Appendix K Specimen WinBUGS code

All synthesis models performed for this guideline conformed to the principles set out in Appendix D.

Random-effects network meta-analysis for dichotomous data

```
# Binomial likelihood, logit link
# Random-effects model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                             # indexes studies
  mu[i] ~ dnorm(0, .0001)                            # vague priors for all trial baselines
  delta[i,1] <- 0                                    # effect is zero for control arm
  w[i,1] <- 0                                        # multi-arm adjustment = zero for ctrl
  for (j in 1:NumArms[i]) {                          # indexes arms
    k[i,j]       ~ dbin(p[i,j],N[i,j])               # binomial likelihood
    logit(p[i,j]) <- mu[i] + delta[i,j]              # model for linear predictor
    rhat[i,j]    <- p[i,j] * N[i,j]                  # expected value of the numerators
    dev[i,j]     <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                   + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                     # deviance contribution
    dummy[i,j]   <- ArmNo[i,j]                       # data not used in this model
    }                                                # close arm loop
  for (j in 2:NumArms[i]) {                          # indexes arms
    delta[i,j]  ~  dnorm(md[i,j],taud[i,j])          # trial-specific LOR distributions
    md[i,j]     <- d[Rx[i,j]] - d[Rx[i,1]] + sw[i,j] # mean of LOR distributions (with
                                                       multi-arm trial correction)
    taud[i,j]   <- tau *2*(j-1)/j                    # precision of LOR distributions (with
                                                       multi-arm trial correction)
    w[i,j]      <- (delta[i,j] - d[Rx[i,j]] + d[Rx[i,1]])
                                                     # adjustment for multi-arm RCTs
    sw[i,j]     <- sum(w[i,1:j-1])/(j-1)             # cumulative adjustment for multi-arm
                                                       trials
    }
  resdev[i]     <- sum(dev[i,1:NumArms[i]])          # summed deviance contribution
  dummy2[i]     <- Yrs[i] * RefID[i]                 # data not used in this model
  }                                                  # close study loop
totresdev     <- sum(resdev[])                       # total residual deviance

d[1]<-0                                              # effect is 0 for reference treatment
for (j in 2:NumRx) {                                 # indexes treatments
  d[j] ~ dnorm(0, .0001)                             # vague priors for treatment effects
  }                                                  # close treatment loop
sd  ~  dunif(0,5)                                    # vague prior for between-trial SD
tau <- pow(sd,-2)                                    # between-trial precision

# Provide estimates of treatment effects T[k] on the natural (probability) scale
AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  logit(Tmean[j]) <- AMean + d[j]
  logit(Tpred[j]) <- APred + d[j]
```

```
    }


  # pairwise ORs and LORs for all possible pairwise comparisons
  for (c in 1:(NumRx-1)) {
    for (j in (c+1):NumRx) {
      lOR[c,j] <- (d[j]-d[c])
      OR[c,j]  <- exp(d[j]-d[c])
      }
    }


  # ranking on relative scale
  for (j in 1:NumRx) {
    rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
    best[j]     <- equals(rk[j],1)                   # probability that treat j is best
    for (h in 1:NumRx) {
      pRk[h,j]  <- equals(rk[j],h)                   # probability that treat j is hth best
      }
    }
  dummy3        <- YrsA                               # not used in this model
}
```

Random-effects network meta-analysis for continuous data

```
# Normal likelihood, identity link
# Random-effects model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                             # indexes studies
  w[i,1]      <- 0                                   # multi-arm adjustment = 0 for control
  delta[i,1]  <- 0                                   # treatment effect is 0 for control
  mu[i]        ~ dnorm(0, .0001)                     # vague priors for all trial baselines
  for (j in 1:NumArms[i]) {                          # indexes arms
    se[i,j]    <- SD[i,j] / sqrt(N[i,j])
    var[i,j]  <- pow(se[i,j],2)                      # calculate variances
    prec[i,j] <- 1/var[i,j]                          # set precisions
    MC[i,j]    ~ dnorm(theta[i,j], prec[i,j])        # normal likelihood
    theta[i,j] <- mu[i] + delta[i,j]                 # model for linear predictor
    dev[i,j]   <- (MC[i,j] - theta[i,j]) * (MC[i,j]
                  - theta[i,j]) * prec[i,j]          # deviance contribution
    dummy[i,j] <- ArmNo[i,j]                         # data not used in this model
    }                                                # close arm loop
  for (j in 2:NumArms[i]) {                          # indexes arms
    delta[i,j] ~ dnorm(md[i,j],taud[i,j])            # trial-specific MD distributions
    md[i,j]    <- d[Rx[i,j]] - d[Rx[i,1]] + sw[i,j]  # mean of MD dists, with multiarm
    taud[i,j]  <- tau *2*(j-1)/j                     # precision of MD dists, with multiarm
    w[i,j]     <- (delta[i,j] - d[Rx[i,j]] + d[Rx[i,1]]) # adjustment, multi-arm RCTs
    sw[i,j]    <- sum(w[i,1:j-1])/(j-1)              # cumulative adjustment for multi-arm
    }
  resdev[i]    <- sum(dev[i,1:NumArms[i]])           # summed deviance contribution
  dummy2[i]    <- Yrs[i] * RefID[i]                  # data not used in this model
  }                                                  # close study loop
totresdev      <- sum(resdev[])                      # total residual deviance

d[1]<-0                                              # effect is 0 for reference treatment
for (j in 2:NumRx) {                                 # indexes treatments
  d[j] ~  dnorm(0, .0001)                            # vague priors for treatment effects
```

```
  }                                                 # close treatment loop
sd   ~ dunif(0,5)                                   # vague prior for between-trial SD
tau  <- pow(sd,-2)                                  # between-trial precision


# Provide estimates of treatment effects T[j] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA

AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  Tmean[j] <- AMean + d[j]
  Tpred[j] <- APred + d[j]
  }


# pairwise MDs for all possible pairwise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    MD[c,j] <- (d[j] - d[c])
    }
  }


# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]      <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]    <- equals(rk[j],1)                 # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j] <- equals(rk[j],h)                 # probability that treat j is hth best
    }
  }
dummy3      <- YrsA                              # data not used in this model
}
```

Random-effects network meta-analysis for categorical data

```
# Binomial likelihood, probit link (different categories)
# Random-effects model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:numStudies) {                    # indexes studies
  w[i,1]      <- 0                           # multi-arm adjustment =0 for control arm
  delta[i,1] <- 0                            # treatment effect =0 for control arm
  mu[i]       ~  dnorm(0, .0001)             # vague priors for all trial baselines
  for (j in 1:numArms[i]) {                  # indexes arms
    p[i,j,1] <- 1                            # Pr(score>0 = 1)
    for (c in 1:numCats[i]-1) {              # indexes categories
      n[i,j,c]      <- N[i,j] - sum(k[i,j,1:c]) + k[i,j,c]
                                             # calculate ns for each consecutive category
      k[i,j,c]      ~  dbin(q[i,j,c],n[i,j,c]) # binomial likelihood
      q[i,j,c]      <- 1-(p[i,j,C[i,c+1]]/p[i,j,C[i,c]])
                                             # conditional probabilities
      theta[i,j,c] <- mu[i] + delta[i,j] + z[C[i,c+1]-1]
                                             # linear predictor
      rhat[i,j,c]  <- q[i,j,c] * n[i,j,c]    # predicted number events
      dv[i,j,c]     <- 2 * (k[i,j,c]*(log(k[i,j,c]) - log(rhat[i,j,c]))
                     +(n[i,j,c] - k[i,j,c]) * (log(n[i,j,c]-k[i,j,c])
```

```
                      - log(n[i,j,c] - rhat[i,j,c])))
                                          # deviance contribution
      }                                   # close category loop
    for (c in 2:numCats[i]) {             # indexes categories again
      p[i,j,C[i,c]]      <- 1 - phi(theta.adj[i,j,c])
                                          # link function
      theta.adj[i,j,c]   <- step(-5-theta[i,j,c-1]) * -5
                            + step(theta[i,j,c-1]-5) * 5
                            + step(5-theta[i,j,c-1]) * step(theta[i,j,c-1]+5)
                              * theta[i,j,c-1]
                                          # constrain theta to [-5,5] to avoid
                                          # numerical errors when using phi()
      }                                   # close second category loop
    dev[i,j] <- sum(dv[i,j,1:numCats[i]-1])  # deviance contribution of each arm
    dummy[i,j] <- ArmNo[i,j]              # data not used in this model
    }                                     # close arm loop
  for (j in 2:numArms[i]) {               # indexes arms
    delta[i,j] ~  dnorm(md[i,j], taud[i,j])
    md[i,j]    <- d[Rx[i,j]] - d[Rx[i,1]] + sw[i,j]
                                          # mean of LHR distributions, with multi-arm
                                            trial correction
    taud[i,j]  <- tau * 2 * (j-1) / j     # precision of LHR distributions, with multi-arm
                                            trial correction
    w[i,j]     <- (delta[i,j] - d[Rx[i,j]] + d[Rx[i,1]])
                                          # adjustment, multi-arm RCTs
    sw[i,j]    <- sum(w[i,1:j-1]) / (j-1) # cumulative adjustment for multi-arm trials
    }
  resdev[i]  <- sum(dev[i,1:numArms[i]])  # summed residual deviance for this trial
  dummy2[i]  <- RefID[i] + juncture[i]    # data not used in this model
  }                                       # close study loop

z[1] <- 0                                 # set z=0 for bottom category
for (j in 2:maxNumCats-1) {
  zz[j] ~  dunif(0,5)                     # prior for difference between z[j] and z[j-1]
  z[j]  <- z[j-1] + zz[j]                 # prior for z[j]
  }
totresdev <- sum(resdev[])                # total residual deviance

d[1] <- 0                                 # effect is zero for reference treatment
for (j in 2:numRx) {                      # indexes treatments
  d[j] ~ dnorm(0, .0001)                  # vague priors for treatment effects
  }
sd  ~  dunif(0, 5)                        # vague prior for between-trial SD
tau <- pow(sd, -2)                        # between-trial precision

# z-scores for all possible pairwise comparisons
for (c in 1:(numRx-1)) {
  for (j in (c+1):numRx) {
    zscore[c,j]      <- d[j] - d[c]
    }
  }

# Provide estimates of treatment effects T[k] on the natural (probability) scale
# at each juncture
for (j in 1:numJunctures) {
  AMean[j] ~ dnorm(meanA[j], precA[j])
  APred[j] ~ dnorm(predA[j], predPrecA[j])
  for (i in 1:numRx) {
    # calculate prob of achieving each level
    for (c in 1:maxNumCats-1) {
      Tmean[j,i,c] <- 1 - phi(AMean[j] + d[i] + z[c])
      Tpred[j,i,c] <- 1 - phi(APred[j] + d[i] + z[c])
```

```
      }
    }
  }

# ranking on relative scale
for (j in 1:numRx) {
  rk[j]       <- blnHiGood * (numRx+1 - rank(d[],j)) + (1-blnHiGood) * rank(d[],j)
  best[j]     <- equals(rk[j],1)                    # probability that treat j is best
  for (h in 1:numRx) {
    pRk[h,j]  <- equals(rk[j],h)                    # probability that treat j is hth best
    }
  }
}
```

Random-effects network meta-analysis for categorical data, with adjustment for dose

```
# Binomial likelihood, probit link (different categories)
# Random-effects model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# and
# Dias, S., Sutton, A.J., Welton, N.J. & Ades, A.E.
# NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression,
# bias and bias-adjustment. 2011.
#
# http://www.nicedsu.org.uk

model {
for(i in 1:numStudies) {                    # indexes studies
  w[i,1]     <- 0                           # multi-arm adjustment =0 for control arm
  delta[i,1] <- 0                           # treatment effect =0 for control arm
  mu[i]      ~ dnorm(0, 0.01)               # vague priors for all trial baselines
  for (j in 1:numArms[i]) {                 # indexes arms
    p[i,j,1] <- 1                           # Pr(score>0 = 1)
    X.CDose[i,j] <- (X.Dose[RefID[i],ArmNo[i,j]] - avgD[Rx[i,j]]) / 1000
                                            # centre dose covariate and divide by
                                            # 1000 (which calms WinBUGS down)
    BX[i,j] <- B[Rx[i,j]] * X.CDose[i,j] - B[Rx[i,1]] * X.CDose[i,1]
                                            # multiply centred dose covariate for arm and
                                            # 'control' by treatment-specific
                                            # dose--response coefficients
    for (c in 1:numCats[i]-1) {             # indexes categories
      n[i,j,c]     <- N[i,j] - sum(k[i,j,1:c]) + k[i,j,c]
                                            # calculate ns for each consecutive category
      k[i,j,c]     ~ dbin(q[i,j,c], n[i,j,c]) # binomial likelihood
      q[i,j,c]     <- 1-(p[i,j,C[i,c+1]]/p[i,j,C[i,c]])
                                            # conditional probabilities
      theta[i,j,c] <- mu[i] + delta[i,j] + z[C[i,c+1]-1] + BX[i,j]
                                            # linear predictor
      rhat[i,j,c]  <- q[i,j,c] * n[i,j,c]   # predicted number events
      dv[i,j,c]    <- 2 * (k[i,j,c]*(log(k[i,j,c]) - log(rhat[i,j,c]))
                    +(n[i,j,c] - k[i,j,c]) * (log(n[i,j,c]-k[i,j,c])
                    - log(n[i,j,c] - rhat[i,j,c])))
                                            # deviance contribution
      }
    dev[i,j] <- sum(dv[i,j,1:numCats[i]-1)) # deviance contribution of each arm
    for (c in 2:numCats[i]) {               # indexes categories
```

```
      p[i,j,C[i,c]]  <- 1 - phi.adj[i,j,c]    # link function
      phi.adj[i,j,c] <- step(5+theta[i,j,c-1])
                       * (step(theta[i,j,c-1]-5)
                       + step(5-theta[i,j,c-1]) * phi(theta[i,j,c-1]))
                                            # adjust phi(x) for values that can give
                                            # numerical errors when x< -5, phi(x)=0,
                                            # when x> 5, phi(x)=1
      }
    dummy[i,j] <- X.FixedDose[RefID[i],ArmNo[i,j]]  # data not used in this model
    }
  for (j in 2:numArms[i]) {                  # indexes arms
    delta[i,j] ~  dnorm(md[i,j], taud[i,j])
    md[i,j]    <- d[Rx[i,j]] - d[Rx[i,1]] + sw[i,j]
                                            # mean of LHR distributions, with multi-arm
                                            # trial correction
    taud[i,j]  <- tau * 2 * (j-1) / j       # precision of LHR distributions, with multi-
                                            # arm trial correction
    w[i,j]     <- (delta[i,j] - d[Rx[i,j]] + d[Rx[i,1]])
                                            # adjustment, multi-arm RCTs
    sw[i,j]    <- sum(w[i,1:j-1]) / (j-1)   # cumulative adjustment for multi-arm trials
    }
  dummy2[i] <- juncture[i]
  resdev[i] <- sum(dev[i,1:numArms[i]])      # summed residual deviance for this trial
  }
sd  ~  dunif(0, 2)                           # vague prior for between-trial SD
tau <- pow(sd, -2)                           # between-trial precision

z[1] <- 0                                    # set z=0 for bottom category
for (j in 2:maxNumCats-1) {
  zz[j] ~  dunif(0,5)                        # prior for difference between z[j] and z[j-1]
  z[j]  <- z[j-1] + zz[j]                    # prior for z[j]
  }
totresdev <- sum(resdev[])                   # total residual deviance

# calculate mean dose (for centring covariates)
for (t in 1:numRx) {                         # indexes treatments
  for (s in 1:numStudies) {                  # indexes studies
    for (a in 1:numArms[s]) {                # indexes arms
      dd[s,a,t] <- X.Dose[RefID[s],ArmNo[s,a]] * equals(Rx[s,a], t)
                                            # record doses where treatment in arm a is t
      nn[s,a,t] <- equals(Rx[s,a], t)        # record a 1 where treatment in arm a is t
      }                                      # close arm loop
    ddd[t,s] <- sum(dd[s,1:numArms[s],t])    # sum doses for treatment t for study s
    nnn[t,s] <- sum(nn[s,1:numArms[s],t])    # count arms with treatment t for study s
    }                                        # close study loop
  avgD[t] <- sum(ddd[t,1:numStudies]) / sum(nnn[t,1:numStudies])
                                            # sum doses for all study-arms, divide by
                                            # no. of arms to calculate average dose
  }                                          # close treatment loop


d[1]  <- 0                                   # effect is zero for placebo
B[1]  <- 0                                   # dose--response coefficient is 0 for placebo
bSD <- 2                                     # moderately vague SD for dose--response prior
prec  <- pow(bSD, -2)                        # convert SD to precision
for (j in 2:numRx) {                         # indexes treatments
  d[j] ~  dnorm(0, .0001)                    # vague priors for treatment effects
  B[j] ~  dnorm(0, prec)                     # priors for dose--response coefficients
  }                                          # close treatment loop

# fit basic parameters (relative effects) at specified covariate values
```

```
for (t in 1:numRx) {                            # indexes treatments
  dz[t] <- d[t] + X.FitVal[t] / 1000 * B[t]     # fit at specified value
  }                                             # close treatment loop


# pairwise z-scores for all possible comparisons
for (c in 1:(numRx-1)) {                        # indexes treatments
  for (j in (c+1):numRx) {                      # indexes comparators
    zscore[c,j] <- dz[j] - dz[c]                # calculate z
    }                                           # close comparator loop
  }                                             # close treatment loop


# ranking on relative scale
for (j in 1:numRx) {                            # indexes treatments
  rk[j]       <- blnHiGood * (numRx+1 - rank(dz[],j)) + (1-blnHiGood) * rank(dz[],j)
                                                # compute ranks (invert if necessary)
  best[j]     <- equals(rk[j],1)                # probability that treat j is best
  for (h in 1:numRx) {                          # index ranks
    pRk[h,j]  <- equals(rk[j],h)                # probability that treat j is hth best
    }                                           # close rank loop
  }                                             # close treatment loop


# Provide estimates of treatment effects T[k] on the natural (probability) scale
# at each juncture
for (j in 1:numJunctures) {
  AMean[j] ~ dnorm(meanA[j], precA[j])
  APred[j] ~ dnorm(predA[j], predPrecA[j])
  for (i in 1:numRx) {
    # calculate prob of achieving each level
    for (c in 1:maxNumCats-1) {
      Tmean[j,i,c] <- 1 - phi(AMean[j] + dz[i] + z[c])
      Tpred[j,i,c] <- 1 - phi(APred[j] + dz[i] + z[c])
      }
    }
  }
}
```