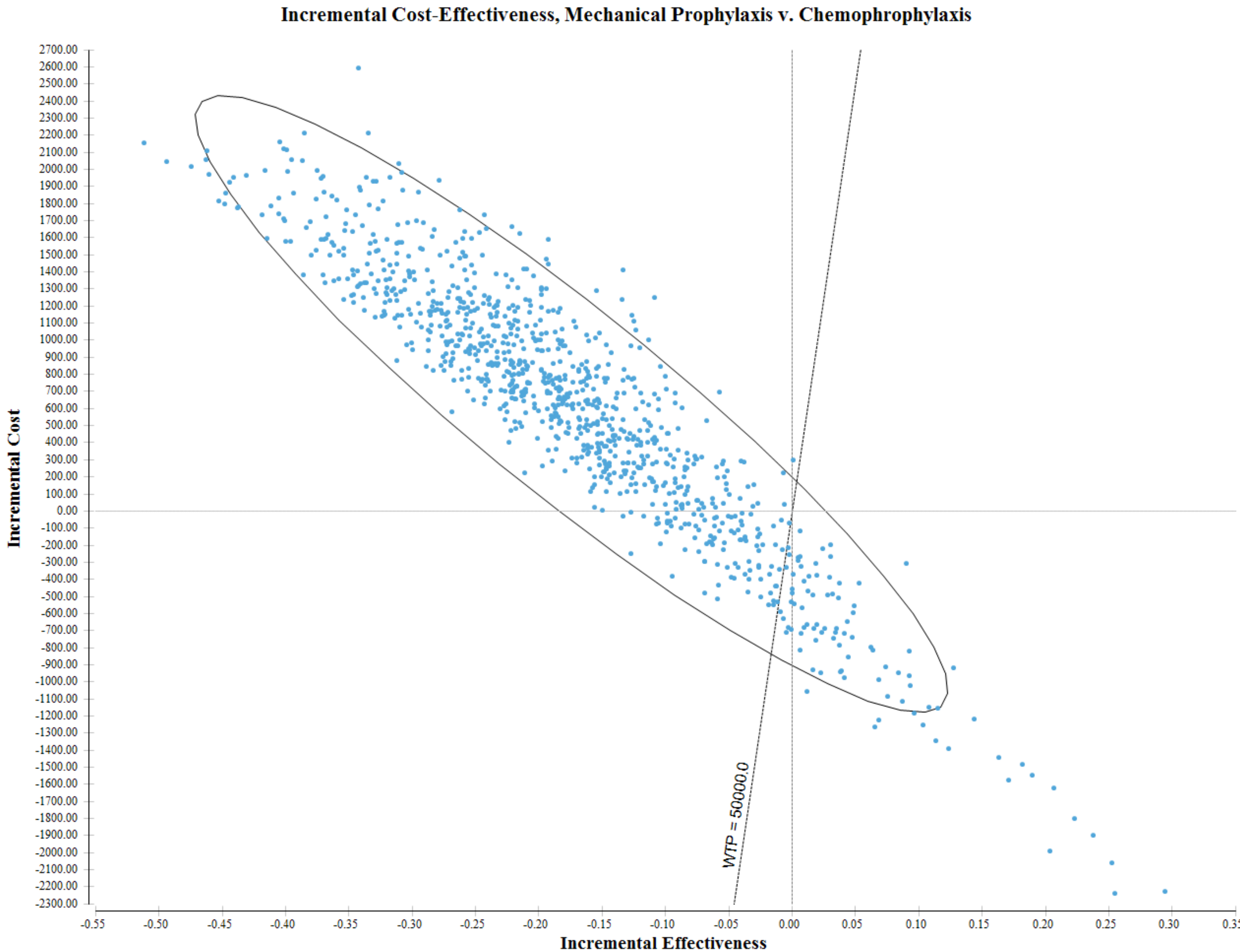
"ICE Report"

Incremental CE Plot Report Chemophrophylaxis v. Mechanical Prophylaxis

COMPONENT	QUADRANT	INCREFF	INCRCOST	INCRCE	FREQUENCY	PROPORTION
C1	IV	IE>0	IC<0	Superior	0	0
C2	I	IE>0	IC>0	ICER<50000.0	0	0
C3	III	IE<0	IC<0	ICER>50000.0	0	0
C4	I	IE>0	IC>0	ICER>50000.0	1	0.001
C5	III	IE<0	IC<0	ICER<50000.0	0	0
C6	II	IE<0	IC>0	Inferior	999	0.999
Indiff	origin	IE=0	IC=0	0/0	0	0

- In this hypothetical example (with entirely made-up data) Mechanical Prophylaxis is cost-effective compared to Chemo Prophylaxis 99.9% of the time
  - Costs less AND provides more health benefit

ICERs in multiple quadrants



ICE report, multiple quadrants

Incremental CE Plot Report Mechanical Prophylaxis v. Chemophrophylaxis

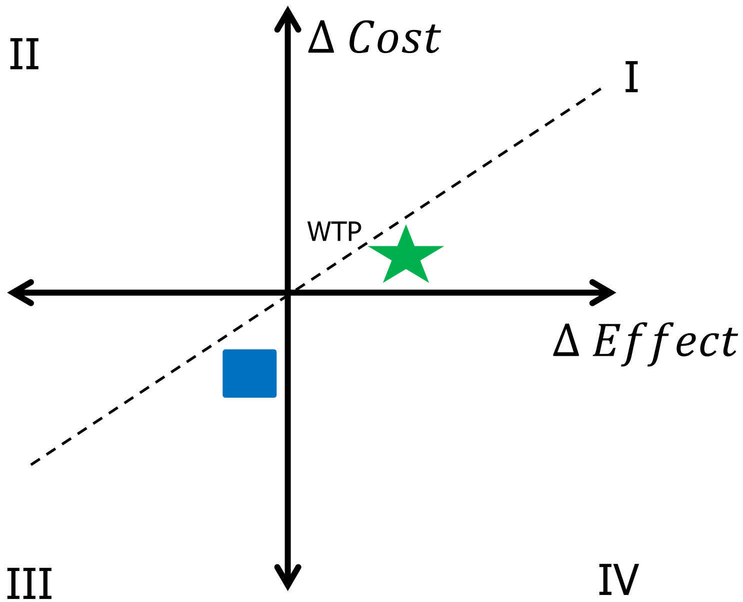
COMPONENT	QUADRANT	INCREFF	INCRCOST	INCRCE	FREQUENCY	PROPORTION
C1	IV	IE>0	IC<0	Superior	82	0.082
C2	I	IE>0	IC>0	ICER<50000.0	0	0
C3	III	IE<0	IC<0	ICER>50000.0	9	0.009
C4	I	IE>0	IC>0	ICER>50000.0	1	0.001
C5	III	IE<0	IC<0	ICER<50000.0	98	0.098
C6	II	IE<0	IC>0	Inferior	810	0.81
Indiff	origin	IE=0	IC=0	0/0	0	0

Ways one should not show uncertainty in the ICER

- Show only the numeric value of the ICER and Confidence Interval

- $ICER = \frac{Cost\ A - Cost\ B}{Effect\ A - Effect\ B} = \frac{-40{,}000}{-1} = \frac{\$40{,}000}{QALY}$

- $ICER = \frac{Cost\ A - Cost\ B}{Effect\ A - Effect\ B} = \frac{40{,}000}{1} = \frac{\$40{,}000}{QALY}$



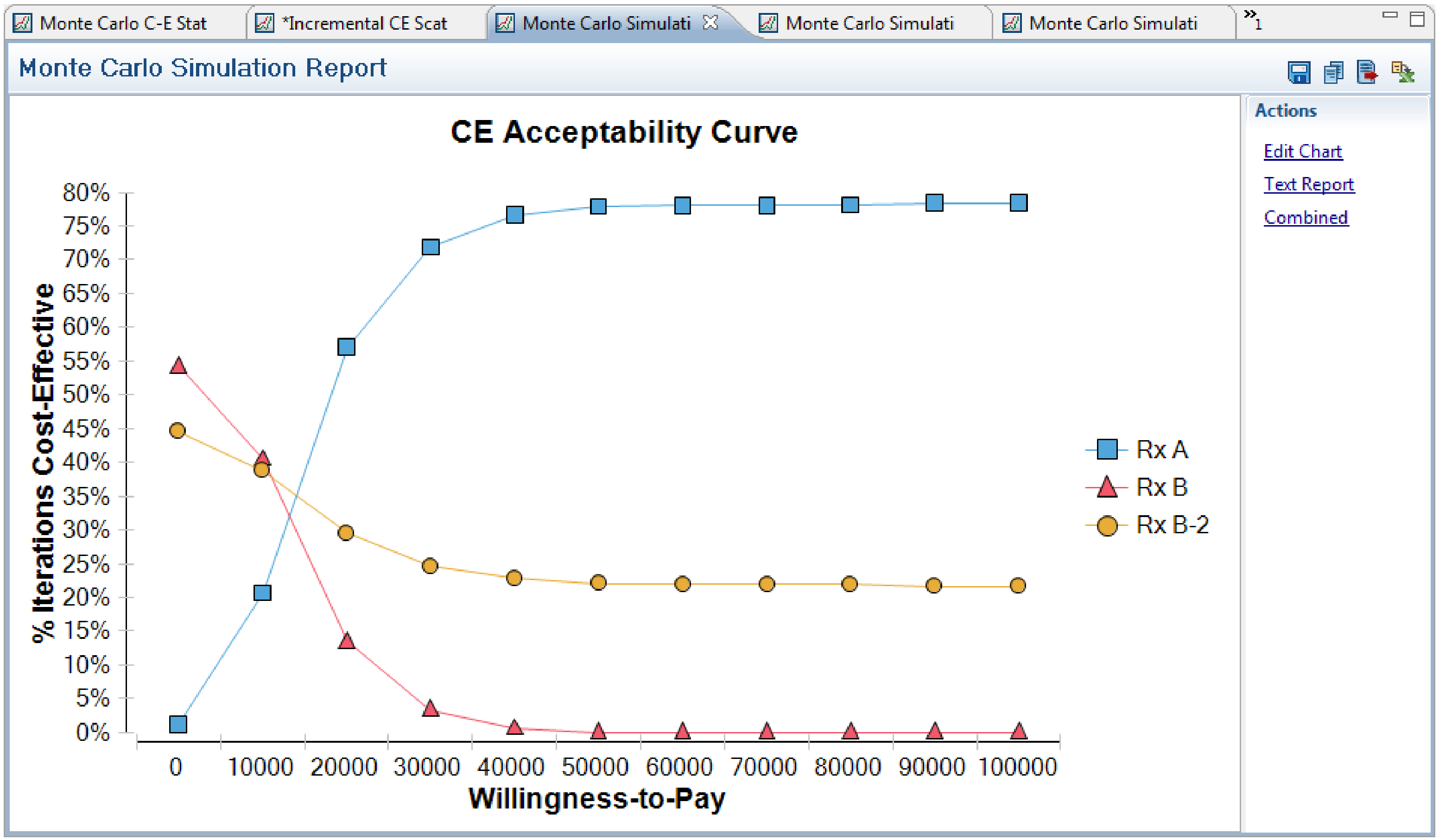
Willingness to pay (WTP)

- Previously, I had to specify my WTP

- What if you don't know what that is?
  - Or different decision makers have different WTP?

- Use a Cost-Effectiveness Acceptability Curve
  - Percentage of iterations that favor each strategy, over a range of WTP

Cost–effectiveness acceptability curves – hypothetical



Net Benefits

- Combine information on costs, outcomes, and willingness to pay
  - Net Monetary Benefits
- Positive number indicates technology is cost-effective
- *Use when you are very certain about your WTP*

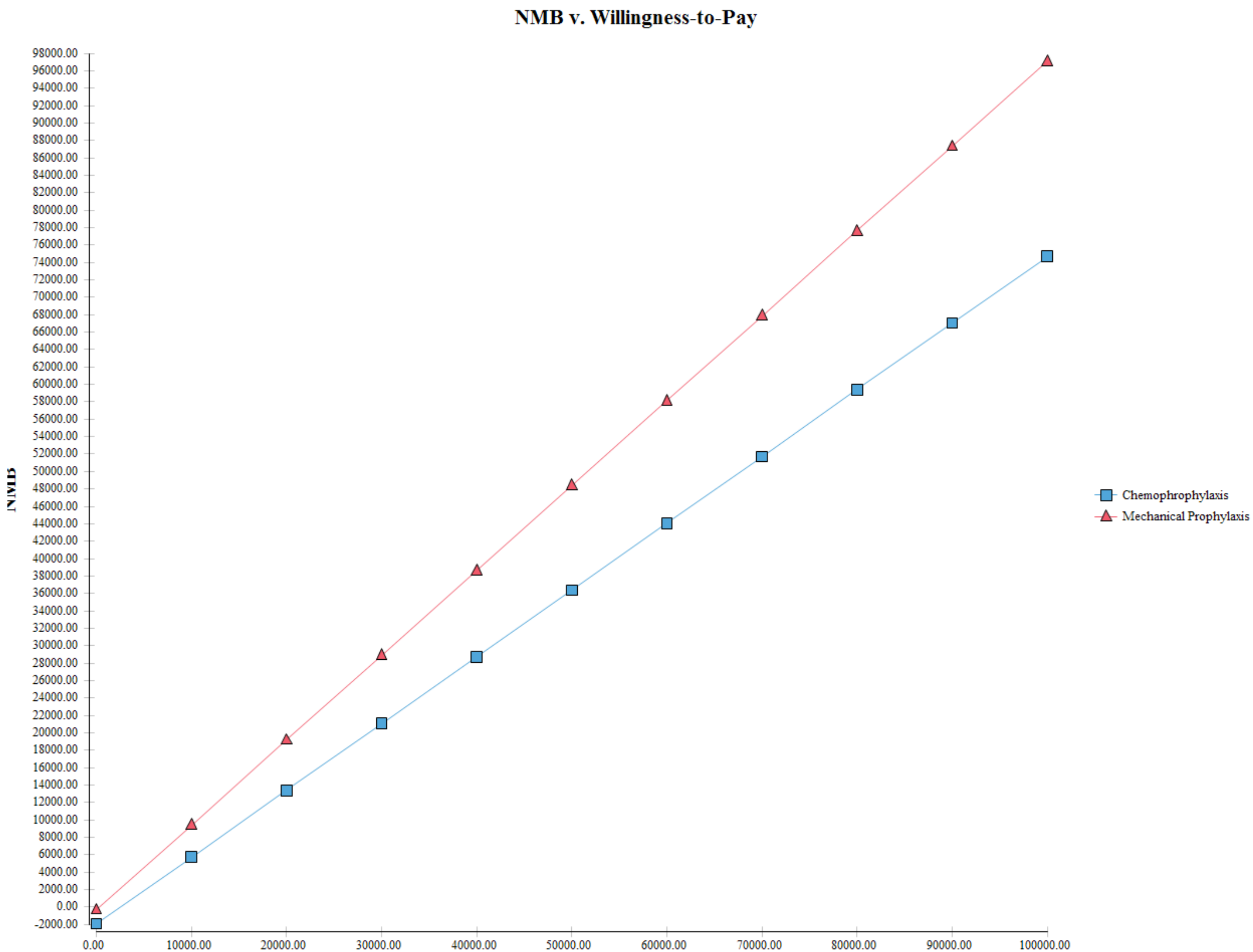
Net Monetary benefits

- Net Monetary Benefits

NMB = (Δ Effect * WTP) – Δ Cost

(-0.11 * $50,000) – $1,057 = $-6,557

TreeAge- Net Monetary benefits



3 ways to show uncertainty in the ICER

1) Cost-effectiveness planes/quadrant
2) Cost-effectiveness acceptability curve
3) Net monetary benefits (only if you are certain on your WTP)

How many iterations in a PSA?

- More distributions = more iterations
- Stop when the simulations generate mean values (without seeding) that are very similar

Monte Carlo C-E Statistics

Attribute	Statistic	Mechanical Prophylaxis	Chemophrophyl...
Cost			
	Mean	295.98	1371.17
	Std Deviation	14.14	966.99
	Minimum	258.19	614.93
	2.5%	270.26	625.63
	10%	278.24	645.27
	Median	295.36	944.17
	90%	315.24	2839.58
	97.5%	325.44	4053.16
	Maximum	338.22	5235.56
	Size (n)	1000.00	1000.00
	Variance	199.99	935077.00
	Variance/Size	0.20	935.08
	SQRT[Varianc...	0.45	30.58
Eff			
	Mean	0.97	0.86

Monte Carlo C-E Statistics

Attribute	Statistic	Mechanical Prophylaxis	Chemophrophyl...
Cost			
	Mean	295.92	1351.17
	Std Deviation	13.87	900.21
	Minimum	258.06	613.43
	2.5%	270.30	631.42
	10%	277.89	651.39
	Median	294.83	950.08
	90%	313.93	2682.31
	97.5%	322.97	3850.64
	Maximum	347.62	5115.89
	Size (n)	1000.00	1000.00
	Variance	192.33	810375.85
	Variance/Size	0.19	810.38
	SQRT[Varianc...	0.44	28.47
Eff			
	Mean	0.97	0.86

100 iterations

Monte Carlo C-E Statistics

Attribute	Statistic	Mechanical Prophylaxis	Chemophrophyl...
Cost			
	Mean	297.80	1413.88
	Std Deviation	13.17	919.06
	Minimum	269.18	613.56
	2.5%	278.24	620.09
	10%	281.11	654.41
	Median	295.40	1056.64
	90%	315.54	2697.37
	97.5%	324.32	3593.22
	Maximum	336.49	5047.80
	Size (n)	100.00	100.00
	Variance	173.49	844673.03
	Variance/Size	1.73	8446.73
	SQRT[Varianc...	1.32	91.91
Eff			
	Mean	0.97	0.85

Monte Carlo C-E Statistics

Attribute	Statistic	Mechanical Prophylaxis	Chemophrophyl...
Cost			
	Mean	296.30	1274.05
	Std Deviation	14.44	891.76
	Minimum	260.79	614.87
	2.5%	261.01	626.80
	10%	280.79	641.58
	Median	296.48	929.81
	90%	315.42	2678.31
	97.5%	322.91	3994.27
	Maximum	335.50	4528.79
	Size (n)	100.00	100.00
	Variance	208.37	795237.48
	Variance/Size	2.08	7952.37
	SQRT[Varianc...	1.44	89.18
Eff			
	Mean	0.97	0.88

PSA Summary

- Looks at model results when multiple sources of uncertainty are evaluated simultaneously

- Results presented in terms of:
  - C-E planes (quadrants)
  - C-E acceptability curves
  - Net Monetary Benefits

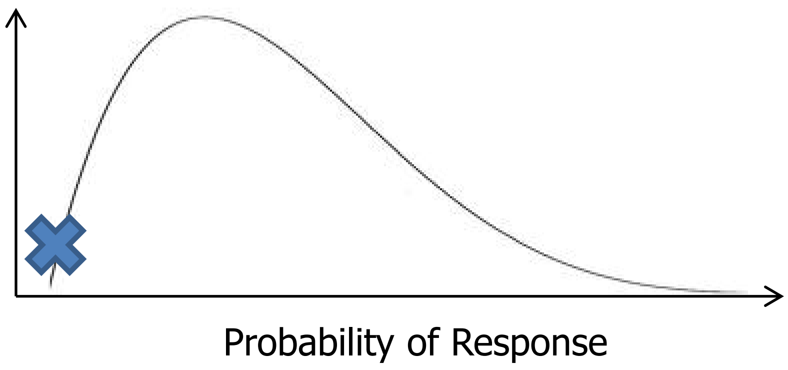
- Required in order to publish in a peer-reviewed journal!

Joint Parameter Uncertainty

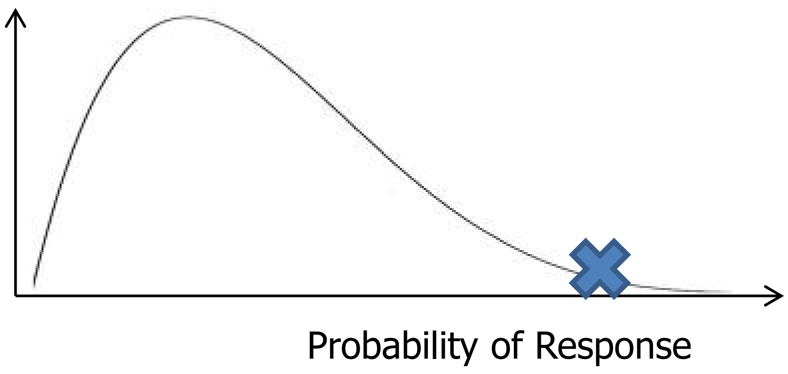
Joint Parameter uncertainty

The model will assume no covariance between parameters unless you specify otherwise

Probability of response at 26 weeks



Probability of response at 52 weeks



Accommodating Joint Parameter uncertainty

- Define one variable in terms of the other

  X = Y+ (Y*0.2)

- Use a table to link variables, have PSA identify Index
  - Variable X = if(PSA = 1; Table 1[Index; 1]; 0.55)
  - Variable Y = if(PSA = 1; Table 1[Index; 2]; 0.65)

Index	X	Y
1	0.60	0.67
2	0.480	0.89
3	0.89	0.93

- *If the PSA indicator is turned on:*
  - *go to Table 1, choose the row (Index) corresponding with the model cycle we are in and use the value in column 1*
- *otherwise, use a value of 0.55*

SUMMARY

Summary

- All model inputs have uncertainty
- Test how this uncertainty affects model results
  - Do so by varying model inputs
- Tornado diagrams: first-pass understanding of the most important variables in your model
- Need to run a PSA in order to fully evaluate the combination of uncertainty in all/most model inputs on robustness of model results
  - Be careful to accommodate joint parameter uncertainty

References

- General Overview:
  - Hunink M, Glasziou P, Siegel J, et al. "Chapter 11: Variability and Uncertainty" in Decision Making in Health and Medicine: Integrating Evidence and Values. Cambridge, UK: Cambridge Press, 2004. 339-363.

- Best Practices:
  - Briggs et al. Model Parameter Estimation and Uncertainty: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force – 6. *Value in Health*, 2012, 15: 835-842.

QUESTIONS?