MAS281 Osteoporosis Drug Comparison

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Task 1: Derivation of mean costs and QALY's over 3 years for each drug.

We must first think about all possible scenarios that a patient may find themselves in.

For a patient taking drug_j , in any given year, since we do not consider more than 1 fracture per year, a patient may either fracture, or not fracture a bone. We have 2 outcomes to consider each year, and 3 years to consider in total, therefore there are 2^3 possible timelines to consider.

Let F denote the event a patient fractures a bone during year_n. Let N denote the event a patient does not fracture a bone during year_n. Then the 8 possible timelines are as follows:

- 1. NNN
- 2. NNF
- 3. NFN
- 4. *NFF*
- 5. NNF
- 6. FNF
- 7. *FFN*
- 8. *FFF*

Where column_n respresents year_n and row_i represents timeline_i.

Next we want to account for the probability that each event will occur.

Let $P(F|N) = \theta_j = \theta$ denote the unknown probability that a patient with no previous fractures will fracture a bone during Year_n, then $P(N|N) = (1 - \theta_j) = \gamma$ is the unknown probability that a patient with no previous fractures will not fracture a bone during Year_n. Let $P(F|F) = \phi_j = \phi$ denote the unknown probability that a patient with at least 1 previous fracture will fracture a bone in Year_n, then $P(N|F) = (1 - \phi_j) = \delta$ is the unknown probability that a patient with at least one previous fracture will not fracture a bone. Since every patient begins Year 1 with no fractures, ϕ terms will only appear after an F has appeared in the timelines, with θ terms appearing everywhere

else. So the probabilities are:

1.
$$P(NNN) = P(N|N)^3 = \gamma^3$$

2. $P(NNF) = P(N|N)^2 P(F|N) = \gamma^2 \theta$
3. $P(NFN) = P(N|N) P(F|N) P(N|F) = \gamma \theta \delta$
4. $P(NFF) = P(N|N) P(F|N) P(F|F) = \gamma \theta \phi$
5. $P(FNN) = P(F|N) P(N|F)^2 = \theta \delta^2$
6. $P(FNF) = P(F|N) P(N|F) P(F|F) = \theta \delta \phi$
7. $P(FFN) = P(F|N) P(F|F) P(N|F) = \theta \phi \delta$
8. $P(FFF) = P(F|N) P(F|F)^2 = \theta \phi^2$

Now we want to know how many QALY's a patient will accumulate over the course of their treatment in each scenario.

Let $Q_f = Q$ denote the number of QALY's gained in year_n by a patient who fractures a bone in year_n, i.e we add Q QALY's to the patients total QALY's for each F in timeline_i. Let 1 be the number of QALY's gained in year_n by a patient who does not fracture a bone in year_n, i.e we add 1 full QALY to the patients total QALY's for each N in timeline_i. Let Q(X) be a function measuring the total QALY's gained, then the total QALY's accumulated for each timeline is:

$$\begin{aligned} &1. &Q(NNN) = 3Q(N) &= 3 \\ &2. &Q(NNF) = 2Q(N) + Q(F) &= 2 + Q \\ &3. &Q(NFN) = 2Q(N) + Q(F) &= 2 + Q \\ &4. &Q(NFF) = Q(N) + 2Q(F) &= 1 + 2Q \\ &5. &Q(FNN) = 2Q(N) + Q(F) &= 2 + Q \\ &6. &Q(FNF) = Q(N) + 2Q(F) &= 1 + 2Q \\ &7. &Q(FFN) = Q(N) + 2Q(F) &= 1 + 2Q \\ &8. &Q(FFF) = 3Q(F) &= 3Q \end{aligned}$$

Finally we need to consider the total cost of patient care over the full course of treatment for each scenario.

Let $B_j = B$ denote the base cost of treatment for drug_j per year in £'s. Since each patient takes the same drug per year for 3 years, each timeline accumulates a base cost of 3B. Let $T_f = T$ denote the extra cost associated from care given to a patient with a fracture in year_n. Then for each F in timeline_i we add a cost of T to the total cost for care. Let T(X) be the function measuring the total cost of treatment, then the total cost for each timeline is:

1.
$$T(NNN) = 3T(N)$$
 = 3B
2. $T(NNF) = 2T(N) + T(F)$ = 3B + T
3. $T(NFN) = 2T(N) + T(F)$ = 3B + T
4. $T(NFF) = T(N) + 2T(F)$ = 3B + 2T
5. $T(FNN) = 2T(N) + T(F)$ = 3B + T
6. $T(FNF) = T(N) + 2T(F)$ = 3B + 2T
7. $T(FFN) = T(N) + 2T(F)$ = 3B + 2T
8. $T(FFF) = 3T(F)$ = 3B + 3T

We now have all the information we need to derive the formula for the mean QALY's gained and mean cost of treatment.

For each drug the timeline structure is identical, only we substitute in θ_1 , ϕ_1 , B_1 for drug 1, and θ_2 , ϕ_2 , B_2 for drug 2. Then compiling the above information we derive the following formula:

$$E_i = 3Q(\theta\phi^2) + (1+2Q)(2\theta\phi\delta + \gamma\theta\phi) + (2+Q)(\theta\delta^2 + \gamma\theta\delta + \gamma^2\theta) + 3\gamma^3$$
(1)

$$C_{i} = (3B + 3T)(\theta\phi^{2}) + (3B + 2T)(2\theta\phi\delta + \gamma\theta\phi) + (3B + T)(\theta\delta^{2} + \gamma\theta\delta + \gamma^{2}\theta) + (3B)3\gamma^{3}$$
 (2)

where E_j represents the mean QALY's for drug_j over 3 years, and C_j represents the mean cost of drug_j (in £'s) over 3 years.

Task 2. Calculate the ICER for given parameters.

Given the parameters

$$\theta_1 = 0.35$$
, $\theta_2 = 0.125$ $\phi_1 = 0.45$, $\phi_2 = 0.27$, $Q_f = 0.6$, $T_f = 5000$,

and drug costs, $B_1 = 5000$, $B_2 = 8000$. Then

$$\gamma_1 = (1 - \theta_1) = 0.65, \quad \gamma_2 = (1 - \theta_2) = 0.875, \quad \delta_1 = (1 - \phi_1) = 0.55, \quad \delta_2 = (1 - \phi_2) = 0.73.$$

Inputting everything into (1) and (2) yields the following values for the mean costs and QALY's of each drug:

$$E_1 = [(3 \times 0.6)(0.35 \times 0.45^2)] + [(1 + 2 \times 0.6)(2 \times 0.35 \times 0.45 \times 0.55 + 0.65 \times 0.35 \times 0.45)] + [(2 + 0.6)(0.35 \times 0.55^2 + 0.65 \times 0.35 \times 0.55 + 0.65^2 \times 0.35)] + [3 \times 0.65^3] = 2.5429$$

$$E_1 = [(3 \times 0.6)(0.125 \times 0.27^2)] + [(1 + 2 \times 0.6)(2 \times 0.125 \times 0.27 \times 0.73 + 0.875 \times 0.125 \times 0.27)] + [(2 + 0.6)(0.125 \times 0.73^2 + 0.875 \times 0.125 \times 0.73 + 0.875^2 \times 0.125)] + [3 \times 0.875^3] = 2.829156$$

$$C_{1} = [(3 \times 5000 + 3 \times 5000)(0.35 \times 0.45^{2})] + [(3 \times 5000 + 2 \times 5000)(2 \times 0.35 \times 0.45 \times 0.55 + 0.65 \times 0.35 \times 0.45)] + [(3 \times 5000 + 5000)(0.35 \times 0.55^{2} + 0.65 \times 0.35 \times 0.55 + 0.65^{2} \times 0.35)] + [(3 \times 5000)(0.65^{3})] = 20713.75$$

$$C_2 = [(3 \times 5000 + 3 \times 5000)(0.125 \times 0.27^2)] + [(3 \times 5000 + 2 \times 5000)(2 \times 0.125 \times 0.27 \times 0.73 + 0.875 \times 0.125 \times 0.27)] + [(3 \times 5000)(0.125 \times 0.73^2 + 0.875 \times 0.125 \times 0.73 + 0.875^2 \times 0.125)] + [(3 \times 5000)(0.875^3)] = 26135.55$$

Next we want to calculate the ICER for drug 2 against drug 1 using the following formula:

$$ICER = \frac{C_1 - C_2}{E_1 - E_2}.$$
 (3)

Then (3) yields the ICER = 18940.36. We suppose NICE will pay no more than $\lambda = £30,000$ per QALY gained. Since the $ICER < \lambda$, we should switch to drug 2 in this case. This is because

although we pay an extra £5422 for drug 2, we gain an extra 0.29 QALY's. Alternatively we can say by staying with drug 1 we save £5422, but we lose a potential 0.29 QALY's to make that saving which is not worthwhile. Either way it is clear that drug 2 is the better choice given our budget.

Task 3. R-function to calculate the mean cost and mean QALY's gained per patient.

```
# Calculates mean QALY's and costs for drug1 and drug 2 treatment.
FractureModel <- function(gamma1, gamma2,
                             delta1, delta2,
                             phi1, phi2,
                             theta1, theta2,
                             B1, B2, Qf, Tf){
# Drug 1 Treatment.
  # Timeline NNN.
  p.path1.1 <- gamma1*gamma1*gamma1</pre>
  QALYgain.path1.1 <- 1+1+1
  cost.path1.1 <- 3*B1
  # Timeline NNF
  p.path2.1 <- gamma1*gamma1*theta1</pre>
  QALYgain.path2.1 <- 1+1+Qf
  cost.path2.1 \leftarrow 3*B1+Tf
  # Timeline NFN.
  p.path3.1 <- gamma1*theta1*delta1</pre>
  QALYgain.path3.1 <- 1+1+Qf
  cost.path3.1 \leftarrow 3*B1+Tf
  # Timeline NFF
  p.path4.1 <- gamma1*theta1*phi1</pre>
  QALYgain.path4.1 <- 1+Qf+Qf
  cost.path4.1 <- 3*B1+Tf+Tf</pre>
  # Timeline FNN.
  p.path5.1 <- theta1*delta1*delta1</pre>
  QALYgain.path5.1 <- 1+1+Qf
  cost.path5.1 \leftarrow 3*B1+Tf
  # Timeline FNF.
  p.path6.1 <- theta1*delta1*phi1</pre>
  QALYgain.path6.1 <- 1+Qf+Qf
  cost.path6.1 <- 3*B1+Tf+Tf</pre>
```

```
# Timeline FFN.
 p.path7.1 <- theta1*phi1*delta1</pre>
  QALYgain.path7.1 <- 1+Qf+Qf
  cost.path7.1 <- 3*B1+Tf+Tf</pre>
  # Timeline FFF.
 p.path8.1 <- theta1*phi1*phi1</pre>
  QALYgain.path8.1 <- Qf+Qf+Qf
  cost.path8.1 <- 3*B1+Tf+Tf+Tf</pre>
  # Expected QALY gain drug 1.
 E1 <- p.path1.1*QALYgain.path1.1+
   p.path2.1*QALYgain.path2.1+
   p.path3.1*QALYgain.path3.1+
   p.path4.1*QALYgain.path4.1+
    p.path5.1*QALYgain.path5.1+
    p.path6.1*QALYgain.path6.1+
    p.path7.1*QALYgain.path7.1+
    p.path8.1*QALYgain.path8.1
  # Expected costs for drug 1.
  C1 <- p.path1.1*cost.path1.1+
   p.path2.1*cost.path2.1+
   p.path3.1*cost.path3.1+
   p.path4.1*cost.path4.1+
   p.path5.1*cost.path5.1+
   p.path6.1*cost.path6.1+
    p.path7.1*cost.path7.1+
   p.path8.1*cost.path8.1
# Drug 2 Treatment.
    # Timeline NNN.
    p.path1.2 <- gamma2*gamma2*gamma2</pre>
  QALYgain.path1.2 <- 1+1+1
  cost.path1.2 <- 3*B2
  # Timeline NNF
 p.path2.2 <- gamma2*gamma2*theta2</pre>
  QALYgain.path2.2 <- 1+1+Qf
 cost.path2.2 \leftarrow 3*B2+Tf
  # Timeline NFN.
 p.path3.2 <- gamma2*theta2*delta2</pre>
  QALYgain.path3.2 <- 1+1+Qf
  cost.path3.2 \leftarrow 3*B2+Tf
  # Timeline NFF
```

```
p.path4.2 <- gamma2*theta2*phi2</pre>
QALYgain.path4.2 <- 1+Qf+Qf
cost.path4.2 <- 3*B2+Tf+Tf</pre>
# Timeline FNN.
p.path5.2 <- theta2*delta2*delta2</pre>
QALYgain.path5.2 <- 1+1+Qf
cost.path5.2 \leftarrow 3*B2+Tf
# Timeline FNF.
p.path6.2 <- theta2*delta2*phi2</pre>
QALYgain.path6.2 <- 1+Qf+Qf
cost.path6.2 <- 3*B2+Tf+Tf</pre>
# Timeline FFN.
p.path7.2 <- theta2*phi2*delta2</pre>
QALYgain.path7.2 <- 1+Qf+Qf
cost.path7.2 <- 3*B2+Tf+Tf</pre>
# Timeline FFF.
p.path8.2 <- theta2*phi2*phi2</pre>
QALYgain.path8.2 <- Qf+Qf+Qf
cost.path8.2 <- 3*B2+Tf+Tf+Tf</pre>
# Expected QALY gain drug 2.
E2 <- p.path1.2*QALYgain.path1.2+
      p.path2.2*QALYgain.path2.2+
      p.path3.2*QALYgain.path3.2+
      p.path4.2*QALYgain.path4.2+
      p.path5.2*QALYgain.path5.2+
      p.path6.2*QALYgain.path6.2+
      p.path7.2*QALYgain.path7.2+
      p.path8.2*QALYgain.path8.2
 # Expected costs for drug 2.
 C2 <- p.path1.2*cost.path1.2+
       p.path2.2*cost.path2.2+
       p.path3.2*cost.path3.2+
       p.path4.2*cost.path4.2+
       p.path5.2*cost.path5.2+
       p.path6.2*cost.path6.2+
       p.path7.2*cost.path7.2+
       p.path8.2*cost.path8.2
  list(QALYgain.drug1=E1,
       QALYgain.drug2=E2,
       cost.drug1=C1,
```

```
cost.drug2=C2)
}
# Parameters given in Task 2.
theta1 <- 0.35
gamma1 <- 1-theta1
phi1 <- 0.45
delta1 <- 1-phi1
theta2 <- 0.125
gamma2 <- 1-theta2</pre>
phi2 <- 0.27
delta2 <- 1-phi2
B1 <- 5000
B2 <- B1 + 3000
Qf \leftarrow 0.6
Tf <- 5000
Lambda <- 30000 # Assume NICE will pay up to £30,000 per QALY gained.
# stores values for E1, E2, C1, C2.
outputs <- FractureModel(gamma1, gamma2,</pre>
                           delta1, delta2,
                           phi1, phi2,
                           theta1, theta2,
                           B1, B2, Qf, Tf)
# If negative, drug 2 is more cost effective than drug 1.
INB <- as.integer(Lambda*(outputs$QALYgain.drug1-outputs$QALYgain.drug2)-</pre>
                     (outputs$cost.drug1-outputs$cost.drug2))
# Drug 1 becomes more cost effective if we are only prepared to
# pay less than the ICER ouput per QALY gained.
ICER <- as.integer((outputs$cost.drug1-outputs$cost.drug2) /</pre>
                      (outputs$QALYgain.drug1-outputs$QALYgain.drug2))
outputs
## $QALYgain.drug1
## [1] 2.5429
##
## $QALYgain.drug2
## [1] 2.829156
##
## $cost.drug1
## [1] 20713.75
##
## $cost.drug2
## [1] 26135.55
```

INB

[1] -3165

ICER

[1] 18940

The INB is negative here confirming that drug 2 is the more cost effective choice for the given parameters and the price we are willing to pay per extra QALY.

The ICER is the same value as in task 2, confiming the derived formula for the mean costs and QALY's are correct. The value of the ICER tells us that drug 1 will only become more cost effective for these parameters choices if we are not prepared to pay more than approximately £18940 per extra QALY gained. We are prepared to pay £30,000 so again drug 2 is the most cost effective option.

Task 4. Probabilistic Sensitivity Analysis.

We now do not know the values for any of the parameters, but we have some data on the effectiveness of each drug which will help us deduce what values the parameters are likely to take. We must consider which drug is likeliest to be the most cost effective, how big is the possibility we make the wrong choice, and what are the implications of making the wrong choice.

We know $Q \sim N(0.6, 0.02^2)$, $\ln T \sim N(8.5, 0.1^2)$, and the cost for drug 1 and 2 are still £5000 and £8000 per year respectively. But we must use the data samples to approximate the distributions of the other parameters. This is done by using the result Beta(1 + successes, 1 + failures), which is the formula for the posterior distributions of the estimators, given the binomially distributed observed data. (Result derived from Baye's Theorem for distributions).

Define $S_i(X)$ be the function that counts "successes" for drug_i, then from the data we get:

$$S_1(N|N) = 47, S_1(N|F) = 30, S_1(F|F) = 25, S_1(F|N) = 25$$

 $S_2(N|N) = 70, S_2(N|F) = 22, S_2(F|F) = 8, S_2(F|N) = 10.$

The posterior distributions for each parameter are then as follows;

$$\hat{\gamma}_{1} \sim Beta(1 + S(N|N), 1 + S(F|N)) = Beta(48, 26)$$

$$\hat{\theta}_{1} \sim Beta(1 + S(F|N), 1 + S(N|N)) = Beta(26, 48)$$

$$\hat{\delta}_{1} \sim Beta(1 + S(N|F), 1 + S(F|F)) = Beta(31, 26)$$

$$\hat{\phi}_{1} \sim Beta(1 + S(F|F), 1 + S(N|F)) = Beta(26, 31)$$

$$\hat{\gamma}_{2} \sim Beta(1 + S(N|N), 1 + S(F|N)) = Beta(71, 11)$$

$$\hat{\theta}_{2} \sim Beta(1 + S(F|N), 1 + S(N|N)) = Beta(11, 71)$$

$$\hat{\delta}_{2} \sim Beta(1 + S(N|F), 1 + S(F|F)) = Beta(23, 9)$$

$$\hat{\phi}_{2} \sim Beta(1 + S(F|F), 1 + S(N|F)) = Beta(9, 23)$$

We now want to find the probability that staying with drug 1 is the correct decision, (i.e P[INB>0]).

```
# Number of simulations we want to run.
N <- 10000
# Take N random samples of Estimators from their corresponding distributions
theta1 <- rbeta(N,26,48)
gamma1 <- rbeta(N,48,26)
phi1 \leftarrow rbeta(N, 26, 31)
delta1 <- rbeta(N,31,26)</pre>
theta2 <- rbeta(N,11,71)
gamma2 <- rbeta(N,71,11)</pre>
phi2 \leftarrow rbeta(N,9,23)
delta2 \leftarrow rbeta(N,32,9)
B1 <- 5000
B2 <- B1 + 3000
Qf <- rnorm(N, 0.6, 0.2)
Tf \leftarrow exp(rnorm(N, 8.5, 0.1))
Lambda <- 30000
# Stores E1, E2, C1, C2, for each set of randomly sampled estimators.
outputs <- FractureModel(gamma1, gamma2,
                           delta1, delta2,
                           phi1, phi2,
                           theta1, theta2,
                           B1, B2, Qf, Tf)
# If negative, drug 2 is more cost effective than drug 1.
INB <- as.integer(Lambda*(outputs$QALYgain.drug1-outputs$QALYgain.drug2)-
                     (outputs$cost.drug1-outputs$cost.drug2))
# Drug 1 becomes more cost effective if we are not prepared to
# pay more than the ICER output per QALY gained.
ICER <- as.integer((outputs$cost.drug1-outputs$cost.drug2) /</pre>
                      (outputs$QALYgain.drug1-outputs$QALYgain.drug2))
# Histogram of INB samples with it's distribution overlayed
hist(INB,probability=TRUE,
     xlim=c(-max(abs(INB)), max(abs(INB))),
     ylim=c(0,0.00004),
     xlab="Incremental Net Benefit (INB)",
     ylab="Probability Density",
     main="Fig.1:Incremental Net Benefit Distribution")
curve(dnorm(x,mean(INB),sqrt(var(INB))),
      col="red",lwd=2,add=TRUE)
abline(v=mean(INB),
       col="blue", lwd=2)
```



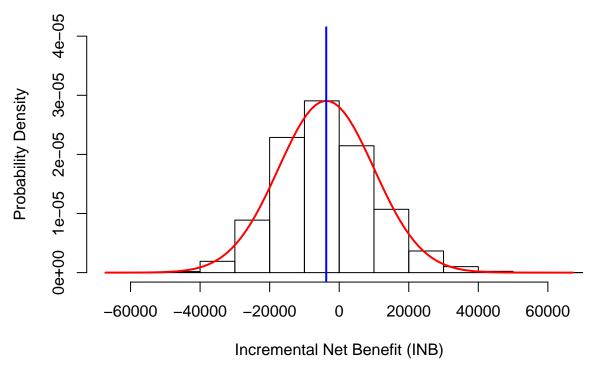


Fig.1: Here, the $INB \sim N(-3729, 13726^2)$ distributed. The histogram tells us that it is not clear whether drug 1 or drug 2 is more cost effective. Although the mean of the INB is negative, meaning drug 2 is more cost effective, 37.1% of the time the INB>0 meaning drug 1 is in fact the correct decision. Also the variance is large enough to cause concern about making the wrong decision as the chance of the INB taking a large positive or negative value is not negligible, i.e 15.9% of the time the INB<(-20000) or 20000 <INB. It is therefore not clear what the best decision is simplying by looking at the histogram and further investigation is required.

Fig.2: Cost-Effectiveness Graph

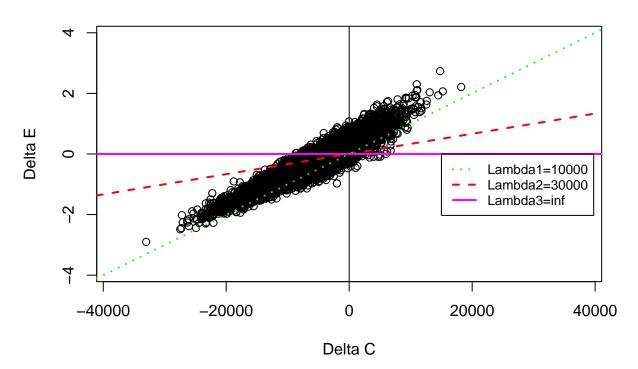


Fig.2: The plot shows the cost effectiveness line for different choices of λ . Points above the line are cases where drug 1 is more cost effective than drug 2. For increasing λ , the proportion of points that indicate drug 2 is more cost effective increases. Note that there is a clear limit to how certain we can be that drug 2 is more cost effective. Taking λ to infinity (the horizontal line), tells us we can never be confident we are making the correct decision if we pick drug 2, no matter how much money we wish to invest, so arbitrarily increasing our budget has little effect on our certainty about making the right choice in regards to drug 2.

The dotted line ($\lambda = 10000$) tells us that drug 1 is likely a better choice for a tight budget. For $\lambda = 30000$, we do not have compelling evidence that one drug is more cost effective than the other. 0.629 is the probability that picking drug 2 is the correct decision for $\lambda = 30000$, which is not strong enough to base a decision on.

```
Lambda <- seq(from=0,to=80000,by=100)
n <- length(Lambda)
CEAC <- rep(0,n)
for(i in 1:n){
    CEAC[i]<-mean(Lambda[i]*deltaE-deltaC>0)
```

Fig.3: INB > 0 for varying Lambda Values

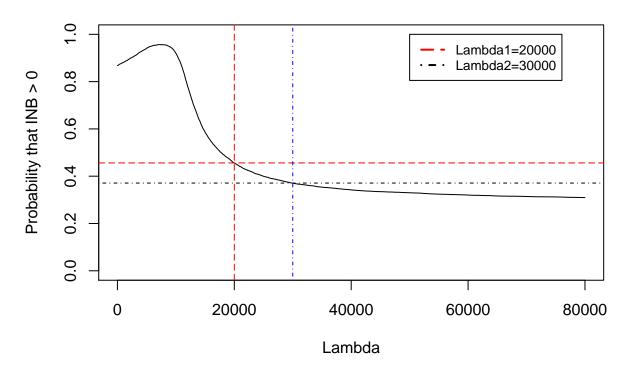


Fig.3: Shows the probability that drug 1 is the correct decision for different values of lambda. For $\lambda = 20000$ and $\lambda = 30000$ we can only be 54.39% and 62.9% sure that switching to drug 2 is the correct decision respectively. For smaller values of λ we see a dramatic increase in the certainty for choosing drug 1.

```
list(greaterThan20000=mean(30000*deltaE-deltaC>20000),
greaterThan10000=mean(30000*deltaE-deltaC>10000),
lessThan0=mean(30000*deltaE-deltaC<0),</pre>
```

```
lessThanMinus10000=mean(30000*deltaE-deltaC< -10000),
lessThanMinus20000=mean(30000*deltaE-deltaC< -20000))</pre>
```

```
## $greaterThan20000
## [1] 0.0493
##
## $greaterThan10000
## [1] 0.1564
##
## $lessThan0
## [1] 0.629
##
## $lessThanMinus10000
## [1] 0.3384
##
## $lessThanMinus20000
## [1] 0.1097
```

Taking a look at some milestone values from the INB distribution we see that the probability of the INB being over 10000 when we pick drug 2 is 0.1564, whereas the probability of the INB being less than -10000 when we pick drug 1 is approximately double that, i.e0.3384. Likewise the probability of being over 20000 when picking drug 2 is around half the probability of being under -20000 when picking drug 1, 0.0493 and 0.1097 respectively. Also we have a 62.9% chance of having the INB less than zero.

This is some evidence to suggest that drug 2 is the better choice however it is weak at best.

5. Conclusion

After performing the analysis we have not seen compelling evidence in support of switching to drug 2, nor have we seen compelling evidence to reject drug 2. We have been unable to find a way to reduce our uncertainty in making the wrong decision or reduce the cosequences of making the wrong decision. Therefore the correct decision is to collect a larger sample of data to investigate the cost effectiveness of drug 2 further.