Supporting materials

Supplementary models

Details of the individual patient data network meta-analysis models including treatment by covariate interactions that were applied are given below.

Notation

Let *i* denote the trial where $i = 1, \ldots \ldots, NS$ and *NS* is the number of independent trials; let *j* the patient where $j = 1, \ldots \ldots, NP_i$ such that NP_i is the number of patients in trial *i*; and let *k* be the trial arm where $k = 1, \ldots \ldots, NA_i$ and NA_i is the number of arms in trial *i*.

Suppose $y_{ijk} = 1$ if patient *j* in trial *i* in arm *k* experiences the event and $y_{ijk} = 0$ if patient *j* in trial *i* in arm *k* does not experience the event. Assume that the outcomes of patients, y_{ijk}, are independent and distributed as $y_{ijk} \sim bernoulli(p_{ijk})$ where p_{ijk} is the probability of an event for patient *j* in trial *i* in arm *k*. Let x_{ijk} be a patient-level covariate for patient *j* in trial *i* in arm *k* (such as, a continuous covariate value or an indicator variable for a dichotomous covariate).

Let t_{ik} denote the treatment given in trial *i* in arm *k* where $t_{ik} \in \{1, \ldots \ldots, NT\}$ and *NT* is the number of treatments in the network. Also specify that the node being split is $(\hat{t}, t^*)$ where $\hat{t} \neq t^*$ and $\hat{t} < t^*$. For example, if one wants to split the node (*3*, *4*) then $\hat{t} = 3$ and $t^* = 4$.

Model S1. NMA model including treatment by covariate interaction

Assuming no multi-arm trials exist, the random-effects model is given as follows:

$$logit(p_{jik}) = \begin{cases} \mu_i + \beta_{0i} x_{jik} & if\ k = 1 \\ \mu_i + \beta_{0i} x_{jik} + \delta_{i,\,1k} + \beta_{t_{i1},t_{ik}} x_{jik} & if\ k \neq 1 \end{cases}$$

where μ_i is the log odds of an event in arm *1* of trial *i*; β_{0i} is a study-specific regression parameter that represents the difference in the log odds of an event in arm *1* of trial *i* per unit increase in the covariate x_{ijk}; $\beta_{t_{i1},t_{ik}}$ represents the difference in the log odds ratio of t_{ik} vs. t_{i1} per unit increase in the covariate and $\beta_{t_{i1},t_{ik}}$=$\beta_{1,t_{ik}}$-$\beta_{1,t_{i1}}$; and $\delta_{i,\,1k}$ represents the trial-specific log odds ratio of t_{ik} vs. t_{i1}. The trial-specific log odds ratios, $\delta_{i,\,1k}$ are assumed to be realisations from a normal distribution where

$$\delta_{i,1k} \sim N\left(d_{t_{i1},t_{ik}},\ \sigma^2\right)$$

and

$$d_{t_{i1},t_{ik}} = d_{1,t_{ik}} - d_{1,t_{i1}}$$

In this model, $d_{t_{i1},t_{ik}}$ represents the log odds ratio of t_{ik} vs. t_{i1}. The fixed-effect model is given by setting $\sigma^2 = 0$.

Under a Bayesian framework, prior distributions are specified for μ_i, β_{0i}, $d_{1,t_{ik}}$, $\beta_{1,t_{ik}}$ and σ^2.

The model can also be applied to datasets with multi-arm trials but the correlation between trial-specific treatment effects must be taken into account. For each multi-arm trial *i* with *m*

arms, the trial-specific treatment effects are taken to be a realisation from a multivariate normal distribution

$$\begin{pmatrix} \delta_{i,\,12} \\ \vdots \\ \delta_{i,\,1m} \end{pmatrix} \sim N\left(\begin{pmatrix} d_{1,t_{i2}} - d_{1,t_{i1}} \\ \vdots \\ d_{1,t_{im}} - d_{1,t_{i1}} \end{pmatrix}, \begin{pmatrix} \tau^2 & \ldots & \tau^2/2 \\ \vdots & \ddots & \vdots \\ \tau^2/2 & \ldots & \tau^2 \end{pmatrix} \right)$$

that can be decomposed into a series of conditional univariate normal distributions.

Model S2. NMA node-splitting model including treatment by covariate interaction

When there are no multi-arm trials, the random-effects model is specified as follows:

$$logit\left(p_{ijk}\right) = \begin{cases} \mu_i + \beta_{0i} x_{ijk} & if\ k = 1 \\ \mu_i + \beta_{0i} x_{ijk} + \delta_{i,\,1k} + \beta_{t_{i1},t_{ik}} x_{ijk} & if\ k \neq 1\ and\ t_{i1} \neq \hat{t} \text{ and/or } t_{ik} \neq t^* \\ \mu_i + \beta_{0i} x_{ijk} + \delta_{i,\,1k} + \beta^{dir} x_{ijk} & if\ k \neq 1\ and\ t_{i1} = \hat{t} \text{ and } t_{ik} = t^* \end{cases}$$

and where β^{dir} represents the difference in the log odds ratio of t^* vs. $\hat{t}$ per unit increase in the covariate estimated using direct evidence; $\beta_{t_{i1},t_{ik}}$ represents the difference in the log odds ratio of t_{ik} vs. t_{i1} per unit increase in the covariate estimated using all trials that did not allocate $t^*$and $\hat{t}$ (i.e. using indirect evidence); and $\delta_{i,\,1k}$ represents the trial-specific log odds ratio of t_{ik} vs. t_{i1}. The trial-specific log odds ratios, $\delta_{i,\,1k}$ are assumed to be realisations from a normal distribution where

$$\delta_{i,1k} \sim N\left(d^{dir},\ \sigma^2\right)$$

if trial *i* allocated $t^*$and $\hat{t}$, that is, $t_{i1} = \hat{t}$ and $t_{ik} = t^*$; whereas

$$\delta_{i,1k} \sim N\left(d_{t_{i1},t_{ik}},\ \sigma^2\right)$$

and the treatment effects satisfy the consistency equation $d_{t_{i1},t_{ik}} = d_{1,t_{ik}} - d_{1,t_{i1}}$

if trial *i* did not allocate $t^*$and $\hat{t}$, that is, $t_{i1} \neq \hat{t}$ and/or $t_{ik} \neq t^*$.

In this model $d_{t_{i1},t_{ik}}$ represents the mean log odds ratio of t_{ik} vs. t_{i1} when the covariate value is zero estimated using all studies that did not allocate t^* and $\hat{t}$ (i.e. using indirect evidence); and d^{dir} represents the mean log odds ratio of t^*vs. $\hat{t}$ when the covariate value is zero estimated using direct evidence.

Under a Bayesian framework, prior distributions are specified for $\mu_i, \beta_{0i},\ d_{1,t_{ik}}, \beta_{1,t_{ik}},\ d^{dir}$, β^{dir} and σ^2.

Multiple node-splitting models are usually applied. One model can be applied for each comparison providing both direct and indirect evidence are available for that comparison.

Node-splitting models can accommodate multi-arm trials as described elsewhere (Dias et al., 2010a, van Valkenhoef et al., 2016). If one wants to split node (t_{i1}, t_{ik}) then a multi-arm trial *i* will contribute direct evidence to the treatment effect (d^{dir}) because $\hat{t} = t_{i1}$. However, if one splits another node (e.g. (t_{i2}, t_{i3})) then $\hat{t} \neq t_{i1}$ therefore, the multi-arm trial would not contribute direct evidence to the estimation of the treatment effect (d^{dir}), therefore, to overcome this problem and to utilise all the direct evidence, if the multi-arm trial compared the two treatments t^* and $\hat{t}$, in addition to other treatments, treatment $\hat{t}$ is taken to be the

baseline treatment t_{i1} for that study. For example, if a trial *i* compared treatments *1*, *3* and *4*, and one wants to split node (*1*, *3*) then $\hat{t} = t_{i1} = 1$ and the model would be as follows:

$logit(p_{ij1}) = \mu_i + \beta_{0i}x_{ij1}$ for treatment *1*,

$logit(p_{ij2}) = \mu_i + \beta_{0i}x_{ij2} + \delta_{i,\,12} + \beta^{dir}x_{ij2}$ for treatment *3* where $\delta_{i,\,12} \sim N\left(d^{dir}, \tau^2\right)$, and

$logit(p_{ij3}) = \mu_i + \beta_{0i}x_{ij3} + \delta_{i,\,13} + \beta_{1,4}x_{ij3}$ for treatment *4* where $\delta_{i,\,13} \sim N\left(d_{1,4}, \tau^2\right)$.

Whereas, for the same trial, if one wants to split node (*3*, *4*) instead, then we fix $\hat{t} = t_{i1} = 3$ and the model is

$logit(p_{ij2}) = \mu_i + \beta_{0i}x_{ij2} + \delta_{i,\,12} + \beta_{3,1}x_{ij2}$ for treatment *1* where $\delta_{i,\,12} \sim N\left(d_{3,1}, \tau^2\right)$.

$logit(p_{ij1}) = \mu_i + \beta_{0i}x_{ij1}$ for treatment *3*, and

$logit(p_{ij3}) = \mu_i + \beta_{0i}x_{ij3} + \delta_{i,\,13} + \beta^{dir}x_{ij3}$ for treatment *4* where $\delta_{i,\,13} \sim N\left(d^{dir}, \tau^2\right)$.

Code for Model S1

Winbugs code (saved as winbugs file "NMA RE IPD COVM1.odc")

```
model{
for(i in 1:ns){                                  #LOOP FOR EACH TRIAL
   w[i,1] <- 0                                   #W IS ZERO FOR ARM 1 OF EACH TRIAL
   delta[i,1] <- 0                               #TREATMENT EFFECT IS ZERO FOR ARM 1 OF EACH TRIAL
   mu[i] ~ dnorm(0,0.00001)                      #PRIOR DISTRIBUTION FOR MU
   beta0[i] ~ dnorm(0,0.00001)                   #PRIOR DISTRIBUTION FOR BETA0
      for (k in 2:na[i]) {                       #LOOP FOR EACH ARM
        delta[i,k] ~ dnorm(md[i,k], taud[i,k])   #DISTRIBUTION OF TRIAL-SPECIFIC TREATMENT EFFECTS
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]  #MEAN OF DISTRIBUTION (CORRECTED FOR MULTI-ARM
TRIALS)
        taud[i,k] <- tau *2*(k-1)/k              #PRECISION OF DISTRIBUTION (CORRECTED FOR MULTI-ARM
TRIALS)
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) #ADJUSTMENTS FOR MULTI-ARM TRIALS
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)         #ADJUSTMENTS FOR MULTI-ARM TRIALS
                  }
            }
for(l in 1:np)  {                                                    #LOOP FOR EACH PATIENT
  y[l]~dbern(p[l])                                                   #BERNOULLI LIKELIHOOD
  logit(p[l])<-mu[s[l]] + (beta0[s[l]]*(x[l]-mx)) + delta[s[l],arm[l]] + (beta[tipd[l]]-beta[b[l]]) * (x[l]-mx)
                                                                     #LINEAR PREDICTOR
  rhat[l] <- p[l]                                                    #MODEL PREDICTION
  dev[l] <- 2*(y[l] * (log(y[l]/rhat[l])) + (1-y[l]) * (log((1-y[l])/(1-rhat[l]))))    #DEVIANCE
            }

totresdev <- sum(dev[])                          #TOTAL RESIDUAL DEVIANCE

d[1]<-0                                          #LOG ODDS RATIO IS ZERO FOR REFERENT TREATMENT
beta[1] <- 0                                     #COEFFICIENT IS ZERO FOR REFERENT TREATMENT

sd ~ dunif(0,10)                                 #PRIOR DISTRIBUTION FOR BETWEEN TRIAL STANDARD
                                                  DEVIATION
tau <- pow(sd,-2)                                #BETWEEN TRIAL PRECISION
tausq <- sd*sd                                   #BETWEEN TRIAL VARIANCE

for (k in 2:nt){
   d[k] ~ dnorm(0,0.00001)                       #PRIOR DISTRIBUTIONS
   beta[k]~dnorm(0,0.00001)
            }

for (k in 1:nt){                                 #CALCULATE THE LOG ODDS RATIO FOR BASIC
                                                  PARAMETERS AT EACH COVARIATE VALUE
   for (j in 1:nz) {
      dz[j,k] <- d[k] - (beta[k])*(mx-z[j]) }
                  }

for (c in 1:(nt-1)){                             #CALCULATE, FOR EACH COMPARISON, THE
                                                  COEFFICIENT, ODDS RATIO AND LOG ODDS RATIO AT
                                                  MEAN COVARIATE VALUE.
    for (k in (c+1):nt)  {
        betas[c,k] <- beta[k] - beta[c]
        or[c,k] <- exp(d[k] - d[c])
        lor[c,k] <- (d[k]-d[c])
           for (j in 1:nz) {

                                                 #CALCULATE, FOR EACH COMPARISON, ODDS RATIO AND
                                                  LOG ODDS RATIO AT DIFFERENT COVARIATE VALUES
              orz[j,c,k] <- exp(dz[j,k] - dz[j,c])
              lorz[j,c,k] <- (dz[j,k]-dz[j,c])
                        }
                    }
                }
}
```

Dataset 1 (saved a csv file"utf_ipdacc.csv")
#t1= treatment in arm 1, t2=treatment in arm 2, t3=treatment in arm 3.
#na=number of arms
#Note that each row represents one study and the studies are in the same order as in dataset 2.

t1	t2	t3	na
1	2	NA	2
1	2	NA	2
1	2	3	3
1	2	3	3
1	2	3	3
1	2	3	3
1	2	3	3
1	2	4	3
1	2	4	3
1	3	NA	2
1	3	NA	2
1	3	NA	2
1	3	NA	2
1	3	4	3
1	3	4	3
1	3	4	3
1	3	4	3

Dataset 2 (saved as csv file "utf_ipdacc2.csv")
(one row per patient)
#age=covariate
#y=binary IPD outcome
#tipd=treatment
#s=study
#b=baseline treatment in that study
#arm=study arm (i.e. 1, 2, 3)
#note that arm 1 of each study is the baseline treatment for that study.

age	y	tipd	s	b	arm
21	1	1	1	1	1
29	1	1	1	1	1
.	.	.	.	.	.
.	.	.	.	.	.

R code

```
#INSTALL R PACKAGES
library(R2WinBUGS)
library(coda)

#CHOOSE WORKING DIRECTORY
working.directory="c:\\dir"
setwd(working.directory)

#IMPORT DATA
dat1 = read.csv("utf_ipdacc.csv")
dat2 = read.csv("utf_ipdacc2.csv")

#DEFINE VARIABLES THAT NEED TO BE ENTERED INTO THE WINBUGS MODEL
na=dat1$na                                          #NUMBER OF ARMS IN EACH STUDY
t=cbind(dat1$t1,dat1$t2,dat1$t3, deparse.level = 0) #TREATMENT NUMBER
s=dat2$s                                            #STUDY NUMBER
y=dat2$y                                            #OUTCOME
arm=dat2$arm                                        #STUDYARM
x=dat2$age/12                                       #COVARIATE VALUES
b=dat2$b                                            #BASELINE TREATMENT
tipd=dat2$tipd                                      #TREATMENT (IPD VERSION)
mx=mean(x)                                          #AVERAGE COVARIATE VALUE
z=c(1,2,3,4,5, mx,0)                                #CHOSEN COVARIATE VALUES AT WHICH TREATMENT
EFFECTS  ARE REQUIRED TO BE ESTIMATED
nz=length(z)                                        #NUMBER OF CHOSEN COVARIATE VALUES
```

```
ns=max(s)                                   #NUMBER OF TRIALS
nt=max(tipd)                                #NUMBER OF TREATMENTS
np=length(y)                                #NUMBER OF PATIENTS

#LIST DATA FOR ENTRY INTO WINBUGS
data= list("y", "s","arm", "tipd", "b", "x", "z", "mx", "t", "na", "ns","nt", "np", "nz")

#DEFINE INITIAL VALUES FOR ENTRY INTO WINBUGS
inits1 = list(d=c(NA,0,0,0), sd=1, mu=c(0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0), beta0=c(0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0),
beta=c(NA,0,0,0))

#WINBUGS MODEL
Models1 = bugs (data, inits1, model.file= "NMA RE IPD COVM1.odc",
parameters.to.save= c("mu", "d",  "totresdev", "or", "lor", "sd", "tausq", "dz", "betas", "beta", "orz", "lorz", "beta0"),
n.chains=1, n.iter=300000, n.burnin=100000, n.thin=5,codaPkg=FALSE, bugs.directory="c:/Program Files/WinBUGS14/",
working.directory=working.directory)
```

Code for model S2

Winbugs code (saved as winbugs file "NMA RE IPD DSPLIT BETASPLIT.odc")

```
model{
for(i in 1:ns){                                  #LOOP FOR EACH TRIAL
   w[i,1] <- 0                                   #W IS ZERO FOR ARM 1 OF EACH TRIAL
     j[i,1] <-0                                  #J IS ZERO FOR ARM 1 OF EACH TRIAL
    delta[i,bi[i]] <- 0                          #TREATMENT EFFECT IS ZERO FOR ARM 1 OF EACH TRIAL
   mu[i] ~ dnorm(0,0.00001)                      #PRIOR DISTRIBUTION FOR MU
   beta0[i] ~ dnorm(0,0.00001)                   #PRIOR DISTRIBUTION FOR BETA0
           for (k in 1:na[i]) {                  #LOOP FOR EACH ARM
              index[i,k] <- split[i] * (equals(t[i,k], pair[1]) + equals(t[i,k], pair[2]))  #INDICATES IF ARM IS TO BE SPLIT
                                  }
       for (k in 2:na[i]) {
           delta[i,si[i,k]] ~ dnorm(md[i,si[i,k]],taud[i,si[i,k]])                  #DISTRIBUTION OF TRIAL-
                                                                                    SPECIFIC TREATMENT EFFECTS
           md[i,si[i,k]] <-  (d[si[i,k]] - d[bi[i]] + sw[i,k])*(1-index[i,m[i,k]]) + direct*index[i,m[i,k]]
                                                                                    #MEAN OF DISTRIBUTION
                                                                                     (CORRECTED FOR MULTI-ARM
                                                                                     TRIALS) SPLIT INTO DIRECT AND
                                                                                     INDIRECT
             j[i,k] <- k - (equals(1, split[i]) * step(k-3))
           taud[i,si[i,k]] <- tau *2*(j[i,k]-1)/j[i,k]                              #PRECISION OF DISTRIBUTION
                                                                                    (CORRECTED FOR MULTI-ARM
                                                                                    TRIALS)
           w[i,k] <- (delta[i,si[i,k]]  - d[si[i,k]] + d[bi[i]]) * (1-index[i,k])   #ADJUSTMENTS FOR MULTI-ARM
                                                                                     TRIALS
           sw[i,k] <- sum(w[i,1:k-1])/(j[i,k]-1)                                    #ADJUSTMENTS FOR MULTI-ARM
                                                                                    TRIALS
                        }
             }

for(l in 1:np)  {                                                                   #LOOP FOR EACH PATIENT
  y[l]~dbern(p[l])                                                                 #BERNOULLI LIKELIHOOD
     logit(p[l])<-mu[s[l]]  +  beta0[s[l]]*(x[l]-mx)  +  delta[s[l], tipd[l]] + (deltab[l]*(1-equals(tipd[l],bi[s[l]])) )
                                                                                    #LINEAR PREDICTOR
  rhat[l] <- p[l]                                                                   #MODEL PREDICTION
  dev[l] <- 2*(y[l] * (log(y[l]/rhat[l])) + (1-y[l]) * (log((1-y[l])/(1-rhat[l]))))  #DEVIANCE
     index2[l] < - split[s[l]] *  (equals(tipd[l], pair[1]) + equals(tipd[l], pair[2]))  #INDICATES IF ARM IS TO BE SPLIT
     deltab[l] <-  (beta[tipd[l]] - beta[bi[s[l]]] )*(x[l]-mx)*(1-index2[l]) + directbeta*(x[l]-mx)*(index2[l])
                                                                                    #TREATMENT BY COVARIATE
                                                                                     INTERACTION TERM SPLIT INTO
                                                                                     DIRECT AND INDIRECT
              }

totresdev <- sum(dev[])                          #TOTAL RESIDUAL DEVIANCE

direct ~ dnorm(0,0.00001)                        #PRIOR DISTRIBUTION OF LOG ODDS RATIO FROM
                                                  DIRECT EVIDENCE
directbeta ~ dnorm(0,0.00001)                    #PRIOR DISTRIBUTION OF COEFFICIENT FROM DIRECT
                                                  EVIDENCE
d[1]<-0                                          #LOG ODDS RATIO IS ZERO FOR REFERENT TREATMENT
beta[1] <- 0                                     #COEFFICIENT IS ZERO FOR REFERENT TREATMENT

sd ~ dunif(0,10)                                 #PRIOR DISTRBIUTION FOR BETWEEN TRIAL STANDARD
                                                  DEVIATION
tau <- pow(sd,-2)                                #BETWEEN TRIAL PRECISION
tausq <- sd*sd                                   #BETWEEN TRIAL VARIANCE

for (k in 2:nt){
   d[k] ~ dnorm(0,0.00001)                       #PRIOR DISTRIBUTIONS FOR LOG ODDS RATIO  AND
                                                  COEFFICIENT FROM INDIRECT EVIDENCE
   beta[k]~dnorm(0,0.00001)
              }

for (k in 1:nt){                                 #CALCULATE THE LOG ODDS RATIO FOR BASIC
```

```
                                                    PARAMETERS AT EACH COVARIATE VALUE FOR
                                                    INDIRECT EVIDENCE

     for (v in 1:nz) { dz[v,k] <- d[k] - (beta[k])*(mx-z[v]) }
                }

for (c in 1:(nt-1)){                                #CALCULATE, FOR EACH COMPARISON, THE
                                                     COEFFICIENT, ODDS RATIO AND LOG ODDS RATIO AT
                                                     MEAN COVARIATE VALUE FOR INDIRECT EVIDENCE.
    for (k in (c+1):nt)  {
          betas[c,k] <- beta[k] - beta[c]
          lor[c,k] <- (d[k]-d[c])
                    for (v in 1:nz) {
                                                    #CALCULATE, FOR EACH COMPARISON, ODDS RATIO AND
                                                     LOG ODDS RATIO AT DIFFERENT COVARIATE VALUES
                                                     FOR INDIRECT EVIDENCE.
          lorz[v,c,k] <- (dz[v,k]-dz[v,c])
                              }
                        }
                }

for (v in 1:nz) {                                   #LOG ODDS RATIO  AND ODDS RATIO AT EACH
                                                     COVARIATE VALUE FOR DIRECT EVIDENCE.

       directz[v] <- direct - (directbeta)*(mx-z[v])
       directorz[v] <-exp(directz[v])
                }

for (v in 1:nz) {
      diff[v] <- directz[v] - lorz[v, pair[1], pair[2]]      #CALCULATE INCONSISTENCY ESTIMATES
      prob[v] <- step(diff[v])                              #CALCULATE P-VALUES
                 }
}
```

R code

```
#INSTALL R PACKAGES
library(R2WinBUGS)
library(coda)

#CHOOSE WORKING DIRECTORY
working.directory="c:\\dir"
setwd(working.directory)

#LOAD FUNCTIONS TO SHAPE DATA

#CHECK IF PAIR(X,Y) IN ROW I OF DATA AND GIVE BASELINE FOR DATA ROW I
PairXY <- function(treat, pair)
{
 N <- nrow(treat)
 out <- cbind(split=rep(0,N), b=rep(0,N))
 for (i in 1:N) {
  pos <- match(pair, treat[i,], nomatch=0)   # lenght = length(pair) = 2
  out[i,1] <- ifelse(prod(pos)>0, 1, 0)      # 1 if pair in line i, 0 o.w.
  out[i,2] <- ifelse(prod(pos)==0, 1, pos[1])
 }
out
}

# GIVES NA-1 INDEXES TO SWEEP NON-BASELINE ARMS ONLY
NonbaseSweep <- function(index, na)
{
 N <- NROW(na)
 C <- max(na)
 out <- matrix(nrow=N, ncol=C)
 for (i in 1:N) {
  for (k in 2:na[i]) {
   out[i,k] <- k - (index[i,"b"] >= k)
```

```
  }
 }
out
}

# BUILDS MATRIX WITH NON-BASELINE TREATMENTS
Sweeptreat <- function(treat, m)
{
 N <- NROW(treat)
 C <- NCOL(m)
 out <- matrix(nrow=N, ncol=C)
 for (i in 1:N) {
  for (k in 2:C) {
    out[i,k] <- treat[i,m[i,k]]
  }
 }
out
}

## BUILDS VECTOR WITH BASELINE TREATMENTS
Basetreat <- function(treat, b)
{
 N <- nrow(treat)
 out <- rep(0,N)
 for (i in 1:N) {
  out[i] <- treat[i,b[i]]
 }
out
}

#IMPORT DATA
dat1 = read.csv("utf_ipdacc.csv")
dat2 = read.csv("utf_ipdacc2.csv")

#DEFINE VARIABLES THAT NEED TO BE ENTERED INTO THE WINBUGS MODEL
na=dat1$na                                          #NUMBER OF ARMS IN EACH STUDY
t=cbind(dat1$t1,dat1$t2,dat1$t3, deparse.level = 0)  #TREATMENT NUMBER
s=dat2$s                                            #STUDY NUMBER
y=dat2$y                                            #OUTCOME
tipd=dat2$tipd                                      #TREATMENT NUMBER
x=dat2$age/12                                       #COVARIATE VALUES
ns=max(s)                                           #NMUBER OF TRIALS
nt=max(tipd)                                        #NUMBER OF TREATMENTS
np=length(y)                                        #NUMBER OF PATIENTS
mx=mean(x)                                          #AVERAGE COVARIATE VALUE
z=c(1,2,3,4,5, mx,0)                                #CHOSEN COVARIATE VALUES AT WHICH TREATMENT
EFFECTS  ARE REQUIRED TO BE ESTIMATED.
nz=length(z)                                        #NUMBER OF CHOSEN COVARIATE VALUES

#DEFINE INITIAL VALUES FOR ENTRY INTO WINBUGS
inits1 = list(direct=0, d=c(NA,0,0,0), mu=rep(0,ns), directbeta=0, beta0=c(0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0),
beta=c(NA,0,0,0), beta=c(NA,0,0,0), sd=1)

#CHOOSE NODE TO SPLIT
pair <- c(2,3)

# CALCULATE SPLIT (=1 IF NODE TO SPLIT IS PRESENT AND 0 OTHERWISE)
checkPair <- PairXY(t, pair)

# BUILD VECTOR BI[I] WITH BASELINE TREATMENT: T[I, B[I]]
bi <- Basetreat(t, checkPair[,"b"])

# INDEXES TO SWEEP NON-BASELINE ARMS ONLY
m <- NonbaseSweep(checkPair, na)

# BUILD MATRIX SI[I,K] WITH NON-BASELINE TREATMENTS: T[I, M[I,K]]
si <- Sweeptreat(t,m)
```

```
#LIST DATA FOR ENTRY INTO WINBUGS
bugs.data(list("y"=y,"s"=s,"tipd"=tipd,
            "na" = na, "nt" = nt, "ns" = ns,"np" = np, "t"=t,
            "split" = checkPair[,"split"], "m" =m,
            "bi" = bi, "si" = si, "pair" = pair, "x"=x, "z"=z, "nz"=nz,"mx"=mx ) )

#WINBUGS MODEL
modelS2=bugs(data = "data.txt",
    inits = inits1, parameters.to.save = c("direct", "d", "lor", "mu", "prob","totresdev", "diff", "directbeta", "directz", "lorz",
"betas", "dz","beta", "sd", "tausq"), model.file = "NMA RE IPD DSPLIT BETASPLIT.odc",
    n.chains = 1,  n.iter = 300000, n.burnin = 100000,  bugs.directory = "C:/Program Files/WinBUGS14/",
working.directory=working.directory)

######REPEAT FOR OTHER NODES
```

Site	Artemisinin-based combination therapies (number of patients that achieved treatment success/number of patients)				Age in years, mean (standard deviation)
	DHAPQ	AQ+AS	AL	CD+A	
Manhica (after CD+A)	94/100	78/97	-	-	2.88 (1.30)
Mbarara (after CD+A)	63/65	59/70	-	-	2.43 (1.07)
Nanoro	187/219	199/290	115/292	-	2.24 (1.18)
Gabon	62/63	67/76	65/70	-	2.83 (1.28)
Afokang	67/72	78/83	84/87	-	2.94 (1.28)
Pamol	60/65	73/79	73/80	-	2.66 (1.36)
Ndola	67/67	63/69	63/75	-	2.45 (1.20)
Manhica (before CD+A)	78/82	70/86	-	42/84	2.82 (1,00)
Mbarara (before CD+A)	72/80	64/79	-	53/80	2.60 (1.10)
Rukara (after CD+A)	46/47	-	46/50	-	3.08 (0.92)
Jinja (after CD+A)	160/167	-	157/168	-	2.33 (1.17)
Tororo (after CD+A)	54/75	-	33/77	-	1.99 (0.99)
Mashesha (after CD+A)	49/52	-	51/52	-	2.90 (1.05)
Rukara (before CD+A)	22/23	-	18/21	4/23	2.71 (1.00)
Jinja (before CD+A)	37/39	-	35/38	34/40	2.62 (1.19)
Tororo (before CD+A)	109/141	-	88/138	71/142	2.11 (0.85)
Mashesha (before CD+A)	23/24	-	23/23	18/24	2.92 (1.09)

Table S1. Summary of the individual patient data (i.e. event rate of each treatment group of each site for treatment success at day 28) and covariate information.

AQ+AS: amodiaquine-artesunate; AL: artemether-lumefantrine; CD+A: chlorproguanil-dapsone plus artesunate; DHAPQ: dihydroartemisinin-piperaquine.

Comparison	Evidence type	Odds ratio Posterior median (posterior 95% credibility interval)					
		Age 1	**Age 2**	**Mean age i.e. 2.5**	**Age 3**	**Age 4**	**Age 5**
AL vs. AQ+AS	**Direct**	0.65 (0.26, 1.76)	0.71 (0.29, 1.81)	0.74 (0.31, 1.87)	0.77 (0.31, 1.96)	0.83 (0.32, 2.26)	0.90 (0.31, 2.72)
	Indirect	2.65 (0.86, 9.44)	1.89 (0.72, 5.88)	1.60 (0.61, 4.90)	1.36 (0.50, 4.26)	0.98 (0.29, 3.58)	0.71 (0.15, 3.37)
CD+A vs. AQ+AS	**Direct**	0.66 (0.13, 3.47)	0.43 (0.10, 1.92)	0.34 (0.08, 1.50)	0.28 (0.06, 1.21)	0.18 (0.04, 0.87)	0.11 (0.02, 0.70)
	Indirect	0.26 (0.06, 1.02)	0.23 (0.06, 0.80)	0.22 (0.06, 0.75)	0.21 (0.06, 0.75)	0.19 (0.04, 0.83)	0.17 (0.03, 1.01)
CD+A vs. AL	**Direct**	0.24 (0.06, 0.82)	0.21 (0.06, 0.62)	0.20 (0.06, 0.58)	0.18 (0.05, 0.56)	0.16 (0.04, 0.59)	0.14 (0.03, 0.70)
	Indirect	0.69 (0.13, 3.25)	0.43 (0.10, 1.68)	0.34 (0.08, 1.30)	0.26 (0.06, 1.04)	0.16 (0.03, 0.75)	0.10 (0.02, 0.62)

Table S2. Odds ratios for treatment success from the NMA node-splitting models including interactions (*model S2*).
AQ+AS: amodiaquine-artesunate; AL: artemether-lumefantrine; CD+A: chlorproguanil-dapsone plus artesunate; DHAPQ: dihydroartemisinin-piperaquine.

Comparison	Log odds ratio Posterior median (posterior 95% credibility interval)					
	Age 1	**Age 2**	**Mean age i.e. 2.5**	**Age 3**	**Age 4**	**Age 5**
AL vs. AQ+AS	0.05 (-0.74, 0.92)	0.05 (-0.67, 0.87)	0.06 (-0.67, 0.87)	0.06 -0.68, 0.88	0.07 -0.75, 0.94	0.08 -0.86, 1.05
CD+A vs. AQ+AS	-0.93 (-2.02, 0.11)	-1.20 (-2.18, -0.27)	-1.34 (-2.30, -0.42)	-1.47 -2.45, -0.54	-1.74 -2.83, -0.70	-2.02 -3.30, -0.77
CD+A vs. AL	-0.98 (-2.07, -0.01)	-1.25 (-2.24, -0.41)	-1.39 (-2.36, -0.56)	-1.53 -2.51, -0.68	-1.82 -2.89, -0.82	-2.10 -3.37, -0.88

Table S3. Selected results for treatment success from the NMA model including interactions (*model S1*).
AQ+AS: amodiaquine-artesunate; AL: artemether-lumefantrine; CD+A: chlorproguanil-dapsone plus artesunate; DHAPQ: dihydroartemisinin-piperaquine. The between trial variance was 0.77 (0.27, 2.07).

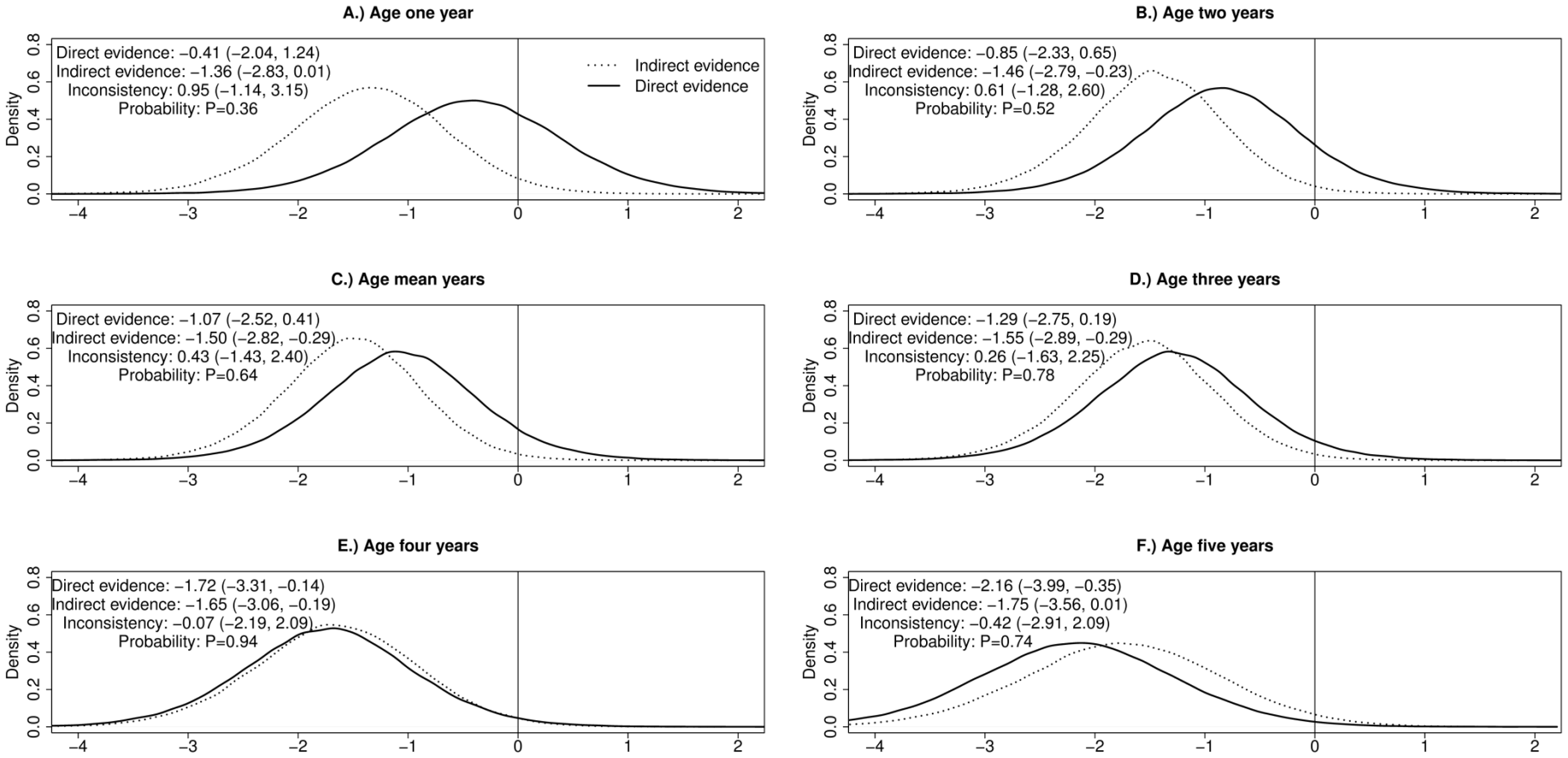

Figure S1. Posterior distributions of log odds ratios at various ages for treatment success for CD+A versus AQ+AS.

The mean age was 2.5 years.

AQ+AS: amodiaquine-artesunate; CD+A: chlorproguanil-dapsone plus artesunate.

Posterior median (95% credibility interval) presented.

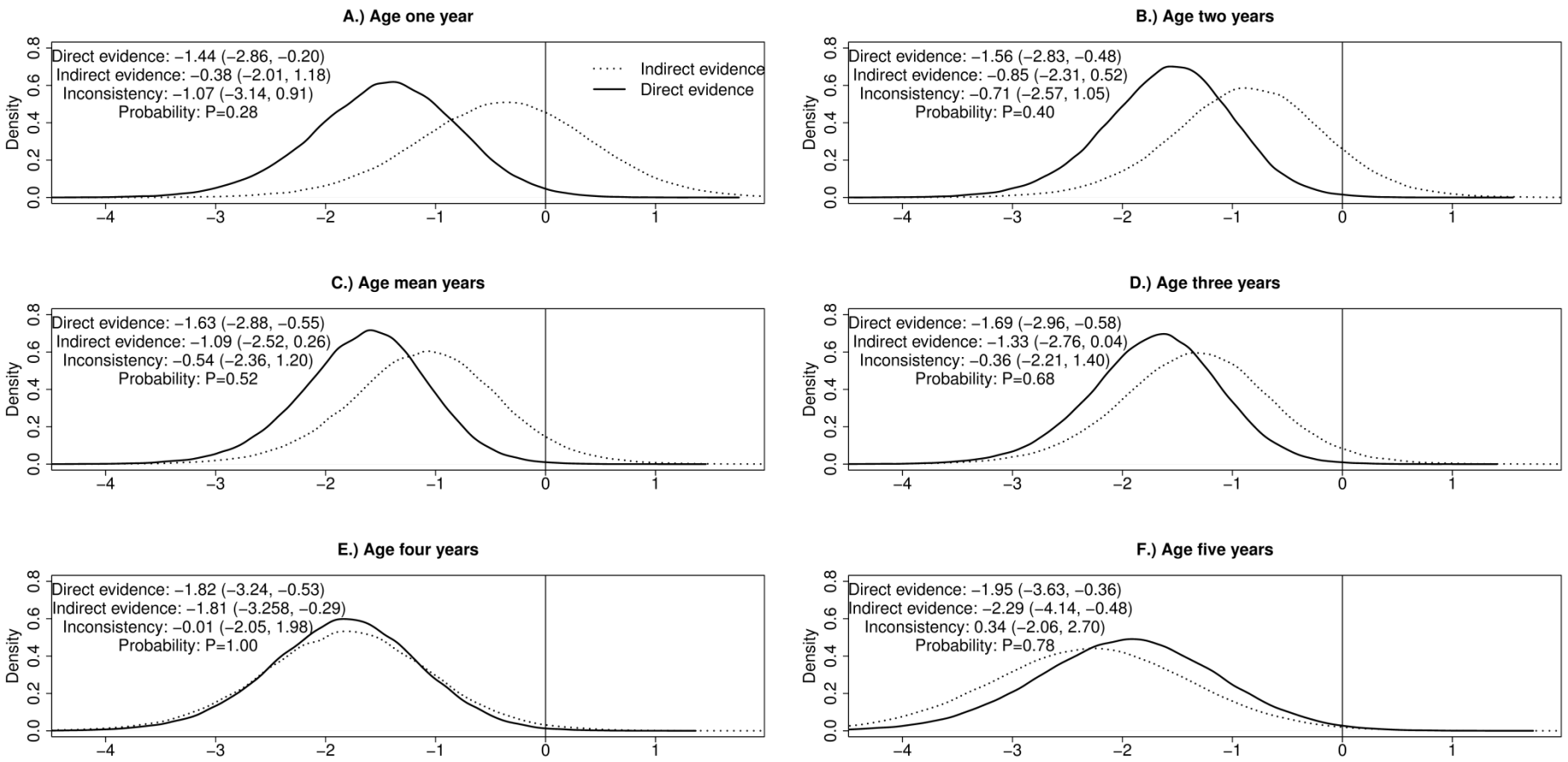

Figure S2. Posterior distributions of log odds ratios at various ages for treatment success for CD+A versus AL.

The mean age was 2.5 years.

AL: artemether-lumefantrine; CD+A: chlorproguanil-dapsone plus artesunate.

Posterior median (95% credibility interval) presented.