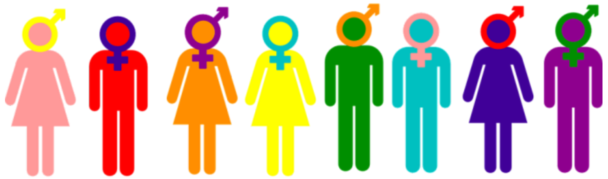
Modelling Uncertainty in R

Making the right choice?

Sources of Uncertainty

- Stochastic uncertainty
  - Variability that naturally occurs between individuals with identical information

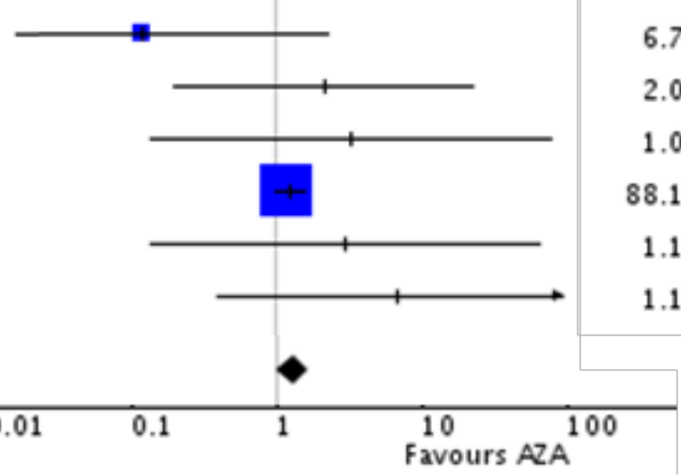
- Heterogeneity
  - Extent to which uncertainty can be explained by the characteristics of individuals, e.g. age, gender, other risk factors



- Parameter uncertainty
  - Refers to the uncertainty surrounding the estimation of input parameters from data sources

Sources of Uncertainty

Example of parameter uncertainty – combining evidence from multiple studies

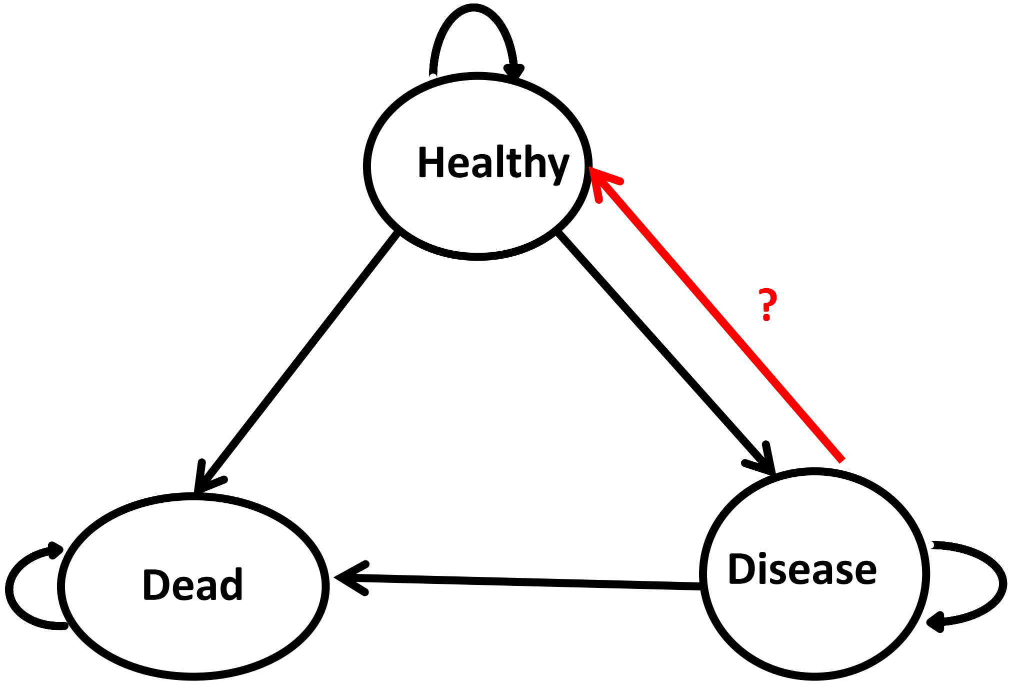


Review: Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease
Comparison: 1 Azathioprine versus placebo
Outcome: 3 Adverse events

Study or subgroup	AZA n/N	Placebo n/N	Weight	Risk Ratio M-H,Fixed,95% CI
Candy 1995	0/33	2/19	6.7 %	0.12 [0.01, 2.33]
Lémann 2005	2/40	1/43	2.0 %	2.15 [0.20, 22.81]
O'Donoghue 197	1/24	0/27	1.0 %	3.36 [0.14, 78.79]
Panes 2013	54/68	40/63	88.1 %	1.25 [1.00, 1.56]
Rosenberg 1975	1/10	0/10	1.1 %	3.00 [0.14, 65.90]
Willoughby 1971	3/11	0/11	1.1 %	7.00 [0.40, 121.39]
				1.29 [1.02, 1.64]

Sources of Uncertainty

- Structural uncertainty
  - assumptions inherent in the decision model
  - e.g. if patients attain a certain level of disease, can those patients be classified as cured? i.e. transition from disease to healthy?



Deterministic sensitivity analysis

- Parameter values are varied manually to test the sensitivity of the model's results to specific parameters or sets of parameters.

- Useful for identifying the parameters which are driving the decision or identifying the critical parameter values above which the decision may be expected to change i.e. threshold analysis

- E.g. one-way sensitivity analysis, multiway (multivariate) sensitivity analysis, scenario analysis

Example

Aflibercept for visual impairment due to diabetic macular oedema – Submission from the technology manufacturer (June 2012)

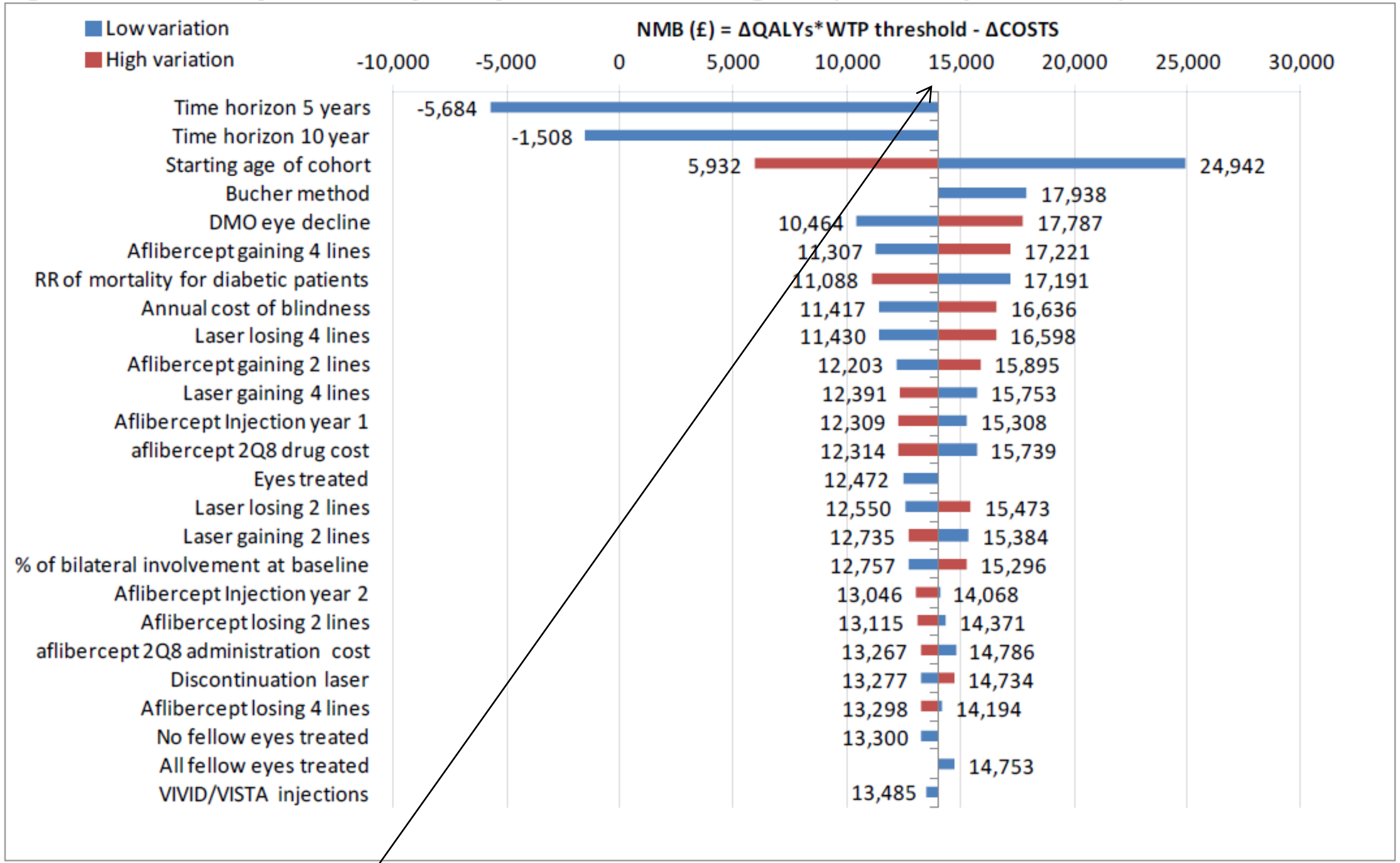
http://www.nice.org.uk/guidance/TA346/documents/macular-oedema-diabetic-aflibercept-committee-papers4

Parameter	Base case value	Lower value	Upper value	Reference
Starting age of cohort	63	58	68	±5 years
% of bilateral involvement at baseline	0.647	0.37	0.56	± 20% of the mean value
Annual incidence of FEI	0.1	0.08	0.12	± 20% of the mean value
Proportion of FE treated	0.5	0.40	0.60	± 20% of the mean value
% of shared visit between eyes (VEG-F)	0.877	0.70	1.05	± 20% of the mean value
% of shared visit between eyes (laser)	0.914	0.73	1.10	± 20% of the mean value
% of shared injection/monitoring visits (VEG-F)	0.5	0.40	0.60	± 20% of the mean value
% of shared injection/monitoring visits (laser)	0	0.00	0.00	± 20% of the mean value
Discounting				
Discounting of costs	0.035	0.02	0.06	± 20% of the mean value
Discounting of outcomes	0.035	0.02	0.06	± 20% of the mean value
Mortality				
RR of mortality for diabetic patients	1.95	1.64	2.33	(Preis et al., 2009)(68)
RR of mortality with one eye blind	1.23	1.16	1.31	(Christ et al., 2008)(12)
Costs				
Cost of aflibercept	816	652.80	979.20	± 20% of the mean value
Cost of ranibizumab	742.17	593.74	890.60	± 20% of the mean value
Cost of laser	117	93.60	140.40	± 20% of the mean value
Monitoring visit costs	139.22	111.38	167.06	± 20% of the mean value
Cataract cost	1146.87	917.50	1376.24	± 20% of the mean value
Endophthalmitis cost	1541.74	1233.39	1850.09	± 20% of the mean value
Retinal detachment cost	1843.16	1474.53	2211.79	± 20% of the mean value
Vitreous haemorrhage cost	1666.58	1333.26	1999.90	± 20% of the mean value
Glaucoma cost	1151.00	920.80	1381.20	± 20% of the mean value

Example

Aflibercept for visual impairment due to diabetic macular oedema – Submission from the technology manufacturer (June 2012)

Figure 71: One-way sensitivity analysis – tornado diagram (aflibercept vs. laser)

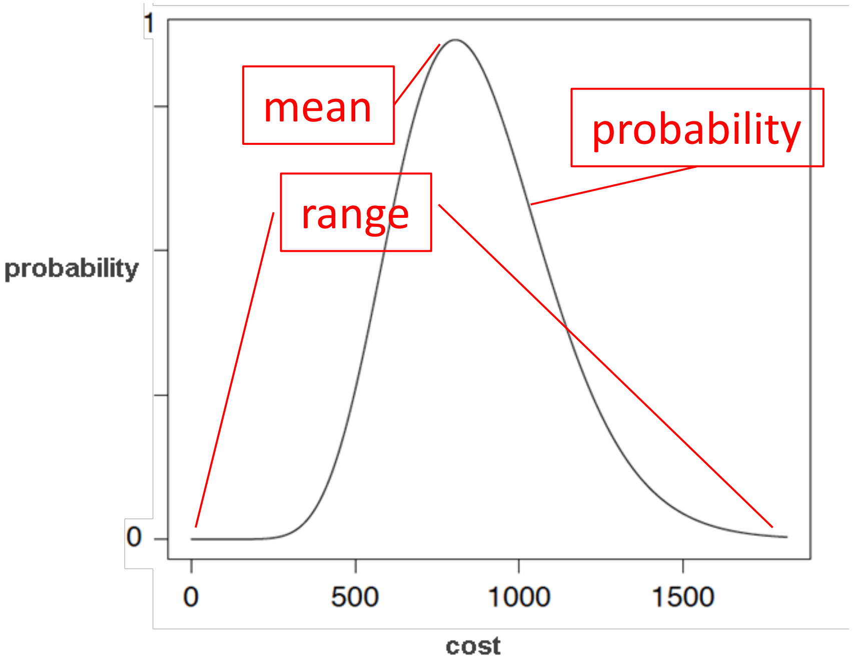


The axis is centered around the base case ICER

Probabilistic sensitivity analysis

- For each parameter, instead of using mean values, best-estimate or upper/lower limit, a probability distribution is specified e.g. normal, log-normal, beta, gamma etc.

- The distribution represents both the range of values that the parameter can take as well as the probability that it takes any particular value

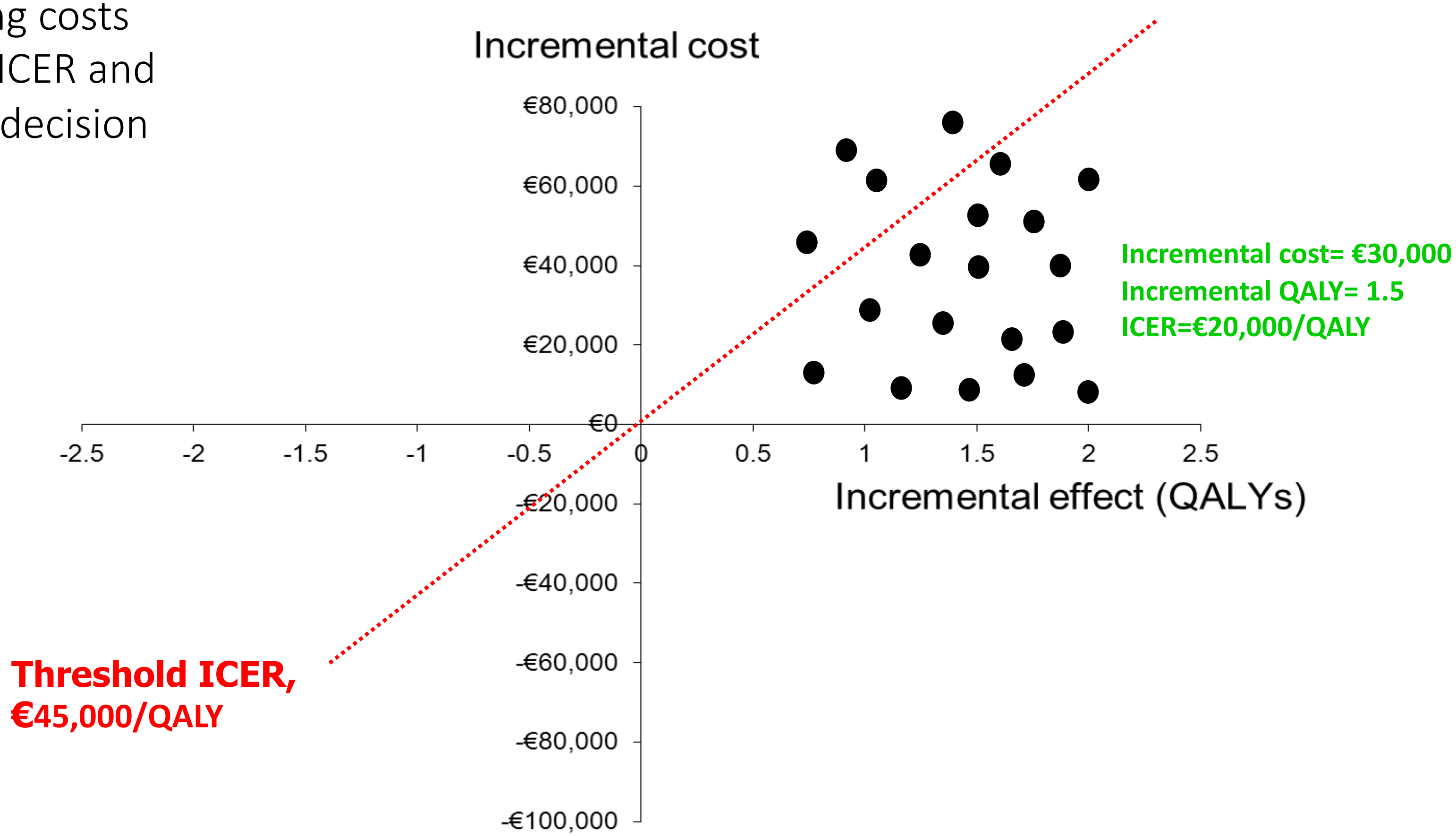


Probabilistic sensitivity analysis

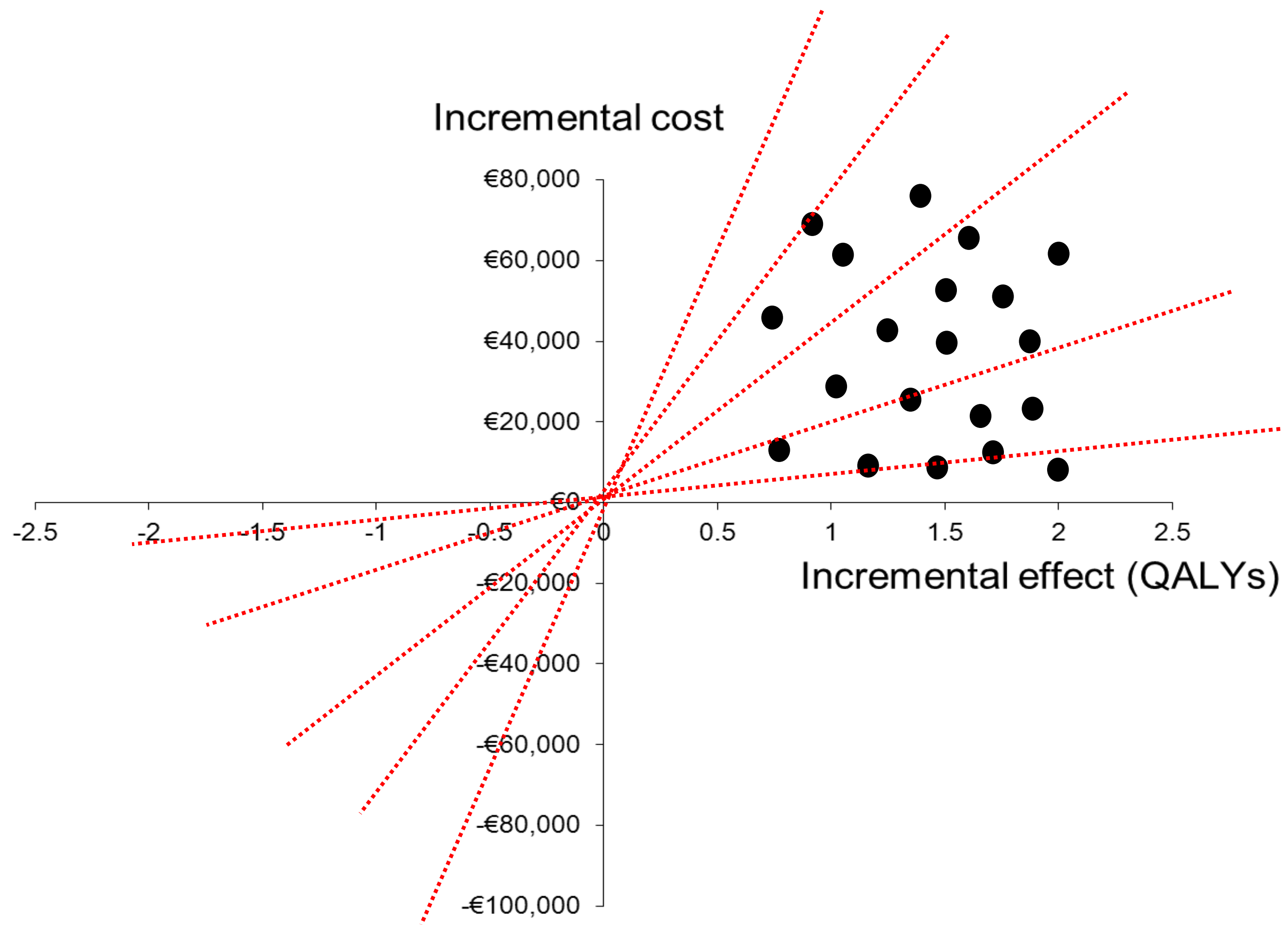
- Uncertainty is then propagated through the model by randomly selecting values from these distributions for each model parameter: repeatedly e.g. 1000 times
- Cost/QALY pair recorded for each iteration
- The choice of distribution should reflect the characteristics of the distribution and the nature of the data, be they cost, utility, probabilities, treatment effects etc.

Incremental cost effectiveness plane

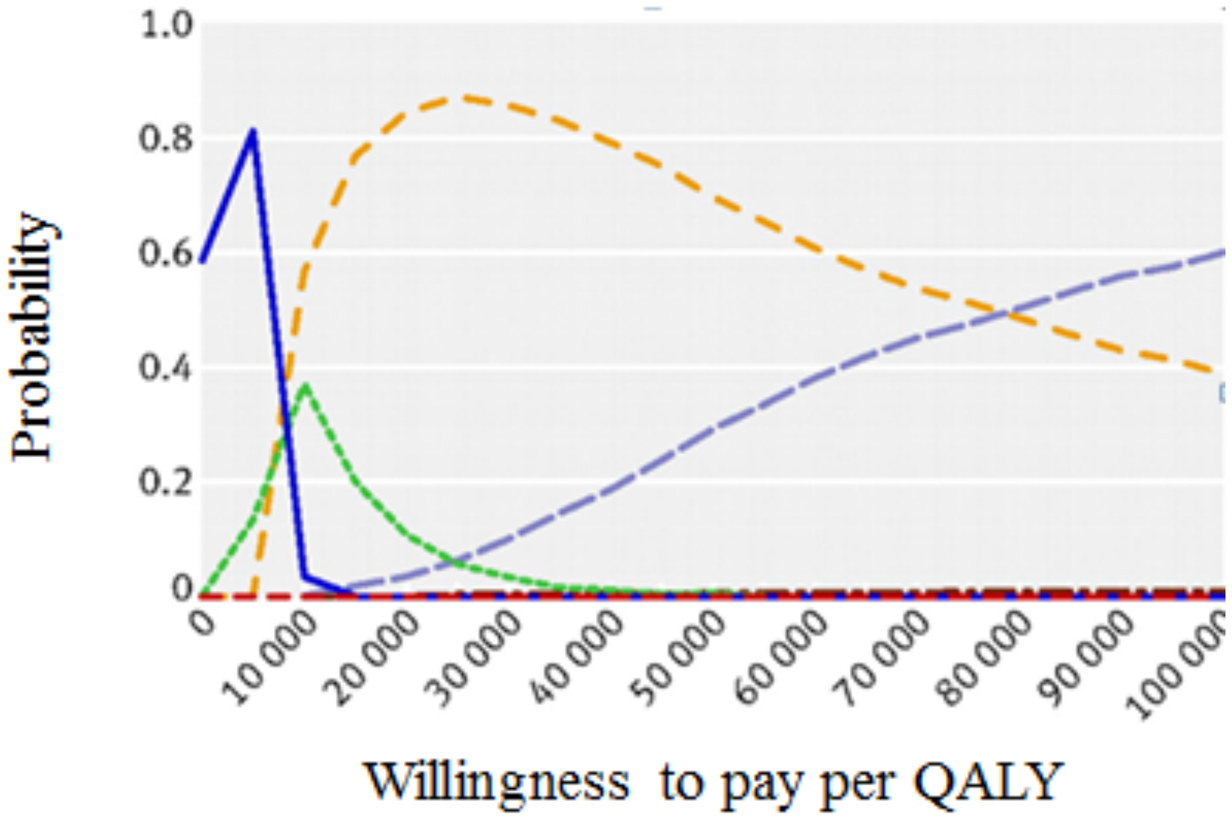
Uncertainty surrounding costs and QALYs can change ICER and potentially change the decision



Willingness to pay threshold



Cost-effectiveness acceptability curve



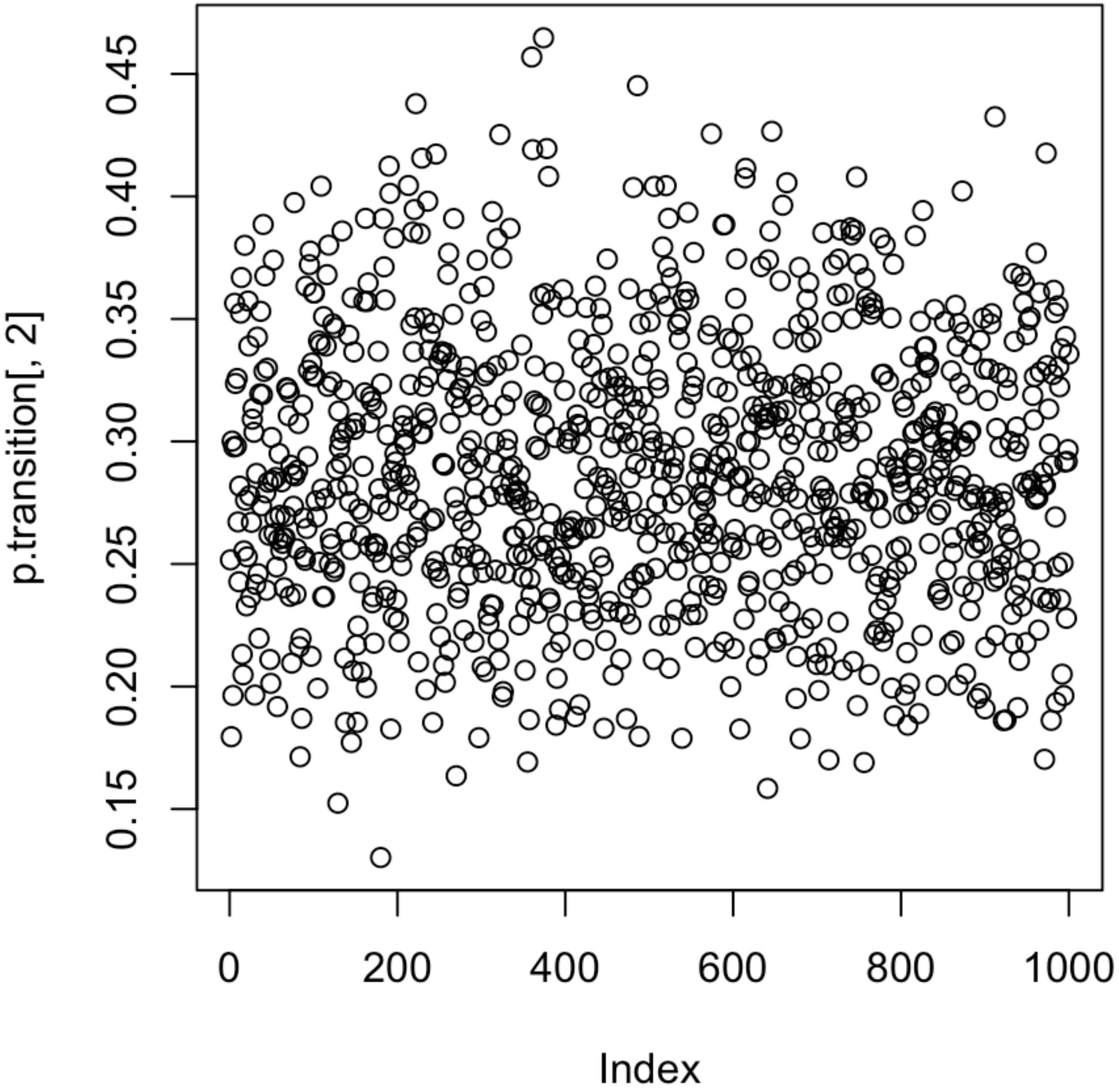
Some R code

```
# Firstly let's define the number of simulations to run and the column names
n.PSA=1000
c.names<-c('ID', 'Beta','Normal')

# Now create some space to fill in the blanks
p.transition<-array(NA,dim=c(n.PSA,3),
                    dimnames=list(NULL,c.names))
```

```
# I want to make the first column the simulation numbers from 1:1000
p.transition[,1]<- 1:n.PSA

# I want to make the second column a random value from the beta distribution with parameters 1 and 2 as specified
p.transition[,2]<- rbeta(n.PSA, 20, 50)
```

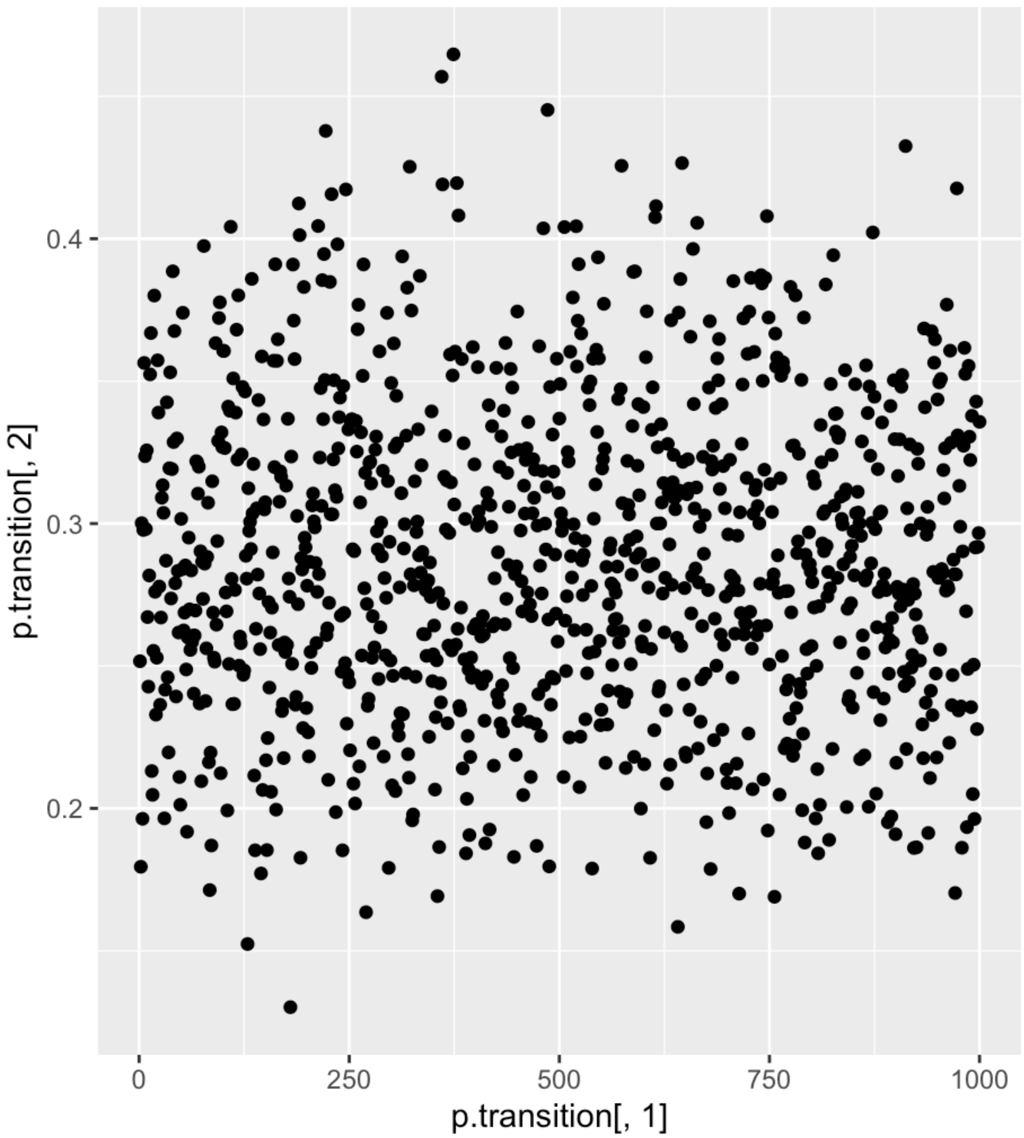
Plots

```
# Is what we have done reasonable?
range(p.transition[,2])
mean(p.transition[,2])

# We could plot these random samples
plot(p.transition[,2])
```



Nicer plots

```
# There are nicer ways to make graphs
library(ggplot2)

qplot(p.transition[,1],p.transition[,2], geom=c("point"))
```



Other distributions

```
# Let's do this for the normal distribution too and add into column 3
p.transition[,3]<- rnorm(n.PSA, -0.1,.3)
qplot(p.transition[,1],p.transition[,3], geom=c("point"))


# To plot the density function, ggplot likes things as a data frame
data<-as.data.frame(p.transition)



# Look at the different shapes and the x axis values for the types of distributions
ggplot(data, aes(x = Beta)) +
  geom_density()

ggplot(data, aes(x = Normal)) +
  geom_density()
```

Compare