National Institute for Health and Care Excellence

Final

Acne vulgaris: management

TSU NMA software code (moderate to severe acne)

NICE guideline NG198

Supplement 7

June 2021

Final

Supplementary material was developed by the National Guideline Alliance which is part of the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-4147-6

Contents

TSU NMA software code (moderate to severe acne)

Efficacy (% change in total lesion count from baseline)

A.1: Efficacy, base-case model (OpenBUGS)

```
# Arm and Trial-level data
# Random effects model for multi-arm trials
# Fixed class effects
model{                          # *** PROGRAM STARTS
for(i in 1:ns.a){                # LOOP THROUGH STUDIES WITH ARM DATA
   w[i,1] <- 0              # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   }

# trials reporting percent CFB
for(i in 1:ns.a1){                  # LOOP THROUGH STUDIES WITH %CFB ARM DATA
   for (k in 1:na[i]) {           #  LOOP THROUGH ARMS
      pCFB.se[i,k] <- pCFB.sd[i,k]/sqrt(n[i,k]) # calculate standard error
      pCFB.var[i,k] <- pow(pCFB.se[i,k],2)   # calculate variances
      pCFB.prec[i,k] <- 1/pCFB.var[i,k]      # set precisions
      pCFB[i,k] ~ dnorm(theta[i,k],pCFB.prec[i,k]) # normal likelihood

      theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor

      #Deviance contribution
      dev[i,k] <- (pCFB[i,k]-theta[i,k])*(pCFB[i,k]-theta[i,k])*pCFB.prec[i,k]
      }
   resdev[i] <- sum(dev[i,1:na[i]]
   )
```

```
}
# trials reporting CFB + B      # LOOP THROUGH STUDIES WITH CFB+B ARM DATA
for(i in (ns.a1+1):(ns.a1+ns.a2)){
   for (k in 1:na[i]) {          #  LOOP THROUGH ARMS
      x.se[i,k] <- x.sd[i,k]/sqrt(n[i,k])    # calculate standard error
      x.var[i,k] <- pow(x.se[i,k],2)   # calculate variances
      x.prec[i,k] <- 1/x.var[i,k]      # set precisions
      x[i,k] ~ dnorm(mu.X[i,k],x.prec[i,k]) # indpt normal likelihood for baseline mean
      mu.X[i,k] ~ dnorm(0,.0001)        # flat prior for baseline mean in likelihood

      CFB.se[i,k] <- CFB.sd[i,k]/sqrt(n[i,k])     # calculate standard error
      CFB.var[i,k] <- pow(CFB.se[i,k],2)   # calculate variances
      CFB.prec[i,k] <- 1/CFB.var[i,k]      # set precisions
      mu.CFB[i,k] <- mu.X[i,k]*(theta[i,k]/100)# calculate mean for CFB likelihood
      CFB[i,k] ~ dnorm(mu.CFB[i,k],CFB.prec[i,k]) # indpt normal likelihood for baseline mean

      theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor

      #Deviance contribution
      dev[i,k] <- (CFB[i,k]-mu.CFB[i,k])*(CFB[i,k]-mu.CFB[i,k])*CFB.prec[i,k]
      }
   resdev[i] <- sum(dev[i,1:na[i]]
   )
}
# trials reporting B + F
for(i in (ns.a1+ns.a2+1):ns.a){          # LOOP THROUGH STUDIES WITH B+F ARM DATA
   for (k in 1:na[i]) {            #  LOOP THROUGH ARMS
      #Calculate standard errors
      x.se[i,k] <- x.sd[i,k]/sqrt(n[i,k])
      y.se[i,k] <- y.sd[i,k]/sqrt(n[i,k])
      #Set precision matrix
```

```
      Sigma[i,k,1,1]<-pow(x.se[i,k],2)
      Sigma[i,k,2,2]<-pow(y.se[i,k],2)
      Sigma[i,k,1,2]<-corr[i]*x.se[i,k]*y.se[i,k]
      Sigma[i,k,2,1]<-Sigma[i,k,1,2]
      Prec[i,k,1:2,1:2]<-inverse(Sigma[i,k,1:2,1:2])
      #Set up vector for baseline and follow-up means
      y.XY[i,k,1]<-x[i,k]
      y.XY[i,k,2]<-y[i,k]

      # Bivariate normal likelihood for baseline and follow-up
      y.XY[i,k,1:2]~dmnorm(mu.XY[i,k,1:2],Prec[i,k,1:2,1:2])
      mu.XY[i,k,2]<- mu.XY[i,k,1]*(1-(theta[i,k]/100))
      mu.XY[i,k,1] ~ dnorm(0,.0001)        # flat prior for baseline mean in likelihood

      theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor

      #Deviance contribution
      for (j in 1:2){
         diff[i,k,j]<- y.XY[i,k,j]-mu.XY[i,k,j]
         z[i,k,j]<- inprod(Prec[i,k,j,1:2],diff[i,k,1:2])
         }
      dev[i,k]<-inprod(diff[i,k,1:2],z[i,k,1:2])
      }
   resdev[i] <- sum(dev[i,1:na[i]])
   }
# 2-arm trials reporting contrasts (e.g., split-face trials)
for(i in (ns.a+1):(ns.a+ns.t2)){        # LOOP THROUGH STUDIES WITH TRIAL DATA
   w[i,1] <- 0              # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0          # treatment effect is zero for control arm
   var[i,2] <- pow(se.T[i,2],2)   # calculate variances
   prec[i,2] <- 1/var[i,2]      # set precisions
```

```
   y.T[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood
   # Deviance contribution
   dev[i,2] <- (y.T[i,2]-delta[i,2])* (y.T[i,2]-delta[i,2])* prec[i,2]
   # summed residual deviance contribution for this trial
   resdev[i] <- dev[i,2]
   }
#RE Model (ARM AND TRIAL DATA)
for(i in 1:ns){                  # LOOP THROUGH STUDIES WITH ARM DATA
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
      # trial-specific RE distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
      # mean of RE distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
      # precision of RE distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
      # adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
      # cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
}

totresdev <- sum(resdev[])           #Total Residual Deviance
# Reference treatment currently Placebo (ref=1)
d[ref]<-0       # treatment effect is zero for reference treatment
D[class[ref]]<-0
# priors for mean class effect
for (j in 2:nc){
   D[j]~dnorm(0,.0001)
   }
# treatment effect = mean class effect
```

```
for (j in 2:nt){
   d[j] <- D[class[j]]
   }
#
sd ~ dunif(0,25)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
#
# pairwise mean differences for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
  for (k in (c+1):nt)  { mean.diff[c,k] <- d[k]-d[c] }
   }
# pairwise differences for classes
for (c in 1:(nc-1)){
   for (k in (c+1):nc){
      diffClass[c,k] <- D[k] - D[c]
      }
   }
# rank all classes
# ranking on relative scale
for (k in 1:nc){
   # rk[k] <- rank(D[],k)           # assumes lower values are “good”
   rk[k] <- nc+1-rank(D[],k)          # assumes higher values are “good”
   best[k] <- equals(rk[k],1)     #calculate probability that treat k is best
   # calculate probability that treat k is h-th best
   for (h in 1:nc){ prob[h,k] <- equals(rk[k],h) }
   }
# ranking on relative scale - males
for (k in 1:18){ D.m[k] <- D[k]}
for (k in 19:(nc-2)){ D.m[k] <- D[k+2]}
for (k in 1:(nc-2)){
   rk.m[k] <- (nc-2)+1-rank(D.m[],k)          # assumes higher values are “good”
```

```
    best.m[k] <- equals(rk.m[k],1)      #calculate probability that treat k is best
    # calculate probability that treat k is h-th best
    for (h in 1:nc){ prob.m[h,k] <- equals(rk.m[k],h) }
    }
}                                   # *** PROGRAM ENDS
```

A.2: Efficacy, node-splitting, class-level

A.2.1: R Code (requires R2OpenBUGS package)

```
##############################################################################
# Node-splitting for Acne Guideline - Efficacy at Class Level
# R script to run node-split for the MTC Random study effects, fixed
# class effects model using OpenBUGS
#
# Uses R2OpenBUGS package
#
# EFficacy
#  1. Need to include in the working directory the following files:
#           efficacy_class.txt --- text file with data
#           rse fce node-splitR2_v2_efficacy_class.txt --- text file holding BUGS code
#
#   2. Output files will be
#           data.txt --- holds all data as used by BUGS
#           log.odc and log.txt --- hold WinBUGS output
#           inits1.txt --- holds initial values as read by BUGS
#           script.txt --- BUGS script file with all commands to execute
#
#   3. Output files for each node should be transferred to a new directory
#      as they will be overwritten in each new run
#
#   4. Youmay need to edit the OpenBUGS location 'bd'
#
```

```
#   5. You will need to edit the working directory 'pathname'
#      to suit your computer settings
#
#   6. Run script file
#
#
###############################################################################
#
# Declare the directory where OpenBUGS is found in this computer
bd <- "C:/Program Files (x86)/OpenBUGS/OpenBUGS323/OpenBUGS.exe"
#
# Declare working directory
pathname <- "C:/Acne/M2S/Efficacy"
setwd(pathname)
#
# load package to call OpenBUGS
library(R2OpenBUGS)
#
# LOAD DATA MANIPULATING FUNCTIONS:
#
PairXY <- function(treat, na, pair)
  # Check if pair(X,Y) in row i of data
  # and reorder treatments in trial as appropriate
{
  N <- nrow(treat)
  multi <- rep(NA,length(na))
  split.ind <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  split.ind1 <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  split.ind2 <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  spliti <- rep(NA,length(na))
  split1i <- rep(NA,length(na))
```

```
  split2i <- rep(NA,length(na))
  pair1 <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  pair2 <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  k.ind <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  for (i in 1:N) {
    # is trial i a multiarm trial?
    multi[i] <- 1*(na[i]>2)
    for (k in 1:na[i]){
      # which arms contain a treatment in the pair?
      split.ind[i,k] <- 1*(treat[i,k]==pair[1])+1*(treat[i,k]==pair[2])
      # which arms contain the treatment in pair[1]?
      split.ind1[i,k] <- 1*(treat[i,k]==pair[1])
      # which arms contain the treatment in pair[2]?
      split.ind2[i,k] <- 1*(treat[i,k]==pair[2])
    }
    # does trial i contain multiples of pair[1]?
    split1i[i] <- 1*(sum(split.ind1[i,1:na[i]])>1)
    # does trial i contain multiples of pair[2]?
    split2i[i] <- 1*(sum(split.ind2[i,1:na[i]])>1)
    # does trial i contain both treatments in the pair?
    # (minus duplicates in multiarm trials that have one treatment (only) in pair)
    spliti[i] <- 1*((sum(split.ind[i,1:na[i]])-split1i[i]*(sum(split.ind1[i,1:na[i]])-split1i[i])-
split2i[i]*(sum(split.ind2[i,1:na[i]])-split2i[i]))>1)
    for (k in 1:na[i]) {
      # which arms contain the first element in the pair
      pair1[i,k] <- k*(1*(treat[i,k]==pair[1]))
      # which arms contain the second element in the pair
      pair2[i,k] <- k*(1*(treat[i,k]==pair[2]))
    }
    for (k in 1:na[i]) {
      # reposition order of arms within a trial according to node being split
```

```
    # k.ind ensures a treatment in the pair is in the baseline arm, where the
    # multi-arm trial contains both treatments in the pair

    # multi-arm trial contains both treatments in the pair
    # If a multi-arm trial does not contain the node, arm order stays the same
    k.ind[i,k]<-(k*((1-multi[i])+multi[i]*(1-spliti[i])+multi[i]*spliti[i]*(1*(split.ind[i,1]==1)))

      # If a multi-arm trial contains the node, the treatment in pair[1] is not duplicated in trial,
      # the baseline arm does not contain a treatment in the node, and the treatment
      # in arm k is pair[1], make this treatment baseline treatment
      + multi[i]*spliti[i]*(1-split1i[i])*(1-(1*(split.ind[i,1]==1)))*(1*(treat[i,k]==pair[1]))

      # If a multi-arm trial contains the node, the treatment in pair[1] is duplicated in trial,
      # the treatment in pair[2] is not duplicated in trial, the baseline arm does not contain
      # a treatment in the node, and the treatment in arm k is pair[2], make this treatment
baseline treatment
      + multi[i]*spliti[i]*split1i[i]*(1-split2i[i])*(1-(1*(split.ind[i,1]==1)))*(1*(treat[i,k]==pair[2]))

      # If a multi-arm trial contains the node, the treatment in pair[1] is not duplicated in trial,
      # the baseline arm does not contain a treatment in the node, and k is baseline arm,
      # move treatment to come after baseline treatment
      + sum(pair1[i,1:na[i]])*(1-split1i[i])*multi[i]*spliti[i]*(1-(1*(split.ind[i,1]==1)))*(1*(k==1))

      # If a multi-arm trial contains the node, the treatment in pair[1] is duplicated in trial,
      # the treatment in pair[2] is not duplicated in trial, the baseline arm does not contain a
      # treatment in the node, and k is baseline arm, move treatment to come after baseline
treatment
      + sum(pair2[i,1:na[i]])*split1i[i]*(1-split2i[i])*multi[i]*spliti[i]*(1-
(1*(split.ind[i,1]==1)))*(1*(k==1))

      # If a multi-arm trial contains the node, the treatment in pair[1] are not duplicated in
trial,
```

```
        # the baseline arm does not contain a treatment in the node, k is NOT baseline arm,
        # and treatment in arm k is NOT pair[1], arm order stays the same
        + k*multi[i]*spliti[i]*(1-split1i[i])*(1-(1*(split.ind[i,1]==1)))*(1-(1*(k==1)))*(1-
(1*(treat[i,k]==pair[1])))


        # If a multi-arm trial contains the node, the treatment in pair[1] is duplicated in trial,
        # the treatment in pair[2] is not duplicated in trial, the baseline arm does not contain a
treatment in the node, k is NOT baseline arm,
        # and treatment in arm k is NOT pair[2], arm order stays the same
        + k*multi[i]*spliti[i]*split1i[i]*(1-split2i[i])*(1-(1*(split.ind[i,1]==1)))*(1-(1*(k==1)))*(1-
(1*(treat[i,k]==pair[2]))))
    }
  }
  k.ind
}
#############################################################################
#
# load data for MTC
MTCData <- read.table("efficacy_class.txt", header=TRUE)
n <- data.matrix(MTCData[,c("n1", "n2", "n3", "n4")])
x <- data.matrix(MTCData[,c("x1", "x2", "x3", "x4")])
x.sd <- data.matrix(MTCData[,c("x.sd1", "x.sd2", "x.sd3", "x.sd4")])
y <- data.matrix(MTCData[,c("y1", "y2", "y3", "y4")])
y.sd <- data.matrix(MTCData[,c("y.sd1", "y.sd2", "y.sd3", "y.sd4")])
CFB <- data.matrix(MTCData[,c("CFB1", "CFB2", "CFB3", "CFB4")])
CFB.sd <- data.matrix(MTCData[,c("CFB.sd1", "CFB.sd2", "CFB.sd3", "CFB.sd4")])
pCFB <- data.matrix(MTCData[,c("pCFB1", "pCFB2", "pCFB3", "pCFB4")])
pCFB.sd <- data.matrix(MTCData[,c("pCFB.sd1", "pCFB.sd2", "pCFB.sd3", "pCFB.sd4")])
y.T <- data.matrix(cbind(rep(NA,length(n[,1])),MTCData[,c("y.T2","y.T3","y.T4")]))
se.T <- data.matrix(cbind(rep(NA,length(n[,1])),MTCData[,c("se.T2","se.T3","se.T4")]))
V <- data.matrix(MTCData["V"])
corr <- data.matrix(MTCData["corr"])
```

```
c <- data.matrix(MTCData[,c("c1", "c2", "c3", "c4")])
na <- data.matrix(MTCData[,"na"])
#Class when running model at class level
class <- 1:max(c,na.rm = TRUE)
nt <- max(c, na.rm=TRUE)
nc <- max(class)
ns <- nrow(n)
ns.a <- 48  #studies reporting arm-level data
ns.a1 <- 29   #pCFB studies
ns.a2 <- 11   #CFB studies
ns.t2 <- 7    #2-arm studies reporting contrasts
ref <- 1    #reference treatment
#
initv1 <- list(direct=0,  D=c(NA,rep(0,nc-1)), mu=rep(0,ns.a), sd=1)
initv2 <- list(direct=0.05,  D=c(NA,rep(-1.2,nc-1)), mu=rep(0.5,ns.a), sd=3)
#############################################################################
#
# Check which notes to split
#
library(gemtc)
ns.data<-mtc.data.studyrow(MTCData,
                           armVars=c('treatment'='c'),
                           nArmsVar='na',
                           studyVars=c(),
                           studyNames=MTCData$study,
                           treatmentNames=NA,
                           patterns=c('%s', '%s%d'))
net<-mtc.network(data.ab=ns.data,description="Efficacy_trt")
## Print which nodes to split
splitcomps<-mtc.nodesplit.comparisons(net)
print(splitcomps)
```

```
#
#############################################################################
##
#  NODE-SPLITTING ROUTINE
#############################################################################
##
#
#
# Define nodes to split
pair<-splitcomps
pair
# Run node split models
for(j in 1:length(pair[,1])){
  print(pair[j,])

  k.ind <- PairXY(treat=c,na=na[,1],pair=as.numeric(pair[j,]))

  # Setup subdirectory to hold results for each node-split
  dir.create(paste("REFCEnode",pair[j,1],"_",pair[j,2],sep=""))

  # Build data file: stored in the working directory as "data.txt"
  bugs.data(list("n"=n,"x"=x,"x.sd"=x.sd,"y"=y,"y.sd"=y.sd,
                 "CFB"=CFB,"CFB.sd"=CFB.sd,"pCFB"=pCFB,"pCFB.sd"=pCFB.sd,
                 "y.T"=y.T,"se.T"=se.T,"V" = V[,1],"corr" = corr[,1],
                 "t"=c, "class"=class,
                 "na" = na[,1], "ns.a" = ns.a, "ns.a1" = ns.a1, "ns.a2" = ns.a2,
                 "nt" = nt, "nc" = nc, "ns" = ns, "ns.t2" = ns.t2,
                 "ref" = ref, "pair" = as.numeric(pair[j,]), "k.ind" = k.ind) )

  # Call OpenBUGS
  #
  bugs(data = "data.txt",
```

```
    inits = list(initv1,initv2),
    #inits = list(initv1),
    parameters.to.save = c("direct", "d", "prob","totresdev","indirect","sd"),
    model.file = "rse fce node-splitR2_v2_efficacy_class.txt",
    n.chains = 2,
    n.iter = 120000,
    n.burnin = 40000,
    n.thin = 1,
    OpenBUGS.pgm = bd,
    debug = FALSE,
    save.history = TRUE,
    useWINE=FALSE)
  #
  # Copy input and output files to relevant directory
  file.copy("data.txt", paste("REFCEnode",pair[j,1],"_",pair[j,2],"/data.txt",sep=""),
overwrite=TRUE)
  file.copy(paste(tempdir(),"/log.odc",sep=""),
paste(pathname,"/REFCEnode",pair[j,1],"_",pair[j,2],"/log.odc",sep=""), overwrite=TRUE)
  file.copy(paste(tempdir(),"/log.txt",sep=""),
paste(pathname,"/REFCEnode",pair[j,1],"_",pair[j,2],"/log.txt",sep=""), overwrite=TRUE)
  file.copy(paste(tempdir(),"/inits1.txt",sep=""),
paste(pathname,"/REFCEnode",pair[j,1],"_",pair[j,2],"/inits1.txt",sep=""), overwrite=TRUE)
  file.copy(paste(tempdir(),"/script.txt",sep=""),
paste(pathname,"/REFCEnode",pair[j,1],"_",pair[j,2],"/script.txt",sep=""), overwrite=TRUE)
  #
  # REPEAT FOR ALL OTHER NODES
}
```

A.2.2 OpenBUGS Code

```
model{                          # *** PROGRAM STARTS
for(i in 1:ns.a){               # LOOP THROUGH STUDIES WITH ARM DATA
   w[i,1] <- 0              # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
```

```
  }


# trials reporting percent CFB
for(i in 1:ns.a1){                  # LOOP THROUGH STUDIES WITH %CFB ARM DATA
  for (k in 1:na[i]) {            #  LOOP THROUGH ARMS
    pCFB.se[i,k.ind[i,k]] <- pCFB.sd[i,k.ind[i,k]]/sqrt(n[i,k.ind[i,k]])  # calculate standard error
    pCFB.var[i,k.ind[i,k]] <- pow(pCFB.se[i,k.ind[i,k]],2)   # calculate variances
    pCFB.prec[i,k.ind[i,k]] <- 1/pCFB.var[i,k.ind[i,k]]      # set precisions
    pCFB[i,k.ind[i,k]] ~ dnorm(theta[i,k],pCFB.prec[i,k.ind[i,k]]) # normal likelihood
    theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
    #Deviance contribution
    dev[i,k] <- (pCFB[i,k.ind[i,k]]-theta[i,k])*(pCFB[i,k.ind[i,k]]-
theta[i,k])*pCFB.prec[i,k.ind[i,k]]
    split[i,k] <- equals(t[i,k.ind[i,1]], pair[1]) * equals(t[i,k.ind[i,k]], pair[2]) -
equals(t[i,k.ind[i,1]], pair[2]) * equals(t[i,k.ind[i,k]], pair[1])
      }
  resdev[i] <- sum(dev[i,1:na[i]])
}
# trials reporting CFB + B      # LOOP THROUGH STUDIES WITH CFB+B ARM DATA
for(i in (ns.a1+1):(ns.a1+ns.a2)){
  for (k in 1:na[i]) {          #  LOOP THROUGH ARMS
    x.se[i,k.ind[i,k]] <- x.sd[i,k.ind[i,k]]/sqrt(n[i,k.ind[i,k]])     # calculate standard error
    x.var[i,k.ind[i,k]] <- pow(x.se[i,k.ind[i,k]],2)   # calculate variances
    x.prec[i,k.ind[i,k]] <- 1/x.var[i,k.ind[i,k]]      # set precisions
    x[i,k.ind[i,k]] ~ dnorm(mu.X[i,k],x.prec[i,k.ind[i,k]]) # indpt normal likelihood for baseline
mean
    mu.X[i,k] ~ dnorm(0,.0001)I(0,)                    # flat prior for baseline mean in likelihood

    CFB.se[i,k.ind[i,k]] <- CFB.sd[i,k.ind[i,k]]/sqrt(n[i,k.ind[i,k]])      # calculate standard error
    CFB.var[i,k.ind[i,k]] <- pow(CFB.se[i,k.ind[i,k]],2)   # calculate variances
    CFB.prec[i,k.ind[i,k]] <- 1/CFB.var[i,k.ind[i,k]]      # set precisions
    mu.CFB[i,k] <- mu.X[i,k]*(theta[i,k]/100)# calculate mean for CFB likelihood
```

```
      CFB[i,k.ind[i,k]] ~ dnorm(mu.CFB[i,k],CFB.prec[i,k.ind[i,k]]) # indpt normal likelihood for
baseline mean

      theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor

      #Deviance contribution

      dev[i,k] <- (CFB[i,k.ind[i,k]]-mu.CFB[i,k])*(CFB[i,k.ind[i,k]]-
mu.CFB[i,k])*CFB.prec[i,k.ind[i,k]]

      split[i,k] <- equals(t[i,k.ind[i,1]], pair[1]) * equals(t[i,k.ind[i,k]], pair[2]) -
equals(t[i,k.ind[i,1]], pair[2]) * equals(t[i,k.ind[i,k]], pair[1])

      }

   resdev[i] <- sum(dev[i,1:na[i]])

}

# trials reporting B + F

for(i in (ns.a1+ns.a2+1):ns.a){          # LOOP THROUGH STUDIES WITH B+F ARM DATA

   for (k in 1:na[i]) {            #  LOOP THROUGH ARMS

      #Calculate standard errors

      x.se[i,k.ind[i,k]] <- x.sd[i,k.ind[i,k]]/sqrt(n[i,k.ind[i,k]])

      y.se[i,k.ind[i,k]] <- y.sd[i,k.ind[i,k]]/sqrt(n[i,k.ind[i,k]])

      #Set precision matrix

      Sigma[i,k.ind[i,k],1,1]<-pow(x.se[i,k.ind[i,k]],2)

      Sigma[i,k.ind[i,k],2,2]<-pow(y.se[i,k.ind[i,k]],2)

      Sigma[i,k.ind[i,k],1,2]<-corr[i]*x.se[i,k.ind[i,k]]*y.se[i,k.ind[i,k]]

      Sigma[i,k.ind[i,k],2,1]<-Sigma[i,k.ind[i,k],1,2]

      Prec[i,k.ind[i,k],1:2,1:2]<-inverse(Sigma[i,k.ind[i,k],1:2,1:2])

      #Set up vector for baseline and follow-up means

      y.XY[i,k.ind[i,k],1]<-x[i,k.ind[i,k]]

      y.XY[i,k.ind[i,k],2]<-y[i,k.ind[i,k]]


      # Bivariate normal likelihood for baseline and follow-up

      y.XY[i,k.ind[i,k],1:2]~dmnorm(mu.XY[i,k,1:2],Prec[i,k.ind[i,k],1:2,1:2])

      mu.XY[i,k,2]<- mu.XY[i,k,1]*(1-(theta[i,k]/100))

      mu.XY[i,k,1] ~ dnorm(0,.0001)I(0,)                    # flat prior for baseline mean in
likelihood
```

```
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor


        #Deviance contribution
        for (j in 1:2){
                    diff[i,k,j]<- y.XY[i,k.ind[i,k],j]-mu.XY[i,k,j]
                    z[i,k,j]<- inprod(Prec[i,k.ind[i,k],j,1:2],diff[i,k,1:2])
                    }
        dev[i,k]<-inprod(diff[i,k,1:2],z[i,k,1:2])


        split[i,k] <- equals(t[i,k.ind[i,1]], pair[1]) * equals(t[i,k.ind[i,k]], pair[2]) -
equals(t[i,k.ind[i,1]], pair[2]) * equals(t[i,k.ind[i,k]], pair[1])
        }
    resdev[i] <- sum(dev[i,1:na[i]])
}
# 2-arm trials reporting contrasts (e.g., split-face trials)
for(i in (ns.a+1):(ns.a+ns.t2)){        # LOOP THROUGH STUDIES WITH TRIAL DATA
    w[i,1] <- 0              # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0          # treatment effect is zero for control arm
    var[i,2] <- pow(se.T[i,2],2)   # calculate variances
    prec[i,2] <- 1/var[i,2]      # set precisions
    y.T[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood
#Deviance contribution
    dev[i,2] <- (y.T[i,2]-delta[i,2])*
                    (y.T[i,2]-delta[i,2])* prec[i,2]
    split[i,2] <- equals(t[i,1], pair[1]) * equals(t[i,2], pair[2]) - equals(t[i,1], pair[2]) * equals(t[i,2],
pair[1])
    #  summed residual deviance contribution for this trial
    resdev[i] <- dev[i,2]
    }
# 4-arm trials reporting contrasts
# No k.ind for Thiboutot 2002 because code can't handle double nodes
```

```
for(i in (ns.a+ns.t2+1):ns){       # LOOP THROUGH STUDIES WITH TRIAL DATA
   w[i,1] <- 0              # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0          # treatment effect is zero for control arm
   for (k in 2:na[i]) {          #  LOOP THROUGH ARMS
      var[i,k] <- pow(se.T[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
      }
   for(k in 2:na[i]){
      split[i,k] <- equals(t[i,1], pair[1]) * equals(t[i,k], pair[2]) - equals(t[i,k], pair[2]) *
equals(t[i,k], pair[1])
      }

   for (k in 1:(na[i]-1)){              # set variance-covariance matrix
      for (j in 1:(na[i]-1)){
                  Sigma2[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,(k+1)]*equals(j,k)
                  }
      }
   Omega2[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma2[i,,]) # Precision matrix

   # multivariate normal likelihood for 4-arm trials
   y.T[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega2[i,1:(na[i]-1),1:(na[i]-1)])

   # Deviance contribution for trial i
   for (k in 1:(na[i]-1)){              # multiply vector & matrix
                  ydiff[i,k] <- y.T[i,(k+1)] - delta[i,(k+1)]
                  z2[i,k] <- inprod(Omega2[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
                  }
   resdev[i] <- inprod(ydiff[i,1:(na[i]-1)], z2[i,1:(na[i]-1)])
   }
#RE Model (ARM AND TRIAL DATA)
for(i in 1:ns){              # LOOP THROUGH STUDIES WITH ARM DATA
```

```
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
                  # trial-specific RE distributions
                  delta[i,k] ~ dnorm(md[i,k],taud[i,k])
                  # mean of RE distributions, with multi-arm trial correction
                  md[i,k] <-  (d[t[i,k.ind[i,k]]] - d[t[i,k.ind[i,1]]])*(1-abs(split[i,k])) + direct * split[i,k]
+ sw[i,k]
                  # precision of RE distributions (with multi-arm trial correction)
                  taud[i,k] <- tau *2*(k-1)/k
                  # adjustment, multi-arm RCTs
                  w[i,k] <- delta[i,k] - ((d[t[i,k.ind[i,k]]] - d[t[i,k.ind[i,1]]])*(1-abs(split[i,k])) + direct *
split[i,k] )
                  # cumulative adjustment for multi-arm trials
                  sw[i,k] <- sum(w[i,1:k-1])/(k-1)
                  }
   }
totresdev <- sum(resdev[])          #Total Residual Deviance
#
# Reference treatment currently Placebo (ref=1)
d[ref]<-0      # treatment effect is zero for reference treatment
D[class[ref]]<-0
#
# priors for mean class effect
for (j in 2:nc){
   D[j]~dnorm(0,.0001)
   }
# treatment effect = mean class effect
for (j in 2:nt){
   d[j] <- D[class[j]]
   }
#
direct ~ dnorm(0,.0001)     # vague prior for direct comparison parameter
indirect <- mean.diff[pair[1], pair[2]]
```

```
#
#calculate difference between direct and lor
diff.ns <- direct - indirect
# calculate p-value
prob <- step(diff.ns)
#
sd ~ dunif(0,25)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
#
# pairwise mean differences for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
   for (k in (c+1):nt)  {
                  mean.diff[c,k] <- d[k]-d[c]
                  mean.diff[k,c] <- -mean.diff[c,k]
                  }
   }
}                              # *** PROGRAM ENDS
```

Discontinuation for any reason

A.3: Discontinuation for any reason, base-case model (WinBUGS)

Note: Same code run separately for female and male populations

```
model{
for(i in 1:ns){                 # LOOP OVER ALL STUDIES
   mu[i] ~ dnorm(0,.0001)         # vague priors for all trial baselines
   for (k in 1:na[i]){            # LOOP OVER ARMS
         r[i,k] ~ dbin(p[i,k],n[i,k])  # binomial likelihood
         logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]] # model for linear predictor
         rhat[i,k] <- p[i,k] * n[i,k]  # expected value of the numerators
         #Deviance contribution
         dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) -
log(n[i,k]-rhat[i,k])))
```

```
        }
    # Summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {            # RE model for treatment effects
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])  # trial-specific LOR distributions
        # mean of LOR distributions (with multi-arm trial correction)
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
        # precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
        # adjustment for multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
        # cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
        }
    }
totresdev <- sum(resdev[])        # Total Residual Deviance
#
# Reference treatment
d[ref]<-0       # treatment effect is zero for reference treatment
D[class[ref]]<-0
#
# vague prior for class effects
for (j in 2:nc){
    D[j] ~ dnorm(0, .0001)
    }
for (j in 2:nt){
    d[j] <- D[class[j]]
    }
#
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
```

```
#
# pairwise ORs and LORs for all possible pair-wise treatment comparisons
for (c in 1:(nt-1)){
   for (k in (c+1):nt){
         or[c,k] <- exp(d[k] - d[c])
         lor[c,k] <- (d[k]-d[c])
         }
   }
#
# pairwise differences for classes
for (c in 1:(nc-1)){
   for (k in (c+1):nc){
         diffClass[c,k] <- D[k] - D[c]
         orClass[c,k] <- exp(D[k] - D[c])
         }
    }
# ranking on relative scale
for (k in 1:nc){
   rkClass[k] <- rank(D[],k)
   bestClass[k] <- equals(rkClass[k],1) # Smallest is best (i.e. rank 1)
   # prob class k is h-th best, prob[1,k]=best[k]
   for (h in 1:nc) { probClass[h,k] <- equals(rkClass[k],h) }
   }
#
}                              # *** PROGRAM ENDS
```

A.4: Discontinuation for any reason, node-splitting, class-level

A.4.1: R Code (requires R2OpenBUGS package)

```
#############################################################################
# Node-splitting for Acne Guideline - Discontinuation (any)
# R script to run node-split for the MTC Random study effects, fixed
```

```
# class effects model using OpenBUGS
#
# Uses R2OpenBUGS package
#
# Discontinuation (any reason)
#  1. Need to include in the working directory the following files:
#           Disc any_UK.txt --- text file with data
#           rse fce node-splitR2_v3.txt --- text file holding BUGS code
#
#   2. Output files will be
#           coda1.txt  --- holds coda output
#           codaIndex.txt --- holds indexes to coda output
#           data.txt --- holds all data as used by BUGS
#           log.odc and log.txt --- hold WinBUGS output
#           inits1.txt --- holds initial values as read by BUGS
#           script.txt --- BUGS script file with all commands to execute
#
#   3. Output files for each node should be transferred to a new directory
#      as they will be overwritten in each new run
#
#   4. You may need to edit the OpenBUGS location 'bd'
#
#   5. You will need to edit the working directory 'pathname'
#      to suit your computer settings
#
#   6. Run script file
#
#   7. To repeat for other node-splits need to change variable 'pair'
#      and edit output file names
#
################################################################################
```

```
#
# Declare the directory where OpenBUGS is found in this computer
bd <- "C:/Program Files (x86)/OpenBUGS/OpenBUGS323/OpenBUGS.exe"
#
# Declare working directory
pathname <- "C:/Acne/M2S/Disc Any/"
setwd(pathname)
#
# load package to call OpenBUGS
library(R2OpenBUGS)
#
# LOAD DATA MANIPULATING FUNCTIONS:
#
PairXY <- function(treat, na, pair)
  # Check if pair(X,Y) in row i of data
  # and reorder treatments in trial as appropriate
{
  N <- nrow(treat)
  multi <- rep(NA,length(na))
  split.ind <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  split.ind1 <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  split.ind2 <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  spliti <- rep(NA,length(na))
  split1i <- rep(NA,length(na))
  split2i <- rep(NA,length(na))
  pair1 <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  pair2 <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  k.ind <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  for (i in 1:N) {
    # is trial i a multiarm trial?
    multi[i] <- 1*(na[i]>2)
```

```
  for (k in 1:na[i]){
    # which arms contain a treatment in the pair?
    split.ind[i,k] <- 1*(treat[i,k]==pair[1])+1*(treat[i,k]==pair[2])
    # which arms contain the treatment in pair[1]?
    split.ind1[i,k] <- 1*(treat[i,k]==pair[1])
    # which arms contain the treatment in pair[2]?
    split.ind2[i,k] <- 1*(treat[i,k]==pair[2])
  }
  # does trial i contain multiples of pair[1]?
  split1i[i] <- 1*(sum(split.ind1[i,1:na[i]])>1)
  # does trial i contain multiples of pair[2]?
  split2i[i] <- 1*(sum(split.ind2[i,1:na[i]])>1)
  # does trial i contain both treatments in the pair?
  # (minus duplicates in multiarm trials that have one treatment (only) in pair)
  spliti[i] <- 1*((sum(split.ind[i,1:na[i]])-split1i[i]*(sum(split.ind1[i,1:na[i]])-split1i[i])-
split2i[i]*(sum(split.ind2[i,1:na[i]])-split2i[i]))>1)
  for (k in 1:na[i]) {
    # which arms contain the first element in the pair
    pair1[i,k] <- k*(1*(treat[i,k]==pair[1]))
    # which arms contain the second element in the pair
    pair2[i,k] <- k*(1*(treat[i,k]==pair[2]))
  }
  for (k in 1:na[i]) {
    # reposition order of arms within a trial according to node being split
    # k.ind ensures a treatment in the pair is in the baseline arm, where the
    # multi-arm trial contains both treatments in the pair
        # If a multi-arm trial does not contain the node, arm order stays the same
    k.ind[i,k]<-(k*((1-multi[i])+multi[i]*(1-spliti[i])+multi[i]*spliti[i]*(1*(split.ind[i,1]==1)))


        # If a multi-arm trial contains the node, the treatment in pair[1] is not duplicated in
trial,
        # the baseline arm does not contain a treatment in the node, and the treatment
```

```
            # in arm k is pair[1], make this treatment baseline treatment
             + multi[i]*spliti[i]*(1-split1i[i])*(1-(1*(split.ind[i,1]==1)))*(1*(treat[i,k]==pair[1]))


            # If a multi-arm trial contains the node, the treatment in pair[1] is duplicated in
trial,
            # the treatment in pair[2] is not duplicated in trial, the baseline arm does not
contain
            # a treatment in the node, and the treatment in arm k is pair[2], make this
treatment baseline treatment
            + multi[i]*spliti[i]*split1i[i]*(1-split2i[i])*(1-
(1*(split.ind[i,1]==1)))*(1*(treat[i,k]==pair[2]))


            # If a multi-arm trial contains the node, the treatment in pair[1] is not duplicated in
trial,
            # the baseline arm does not contain a treatment in the node, and k is baseline
arm,
            # move treatment to come after baseline treatment
            + sum(pair1[i,1:na[i]])*(1-split1i[i])*multi[i]*spliti[i]*(1-
(1*(split.ind[i,1]==1)))*(1*(k==1))


            # If a multi-arm trial contains the node, the treatment in pair[1] is duplicated in
trial,
            # the treatment in pair[2] is not duplicated in trial, the baseline arm does not
contain a
            # treatment in the node, and k is baseline arm, move treatment to come after
baseline treatment
            + sum(pair2[i,1:na[i]])*split1i[i]*(1-split2i[i])*multi[i]*spliti[i]*(1-
(1*(split.ind[i,1]==1)))*(1*(k==1))


            # If a multi-arm trial contains the node, the treatment in pair[1] are not duplicated
in trial,
            # the baseline arm does not contain a treatment in the node, k is NOT baseline
arm,
            # and treatment in arm k is NOT pair[1], arm order stays the same
            + k*multi[i]*spliti[i]*(1-split1i[i])*(1-(1*(split.ind[i,1]==1)))*(1-(1*(k==1)))*(1-
(1*(treat[i,k]==pair[1])))
```

```
            # If a multi-arm trial contains the node, the treatment in pair[1] is duplicated in
trial,
            # the treatment in pair[2] is not duplicated in trial, the baseline arm does not
contain a treatment in the node, k is NOT baseline arm,
            # and treatment in arm k is NOT pair[2], arm order stays the same
            + k*multi[i]*spliti[i]*split1i[i]*(1-split2i[i])*(1-(1*(split.ind[i,1]==1)))*(1-(1*(k==1)))*(1-
(1*(treat[i,k]==pair[2])))
   }
 }
 k.ind
}
#############################################################################
#
# load data for MTC
MTCData <- read.table("Disc any_UK.txt", header=TRUE)
r <- data.matrix(MTCData[,c("r1", "r2", "r3", "r4")])
n <- data.matrix(MTCData[,c("n1", "n2", "n3", "n4")])
c <- data.matrix(MTCData[,c("c1", "c2", "c3", "c4")])
na <- data.matrix(MTCData["na"])
#Class when running model at class level
class <- 1:max(c,na.rm = TRUE)
nt <- max(c, na.rm=TRUE)
nc <- max(class)
ns <- nrow(r)
ref <- 1    #reference treatment
#
# define initial values
initv1 <- list(direct=0,  D=c(NA,rep(0,nc-1)), mu=rep(0,ns), sd=1)
initv2 <- list(direct=0.05,  D=c(NA,rep(-1.2,nc-1)), mu=rep(0.5,ns), sd=3)
#############################################################################
#
# Check which notes to split
#
```

```
library(gemtc)
ns.data<-mtc.data.studyrow(MTCData,
                    armVars=c('treatment'='c', 'responders'='r', 'sampleSize'='n'),
                    nArmsVar='na',
                    studyVars=c(),
                    studyNames=MTCData$studyid,
                    treatmentNames=NA,
                    patterns=c('%s', '%s%d'))
net<-mtc.network(data.ab=ns.data,description="Disc any_trt")
## Print which nodes to split
splitcomps<-mtc.nodesplit.comparisons(net)
print(splitcomps)
#
################################################################################
##
#  NODE-SPLITTING ROUTINE
################################################################################
##
#
#
# Define nodes to split
pair<-splitcomps
pair
# Run node split models
for(j in 1:length(pair[,1])){
  print(pair[j,])

  k.ind <- PairXY(treat=c,na=na[,1],pair=as.numeric(pair[j,]))

  # Setup subdirectory to hold results for each node-split
  dir.create(paste("REFCEnode",pair[j,1],"_",pair[j,2],sep=""))
  # Build data file: stored in the working directory as "data.txt"
```

```
  bugs.data(list("r"=r,"n"=n,"t"=c, "class"=class,
                 "na" = na[,1], "nt" = nt, "nc" = nc, "ns" = ns, "ref" = ref,
                 "pair" = as.numeric(pair[j,]), "k.ind" = k.ind))


  # Call OpenBUGS
  #
  bugs(data = "data.txt",
     inits = list(initv1,initv2),
     #inits = list(initv1),
     parameters.to.save = c("direct", "d", "prob","totresdev","indirect","sd"),
     model.file = "rse fce node-splitR2_v3.txt",
     n.chains = 2,
     n.iter = 120000,          #including burn-in iterations
     n.burnin = 40000,
     n.thin = 1,
     OpenBUGS.pgm = bd,
     debug = FALSE,
     save.history = TRUE,
     useWINE=FALSE)
  #
  # Copy input and output files to relevant directory
  file.copy("data.txt", paste("REFCEnode",pair[j,1],"_",pair[j,2],"/data.txt",sep=""),
overwrite=TRUE)
  file.copy(paste(tempdir(),"/log.odc",sep=""),
paste(pathname,"/REFCEnode",pair[j,1],"_",pair[j,2],"/log.odc",sep=""), overwrite=TRUE)
  file.copy(paste(tempdir(),"/log.txt",sep=""),
paste(pathname,"/REFCEnode",pair[j,1],"_",pair[j,2],"/log.txt",sep=""), overwrite=TRUE)
  file.copy(paste(tempdir(),"/inits1.txt",sep=""),
paste(pathname,"/REFCEnode",pair[j,1],"_",pair[j,2],"/inits1.txt",sep=""), overwrite=TRUE)
  file.copy(paste(tempdir(),"/script.txt",sep=""),
paste(pathname,"/REFCEnode",pair[j,1],"_",pair[j,2],"/script.txt",sep=""), overwrite=TRUE)
  #
  # REPEAT FOR ALL OTHER NODES
```

```
}
```

A.4.2 OpenBUGS Code

```
model{
for(i in 1:ns){                 # LOOP OVER ALL STUDIES
   delta[i,1] <- 0  # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]){             # LOOP OVER ARMS
         r[i,k.ind[i,k]] ~ dbin(p[i,k],n[i,k.ind[i,k]])  # binomial likelihood
         logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
         rhat[i,k] <- p[i,k] * n[i,k.ind[i,k]]  # expected value of the numerators
         #Deviance contribution
         dev[i,k] <- 2 * (r[i,k.ind[i,k]] * (log(r[i,k.ind[i,k]])-log(rhat[i,k])) +  (n[i,k.ind[i,k]]-
r[i,k.ind[i,k]]) * (log(n[i,k.ind[i,k]]-r[i,k.ind[i,k]]) - log(n[i,k.ind[i,k]]-rhat[i,k])))
         split[i,k] <- equals(t[i,k.ind[i,1]], pair[1]) * equals(t[i,k.ind[i,k]], pair[2]) -
equals(t[i,k.ind[i,1]], pair[2]) * equals(t[i,k.ind[i,k]], pair[1])
         }
   # Summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {            # RE model for treatment effects
         delta[i,k] ~ dnorm(md[i,k],taud[i,k])  # trial-specific LOR distributions
         # mean of LOR distributions (with multi-arm trial correction)
         md[i,k] <-  (d[t[i,k.ind[i,k]]] - d[t[i,k.ind[i,1]]])*(1-abs(split[i,k])) + direct * split[i,k] + sw[i,k]
         # precision of LOR distributions (with multi-arm trial correction)
         taud[i,k] <- tau *2*(k-1)/k
         # adjustment for multi-arm RCTs
         w[i,k] <- delta[i,k] - ((d[t[i,k.ind[i,k]]] - d[t[i,k.ind[i,1]]])*(1-abs(split[i,k])) + direct *
split[i,k] )
         # cumulative adjustment for multi-arm trials
         sw[i,k] <- sum(w[i,1:k-1])/(k-1)
         }
   }
totresdev <- sum(resdev[])       # Total Residual Deviance
```

```
#
d[ref]<-0       # treatment effect is zero for reference treatment
D[class[ref]]<-0
# vague prior for class effects
for (j in 2:nc){
   D[j] ~ dnorm(0, .0001)
   }
for (j in 2:nt){
   d[j] <- D[class[j]]
   }
direct ~ dnorm(0,.0001)      # vague prior for direct comparison parameter
indirect <- lor[pair[1], pair[2]]
#calculate difference between direct and lor
diff <- direct - indirect
# calculate p-value
prob <- step(diff)
#
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
#
# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)){
   for (k in (c+1):nt){
         or[c,k] <- exp(d[k] - d[c])
         lor[c,k] <- (d[k]-d[c])
         lor[k,c] <- -lor[c,k]
         }
   }
}                              # *** PROGRAM ENDS
```

Discontinuation due to side effects

A.5: Discontinuation due to side effects, base-case model (WinBUGS)

Note: Same code run separately for female and male populations

```
model{
for(i in 1:ns){                 # LOOP OVER ALL STUDIES
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]){             # LOOP OVER ARMS
         r[i,k] ~ dbin(p[i,k],n[i,k])  # binomial likelihood
         logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]] # model for linear predictor
         rhat[i,k] <- p[i,k] * n[i,k]  # expected value of the numerators
         #Deviance contribution
         dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) -
log(n[i,k]-rhat[i,k])))
         }
   # Summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   }
totresdev <- sum(resdev[])       # Total Residual Deviance
#
# Reference treatment
d[ref]<-0      # treatment effect is zero for reference treatment
D[class[ref]]<-0
#
# vague prior for class effects
for (j in 2:nc){
   D[j] ~ dnorm(0, .0001)
   }
for (j in 2:nt){
   d[j] <- D[class[j]]
   }
#
```

```
# pairwise ORs and LORs for all possible pair-wise treatment comparisons
for (c in 1:(nt-1)){
   for (k in (c+1):nt){
         or[c,k] <- exp(d[k] - d[c])
         lor[c,k] <- (d[k]-d[c])
         }
   }
#
# pairwise differences for classes
for (c in 1:(nc-1)){
   for (k in (c+1):nc){
         diffClass[c,k] <- D[k] - D[c]
         orClass[c,k] <- exp(D[k] - D[c])
         }
    }
# ranking on relative scale
for (k in 1:nc){
   rkClass[k] <- rank(D[],k)
   bestClass[k] <- equals(rkClass[k],1) # Smallest is best (i.e. rank 1)
   # prob class k is h-th best, prob[1,k]=best[k]
   for (h in 1:nc) { probClass[h,k] <- equals(rkClass[k],h) }
   }
#
}                              # *** PROGRAM ENDS
```

A.6: Discontinuation due to side effects, bias-adjusted model: Domain 4, Outcome measurement (efficacy) (WinBUGS)

```
model{
for(i in 1:ns){                # LOOP OVER ALL STUDIES
   mu[i] ~ dnorm(0,.0001)         # vague priors for all trial baselines
   beta[i,1] <- 0          #No bias on baseline arm
   for (k in 1:na[i]){            # LOOP OVER ARMS
```

```
        r[i,k] ~ dbin(p[i,k],n[i,k])  # binomial likelihood
        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]] + beta[i,k]*X[i,k]*step(bias[i,b.ind]-2) # model for linear predictor, Bias for high ROB or some concerns
        rhat[i,k] <- p[i,k] * n[i,k]  # expected value of the numerators
        #Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
        }
    for(k in 2:na[i]){
        # model for bias parameter beta
        beta[i,k] ~ dnorm(b, prec.b)
        }
    # Summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    }
totresdev <- sum(resdev[])        # Total Residual Deviance
#
# Reference treatment currently Placebo
d[ref]<-0       # treatment effect is zero for reference treatment
D[class[ref]]<-0
# vague prior for class effects
for (j in 2:nc){
    D[j] ~ dnorm(0, .0001)
    }
for (j in 2:nt){
    d[j] <- D[class[j]]
    }
# bias model prior for variance
sd.b ~ dunif(0,5)
prec.b <- pow(sd.b,-2)
# bias model prior for mean
b ~ dnorm(0,.0001)
```

```
#
# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)){
   for (k in (c+1):nt){
         or[c,k] <- exp(d[k] - d[c])
         lor[c,k] <- (d[k]-d[c])
         }
   }
#
# pairwise differences for classes
for (c in 1:(nc-1)){
   for (k in (c+1):nc){
         diffClass[c,k] <- D[k] - D[c]
         orClass[c,k] <- exp(D[k] - D[c])
         }
   }
#
# ranking on relative scale
for (k in 1:nc){
   rkClass[k] <- rank(D[],k)
   bestClass[k] <- equals(rkClass[k],1) # Smallest is best (i.e. rank 1)
   # prob class k is h-th best, prob[1,k]=best[k]
   for (h in 1:nc) { probClass[h,k] <- equals(rkClass[k],h) }
   }
}                              # *** PROGRAM ENDS
```

A.7: Discontinuation due to side effects, node-splitting, treatment-level

A.7.1: R Code (requires R2OpenBUGS package)

```
#############################################################################
# Node-splitting for Acne Guideline - Discontinuation (due to SE)
# R script to run node-split for the MTC Fixed study effects, fixed
```

```
# class effects model using OpenBUGS
#
# Uses R2OpenBUGS package
#
# Discontinuation (due to SE)
#  1. Need to include in the working directory the following files:
#           Disc se.txt --- text file with data
#           fse fce node-splitR2_v3.txt --- text file holding BUGS code
#
#   2. Output files will be
#           data.txt --- holds all data as used by BUGS
#           log.odc and log.txt --- hold WinBUGS output
#           inits1.txt --- holds initial values as read by BUGS
#           script.txt --- BUGS script file with all commands to execute
#
#   3. Output files for each node should be transferred to a new directory
#      as they will be overwritten in each new run
#
#   4. You may need to edit the OpenBUGS location 'bd'
#
#   5. You will need to edit the working directory 'pathname'
#      to suit your computer settings
#
#   6. Run script file
#
################################################################################
#
# Declare the directory where OpenBUGS is found in this computer
bd <- "C:/Program Files (x86)/OpenBUGS/OpenBUGS323/OpenBUGS.exe"
#
# Declare working directory
```

```
pathname <- "C:/Acne/M2S/Disc SE/"
setwd(pathname)
#
# load package to call OpenBUGS
library(R2OpenBUGS)
#
# LOAD DATA MANIPULATING FUNCTIONS:
#
PairXY <- function(treat, na, pair)
  # Check if pair(X,Y) in row i of data
  # and reorder treatments in trial as appropriate
{
  N <- nrow(treat)
  multi <- rep(NA,length(na))
  split.ind <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  split.ind1 <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  split.ind2 <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  spliti <- rep(NA,length(na))
  split1i <- rep(NA,length(na))
  split2i <- rep(NA,length(na))
  pair1 <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  pair2 <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  k.ind <- matrix(nrow=nrow(treat),ncol=ncol(treat))
  for (i in 1:N) {
    # is trial i a multiarm trial?
    multi[i] <- 1*(na[i]>2)
    for (k in 1:na[i]){
      # which arms contain a treatment in the pair?
      split.ind[i,k] <- 1*(treat[i,k]==pair[1])+1*(treat[i,k]==pair[2])
      # which arms contain the treatment in pair[1]?
      split.ind1[i,k] <- 1*(treat[i,k]==pair[1])
```

```
    # which arms contain the treatment in pair[2]?
    split.ind2[i,k] <- 1*(treat[i,k]==pair[2])
  }
  # does trial i contain multiples of pair[1]?
  split1i[i] <- 1*(sum(split.ind1[i,1:na[i]])>1)
  # does trial i contain multiples of pair[2]?
  split2i[i] <- 1*(sum(split.ind2[i,1:na[i]])>1)
  # does trial i contain both treatments in the pair?
  # (minus duplicates in multiarm trials that have one treatment (only) in pair)
  spliti[i] <- 1*((sum(split.ind[i,1:na[i]])-split1i[i]*(sum(split.ind1[i,1:na[i]])-split1i[i])-
split2i[i]*(sum(split.ind2[i,1:na[i]])-split2i[i]))>1)
  for (k in 1:na[i]) {
    # which arms contain the first element in the pair
    pair1[i,k] <- k*(1*(treat[i,k]==pair[1]))
    # which arms contain the second element in the pair
    pair2[i,k] <- k*(1*(treat[i,k]==pair[2]))
  }
  for (k in 1:na[i]) {
    # reposition order of arms within a trial according to node being split
    # k.ind ensures a treatment in the pair is in the baseline arm, where the
    # multi-arm trial contains both treatments in the pair
    # If a multi-arm trial does not contain the node, arm order stays the same
    k.ind[i,k]<-(k*((1-multi[i])+multi[i]*(1-spliti[i])+multi[i]*spliti[i]*(1*(split.ind[i,1]==1)))

                # If a multi-arm trial contains the node, the treatment in pair[1] is not duplicated in
trial,
                # the baseline arm does not contain a treatment in the node, and the treatment
                # in arm k is pair[1], make this treatment baseline treatment
                + multi[i]*spliti[i]*(1-split1i[i])*(1-(1*(split.ind[i,1]==1)))*(1*(treat[i,k]==pair[1]))

                # If a multi-arm trial contains the node, the treatment in pair[1] is duplicated in
trial,
```

```
            # the treatment in pair[2] is not duplicated in trial, the baseline arm does not
contain

            # a treatment in the node, and the treatment in arm k is pair[2], make this
treatment baseline treatment

            + multi[i]*spliti[i]*split1i[i]*(1-split2i[i])*(1-
(1*(split.ind[i,1]==1)))*(1*(treat[i,k]==pair[2]))


            # If a multi-arm trial contains the node, the treatment in pair[1] is not duplicated in
trial,

            # the baseline arm does not contain a treatment in the node, and k is baseline
arm,

            # move treatment to come after baseline treatment

            + sum(pair1[i,1:na[i]])*(1-split1i[i])*multi[i]*spliti[i]*(1-
(1*(split.ind[i,1]==1)))*(1*(k==1))


            # If a multi-arm trial contains the node, the treatment in pair[1] is duplicated in
trial,

            # the treatment in pair[2] is not duplicated in trial, the baseline arm does not
contain a

            # treatment in the node, and k is baseline arm, move treatment to come after
baseline treatment

            + sum(pair2[i,1:na[i]])*split1i[i]*(1-split2i[i])*multi[i]*spliti[i]*(1-
(1*(split.ind[i,1]==1)))*(1*(k==1))


            # If a multi-arm trial contains the node, the treatment in pair[1] are not duplicated
in trial,

            # the baseline arm does not contain a treatment in the node, k is NOT baseline
arm,

            # and treatment in arm k is NOT pair[1], arm order stays the same

            + k*multi[i]*spliti[i]*(1-split1i[i])*(1-(1*(split.ind[i,1]==1)))*(1-(1*(k==1)))*(1-
(1*(treat[i,k]==pair[1])))


            # If a multi-arm trial contains the node, the treatment in pair[1] is duplicated in
trial,

            # the treatment in pair[2] is not duplicated in trial, the baseline arm does not
contain a treatment in the node, k is NOT baseline arm,

            # and treatment in arm k is NOT pair[2], arm order stays the same
```

```
                + k*multi[i]*spliti[i]*split1i[i]*(1-split2i[i])*(1-(1*(split.ind[i,1]==1)))*(1-(1*(k==1)))*(1-(1*(treat[i,k]==pair[2]))))
    }
  }
  k.ind
}
#############################################################################
#
# load data for MTC
MTCData <- read.table("Disc se_UK_treat.txt", header=TRUE)
r <- data.matrix(MTCData[,c("r1", "r2", "r3", "r4")])
n <- data.matrix(MTCData[,c("n1", "n2", "n3", "n4")])
t <- data.matrix(MTCData[,c("t1", "t2", "t3", "t4")])
na <- data.matrix(MTCData[,"na"])
#Class when running model at treatment level
class <-c(1,1,   1,2,2,3,3,       3,3,4,5,6,       7,7,7,7,7,       8,9,10,11,11,
          12,13,14,15,15,16,16,16,17,17,          18)
nt <- max(t, na.rm=TRUE)
nc <- max(class)
ns <- nrow(r)
ref <- 1    #reference treatment
#
# define initial values
initv1 <- list(direct=0,  D=c(NA,rep(0,nc-1)), mu=rep(0,ns))
initv2 <- list(direct=0.05,  D=c(NA,rep(-1.2,nc-1)), mu=rep(0.5,ns))
#############################################################################
#
# Check which notes to split
#
library(gemtc)
ns.data<-mtc.data.studyrow(MTCData,
                    armVars=c('treatment'='t', 'responders'='r', 'sampleSize'='n'),
```

```
                    nArmsVar='na',
                    studyVars=c(),
                    studyNames=MTCData$study,
                    treatmentNames=NA,
                    patterns=c('%s', '%s%d'))
net<-mtc.network(data.ab=ns.data,description="Disc se_trt")
## Print which nodes to split
splitcomps<-mtc.nodesplit.comparisons(net)
print(splitcomps)
#
#############################################################################
##
#  NODE-SPLITTING ROUTINE
#############################################################################
##
#
# Define nodes to split
pair<-splitcomps
pair
# Run node split models
for(j in 1:length(pair[,1])){
  print(pair[j,])

  k.ind <- PairXY(treat=t,na=na[,1],pair=as.numeric(pair[j,]))

  # Setup subdirectory to hold results for each node-split
  dir.create(paste("FEFCEnode",pair[j,1],"_",pair[j,2],sep=""))

  # Build data file: stored in the working directory as "data.txt"
  bugs.data(list("r"=r,"n"=n,"t"=t, "class"=class,
              "na" = na[,1], "nt" = nt, "nc" = nc, "ns" = ns, "ref" = ref,
              "pair" = as.numeric(pair[j,]), "k.ind" = k.ind))
```

```
  # Call OpenBUGS
  #
  bugs(data = "data.txt",
      inits = list(initv1,initv2),
      #inits = list(initv1),
      parameters.to.save = c("direct", "d", "prob","totresdev","indirect"),
      model.file = "fse fce node-splitR2_v3.txt",
      n.chains = 2,
      n.iter = 120000,          #including burn-in iterations
      n.burnin = 40000,
      n.thin = 1,
      OpenBUGS.pgm = bd,
      debug = TRUE,
      save.history = TRUE,
      useWINE=FALSE)
  #
  # Copy input and output files to relevant directory
  file.copy("data.txt", paste("FEFCEnode",pair[j,1],"_",pair[j,2],"/data.txt",sep=""),
overwrite=TRUE)
  file.copy(paste(tempdir(),"/log.odc",sep=""),
paste(pathname,"/FEFCEnode",pair[j,1],"_",pair[j,2],"/log.odc",sep=""), overwrite=TRUE)
  file.copy(paste(tempdir(),"/log.txt",sep=""),
paste(pathname,"/FEFCEnode",pair[j,1],"_",pair[j,2],"/log.txt",sep=""), overwrite=TRUE)
  file.copy(paste(tempdir(),"/inits1.txt",sep=""),
paste(pathname,"/FEFCEnode",pair[j,1],"_",pair[j,2],"/inits1.txt",sep=""), overwrite=TRUE)
  file.copy(paste(tempdir(),"/script.txt",sep=""),
paste(pathname,"/FEFCEnode",pair[j,1],"_",pair[j,2],"/script.txt",sep=""), overwrite=TRUE)
  #
  # REPEAT FOR ALL OTHER NODES
}
```

A.7.2 OpenBUGS Code

```
model{
```

```
for(i in 1:ns){                 # LOOP OVER ALL STUDIES
   delta[i,1] <- 0  # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]){             # LOOP OVER ARMS
         r[i,k.ind[i,k]] ~ dbin(p[i,k],n[i,k.ind[i,k]])  # binomial likelihood
         logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
         rhat[i,k] <- p[i,k] * n[i,k.ind[i,k]]  # expected value of the numerators
         #Deviance contribution
         dev[i,k] <- 2 * (r[i,k.ind[i,k]] * (log(r[i,k.ind[i,k]])-log(rhat[i,k])) +  (n[i,k.ind[i,k]]-
r[i,k.ind[i,k]]) * (log(n[i,k.ind[i,k]]-r[i,k.ind[i,k]]) - log(n[i,k.ind[i,k]]-rhat[i,k])))
         split[i,k] <- equals(t[i,k.ind[i,1]], pair[1]) * equals(t[i,k.ind[i,k]], pair[2]) -
equals(t[i,k.ind[i,1]], pair[2]) * equals(t[i,k.ind[i,k]], pair[1])
         }
   # Summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {            # FE model for treatment effects
         delta[i,k] <- (d[t[i,k.ind[i,k]]] - d[t[i,k.ind[i,1]]])*(1-abs(split[i,k])) + direct * split[i,k]
         }
   }
totresdev <- sum(resdev[])       # Total Residual Deviance
#
d[ref]<-0       # treatment effect is zero for reference treatment
D[class[ref]]<-0
# vague prior for class effects
for (j in 2:nc){
   D[j] ~ dnorm(0, .0001)
   }
for (j in 2:nt){
   d[j] <- D[class[j]]
   }
direct ~ dnorm(0,.0001)      # vague prior for direct comparison parameter
indirect <- lor[pair[1], pair[2]]
```

```
#calculate difference between direct and lor
diff <- direct - indirect
# calculate p-value
prob <- step(diff)
#
# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)){
   for (k in (c+1):nt){
         or[c,k] <- exp(d[k] - d[c])
         lor[c,k] <- (d[k]-d[c])
         lor[k,c] <- -lor[c,k]
         }
   }
}                              # *** PROGRAM ENDS
```