APPENDIX: Pairwise and Network Meta-analysis – Illustrative examples and WinBUGS code

This appendix gives illustrative WinBUGS code for all the link functions and likelihoods mentioned in the main document, as well as example code for shared parameter models. All programming code is fully annotated. The program codes are printed here, but are also available as WinBUGS system files at www.nicedsu.org.uk. Users are advised to download the WinBUGS files from the website instead of copying and pasting from this document. We have provided the codes as complete programs. However, the majority of each RE program is identical to other RE programs, and similarly for the FE programs. We have therefore highlighted the linear predictor in blue, and the likelihood and deviance calculations in red to emphasise the modular nature of the code.

Tables A1 gives an index of the programmes and their relation to the descriptions in the text. Note that for each example there are random and fixed effects versions of the code. All fixed effects code can be run using the same data structure described for the random effects.

<table>
<thead>
<tr>
<th>Program number</th>
<th>Fixed or Random Effects</th>
<th>Likelihood</th>
<th>Link Function</th>
<th>Example name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (a)</td>
<td>Random (2-arm)</td>
<td>Binomial</td>
<td>logit</td>
<td>Blocker</td>
</tr>
<tr>
<td>(b)</td>
<td>Fixed (2-arm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c)</td>
<td>Random Fixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d)</td>
<td>Fixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (a)</td>
<td>Random Fixed</td>
<td>Poisson</td>
<td>log</td>
<td>Dietary fat</td>
</tr>
<tr>
<td>(b)</td>
<td>Fixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (a)</td>
<td>Random Fixed</td>
<td>Binomial</td>
<td>cloglog</td>
<td>Diabetes</td>
</tr>
<tr>
<td>(b)</td>
<td>Fixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (a)</td>
<td>Random Fixed</td>
<td>Multinomial</td>
<td>log</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>(b)</td>
<td>Fixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (a)</td>
<td>Random Fixed</td>
<td>Normal</td>
<td>identity</td>
<td>Parkinson’s</td>
</tr>
<tr>
<td>(b)</td>
<td>Fixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (a)</td>
<td>Random Fixed</td>
<td>Multinomial</td>
<td>probit</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>(b)</td>
<td>Fixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 (a)</td>
<td>Random Fixed</td>
<td>Normal</td>
<td>identity</td>
<td>Parkinson’s</td>
</tr>
<tr>
<td>(b)</td>
<td>Fixed (difference data)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 (a)</td>
<td>Random Fixed</td>
<td>Normal</td>
<td>identity</td>
<td>Parkinson’s</td>
</tr>
<tr>
<td>(b)</td>
<td>Fixed (shared parameter)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EXAMPLE 1.  Blocker

The first two programmes (Blocker 1(a) and 1(b)) are somewhat apart from the other programmes: these programmes are only capable of processing syntheses of two treatments and 2-arm trials. We include them for the benefit of readers who may wish to start with the simplest possible case and see how the more general code that allows incorporation of multi-arm trials is related to the simpler code. The Blocker example is described in the main paper.¹

Program 1(a): Binomial likelihood, logit link, Random Effects, two treatments (Blocker example). Two-arm trials Only

```r
# Binomial likelihood, logit link, pairwise meta-analysis (2 treatments)
# Random effects model
model{
  for(i in 1:ns){ # LOOP THROUGH STUDIES
    delta[i,] ~ dnorm(0,0.0001) # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
    for (k in 1:2) { # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[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] # expected value of the numerators
      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]))) #Deviance contribution
    }
    resdev[i] <- sum(dev[i,]) # summed residual deviance contribution for this trial
    delta[2] ~ dnorm(d[2],tau) # trial-specific LOR distributions
  }
  totresdev <- sum(resdev[]) #Total Residual Deviance
  d[1] ~ dnorm(0,0.0001) # treatment effect is zero for reference treatment
  d[2] ~ dnorm(0,.0001) # vague prior for treatment effect
  sd ~ dunif(0,5) # vague prior for between-trial SD
  tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
}
```

The data structure has two components: a list specifying the number of studies ns and the main body of data which is in a column format: r[1] and n[1] are the numerators and denominators for the first treatment; r[2] and n[2], the numerators and denominators for the second listed treatment. Both data components need to be loaded into WinBUGS for the program to run. Text can be included after the hash symbol (#) for ease of reference to the original data source.

# Data (Blocker example)
list(ns=22)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>39</td>
<td>3</td>
<td>38</td>
<td>1</td>
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<tr>
<td>14</td>
<td>116</td>
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<td>114</td>
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</tr>
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<td>127</td>
<td>1520</td>
<td>102</td>
<td>1533</td>
<td>4</td>
</tr>
<tr>
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<td>365</td>
<td>28</td>
<td>355</td>
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<td>939</td>
<td>98</td>
<td>945</td>
<td>7</td>
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<td>48</td>
<td>471</td>
<td>60</td>
<td>632</td>
<td>8</td>
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<tr>
<td>37</td>
<td>282</td>
<td>25</td>
<td>278</td>
<td>9</td>
</tr>
<tr>
<td>188</td>
<td>1921</td>
<td>138</td>
<td>1916</td>
<td>10</td>
</tr>
</tbody>
</table>
Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials

52 583 64 873 # 11
47 266 45 263 # 12
16 293 9 291 # 13
45 883 57 858 # 14
31 147 25 154 # 15
38 213 33 207 # 16
12 122 28 251 # 17
6 154 8 151 # 18
3 134 6 174 # 19
40 218 32 209 # 20
43 364 27 391 # 21
39 674 22 680 # 22

Program 1(b): Binomial likelihood, logit link, Fixed Effects, two treatments (Blocker example), Two-arm trials only.

# Binomial likelihood, logit link, pairwise meta-analysis (2 treatments)
# Fixed effect model
model{# *** PROGRAM STARTS
for(i in 1:ns){# LOOP THROUGH STUDIES
mu[i] ~ dnorm(0,.0001)# vague priors for all trial baselines
for (k in 1:2){# LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k])# binomial likelihood
logit(p[i,k]) <- mu[i] + d[k]# model for linear predictor
rhat[i,k] <- p[i,k] * n[i,k]# expected value of the numerators
dev[i] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])))# Deviance contribution
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
}
resdev[i] <- sum(dev[i,])# summed residual deviance contribution for this trial
totresdev <- sum(resdev[])# Total Residual Deviance
d[1]<- 0# treatment effect is zero for reference treatment
d[2] ~ dnorm(0,.0001)# vague prior for treatment effect
}

# Initial values
#chain 1
list(d=c( NA, 0), sd=1, mu=c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0))
#chain 2
list(d=c( NA, -1), sd=4, mu=c(-3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3))
#chain 3
list(d=c( NA, 2), sd=2, mu=c(-3, 5, -1, -3, 7, -3, -4, -3, -3, 0, -3, -3, 0, 3, 5, -3, -1, -3, -7, -3, -3))

All code presented below is completely general and will be suitable for fitting pairwise or network meta-analyses with any number of treatments and multi-arm trials. We also provide an indication of the relevant parameters to monitor for inference and model checking for the various programs.
The nodes to monitor for the fixed effects models are the same as those for the random effects models, except that there is no heterogeneity parameter.

This example and results are described in the main paper\(^1\) (Tables 1 and 3). The WinBUGS code for random effects is given in program 1(c) and the fixed effects code is given in program 1(d).

**Program 1(c): Binomial likelihood, logit link, Random Effects (Blocker example)**

```plaintext
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{
    # *** PROGRAM STARTS
    # LOOP THROUGH STUDIES
    for(i in 1:ns){
        # adjustment for multi-arm trials is zero for control arm
        w[i,1] <- 0
        # treatment effect is zero for control arm
        delta[i,1] <- 0
        # vague priors for all trial baselines
        mu[i] ~ dnorm(0,.0001)
        for (k in 1:na[i])  {
            # binomial likelihood
            r[i,k] ~ dbin(p[i,k],n[i,k])
            logit(p[i,k]) <- mu[i] + delta[i,k]
            # model for linear predictor
            rhat[i,k] <- 2 * (r[i,k] * (log(r[i,k]) - log(rhat[i,k])))
            # Deviance contribution
            dev[i,k] <- 2 * (r[i,k] * (log(r[i,k]) - log(rhat[i,k])))
            # expected value of the numerators
            resdev[i] <- sum(dev[i,1:na[i]])
            # summed residual deviance contribution for this trial
        }
        # LOOP THROUGH ARMS
        resdev[i] <- sum(resdev[i])
        # Total Residual Deviance
        totresdev <- sum(resdev[])
        # *** PROGRAM ENDS
    }
}
```

Alternative prior distributions can be used for the Random Effects Variance. For example, the last two lines above can be replaced by a vague Gamma prior on the precision parameter, which is sometimes also referred to as a vague inverse Gamma prior on the variance:

```plaintext
tau ~ dgamma(.001,.001)       # vague gamma prior on the precision
sd ~ dnorm(0,0.5)             # vague priors for treatment effects
sd ~ dunif(0,0.5)             # between-trial precision = (1/between-trial variance)
```

See the main document for further discussion of prior distributions.

Additional code can be added before the closing brace to estimate all the pair-wise Log Odds Ratios and Odds Ratios, to generate ranking statistics and the probability that each treatment is the best treatment, and to produce estimates of absolute effects, given additional information on the absolute treatment effect on one of the treatments. In addition, given an
assumption about the absolute effect of one treatment, it is possible to express the treatment effect on other scales (risk difference, relative risk), or number needed to treat, and to obtain confidence intervals for all these quantities. This is illustrated below.

The data structure has two components: a list specifying the number of treatments nt and number of studies ns. Both data components need to be loaded into WinBUGS for the program to run. The main body of data is in a vector format, in the order r[,1] then n[,1], the numerators and denominators for the first treatment, then r[,2] then n[,2], the numerators and denominators for the second listed treatment, then r[,1] and t[,2], the treatment number identifiers for the first and second listed treatments, and finally the number of arms in each trial, na[]. The purpose for this structure becomes clearer in datasets with multi-arm trials. An important feature of the code presented is the assumption that the treatments are always presented in ascending (numerical) order and that treatment 1 is taken as the reference treatment. This rule is crucial when conducting network meta-analysis to ensure the correct relative effects are estimated.
We strongly recommend the use of the column data format shown here in preference to the list format that WinBUGS also allows, and the use of comments to add trial names or references. This facilitates data checking.

```
# Data (Blocker example)
list(nt=2, ns=22)
  r[,1] r[,2] t[,1] t[,2] na[]
  3   39   3   38  1  2  2
  14  116  7   114  1  2  2
  11  93   5   69  1  2  2
  127 1520 102 1533 1  2  2
  27  365  28  355  1  2  2
   6   52   4   59  1  2  2
 152  939  98  945  1  2  2
  48  471  60  632  1  2  2
  37  292  25  278  1  2  2
 168 1921 138 1916 1  2  2
  52  583  64  873  1  2  2
  47  266  45  263  1  2  2
  16  293   9  291  1  2  2
  45  883  57  858  1  2  2
  31  147  25  154  1  2  2
  38  213  33  207  1  2  2
  12  122  28  251  1  2  2
   6  154   8  151  1  2  2
   3  134   6  174  1  2  2
  40  218  32  209  1  2  2
  43  364  27  391  1  2  2
  39  674  22  680  1  2  2
END
```

To obtain the posterior summaries of the parameters of interest for inference, the nodes \( \delta \) and \( \sigma_d \) (in the random effects model only) need to be monitored. To obtain the posterior means of the parameters required to assess model fit and model comparison, \( \text{dev}, \text{totresdev} \) and the DIC (from the WinBUGS DIC tool), need to be monitored. In addition, to calculate the leverage for each data point and to draw leverage plots, \( rhat \) needs to be monitored.

**Program 1(d): Binomial likelihood, logit link, Fixed Effects (Blocker example)**

```
# Binomial likelihood, logit link
# Fixed effects model
model{
  for(i in 1:ns){
    mu[i] ~ dnorm(0,.0001)  # vague priors for all trial baselines
    for (k in 1:na[i]) {
      # *** PROGRAM STARTS
      # LOOP THROUGH STUDIES
      # LOOP THROUGH ARMS
```
EXAMPLE 2. Dietary fat

In a Cochrane Review of randomised controlled trials to assess the effect of change in dietary fats on total and cardiovascular mortality,² data extracted was in the form of rates and given as the number of events per person-years observed (Table A2). Most of the trials compared only one reduced fat dietary intervention with a control diet (non-reduced fat). However, the ‘London Corn/Olive’ trial compared two types of reduced fat diets against control (for more details see Hooper et al.²). For the purpose of this example we considered the two different types of diet as the same intervention (treatment 2), but kept the treatment arms separately, so that in a random effects model, this trial will provide two correlated estimates of the trial-specific treatment effect \( \delta_{i2} \) and in the fixed effects model, both arms will contribute to the estimate of the common treatment effect \( d_{12} \).

Table A2 Dietary fat example: Study names and treatment codes for the 10 included studies and person-years and total mortality observed in each study.

<table>
<thead>
<tr>
<th>Study name and ID</th>
<th>Treatment control diet</th>
<th>diet 2</th>
<th>Person-yrs obs control diet</th>
<th>diet 2</th>
<th>Total mortality control diet</th>
<th>diet 2</th>
<th>Number randomised control diet</th>
<th>diet 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.DART</td>
<td>1</td>
<td>2</td>
<td>1917</td>
<td>1925</td>
<td>113</td>
<td>111</td>
<td>1015</td>
<td>1018</td>
</tr>
<tr>
<td>2.London Corn /Olive</td>
<td>1</td>
<td>2</td>
<td>43.6</td>
<td>41.3</td>
<td>38</td>
<td>3</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>3.London Low Fat</td>
<td>1</td>
<td>2</td>
<td>393.5</td>
<td>373.9</td>
<td>24</td>
<td>20</td>
<td>129</td>
<td>123</td>
</tr>
<tr>
<td>4.Minnesota Coronary</td>
<td>1</td>
<td>2</td>
<td>4715</td>
<td>4823</td>
<td>248</td>
<td>269</td>
<td>4516</td>
<td>4516</td>
</tr>
<tr>
<td>5.MRC Soya</td>
<td>1</td>
<td>2</td>
<td>715</td>
<td>751</td>
<td>31</td>
<td>28</td>
<td>194</td>
<td>199</td>
</tr>
<tr>
<td>6.Oslo Diet-Heart</td>
<td>1</td>
<td>2</td>
<td>885</td>
<td>895</td>
<td>65</td>
<td>48</td>
<td>206</td>
<td>206</td>
</tr>
<tr>
<td>7.STARS</td>
<td>1</td>
<td>2</td>
<td>87.8</td>
<td>91</td>
<td>3</td>
<td>1</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>8.Sydney Diet-Heart</td>
<td>1</td>
<td>2</td>
<td>1011</td>
<td>939</td>
<td>28</td>
<td>39</td>
<td>237</td>
<td>221</td>
</tr>
<tr>
<td>9.Veterans Admin</td>
<td>1</td>
<td>2</td>
<td>1544</td>
<td>1588</td>
<td>177</td>
<td>174</td>
<td>422</td>
<td>424</td>
</tr>
<tr>
<td>10.Veterans Diet &amp; Skin CA</td>
<td>1</td>
<td>2</td>
<td>125</td>
<td>123</td>
<td>2</td>
<td>1</td>
<td>67</td>
<td>66</td>
</tr>
</tbody>
</table>

²Hooper et al. (2013). A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials.
The WinBUGS code for random effects is given in program 2(a) and the fixed effects code is given in program 2(b).

**Program 2(a): Poisson likelihood, log link, Random Effects (Dietary fat example)**

```wbr
# Poisson likelihood, log link
# Random effects model for multi-arm trials
model{
  for(i in 1:ns){
    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
  for (k in 1:na[i]) {
    r[i,k] ~ dpois(theta[i,k]) # Poisson likelihood
    theta[i,k] <- lambda[i,k]*E[i,k] # failure rate * exposure
    log(lambda[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
    dev[i,k] <- 2*((theta[i,k] - r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k])) # Deviance contribution
    }
  }
  resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
  for (k in 2:na[i]) {
    delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
    md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions (with multi-arm trial correction)
    taud[i,k] <- tau * 2*(k-1)/k # precision of LOR distributions (with multi-arm trial correction)
  }
  for (k in 2:nt){ # treatment effect is zero for reference treatment
d[k] ~ 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 = (1/between-trial variance)
}

# *** PROGRAM STARTS
# LOOP THROUGH STUDIES
# adjustment for multi-arm trials is zero for control arm
# treatment effect is zero for control arm
# vague priors for all trial baselines
# LOOP THROUGH ARMS
# Poisson likelihood
# failure rate * exposure
# model for linear predictor
#Deviance contribution
}

resdev[i] <- sum(resdev[]) #Total Residual Deviance
for (k in 2:nt){ # treatment effect is zero for reference treatment
  d[k] ~ dnorm(0,0.0001) # vague priors for treatment effects
}
for (k in 1:nt) { log(T[k]) ~ A + d[k] }
```

As before, additional code can be added to monitor all the $K(K-1)/2$ log hazard ratios and hazard ratios when there are more than 2 treatments:

```wbr
# pairwise HRs and LHRs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
  for (k in (c+1):nt) {
    lh[c,k] <- (d[k]-d[c])
    log(lh[c,k]) ~ lh[c,k]
  }
}
or to rank treatments and monitor the probabilities that each is best, and to generate absolute rates for each treatment. For example if, on the basis of some external data we believe that the log-rate for Treatment 1 has mean -3, and precision 1.77, then we can generate absolute rates for other treatments as follows:

```wbr
A ~ dnorm(-3,1.77)
for (k in 1:nt) { log(T[k]) ~ A + d[k] }
```
A further variable that may be required for cost-effectiveness modelling might be the proportion of patients that would be expected to have an event, after a follow-up of, say, 3 months, under each treatment. In this example the rates are per year, so:

```r
for (k in 1:nt) { p[k] <- 1-exp(-T[k]*0.25) }
```

The data structure again has two components: a list specifying the number of treatments `nt` and number of studies `ns`. Both data components need to be loaded into WinBUGS for the program to run. The main body of data is in a vector format, and we need to allow for a 3-arm trial. Three places are therefore required to specify the treatments `t[,]`, the exposure times `E[,]` and the number of events `r[,]` in each arm; “NA” indicates that the data is missing for a particular cell. As before `na[]` is the number of arms in each study. Text can be included after a hash symbol for ease of reference to the original data source.

```
# Data (Dietary fat example)
list(ns=10, nt=2)
1 2 NA 1917 1925 NA 113 111 NA 2 #10 London Corn/Olive
1 2 NA 393.5 373.9 NA 24 20 NA 2 #11 London Low Fat
1 2 NA 4715 4823 NA 248 269 NA 2 #14 Minnesota Coronary
1 2 NA 715 751 NA 31 28 NA 2 #15 MRC Soya
1 2 NA 885 895 NA 65 48 NA 2 #18 Oslo Diet-Heart
1 2 NA 87.8 91 NA 3 1 NA 2 #22 STARS
1 2 NA 1011 939 NA 28 39 NA 2 #23 Sydney Diet-Heart
1 2 NA 1544 1588 NA 177 174 NA 2 #26 Veterans Administration
1 2 NA 125 123 NA 2 1 NA 2 #27 Veterans Diet & Skin CA
END
```

```
# Initial Values
# Initial values for delta can be generated by WinBUGS.
#chain 1
list(d=c( NA, 0), sd=1, mu=c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0))
#chain 2
list(d=c( NA, -1), sd=4, mu=c(-3, -3, -3, -3, -3, -3, -3, -3, -3, -3))
#chain 3
list(d=c( NA, 2), sd=2, mu=c(-3, 5, -1, -3, 7, -3, -4, -3, -3, 0))
```

To get the posterior summaries of the parameters of interest for inference, the nodes `a` and `sd` (in the random effects model only) need to be monitored. To obtain the posterior means of the parameters required to assess model fit and model comparison, `dev`, `totresdev` and the DIC (from the WinBUGS the DIC tool), need to be monitored. In addition, to calculate the leverage for each data point and to draw leverage plots, `theta` needs to be monitored.
Program 2(b): Poisson likelihood, log link, Fixed Effects (Dietary fat)

```
# Poisson likelihood, log link
# Fixed effects model for multi-arm trials
model{
  for(i in 1:ns){
    mu[i] ~ dnorm(0, .0001)
    for (k in 1:na[i]) {
      rf[i,k] ~ dpois(theta[i,k])
      theta[i,k] <- lambda[i,k]*E[i,k]
      log(lambda[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
      dev[i,k] <- 2*(theta[i,k]*rf[i,k] + rf[i,k]*log(rf[i,k]/theta[i,k]))
    }
    resdev[i] <- sum(dev[i,1:na[i]])
  }
  totresdev <- sum(resdev[])
  for (k in 2:nt){ d[k] ~ dnorm(0, .0001) }
}

# Initial Values
#chain 1
list(d=c(NA, 0), mu=c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0))
#chain 2
list(d=c(NA, -1), mu=c(-3, -3, -3, -3, -3, -3, -3, -3, -3, -3))
#chain 3
list(d=c(NA, 2), mu=c(-3, 5, -1, -3, 7, -3, -4, -3, -3, 0))

Results

The results from the two models (3 chains: 20,000 iterations after a burn-in of 20,000 for the FE model and 100,000 iterations after a burn-in of 100,000 for the RE model) are compared in Table A3. The random and fixed effects models are indistinguishable in terms of model fit, and both appear to fit the data well in that $\hat{D}_{re}$ is close to 21, the number of data points. The posterior median of the pooled log-rate of a reduced fat diet, compared to the control diet is -0.01 in the FE model with 95% Credible Interval (-0.11, 0.10) suggesting no difference in the number of cardiovascular mortalities in each group. The posterior medians of the absolute rates of mortality (and their 95% Credible intervals), having assumed that the log-rate of mortality on the control diet has mean -3 and precision 1.77, on the control and reduced fat diets are the same (Table A3).
Table A3 Dietary fat example: posterior mean, standard deviation (sd), median and 95% Credible interval (CrI) for both the fixed and random effects models for the treatment effect $d_{12}$, absolute effects of the control diet ($T_1$) and the reduced fat diet ($T_2$) for a log-rate of mortality on the control diet with mean -3 and precision 1.77, heterogeneity parameter $\tau$ and model fit statistics.

<table>
<thead>
<tr>
<th></th>
<th>FE model</th>
<th></th>
<th></th>
<th></th>
<th>RE model</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>sd</td>
<td>median</td>
<td>CrI</td>
<td>mean</td>
<td>sd</td>
<td>median</td>
<td>CrI</td>
</tr>
<tr>
<td>$d_{12}$</td>
<td>-0.01</td>
<td>0.054</td>
<td>-0.01</td>
<td>(-0.11,0.10)</td>
<td>-0.02</td>
<td>0.09</td>
<td>-0.01</td>
<td>(-0.19,0.16)</td>
</tr>
<tr>
<td>$T_1$</td>
<td>0.06</td>
<td>0.04</td>
<td>0.05</td>
<td>(0.01,0.18)</td>
<td>0.06</td>
<td>0.04</td>
<td>0.05</td>
<td>(0.01,0.18)</td>
</tr>
<tr>
<td>$T_2$</td>
<td>0.06</td>
<td>0.04</td>
<td>0.05</td>
<td>(0.01,0.18)</td>
<td>0.06</td>
<td>0.04</td>
<td>0.05</td>
<td>(0.01,0.18)</td>
</tr>
<tr>
<td>$\tau$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.13</td>
<td>0.12</td>
<td>0.10</td>
<td>(0.00,0.43)</td>
</tr>
<tr>
<td>$D_{res}$</td>
<td>22.32</td>
<td></td>
<td></td>
<td></td>
<td>21.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D_0$</td>
<td>10.9</td>
<td></td>
<td></td>
<td></td>
<td>13.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIC</td>
<td>33.2</td>
<td></td>
<td></td>
<td></td>
<td>34.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Compare to 21 data points

**EXAMPLE 3. Diabetes**

Here we show code for a linear model on the log rate scale based on binomial data gathered at different follow-up times. We use as an illustration a network meta-analysis to assess the incidence of diabetes in randomised controlled trials of antihypertensive drugs. The outcome was new cases of diabetes observed over the trial duration period (measured in years) for 6 different drugs: Diuretic (treatment 1), Placebo (treatment 2), $\beta$ blocker (treatment 3), CCB (treatment 4), ACE inhibitor (treatment 5) and ARB (treatment 6). In this example of a network meta-analysis, the reference treatment chosen was diuretic, as recommended in this field – for more details see Elliott & Meyer. The data are presented in Table A4 and the network diagram in Figure A1.
Appendix to Dias, Sutton, Ades and Welton, MDM 2013
Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials

Table A4 Diabetes example: study names, follow-up time in years, treatments compared, total number of new cases of diabetes and number of patients in each trial arm, where Diuretic = treatment 1, Placebo = treatment 2, β blocker = treatment 3, CCB = treatment 4, ACE inhibitor = treatment 5 and ARB = treatment 6.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study Follow-up (in years)</th>
<th>Treatment arm 1</th>
<th>Treatment arm 2</th>
<th>Treatment arm 3</th>
<th>New cases of diabetes arm 1</th>
<th>New cases of diabetes arm 2</th>
<th>New cases of diabetes arm 3</th>
<th>Total number of patients arm 1</th>
<th>Total number of patients arm 2</th>
<th>Total number of patients arm 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MRC-E</td>
<td>5.8</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>43</td>
<td>34</td>
<td>37</td>
<td>1081</td>
<td>2213</td>
<td>1102</td>
</tr>
<tr>
<td>2. EWPH</td>
<td>4.7</td>
<td>1</td>
<td>2</td>
<td></td>
<td>29</td>
<td>20</td>
<td></td>
<td>416</td>
<td>424</td>
<td></td>
</tr>
<tr>
<td>3. SHEP</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
<td>140</td>
<td>118</td>
<td></td>
<td>1631</td>
<td>1578</td>
<td></td>
</tr>
<tr>
<td>4. HAPPHY</td>
<td>3.8</td>
<td>1</td>
<td>3</td>
<td></td>
<td>75</td>
<td>86</td>
<td></td>
<td>3272</td>
<td>3297</td>
<td></td>
</tr>
<tr>
<td>5. ALLHAT</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>302</td>
<td>154</td>
<td>119</td>
<td>6766</td>
<td>3954</td>
<td>4096</td>
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<tr>
<td>6. INSIGHT</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td></td>
<td>176</td>
<td>136</td>
<td></td>
<td>2511</td>
<td>2508</td>
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<td>7. ANBP-2</td>
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<td>5</td>
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<td>200</td>
<td>138</td>
<td></td>
<td>2826</td>
<td>2800</td>
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</tr>
<tr>
<td>8. ALPINE</td>
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<td>1</td>
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<td></td>
<td>8</td>
<td>1</td>
<td></td>
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<td>196</td>
<td></td>
</tr>
<tr>
<td>9. FEVER</td>
<td>3.3</td>
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<td>4</td>
<td></td>
<td>154</td>
<td>177</td>
<td></td>
<td>4870</td>
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<tr>
<td>10. DREAM</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td></td>
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<tr>
<td>11. HOPE</td>
<td>4.5</td>
<td>2</td>
<td>5</td>
<td></td>
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<td></td>
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<td>2837</td>
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</tr>
<tr>
<td>12. PEACE</td>
<td>4.8</td>
<td>2</td>
<td>5</td>
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<td></td>
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<td></td>
<td>2175</td>
<td>2167</td>
<td></td>
</tr>
<tr>
<td>15. AASK</td>
<td>3.8</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>70</td>
<td>32</td>
<td>45</td>
<td>405</td>
<td>202</td>
<td>410</td>
</tr>
<tr>
<td>16. STOP-2</td>
<td>4</td>
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<td>4</td>
<td>5</td>
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<td>95</td>
<td>93</td>
<td>1960</td>
<td>1965</td>
<td>1970</td>
</tr>
<tr>
<td>17. ASCOT</td>
<td>5.5</td>
<td>3</td>
<td>4</td>
<td></td>
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<td></td>
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<td>7072</td>
<td></td>
</tr>
<tr>
<td>18. NORDIL</td>
<td>4.5</td>
<td>3</td>
<td>4</td>
<td></td>
<td>251</td>
<td>216</td>
<td></td>
<td>5059</td>
<td>5095</td>
<td></td>
</tr>
<tr>
<td>19. INVEST</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td></td>
<td>665</td>
<td>569</td>
<td></td>
<td>8078</td>
<td>8098</td>
<td></td>
</tr>
<tr>
<td>20. CAPPP</td>
<td>6.1</td>
<td>3</td>
<td>5</td>
<td></td>
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<td>337</td>
<td></td>
<td>5230</td>
<td>5183</td>
<td></td>
</tr>
<tr>
<td>21. LIFE</td>
<td>4.8</td>
<td>3</td>
<td>6</td>
<td></td>
<td>320</td>
<td>242</td>
<td></td>
<td>3979</td>
<td>4020</td>
<td></td>
</tr>
<tr>
<td>22. VALUE</td>
<td>4.2</td>
<td>4</td>
<td>6</td>
<td></td>
<td>845</td>
<td>690</td>
<td></td>
<td>5074</td>
<td>5087</td>
<td></td>
</tr>
</tbody>
</table>

Figure A1 Diabetes network: each edge represents a treatment, connecting lines indicate pairs of treatments which have been directly compared in randomised trials. The numbers on the lines indicate the numbers of trials making that comparison and the numbers by the treatment names are the treatment codes used in the modelling.
The WinBUGS code for random effects is given in program 3(a) and the fixed effects code is given in program 3(b).

**Program 3(a): Binomial likelihood, cloglog link, Random Effects (Diabetes example)**

```plaintext
# Binomial likelihood, cloglog link
# Random effects model for multi-arm trials
model{
   # *** PROGRAM STARTS
   for(i in 1:ns){
      # LOOP THROUGH STUDIES
      w[i,1] ~ dbern(pi[i,k].n[i,k])
      delta[i,1] ~ dnorm(0,.0001)
      for (k in 1:na[i]) {
         # LOOP THROUGH ARMS
         r[i,k] ~ dbin(p[i,k],n[i,k])
         cloglog(p[i,k]) <- log(time[i]) + mu[i] + delta[i,k]
         rhat[i,k] <- p[i,k] * n[i,k]
         dev[i,k] <- 2 * ((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])))
         # Deviance contribution
      }
      resdev[i] <- sum(dev[i,1:na[i]])
      # summed residual deviance contribution for this trial
      for (k in 2:na[i]) {
         # LOOP THROUGH ARMS
         delta[i,k] ~ dnorm(md[i,k],taud[i,k])
         md[i,k] <- d[t[i,k]] - d[t[i,1]] + s[w[i,k]]
         taud[i,k] <- tau * 2*(k-1)/k
         w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
         sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
      totresdev <- sum(resdev[i])
      # Total Residual Deviance
   }
   d[1]<-0
   for (k in 2:nt){
      # LOOP THROUGH ARMS
      d[k] ~ dnorm(md[k],taud[k])
      md[k] <- d[t[k]] - d[t[1]] + s[w[k]]
      taud[k] <- tau * 2*(k-1)/k
      w[k] <- (delta[k] - d[t[k]] + d[t[1]])
      sw[k] <- sum(w[i,1:k-1])/(k-1)
   }
   # *** PROGRAM ENDS
}
```

Additional code to generate all the treatment contrasts, absolute effects, ranking can be added, as with the Poisson – log link models. To generate absolute probabilities for each treatment, if, on the basis of some external data, we believe that the cloglog of the probability of an event for Treatment 1, after a time period of 3 years, has mean -4.2, and precision 1.11, then we can generate absolute probabilities for other treatments as follows:

```plaintext
A ~ dnorm(-4.2,1.11)
for (k in 1:nt) { cloglog(T[k]) <- log(3) + A + d[k]  }
```

The main body of data is in the same format as the binomial likelihood with logit link in Example 1, with an additional vector for follow-up time, `time[]`. Note that treatments are ordered numerically so that the treatment in arm 2 has a higher code than the treatment in arm 1, and the treatment in arm 3 has a higher code than the treatment in arm 2. This is essential to ensure the correct relative effects are obtained.
Data (Diabetes example)
list(ns=22, n=6)

Program 3(b): Binomial likelihood, cloglog link, Fixed Effects (Diabetes example)
Appendix to Dias, Sutton, Ades and Welton, MDM 2013
Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials

# Initial Values
# chain 1
list(d=c(NA,0,0,0,0,0), mu=c(0,0,0,0,0, 0,0,0,0,0,0,0))
# chain 2
list(d=c(NA,1,1,1,1,1), mu=c(0,0,0,0,0, 0,0,0,0,0,0,0))
# chain 3
list(d=c(NA,1,1,1,1,2), mu=c(0,0,0,0,0, 0,0,0,0,0,0,0))

Results

Both fixed and random effects models were fitted (3 chains: 100,000 iterations after a burn-in of 50,000). From the results presented in Table A5, we see that the fixed effects model has a very poor fit and the random effects model should be preferred for inference.

Table A5 Diabetes example: posterior mean, standard deviation (sd), median and 95% Credible interval (CrI) for both the fixed and random effects models for the treatment effects of Placebo ($d_{12}$), β blocker ($d_{13}$), CCB ($d_{14}$), ACE inhibitor ($d_{15}$) and ARB ($d_{16}$) relative to Diuretic; absolute effects of diuretic ($T_1$), Placebo ($T_2$), β blocker ($T_3$), CCB ($T_4$), ACE inhibitor ($T_5$) and ARB ($T_6$); heterogeneity parameter $\tau$ and model fit statistics.

<table>
<thead>
<tr>
<th></th>
<th>FE model</th>
<th></th>
<th>RE model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>sd</td>
<td>median</td>
</tr>
<tr>
<td>$d_{12}$</td>
<td>-0.25</td>
<td>0.06</td>
<td>-0.25</td>
</tr>
<tr>
<td>$d_{13}$</td>
<td>-0.06</td>
<td>0.06</td>
<td>-0.06</td>
</tr>
<tr>
<td>$d_{14}$</td>
<td>-0.25</td>
<td>0.05</td>
<td>-0.25</td>
</tr>
<tr>
<td>$d_{15}$</td>
<td>-0.36</td>
<td>0.05</td>
<td>-0.36</td>
</tr>
<tr>
<td>$d_{16}$</td>
<td>-0.45</td>
<td>0.06</td>
<td>-0.45</td>
</tr>
<tr>
<td>$T_1$</td>
<td>0.065</td>
<td>0.067</td>
<td>0.044</td>
</tr>
<tr>
<td>$T_2$</td>
<td>0.052</td>
<td>0.055</td>
<td>0.034</td>
</tr>
<tr>
<td>$T_3$</td>
<td>0.062</td>
<td>0.064</td>
<td>0.042</td>
</tr>
<tr>
<td>$T_4$</td>
<td>0.051</td>
<td>0.055</td>
<td>0.034</td>
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<td>$T_5$</td>
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<td>0.050</td>
<td>0.031</td>
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<tr>
<td>$T_6$</td>
<td>0.043</td>
<td>0.046</td>
<td>0.028</td>
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<tr>
<td>$\tau$</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

|       |         |       |        |          | FE model |       |       |        |          | RE model |
|-------|---------|-------|--------|----------|----------|-------|-------|--------|----------|
|       |         |       |        |          | mean     | sd    | median | CrI    | mean     | sd    | median | CrI    |
| $D_{res}$ | 78.25   |       |       |          |          |       |       |        | 53.7     |          |       |       |
| pD     | 27.0    |       |       |          |          |       |       |        | 38.0     |          |       |       |
| DIC    | 105.2   |       |       |          |          |       |       |        | 91.7     |          |       |       |

* Compare to 48 data points

The posterior median of the pooled treatment effects, on the complementary log-log scale, of treatments 2 to 6 relative to the reference treatment show a beneficial effect of all the treatment with the exception of treatment 3 (Table A5).

The posterior medians of the absolute probabilities of developing diabetes after a period of three years, assuming that the cloglog of the probability of developing diabetes on Placebo has mean -4.2 and precision 1.11, on each of the treatments are between 3 and 4% (Table A5).
EXAMPLE 4. Schizophrenia

In a network meta-analysis of trials of antipsychotic medication for the prevention of relapse in people with schizophrenia, 17 trials comparing 9 treatments including placebo were included. The data available from each trial are the number of patients in each of three outcome states at the end of follow-up. The outcome states are: relapse ($j=1$), discontinuation of treatment due to intolerable side effects ($j=2$), and discontinuation for other reasons ($j=3$), which might include inefficacy of treatment that did not fulfil all criteria for relapse, or loss to follow-up. Patients not reaching any of these end-points at the end of follow-up were considered as censored observations, and still in remission ($j=4$) (for more details see Ades et al.). The data are presented in Table A6 and the network diagram in Figure A2.

Table A6 Schizophrenia example: study names, follow-up time in weeks, treatments compared, total number of events for each of the four states and total number of patients in each trial arm, where Placebo = treatment 1, Olanzapine = 2, Amisulpride = 3, Zotepine = 4, Aripiprazole = 5, Ziprasidone = 6, Paliperidone = 7, Haloperidol = 8, Risperidone = 9.44

<table>
<thead>
<tr>
<th>Study</th>
<th>follow-up (weeks)</th>
<th>treatment</th>
<th>number of events</th>
<th>total no of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>arm 1</td>
<td>relapse</td>
<td>arm 1 arm 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>arm 2</td>
<td>discontinuation due to intolerable side effects</td>
<td>arm 1 arm 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>arm 1 arm 2</td>
<td>arm 1 arm 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>discontinuation for other reasons</td>
<td>arm 1 arm 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>arm 1 arm 2</td>
<td>arm 1 arm 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient still in remission</td>
<td>arm 1 arm 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>total no of patients</td>
<td>arm 1 arm 2</td>
</tr>
<tr>
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4. Ades et al.
Appendix to Dias, Sutton, Ades and Welton, MDM 2013
Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials

Figure A2 Schizophrenia network: each edge represents a treatment, connecting lines indicate pairs of treatments which have been directly compared in randomised trials. The numbers on the lines indicate the numbers of trials making that comparison and the numbers by the treatment names are the treatment codes used in the modelling.

A random effects model with different between-trial variation for each outcome and a fixed effects model were fitted. The WinBUGS code for the random effects model is given in program 4(a), and the fixed effect code is given in program 4(b).

Program 4(a): Multinomial likelihood (with competing risks), log link, Random Effects (Schizophrenia example)

```r
# Multinomial likelihood, log link (competing risks)
# Random effects model for multi-arm trials
model{
  for(i in 1:ns){
    for (m in 1:3) {
      w[i,1,m] ~ 0  # adjustment for multi-arm trials is zero for control arm
      delta[i,1,m] ~ 0  # treatment effect is zero for control arm
      mu[i,m] ~ dnorm(0,.0001)  # vague priors for all trial baselines
    }
    for (k in 1:na[i]) {
      r[i,k,1:4] ~ dmulti(p[i,k,1:4],n[i,k])
      p[i,k,4] ~ 1 - sum(p[i,k,1:3])
      slam[i,k] ~ sum(lamda[i,k])
      for (m in 1:4) {
        rhat[i,k,m] ~ p[i,k,m]*n[i,k]
        dv[i,k,m] ~ 2*r[i,k,m]*log(r[i,k,m]/rhat[i,k,m])  # predicted number events
      }
      dev[i,k] ~ sum(dv[i,k])  # deviance contribution for arm
    }
    for (m in 1:3) {
      # cumulative pr(failed) at each end point (per year), data in weeks
      p[i,k,m] ~ lamda[i,k,m] * (1-exp(-slam[i,k]*f[i]/52))/slam[i,k]
      log[lamda[i,k,m]] ~ mu[i,m] + delta[i,k,m]  # model for linear predictor for each outcome
    }
  }
}

# *** PROGRAM STARTS
# LOOP THROUGH STUDIES
# LOOP OVER 3 ENDPOINTS
# adjustment for multi-arm trials is zero for control arm
# treatment effect is zero for control arm
# vague priors for all trial baselines

# LOOP THROUGH ARMS
# multinomial likelihood

# sum of the 3 hazard rates
# LOOP OVER ALL ENDPOINTS
# predicted number events
#Deviance contribution

# LOOP THROUGH 3 ENDPOINTS
# LOOP THROUGH ARMS

# cumulative pr(failed) at each end point (per year), data in weeks
# model for linear predictor for each outcome
# LOOP THROUGH ARMS
```

Aripiprazole (5)
Ziprasidone (6)
Olanzapine (2)
Paliperidone (7)
Risperidone (9)
Haloperidol (8)
Amisulpride (3)
Zotepine (4)
Paliperidone (7)
Risperidone (9)
Olanzapine (2)
Ziprasidone (6)
Placebo (1)
Appendix to Dias, Sutton, Ades and Welton, MDM 2013
Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials

\[
\begin{align*}
\text{delta}[i,k,m] & \sim \text{dnorm}(\text{md}[i,k,m], \text{taud}[i,k,m]) \\
\text{md}[i,k,m] & \sim \text{d}[t[i,k,m] - d[t[i,1,m]] + \text{sw}[i,k,m]] \\
\text{taud}[i,k,m] & \sim \text{d}[\text{d}[t[i,k,m] - d[t[i,1,m]], \text{sw}[i,k,m]] \\
\text{w}[i,k,m] & \sim \text{d}[\text{sum}(\text{w}[i,1:k-1,m]/(k-1))]
\end{align*}
\]

\# mean of LHR distributions (with multi-arm correction)
\# precision of LHR distributions with multi-arm correction
\# adjustment for multi-arm RCTs
\# cumulative adjustment for multi-arm trials

\[
\begin{align*}
\text{resdev}[i] & \sim \text{sum}(\text{dev}[i,1:na[i]]) \\
\text{totresdev} & \sim \text{sum}(\text{resdev}) \\
\text{for} (m \in 1:3) \{ \text{# LOOP THROUGH 3 END-POINTS} \\
\text{d}[1,m] & \sim 0 \\
\text{for} (k \in 2:nt) \{ \text{# treatment effect is zero for reference treatment} \\
\text{d}[k,m] & \sim \text{dnorm}(0,.0001) \\
\text{sd}[m] & \sim \text{duni}(0,5) \\
\text{tau}[m] & \sim \text{pow}(\text{sd}[m],-2) \\
\text{A}[m] & \sim \text{dnorm}(\text{meanA}[m], \text{precA}[m]) \\
\text{for} (k \in 1:nt) \{ \text{# LOOP THROUGH TREATMENTS} \\
\text{log}(T[k,m]) & \sim \text{A}[m] + \text{d}[k,m] \\
\text{cumpr}[k,m] & \sim T[k,m] * (1-\exp(-\text{pslam[k]*timeA})/\text{pslam[k]} \# cumulative pr(failed) at each end point
\}
\}
\]}

Additional code to monitor all treatment contrasts and rank treatments can be added as before. Given values for the mean for each outcome, \text{meanA} = c(-0.078,-1.723,-0.7185), and precision, \text{precA} = c(1.6, 1.05, 0.61), of the hazards for each endpoint on Treatment 1, from external sources, absolute effects, and absolute probabilities of the competing outcomes occurring within a given time period, \text{timeA}, say, a 1-month (1/12=0.083 years) interval, could be monitored as follows:

\[
\begin{align*}
\text{for} (k \in 1:nt) \{ \text{pslam[k]} & \sim \text{sum}(\text{T[k,j]}) \}
\text{for} (m \in 1:3) \{ \text{# LOOP THROUGH TREATMENTS, summing the 3 rates} \\
\text{A}[m] & \sim \text{dnorm}(\text{meanA}[m], \text{precA}[m]) \\
\text{for} (k \in 1:nt) \{ \text{# LOOP THROUGH TREATMENTS} \\
\text{log}(T[k,m]) & \sim \text{A}[m] + \text{d}[k,m] \\
\text{cumpr}[k,m] & \sim T[k,m] * (1-\exp(-\text{pslam[k]*timeA})/\text{pslam[k]} \# cumulative pr(failed) at each end point
\}
\}
\]

The data structure again consists of a list specifying the number of treatments \(nt\) and number of studies \(ns\), with the main body of data in a vector format; \(t[j]\) represents the follow-up time in that trial. Only two columns are required for each arm variable since there are no multi-arm trials: \(t[1,1]\) and \(t[1,2]\) the treatment codes; then \(r[k,j]\) the number of events for the \(k\)-th treatment, outcome \(j\); then \(n[1,1]\) and \(n[1,2]\) the total number of individuals in each trial arm; and finally the number of arms in the study, \(na[i]\), and the study identifiers commented out. Both data components need to be loaded into WinBUGS for the program to run.
# Data (Schizophrenia example)

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list(ns=15, nt=9)

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Readers experimenting with this example need to be aware of difficulties with starting values. We have found one set of starting values which converges, but to a different posterior. Examples like this remind us of the importance of careful attention to the technical aspects of fitting models by Bayesian MCMC, and the need to look at the results obtained with different starting values. This is also an example where inverse gamma priors on the between trial variance leads to faster convergence, and avoids spikes in the posterior distributions.  

Program 4(b): Multinomial likelihood (with competing risks), log link, Fixed Effects
(Schizophrenia example)
Results

Results (based on 3 chains: 100,000 iterations after a burn-in of 50,000 for the FE model and 100,000 iterations after a burn-in of 10,000 for the RE model) are presented in Table A7.

Note that the follow-up time data are entered in weeks, while the analysis delivers annual rates. The model fit statistics suggest that the random effects model is a better fit to the data and the DIC shows that this model should be preferred. The log-hazard rates for each of the competing events and the absolute probabilities of the competing outcomes occurring within 1 month (assuming a baseline log-hazard as detailed above) are given in Table A7. For a graphical representation of which treatment is best for each of the competing outcomes and further comments see Ades et al.⁴

Table A7 Schizophrenia example: posterior mean, standard deviation (sd), median and 95% Credible interval (CrI) for both the fixed and random effects models for the treatment effects of Olanzapine ($d_{12}$), Amisulpride ($d_{13}$), Zotepine ($d_{14}$), Aripiprazole ($d_{15}$), Ziprasidone ($d_{16}$), Paliperidone ($d_{17}$), Haloperidol ($d_{18}$) and Risperidone ($d_{19}$) relative to Placebo, absolute probabilities of reaching each of the outcomes for Placebo ($P_{r1}$), Olanzapine ($P_{r2}$), Amisulpride ($P_{r3}$), Zotepine ($P_{r4}$), Aripiprazole ($P_{r5}$), Ziprasidone ($P_{r6}$), Paliperidone ($P_{r7}$), Haloperidol ($P_{r8}$) and Risperidone ($P_{r9}$); heterogeneity parameter $\tau$ for each of the three outcomes, and model fit statistics for the fixed and random effects models.

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<td>$P_{r3}$</td>
<td>0.03</td>
<td>0.04</td>
<td>0.02</td>
<td>(0.00,0.14)</td>
<td>0.05</td>
<td>0.07</td>
<td>0.03</td>
<td>(0.00,0.23)</td>
<td></td>
</tr>
<tr>
<td>$P_{r4}$</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
<td>(0.00,0.06)</td>
<td>0.02</td>
<td>0.04</td>
<td>0.01</td>
<td>(0.00,0.10)</td>
<td></td>
</tr>
<tr>
<td>$P_{r5}$</td>
<td>0.05</td>
<td>0.04</td>
<td>0.03</td>
<td>(0.01,0.16)</td>
<td>0.06</td>
<td>0.08</td>
<td>0.03</td>
<td>(0.00,0.27)</td>
<td></td>
</tr>
<tr>
<td>$P_{r6}$</td>
<td>0.03</td>
<td>0.03</td>
<td>0.02</td>
<td>(0.00,0.11)</td>
<td>0.03</td>
<td>0.05</td>
<td>0.02</td>
<td>(0.00,0.15)</td>
<td></td>
</tr>
<tr>
<td>$P_{r7}$</td>
<td>0.03</td>
<td>0.03</td>
<td>0.02</td>
<td>(0.00,0.12)</td>
<td>0.04</td>
<td>0.06</td>
<td>0.02</td>
<td>(0.00,0.20)</td>
<td></td>
</tr>
<tr>
<td>$P_{r8}$</td>
<td>0.04</td>
<td>0.04</td>
<td>0.03</td>
<td>(0.01,0.14)</td>
<td>0.06</td>
<td>0.07</td>
<td>0.04</td>
<td>(0.00,0.24)</td>
<td></td>
</tr>
<tr>
<td>$P_{r9}$</td>
<td>0.03</td>
<td>0.03</td>
<td>0.02</td>
<td>(0.00,0.10)</td>
<td>0.04</td>
<td>0.06</td>
<td>0.02</td>
<td>(0.00,0.19)</td>
<td></td>
</tr>
<tr>
<td>$\tau$</td>
<td>0.73</td>
<td>0.32</td>
<td>0.66</td>
<td>(0.30,1.53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The data presented in Table A8 are the mean off-time reduction in patients given dopamine Agonists as adjunct therapy in Parkinson’s disease. The data available are the mean, standard deviation and number of patients in each trial arm, for 7 studies of five different treatments: placebo, coded 1, and four active drugs coded 2 to 5. The network diagram is presented in Figure A3.
Table A8 Parkinson’s example: study names, treatments compared, mean off-time reduction with its standard deviation, total number of patients in each trial arm; treatment differences and standard error of the differences; where treatment 1 is a placebo and treatments 2-5 are active drugs.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>y</th>
<th>sd</th>
<th>n</th>
<th>diff</th>
<th>se(diff)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>-1.22</td>
<td>3.7</td>
<td>54</td>
<td>-0.31</td>
<td>0.668</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>-1.53</td>
<td>4.28</td>
<td>95</td>
<td>-0.31</td>
<td>0.668</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>-0.7</td>
<td>3.7</td>
<td>172</td>
<td>-1.7</td>
<td>0.383</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>-2.4</td>
<td>3.4</td>
<td>173</td>
<td>-1.7</td>
<td>0.383</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>-0.3</td>
<td>4.4</td>
<td>76</td>
<td>-2.3</td>
<td>0.718</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>-2.6</td>
<td>4.3</td>
<td>71</td>
<td>-2.3</td>
<td>0.718</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>-1.2</td>
<td>4.3</td>
<td>81</td>
<td>-0.9</td>
<td>0.695</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>-0.24</td>
<td>3</td>
<td>128</td>
<td>-0.35</td>
<td>0.442</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>-0.59</td>
<td>3</td>
<td>72</td>
<td>-0.35</td>
<td>0.442</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>-0.73</td>
<td>3</td>
<td>80</td>
<td>-0.3</td>
<td>0.555</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>-0.18</td>
<td>3</td>
<td>46</td>
<td>-0.3</td>
<td>0.555</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>-2.2</td>
<td>2.31</td>
<td>137</td>
<td>0.55</td>
<td>0.555</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>-2.5</td>
<td>2.18</td>
<td>131</td>
<td>0.55</td>
<td>0.555</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>-1.8</td>
<td>2.48</td>
<td>154</td>
<td>-0.3</td>
<td>0.320</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>-2.1</td>
<td>2.99</td>
<td>143</td>
<td>-0.3</td>
<td>0.320</td>
</tr>
</tbody>
</table>

Figure A3 Parkinson network: each edge represents a treatment, connecting lines indicate pairs of treatments which have been directly compared in randomised trials. The numbers on the lines indicate the numbers of trials making that comparison and the numbers by the treatment names are the treatment codes used in the modelling.

The WinBUGS code for random effects is given in program 5(a) and the fixed effects code is given in program 5(b).

Program 5(a): Normal likelihood, identity link, Random Effects (Parkinson’s example)

```plaintext
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{
  for(i in 1:ns){
    w[i,1] <- 0           # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0
    mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
    for (k in 1:na[i]) {
      var[i,k] <- pow(se[i,k],2) # calculate variances
      prec[i,k] <- 1/var[i,k]   # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # normal likelihood
    }
  }
  for (i in 1:ns){
    w[i,2] <- 0
    delta[i,2] <- 0
    mu[i] ~ dnorm(0,.0001)
    for (k in 1:na[i]) {
      var[i,k] <- pow(se[i,k],2)
      prec[i,k] <- 1/var[i,k]
      y[i,k] ~ dnorm(theta[i,k],prec[i,k])
    }
  }
  # *** PROGRAM STARTS
  # LOOP THROUGH STUDIES
  for (i in 1:ns){
    w[i,3] <- 0
    delta[i,3] <- 0
    mu[i] ~ dnorm(0,.0001)
    for (k in 1:na[i]) {
      var[i,k] <- pow(se[i,k],2)
      prec[i,k] <- 1/var[i,k]
      y[i,k] ~ dnorm(theta[i,k],prec[i,k])
    }
  }
  # LOOP THROUGH ARMS
  for (i in 1:ns){
    w[i,4] <- 0
    delta[i,4] <- 0
    mu[i] ~ dnorm(0,.0001)
    for (k in 1:na[i]) {
      var[i,k] <- pow(se[i,k],2)
      prec[i,k] <- 1/var[i,k]
      y[i,k] ~ dnorm(theta[i,k],prec[i,k])
    }
  }
  # LOOP THROUGH TREATMENTS
  for (i in 1:ns){
    w[i,5] <- 0
    delta[i,5] <- 0
    mu[i] ~ dnorm(0,.0001)
    for (k in 1:na[i]) {
      var[i,k] <- pow(se[i,k],2)
      prec[i,k] <- 1/var[i,k]
      y[i,k] ~ dnorm(theta[i,k],prec[i,k])
    }
  }
}
```
theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k] # Deviance contribution

resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
for (k in 2:na[i]) {
  delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
  md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of treat effects distributions (with multi-arm trial correction)
  taud[i,k] <- tau *2*(k-1)/k # precision of treat effects distributions (with multi-arm trial correction)
  w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs
  sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
}

totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
for (k in 2:nt) { d[k] ~ 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 = (1/between-trial variance)

Additional code to monitor all treatment contrasts and rank treatments can be added as before. Given values for the mean, -0.73, and precision, 21, of the outcome on Treatment 1, from external sources, absolute effects, and the absolute treatment effect, could be monitored by adding the following code:

A ~ dnorm(-.73,21)
for (k in 1:nt) { T[k] <- A + d[k] }

The maximum number of arms is 3, so 3 vectors are needed for the treatment indicators, t[1], t[2], t[3]; the continuous outcomes y[1], y[2], y[3]; and their standard errors se[1], se[2], se[3]; and finally the number of arms, na.[

# Data (Parkinson's example)
list(ns=7, nt=5)
list(t[1], t[2], t[3], y[1], y[2], y[3], se[1], se[2], se[3], na[])

# Initial Values
# Initial values for delta can be generated by WinBUGS.
# chain 1
list(d=c(NA, 0,0,0,0), sd=1, mu=c(0, 0, 0, 0, 0))
# chain 2
list(d=c(NA, -1,-1,-1,1), sd=4, mu=c(-3,-3,-3,3,-3))
# chain 3
list(d=c(NA,2,2,2,2), sd=2, mu=c(-3,5,-1,-3,7,-3,-4))

Program 5(b): Normal likelihood, identity link, Fixed Effects (Parkinson's example)
Appendix to Dias, Sutton, Ades and Welton, MDM 2013
Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials

### # Fixed effects model for multi-arm trials

```r
for(i in 1:ns){
  mu[i] ~ dnorm(0,0.0001)
  for (k in 1:na[i]) {
    var[i,k] <- pow(se[i,k],2)
    prec[i,k] <- 1/var[i,k]
    y[i,k] ~ dnorm(theta[i,k],prec[i,k])
    theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
    dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
  }
  resdev[i] <- sum(dev[i,1:na[i]])
} totresdev <- sum(resdev)
```

### # *** PROGRAM STARTS

```r
# *** PROGRAM STARTS
# LOOP THROUGH STUDIES
# LOOP THROUGH ARMS
# set precisions
# normal likelihood
# model for linear predictor
#Deviance contribution
# summed residual deviance contribution for this trial
#Total Residual Deviance
# treatment effect is zero for reference treatment
# vague priors for treatment effects
# *** PROGRAM ENDS
```

### Initial Values

- **# chain 1**
  ```r
  list(d=c( NA, 0,0,0,0), mu=c(0, 0, 0, 0, 0, 0))
  ```

- **# chain 2**
  ```r
  list(d=c( NA, -1,-3,-1,1), mu=c(-3, -3, -3, -3, -3, -3))
  ```

- **# chain 3**
  ```r
  list(d=c( NA, 2,2,2,2), mu=c(-3, 5, -1, -3, 7, -3, -4))
  ```

### Results

Results (based on 3 chains: 100,000 iterations after a burn-in of 50,000) are presented in Table A9. The random and fixed effects model both fit the data well, and since the random effects model has a higher DIC (due to having a higher effective number of parameters) the FE model should be preferred. The difference in mean of symptoms for each of the treatments compared to placebo and the absolute mean reduction in symptoms (assuming a baseline treatment effect as detailed above) are given in Table A9.
Table A9 Parkinson example: posterior mean, standard deviation (sd), median and 95% Credible interval (CrI) for both the fixed and random effects models for the treatment effects of Treatments 2 to 5 ($d_{12}$ to $d_{15}$) relative to Placebo, absolute effects of Placebo ($T_1$) and treatments 2 to 5 ($T_2$ to $T_5$), heterogeneity parameter $\tau$ and model fit statistics for different data types.

<table>
<thead>
<tr>
<th></th>
<th>FE model</th>
<th>RE model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>sd</td>
</tr>
<tr>
<td>Arm-level data: Example 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$d_{12}$</td>
<td>-1.81</td>
<td>0.33</td>
</tr>
<tr>
<td>$d_{13}$</td>
<td>-0.47</td>
<td>0.49</td>
</tr>
<tr>
<td>$d_{14}$</td>
<td>-0.52</td>
<td>0.48</td>
</tr>
<tr>
<td>$d_{15}$</td>
<td>-0.82</td>
<td>0.52</td>
</tr>
<tr>
<td>$T_1$</td>
<td>-0.73</td>
<td>0.22</td>
</tr>
<tr>
<td>$T_2$</td>
<td>-2.54</td>
<td>0.40</td>
</tr>
<tr>
<td>$T_3$</td>
<td>-1.21</td>
<td>0.53</td>
</tr>
<tr>
<td>$T_4$</td>
<td>-1.25</td>
<td>0.53</td>
</tr>
<tr>
<td>$T_5$</td>
<td>-1.55</td>
<td>0.57</td>
</tr>
<tr>
<td>$\tau$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\bar{D}_{cs}$</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>pD</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>DIC</td>
<td>24.3</td>
<td></td>
</tr>
</tbody>
</table>

Trial-level data (differences): Example 7

<table>
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<tr>
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<th>FE model</th>
<th>RE model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>sd</td>
</tr>
<tr>
<td>$d_{12}$</td>
<td>-1.81</td>
<td>0.33</td>
</tr>
<tr>
<td>$d_{13}$</td>
<td>-0.48</td>
<td>0.49</td>
</tr>
<tr>
<td>$d_{14}$</td>
<td>-0.52</td>
<td>0.48</td>
</tr>
<tr>
<td>$d_{15}$</td>
<td>-0.82</td>
<td>0.52</td>
</tr>
<tr>
<td>$T_1$</td>
<td>-0.73</td>
<td>0.22</td>
</tr>
<tr>
<td>$T_2$</td>
<td>-2.54</td>
<td>0.40</td>
</tr>
<tr>
<td>$T_3$</td>
<td>-1.21</td>
<td>0.53</td>
</tr>
<tr>
<td>$T_4$</td>
<td>-1.25</td>
<td>0.53</td>
</tr>
<tr>
<td>$T_5$</td>
<td>-1.55</td>
<td>0.56</td>
</tr>
<tr>
<td>$\tau$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\bar{D}_{cs}$</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>pD</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>DIC</td>
<td>10.3</td>
<td></td>
</tr>
</tbody>
</table>

Arm and Trial-level data (shared parameter model): Example 8

<table>
<thead>
<tr>
<th></th>
<th>FE model</th>
<th>RE model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>sd</td>
</tr>
<tr>
<td>$d_{12}$</td>
<td>-1.81</td>
<td>0.33</td>
</tr>
<tr>
<td>$d_{13}$</td>
<td>-0.48</td>
<td>0.49</td>
</tr>
<tr>
<td>$d_{14}$</td>
<td>-0.52</td>
<td>0.48</td>
</tr>
<tr>
<td>$d_{15}$</td>
<td>-0.82</td>
<td>0.52</td>
</tr>
<tr>
<td>$T_1$</td>
<td>-0.73</td>
<td>0.22</td>
</tr>
<tr>
<td>$T_2$</td>
<td>-2.54</td>
<td>0.40</td>
</tr>
<tr>
<td>$T_3$</td>
<td>-1.21</td>
<td>0.53</td>
</tr>
<tr>
<td>$T_4$</td>
<td>-1.26</td>
<td>0.53</td>
</tr>
<tr>
<td>$T_5$</td>
<td>-1.56</td>
<td>0.57</td>
</tr>
<tr>
<td>$\tau$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\bar{D}_{cs}$</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>pD</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>DIC</td>
<td>16.3</td>
<td></td>
</tr>
</tbody>
</table>

* compare to 15 data points; † compare to 8 data points; ‡ compare to 11 data points
EXAMPLE 6. Psoriasis

In an HTA report to evaluate the effectiveness of treatments for moderate to severe chronic plaque psoriasis,6 16 trials, comparing 8 treatments were identified: Supportive care (coded 1); Etanercept 25 mg (2); Etanercept 50 mg (3); Efalizumab (4); Ciclosporin (5); Fumaderm (6); Infliximab (7) and Methotrexate (8). The network diagram is presented in Figure A4. Each trial reported the number of patients in mutually exclusive categories representing the percentage improvement in symptoms as measured by the PASI score. Different trials reported on different categories defining 3 cut-points, 50, 75 and 90% improvement, in addition to the scale’s lower and upper bounds (0 and 100% improvement, respectively). In the code below, we define: C=1 representing 0% improvement (the scale’s lower bound); C=2 representing 50% improvement; C=3 representing 75% improvement; and C=4 representing 90% improvement. The data is presented in Table A10.

![Psoriasis network](image)

**Figure A4** Psoriasis network: each edge represents a treatment, connecting lines indicate pairs of treatments which have been directly compared in randomised trials. The numbers on the lines indicate the numbers of trials making that comparison and the numbers by the treatment names are the treatment codes used in the modelling. One trial compared two arms of Ciclosporin with Placebo and another compared two arms of Infliximab with placebo – these comparisons are not represented in the network.

The likelihood contribution of each trial is multinomial and this can be used to model the data directly in WinBUGS. However, since the reported categories are different in different
studies and overlap, it is helpful to re-write the multinomial likelihood as a series of conditional Binomials.

So, for a trial \(i\) reporting the number of patients \(r_{ikj}\) in category \(j=1,\ldots,J_i-1\), we can write

\[
r_{ikj} \sim \text{Binomial}(q_{ikj}, N_{ikj}) \quad j=1,\ldots,J_i-1
\]

where

\[
q_{ik1} = \Pr(\text{PASI score in category 1 of trial } i) \\
q_{ik2} = \Pr(\text{PASI score in category 2 of trial } i \mid \text{not in category 1}) \\
\vdots \\
q_{ikJ_i} = \Pr(\text{PASI score in category } J_i \mid \text{not in categories 1,2,\ldots, } J_i-1)
\]

and \(N_{ikj} = n_{ik} - \sum_{u=1}^{j-1} r_{iku}\).

Noting that the lower and upper bounds of each mutually exclusive category are defined by the cut-points above and the scale’s lower and upper bounds, for arm \(k\) of trial \(i\) we can define \(q_{ikj}\) as the probability of belonging to category \(j\), in arm \(k\) of trial \(i\),

\[
q_{ikj} = \Pr(\text{PASI score in category } j) = \Pr(L_j < \text{PASI score} < U_j)
\]

where \(L_j\) and \(U_j\) define the lower and upper bounds of the interval defining category \(j\). So, for example, for arm 1 of study 1 in Table A10 category 1 is 0-50% improvement so

\[
q_{111} = \Pr(\text{having less than 50% improvement in PASI score}) = \Pr(0 < \text{PASI score} < 50).
\]

Letting \(p_{ikc}\) denote the probability of achieving a PASI score of at least \(c\), in arm \(k\) of trial \(i\), for \(c=50, 75, 90\) we model

\[
\pi_{ikc} = \Pr(\text{PASI score} > c) = \Phi(\theta_{ik} + z_c)
\]

where \(\theta_{ik}\) is the linear predictor and \(\Phi\) is the standard normal cumulative distribution function. Cut-points \(z_{50}, z_{75}\) and \(z_{90}\) have been coded \(z_1, z_2\) and \(z_3\), respectively, in the code below. We set \(z_1=0\) and give non-informative priors to \(z_2\) and \(z_3\).

The terms \(z_c\) can be thought of as the distance on the standard normal scale between the category boundaries. The “fixed effect” model above assumes that these distances are the
same in every trial and for every treatment. An alternative might be that they differ between trials, but that within a trial the distances between categories are the same. This leads us to a “random effects” model in which for each trial $i$, $z_{ic}$ varies around a mean

$$ z_{ic} \sim N(\nu_c, \sigma_z^2). $$

The mean and variance are then given vague priors in the usual way. One interpretation of this model, which can be used with a Fixed or Random treatment effects, is that there may be differences between trials in the way that the underlying symptoms are scored, in this case on the PASI scale. It can be shown that, for $j=1, \ldots, J-1$

$$ q_{ij} = 1 - \frac{\Pr(PASI > C_{j+1})}{\Pr(PASI > C_j)} = 1 - \frac{\pi_{ikC_{j+1}}}{\pi_{ikC_j}} $$

with $C_j$ and $C_{j+1}$ representing the lower and upper bounds of the interval defining category $j$, respectively. Using these relationships simplifies the code and makes it general for any number of categories and cut-off points.
Table A10 Psoriasis example: study names, treatments compared, total number of patients with different percentage improvement and total number of patients in each trial arm, where Supportive Care = treatment 1, Etanercept 25mg = 2, Etanercept 50 mg = 3, Efalizumab = 4, Ciclosporin = 5, Fumaderm = 6, Infliximab = 7, Methotreaxate = 8.31

<table>
<thead>
<tr>
<th>Trial</th>
<th>arm 1</th>
<th>arm 2</th>
<th>arm 3</th>
<th>arm 1 outcomes</th>
<th>arm 2 outcomes</th>
<th>arm 3 outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Elewski 2004</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>175 12 5 1</td>
<td>193 70 59 46 21</td>
<td>196 44 54 56 40 194</td>
</tr>
<tr>
<td>2. Gottlieb 2003</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>49 5 1 0</td>
<td>55 17 23 11 6</td>
<td>57</td>
</tr>
<tr>
<td>3. Lebwohl 2003</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>103 13 5 1</td>
<td>122 112 68 42 10</td>
<td>232</td>
</tr>
<tr>
<td>4. Leonardi 2003</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>142 18 5 1</td>
<td>166 68 39 36 19</td>
<td>162 43 40 45 36 164</td>
</tr>
</tbody>
</table>

Outcomes presented in arm 1 for each category

<table>
<thead>
<tr>
<th>0-50</th>
<th>50-75</th>
<th>75-90</th>
<th>90-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>n[1]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outcomes presented in arm 2 for each category

<table>
<thead>
<tr>
<th>0-50</th>
<th>50-75</th>
<th>75-90</th>
<th>90-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>n[2]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outcomes presented in arm 3 for each category

<table>
<thead>
<tr>
<th>0-50</th>
<th>50-75</th>
<th>75-90</th>
<th>90-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>n[3]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trials presenting outcomes in 4 categories

<table>
<thead>
<tr>
<th>Trial</th>
<th>arm 1</th>
<th>arm 2</th>
<th>arm 3</th>
<th>arm 1 outcomes</th>
<th>arm 2 outcomes</th>
<th>arm 3 outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Gordon 2003</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>161 18 8</td>
<td>187 153 118 98</td>
<td>369</td>
</tr>
</tbody>
</table>

Trials presenting outcomes in 3 categories

<table>
<thead>
<tr>
<th>Trial</th>
<th>arm 1</th>
<th>arm 2</th>
<th>arm 3</th>
<th>arm 1 outcomes</th>
<th>arm 2 outcomes</th>
<th>arm 3 outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. ACD2058g</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>145 25</td>
<td>170 63 99</td>
<td>162</td>
</tr>
<tr>
<td>7. ACD2600g</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>230 33</td>
<td>263 216 234</td>
<td>450</td>
</tr>
<tr>
<td>8. Guenthner 1991</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>10 1</td>
<td>11 0 12</td>
<td>12</td>
</tr>
<tr>
<td>9. IMP24011</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>226 38</td>
<td>264 245 284</td>
<td>529</td>
</tr>
</tbody>
</table>

Trials presenting outcomes in 2 categories (PASI 50)

<table>
<thead>
<tr>
<th>Trial</th>
<th>arm 1</th>
<th>arm 2</th>
<th>arm 3</th>
<th>arm 1 outcomes</th>
<th>arm 2 outcomes</th>
<th>arm 3 outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Altmeyer 1994</td>
<td>1</td>
<td>6</td>
<td>5</td>
<td>50 1</td>
<td>51 37 12</td>
<td>49</td>
</tr>
<tr>
<td>11. Chaudari 2001</td>
<td>1</td>
<td>6</td>
<td>5</td>
<td>9 2</td>
<td>11 2 9</td>
<td>11</td>
</tr>
<tr>
<td>12. Ellis 1991</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>25 0</td>
<td>25 16 9</td>
<td>25 7 13 20</td>
</tr>
<tr>
<td>13. Gottlieb 2004</td>
<td>1</td>
<td>7</td>
<td>7</td>
<td>48 3</td>
<td>51 28 71</td>
<td>99 12 87 99</td>
</tr>
<tr>
<td>14. Heydendael 2003</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>12 30</td>
<td>42 17 26</td>
<td>43</td>
</tr>
<tr>
<td>15. Meffert 1997</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>41 2</td>
<td>43 37 4</td>
<td>41</td>
</tr>
<tr>
<td>16. Van Joost 1988</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>10 0</td>
<td>10 3 7</td>
<td>10</td>
</tr>
</tbody>
</table>
The WinBUGS code for random effects is given in program 6(a) and the fixed effects code is given in program 6(b).

Program 6(a): Conditional Binomial likelihood, probit link, Random Effects (Psoriasis example)

```
# Binomial likelihood, probit link (different categories)  
# Random effects model for multi-arm trials
model{  
  for(i in 1:ns){    
    # *** PROGRAM STARTS    
    # LOOP THROUGH STUDIES
    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
    for (k in 1:na[i]) {  
      p[i,k,1] <- 1    
      # Pr(PASI >0)
      for (j in 1:nc[i] - 1) {  
        r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j])    
        # binomial likelihood
        q[i,k,j] <- 1 - (p[i,k,C[i,j+1]]/p[i,k,C[i,j]])    
        # conditional probabilities
        theta[i,k,j] <- mu[i] + delta[i,k] + z[j]    
        # linear predictor
        rhat[i,k,j] <- q[i,k,j] * n[i,k,j]    
        # predicted number events
        dv[i,k,j] <- 2 * (r[i,k,j]*log(r[i,k,j]) - log(rhat[i,k,j]))  
        #Deviance contribution of each category
        + (r[i,k,j]-r[i,k,j])*log(r[i,k,j]-r[i,k,j]) - log(r[i,k,j]-rhat[i,k,j]))
        #Deviance contribution of each category
        dev[i,k,j] <- sum(dv[i,k,j,1:nc[i]-1])
        # deviance contribution of each arm
        for (j in 2:nc[i]) {    
          p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j]    
          # link function
          # adjust link function phi(x) for extreme values that can give numerical errors
          # when x< -5, phi(x)=0, when x> 5, phi(x)=1
          phi.adj[i,k,j] <- step(5+theta[i,k,j]-1) * (step(theta[i,k,j]-5)+step(5-theta[i,k,j])) * phi(theta[i,k,j]-1)
          #predicted number events
        }    
      }    
      deltal[i,k] ~ dnorm(md[i,k],taud[i,k])    
      # mean of LHR distributions, with multi-arm trial correction
      md[i,k] <- d[i[t[i,k]] - d[i[t[i,1]]] + sw[i,k]    
      # precision of LHR distributions (with multi-arm trial correction)
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)    
      # cumulative adjustment for multi-arm trials
      w[i,k] <- (delta[i,k] - d[i[t[i,k]] + sw[i,k])    
      # adjustment, multi-arm RCTs
      for(k in 2:na[i]) {  
        # LOOP THROUGH ARMS
        z[j]<-0
      }
      z[j+1]<-0
    }  
  }  
  for (k in 2:na[i]) {  
    # LOOP THROUGH CATEGORIES
    r[i,k,1] ~ dbin(q[i,k,1],n[i,k,1])    
    q[i,k,1] <- 1 - (p[i,k,C[i,1]]/p[i,k,C[i,2]])    
    # conditional probabilities
    theta[i,k,1] <- mu[i] + delta[i,k] + z[j]    
    # linear predictor
    rhat[i,k,1] <- q[i,k,1] * n[i,k,1]    
    # predicted number events
    dv[i,k,1] <- 2 * (r[i,k,1]*log(r[i,k,1])-log(rhat[i,k,1]))  
    #Deviance contribution of each category
    # Alternative code to monitor all treatment contrasts and rank treatments can be added as before. Given values for the mean, 1.097, and precision, 123, of the effects on Treatment 1 on the probit scale, from external sources, absolute effects, and absolute probabilities T[j,k] of
    dev[i,k] <- sum(dev[i,k,1:nc[i]-1])
    # deviance contribution of each arm
    for (j in 2:nc[i]) {    
      phi.adj[i,k,j] <- step(5+theta[i,k,j]-1) * (step(theta[i,k,j]-5)+step(5-theta[i,k,j])) * phi(theta[i,k,j]-1)
      #link function
    }    
  }  
}  
for (i in 1:ns) {    
  # *** PROGRAM ENDS    
  # LOOP THROUGH STUDIES
  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
  for (k in 1:na[i]) {  
    p[i,k,1] <- 1
    for (j in 1:nc[i]-1) {
      r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j])  
      q[i,k,j] <- 1 - (p[i,k,C[i,j+1]]/p[i,k,C[i,j]])  
      # conditional probabilities
      theta[i,k,j] <- mu[i] + delta[i,k] + z[j]  
      # linear predictor
      rhat[i,k,j] <- q[i,k,j] * n[i,k,j]  
      # predicted number events
      dv[i,k,j] <- 2 * (r[i,k,j]*log(r[i,k,j]) - log(rhat[i,k,j])) + (r[i,k,j]-r[i,k,j])*log(r[i,k,j]-r[i,k,j]) - log(r[i,k,j]-rhat[i,k,j]))
      #Deviance contribution of each category
      dev[i,k,j] <- sum(dv[i,k,j,1:nc[i]-1])
      # deviance contribution of each arm
      for (j in 2:nc[i]) {
        # LOOP THROUGH CATEGORIES
        p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j]  
        # link function
        # adjust link function phi(x) for extreme values that can give numerical errors
        # when x< -5, phi(x)=0, when x> 5, phi(x)=1
        phi.adj[i,k,j] <- step(5+theta[i,k,j]-1) * (step(theta[i,k,j]-5)+step(5-theta[i,k,j])) * phi(theta[i,k,j]-1)
        #predicted number events
      }  
    }  
    deltal[i,k] ~ dnorm(md[i,k],taud[i,k])  
    # mean of LHR distributions, with multi-arm trial correction
    md[i,k] <- d[i[t[i,k]] - d[i[t[i,1]]] + sw[i,k]  
    # precision of LHR distributions (with multi-arm trial correction)
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)  
    # cumulative adjustment for multi-arm trials
    w[i,k] <- (delta[i,k] - d[i[t[i,k]] + sw[i,k])  
    # adjustment, multi-arm RCTs
    for(k in 2:na[i]) {
      # LOOP THROUGH ARMS
      z[j]<-0
    }
    z[j+1]<-0
  }  
  for (k in 2:na[i]) {
    # LOOP THROUGH CATEGORIES
    r[i,k,1] ~ dbin(q[i,k,1],n[i,k,1])  
    q[i,k,1] <- 1 - (p[i,k,C[i,1]]/p[i,k,C[i,2]])  
    # conditional probabilities
    theta[i,k,1] <- mu[i] + delta[i,k] + z[j]  
    # linear predictor
    rhat[i,k,1] <- q[i,k,1] * n[i,k,1]  
    # predicted number events
    dv[i,k,1] <- 2 * (r[i,k,1]*log(r[i,k,1])-log(rhat[i,k,1]))  
    #Deviance contribution of each category
    # Alternative code to monitor all treatment contrasts and rank treatments can be added as before. Given values for the mean, 1.097, and precision, 123, of the effects on Treatment 1 on the probit scale, from external sources, absolute effects, and absolute probabilities T[j,k] of
    dev[i,k] <- sum(dev[i,k,1:nc[i]-1])  
    # deviance contribution of each arm
    for (j in 2:nc[i]) {
      # LOOP THROUGH CATEGORIES
      p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j]  
      # link function
      # adjust link function phi(x) for extreme values that can give numerical errors
      # when x< -5, phi(x)=0, when x> 5, phi(x)=1
      phi.adj[i,k,j] <- step(5+theta[i,k,j]-1) * (step(theta[i,k,j]-5)+step(5-theta[i,k,j])) * phi(theta[i,k,j]-1)
      #predicted number events
    }
  }
}
```
having over 50, 75 or 90% improvement \( (j=1, 2, 3 \text{ respectively}) \) on treatment \( k \), could be monitored as follows:

\[
A \sim \text{dnorm}(1.097, 123)
\]

# calculate prob of achieving PASI50,75,90 on treat k
for (k in 1:nt) {
  for (j in 1:3) { T[j,k] <- 1 - \text{phi}(A + d[k] + z[j]) }
}

The data structure again consists of a list specifying the number of treatments \( nt \), number of studies \( ns \) and total number of categories \( C_{\text{max}} \), with the main body of data in a vector format. Both data components need to be loaded into WinBUGS for the program to run. Three columns are required for each arm variable since there are four three-arm trials: \( t[,1], t[,2] \) and \( t[,3] \) are the treatment codes; \( na[] \) represents the number of arms and \( nc[] \) the number of cut-offs in that trial; \( C[,1], C[,2], C[,3], C[,4] \) represent the cut-offs used to define the categories reported in each trial – four columns are needed as the maximum number of cut-offs given in a trial is four – these cut-offs are coded 1 to 4 as described above; then \( r[.,k,j] \) the number of events for the \( k \)-th treatment, in category \( j \) given the number of events in categories 1 to \( j-1 \); then \( n[.,k,1] \) represents the total number of individuals in trial arm \( k \), \( n[.,k,2] \) represents the total number of individuals in trial arm \( k \) which were not in category 1 of that trial and \( n[.,k,3] \) represents the total number of individuals in trial arm \( k \) which were not in categories 1 or 2 of that trial. So, for example, for the first trial in Table A10, Elewski 2004, 193 patients were included in arm 1 of the trial. These patients were split between the four categories as follows: 175 out of 193 patients had between 0 and 50% improvement, leaving 18 patients who could belong to any of the other categories, thus \( r_{111}=173, n_{111}=193; 12 \text{ out of 18 patients had between 50 and } 75\% \text{ improvement, leaving 6 patients who could belong to any of the other categories, thus } r_{112}=12, n_{112}=193-175=18; 5 \text{ out of 6 patients had between } 75 \text{ and } 90\% \text{ improvement, leaving 1 patient (who necessarily had over } 90\% \text{ improvement), thus } r_{113}=5, n_{112}=18-12=6 \). All other \( n_{ijk} \) were similarly calculated for the other trials.

Note that for trials reporting \( j \) categories, \( r \) and \( n \) only need to be defined for the first \( j-1 \) categories with the remaining columns coded \text{NA}, and some of the data given below is redundant.

# Data (Psoriasis example)
list(ns=16, nt=8, \( C_{\text{max}}=4 \))
Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials

The parameters to monitor are the same as in Example 1. We may in addition want to monitor node $z$ to obtain the posterior summaries for the different cut-off points.
Program 6(b): Conditional Binomial likelihood, probit link, Fixed Effects (Psoriasis example)

```
# Binomial likelihood, probit link (different categories)
# Fixed effects model for multi-arm trials
model{
  for(i in 1:ns){
    mu[i] ~ dnorm(0,.0001)  # LOOP THROUGH STUDIES
    for (k in 1:na[i]) {
      p[i,k,1] <- 1  # Pr(PASI>0)
    }
    for (j in 1:nc[i]-1) {
      r[i,k,j] <- dbin(q[i,k,j],n[i,k,j])  # binomial likelihood
      theta[i,k,j] <- mu[i] + d[t[i,k]] - d[t[i,1]] + z[j]  # linear predictor
      rhat[i,k,j] <- q[i,k,j] * n[i,k,j]  # predicted number events
      dev[i,k,j] <- 2 * (r[i,k,j] * log(r[i,k,j]) - log(rhat[i,k,j]))  # Deviance contribution of each category
      dv[i,k,j] <- 2 * (log(n[i,k,j] - r[i,k,j]) - log(n[i,k,j] - rhat[i,k,j]))
    }
    dev[i,1] <- sum(dev[i,1:nc[i]-1])  # deviance contribution of each arm
    for (j in 2:nc[i])  {
      p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j]  # link function
      phi.adj[i,k,j] <- step(5+theta[i,k,j]-1) * (step(theta[i,k,j]-5) + step(5-theta[i,k,j]))  # adjust phi(x) for extreme values that can give numerical errors
      # when x< -5, phi(x)=0, when x> 5, phi(x)=1
      z[j] ~ dunif(0,5)  # priors for z, for any number of categories
      z[aux][j] ~ dunif(0,0.5)  # ensures z[j]~Uniform(z[j]-1, z[j]+5)
    }
    resdev[i] <- sum(dev[i,1:na[i]])  # summed residual deviance contribution for this trial
  }
  z[1] ~ dnorm(0,.0001)  # set z50=0
  for(j in 2:Cmax-1) {
    z[aux][j] ~ dunif(0,0.5)  # priors
    z[1] ~ z[1]+z[aux][j]
  }
  totresdev <- sum(resdev[])  # Total Residual Deviance
  d[1] ~ dnorm(0,.0001)  # treatment effect is zero for reference treatment
  for (k in 2:nt) {  d[k] ~ dnorm(0,.0001)  # vague prior for treatment effects
    # *** PROGRAM ENDS
  }
}
```

Results

Results for the fixed and random effects models are presented in Table A11 (results based on 3 chains: 100,000 iterations after a burn-in of 40,000 and 50,000 for the FE and RE models, respectively). From the residual deviance and DIC we conclude that the random effects model should be preferred as it is a better fit to the data and has a smaller DIC. The treatment effects relative to Supportive care (treatment 1) are all below zero which suggests that all
treatments are better than Supportive care at increasing the probability of a reduction in symptoms on the probit scale. The absolute probabilities of achieving a reduction on at least 50, 75 or 90% in symptoms show that, for example, there is on average 0% probability of achieving at least a 90% reduction in symptoms with Supportive care, but this probability is on average 37% with Infliximab.

A model which assumes the cut-points differ between trials and come from a common distribution was also fitted and gave very similar results.

Table A11 Psoriasis example: posterior mean, standard deviation (sd), median and 95% Credible interval (CrI) for the fixed and random effects models for the treatment effects, on the probit scale, of Etanercept 25 mg ($d_{12}$), Etanercept 50 mg ($d_{13}$), Efalizumab ($d_{14}$), Ciclosporin ($d_{15}$), Fumaderm ($d_{16}$), Infliximab ($d_{17}$), and Methotrexate ($d_{18}$) relative to Supportive Care; absolute probabilities of achieving at least 50, 70 or 90% relief in symptoms for each treatment; heterogeneity parameter $\tau$ and model fit statistics.

<table>
<thead>
<tr>
<th></th>
<th>FE model</th>
<th></th>
<th>RE model</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>sd</td>
<td>median</td>
<td>CrI</td>
</tr>
<tr>
<td>$d_{12}$</td>
<td>-1.51</td>
<td>0.10</td>
<td>-1.51</td>
<td>(-1.70,-1.33)</td>
</tr>
<tr>
<td>$d_{13}$</td>
<td>-1.92</td>
<td>0.10</td>
<td>-1.92</td>
<td>(-2.12,-1.72)</td>
</tr>
<tr>
<td>$d_{14}$</td>
<td>-1.19</td>
<td>0.06</td>
<td>-1.19</td>
<td>(-1.30,-1.08)</td>
</tr>
<tr>
<td>$d_{15}$</td>
<td>-1.92</td>
<td>0.34</td>
<td>-1.90</td>
<td>(-2.64,-1.28)</td>
</tr>
<tr>
<td>$d_{16}$</td>
<td>-1.48</td>
<td>0.48</td>
<td>-1.45</td>
<td>(-2.53,-0.63)</td>
</tr>
<tr>
<td>$d_{17}$</td>
<td>9.23</td>
<td>0.27</td>
<td>-2.33</td>
<td>(-2.89,-1.83)</td>
</tr>
<tr>
<td>$d_{18}$</td>
<td>9.61</td>
<td>0.45</td>
<td>-1.60</td>
<td>(-2.52,-0.75)</td>
</tr>
<tr>
<td>$\tau$</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Probability of achieving at least 50% relief in symptoms (PASI50)

<table>
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<th></th>
<th>Supportive Care</th>
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<th>Etanercept 50 mg</th>
<th>Efalizumab</th>
<th>Ciclosporin</th>
<th>Fumaderm</th>
<th>Infliximab</th>
<th>Methotrexate</th>
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<td></td>
<td>0.14</td>
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<td>(0.10,0.18)</td>
<td>0.14</td>
<td>0.02</td>
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<td>(0.10,0.18)</td>
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<td>(0.56,0.75)</td>
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<tr>
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<td>(0.71,0.86)</td>
<td>0.79</td>
<td>0.08</td>
<td>0.80</td>
<td>(0.59,0.93)</td>
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<td>0.08</td>
<td>0.54</td>
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<td>0.63</td>
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<td>0.64</td>
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<td>(0.76,0.97)</td>
<td>0.87</td>
<td>0.08</td>
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<td>(0.66,0.98)</td>
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<tr>
<td></td>
<td>0.68</td>
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<td>0.69</td>
<td>(0.36,0.92)</td>
<td>0.70</td>
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<td>0.73</td>
<td>(0.30,0.98)</td>
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Probability of achieving at least 75% relief in symptoms (PASI75)

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<th>Etanercept 50 mg</th>
<th>Efalizumab</th>
<th>Ciclosporin</th>
<th>Fumaderm</th>
<th>Infliximab</th>
<th>Methotrexate</th>
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</thead>
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<td>0.03</td>
<td>(0.02,0.05)</td>
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<td>0.01</td>
<td>0.03</td>
<td>(0.02,0.05)</td>
</tr>
<tr>
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<td>0.37</td>
<td>(0.27,0.47)</td>
<td>0.38</td>
<td>0.10</td>
<td>0.37</td>
<td>(0.20,0.59)</td>
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<td>(0.42,0.63)</td>
<td>0.53</td>
<td>0.11</td>
<td>0.53</td>
<td>(0.30,0.76)</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.03</td>
<td>0.25</td>
<td>(0.19,0.33)</td>
<td>0.26</td>
<td>0.07</td>
<td>0.25</td>
<td>(0.14,0.41)</td>
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<tr>
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<td>0.13</td>
<td>0.52</td>
<td>(0.27,0.79)</td>
<td>0.57</td>
<td>0.16</td>
<td>0.56</td>
<td>(0.28,0.89)</td>
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<tr>
<td></td>
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<td>(0.11,0.76)</td>
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<td>0.35</td>
<td>(0.06,0.84)</td>
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<tr>
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<td>0.68</td>
<td>0.10</td>
<td>0.68</td>
<td>(0.48,0.86)</td>
<td>0.67</td>
<td>0.13</td>
<td>0.68</td>
<td>(0.37,0.89)</td>
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<tr>
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<td>0.41</td>
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<td>0.40</td>
<td>(0.13,0.75)</td>
<td>0.46</td>
<td>0.21</td>
<td>0.44</td>
<td>(0.10,0.92)</td>
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</table>
### Probability of achieving at least 90% relief in symptoms (PASI90)

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<td>(0.00, 0.01)</td>
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<td>(0.00, 0.01)</td>
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<td></td>
</tr>
<tr>
<td>Etanercept 25 mg</td>
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<td>0.03</td>
<td>0.13</td>
<td>(0.08, 0.19)</td>
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<td>0.13</td>
<td>(0.05, 0.28)</td>
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</tr>
<tr>
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<td>(0.16, 0.32)</td>
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<td>0.09</td>
<td>0.23</td>
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<tr>
<td>Efalizumab</td>
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<td>(0.04, 0.11)</td>
<td>0.08</td>
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<td>0.07</td>
<td>(0.03, 0.15)</td>
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<tr>
<td>Ciclosporin</td>
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<td>0.22</td>
<td>(0.08, 0.50)</td>
<td>0.29</td>
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<td>0.26</td>
<td>(0.08, 0.66)</td>
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<tr>
<td>Fumaderm</td>
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<td>0.11</td>
<td>(0.02, 0.46)</td>
<td>0.16</td>
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<td>0.12</td>
<td>(0.01, 0.58)</td>
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</tr>
<tr>
<td>Infliximab</td>
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<td>0.11</td>
<td>0.37</td>
<td>(0.19, 0.60)</td>
<td>0.37</td>
<td>0.14</td>
<td>0.36</td>
<td>(0.13, 0.67)</td>
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</tr>
<tr>
<td>Methotrexate</td>
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<td>0.22</td>
<td>0.18</td>
<td>0.17</td>
<td>(0.02, 0.72)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

* * compare with 58 data points

### EXAMPLE 7. Parkinson’s Difference (treatment differences as data)

We now assume that the data available for the Parkinson’s example were not the mean off-time reduction for patients in each arm of the trial, but rather the differences in off-time reduction, and their standard errors, between the intervention and control arms for each trial, as presented in the last two columns of Table A8. The data available are therefore the differences, their standard errors and the treatments compared in each trial, coded as before.

Random and fixed effects models were fitted. The code is given below. The coding for the likelihood has been modified to allow for the 3-arm trial. This requires users to set up the data file with all two-arm trials first, then 3-arm trials, then – if any were present – 4-arm trials, and so on.

#### Program 7(a): Normal likelihood, identity link, treatment differences, Random Effects (Parkinson’s Differences)

```plaintext
# Normal likelihood, identity link, trial-level data given as treatment differences
# Random effects model for multi-arm trials
model{  # *** PROGRAM STARTS
    for(i in 1:ns2) {  # LOOP THROUGH 2-ARM STUDIES
        y[i,2] ~ dnorm(delta[i,2],prec[i,2])  # normal likelihood for 2-arm trials
        resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]  # Deviance contribution for trial i
    }
    for(i in (ns2+1):(ns2+ns3)) {  # LOOP THROUGH 3-ARM STUDIES
        for (k in 1:(na[i]-1)) {  # set variance-covariance matrix
            Sigma[i,k,1:(na[i]-1)] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)  # Precision matrix
        }
        Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i])  # Precision matrix
    }
    for (k in 1:3) {  # multivariate normal likelihood for 3-arm trials
        y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])  # Deviance contribution for trial i
    }
    for (k in 1:3) {  # multiply vector & matrix
        ydiff[k]<- y[i,(k+1)] - delta[i,(k+1)]
        z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
    }
}
```
Additional code to monitor all treatment contrasts and rank treatments can be added as before. Given values for the mean, meanA=-0.73, and precision, precA=21, of the effects on Treatment 1, from external sources, absolute effects, could be monitored as follows:

\[
A \sim \text{dnorm(}\text{meanA, precA})
\]

for (k in 1:nt) { T[k] <- A + d[k] }

If trials with four or more arms were included, a further multivariate normal likelihood statement would need to be added and the corresponding variance-covariance and precision matrices built (Sigma2 and Omega2, say). So, for example if \( ns4 \) 4-arm trials were available, we would add the following lines of code to the above, taking care to change all the relevant loops to go through all trials:

\[
\text{for}(i \in (ns2+ns3+1):(ns2+ns3+ns4)) { \\
\text{# LOOP THROUGH 4-ARM STUDIES} \\
\text{for}(k \in 1:((na[i]-1))) { \\
\text{# set variance-covariance matrix} \\
\text{for}(j \in 1:((na[i]-1)) { \\
\text{Sigma2[i,j,k] <- V[i][j] (1-equals(j,k)) + var[i,k+1] * equals(j,k) } \\
\text{}} \\
\text{Omega2[1:((na[i]-1),1:((na[i]-1)) <- inverse(Sigma2[i,i]) #Precision matrix} \\
\text{# multivariate normal likelihood for 4-arm trials} \\
y[i,2:na[i]] ~ \text{dmnorm(delta[i,2:na[i]], Omega2[1:((na[i]-1),1:((na[i]-1))]} \\
\text{}} \\
\text{}} \\
\text{}} \\
\text{}}
\]

If no multi-arm trials are included, the code simplifies to:

\[
\text{# Normal likelihood, identity link, trial-level data given as treatment differences}
\]
The data structure is similar to that of Example 5 but we now have to specify the number of two-arm trials ns2 and the number of three-arm trials ns3. The maximum number of arms is 3, so 3 vectors are needed for the treatment indicators, t[,1] t[,2], t[,3]; for a trial with 3 treatment arms, two treatment differences will be available, so 2 vectors of differences (the continuous outcomes) y[,1] and their standard errors se[,1] are needed; and finally the number of arms, na[] and v[] the variance of the baseline treatment in that trial (needed to adjust for the correlation in multi-arm trials – note that this variable only need to have values assigned when there are multi-arm trials), with NA denoting a missing observation. Note that any three-arm trials need to appear at the end of the column format data.

The parameters to monitor are the same as in Example 5.
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Program 7(b): Normal likelihood, identity link, treatment differences, Fixed Effects (Parkinson’s Differences)

```r
# Normal likelihood, identity link, trial-level data given as treatment differences
# Fixed effects model
model{  
  # *** PROGRAM STARTS
  for(i in 1:ns2) {  
    # LOOP THROUGH 2-ARM STUDIES
    y[i,2] ~ dnorm(delta[i,2], prec[i,2])  
    # normal likelihood for 2-arm trials
    resdev[i] <- (y[i,2]-delta[i,2])^2*prec[i,2]  
    #Deviance contribution for trial i
  }
  for(i in (ns2+1):(ns2+ns3)) {  
    # LOOP THROUGH MULTI-ARM STUDIES
    for (j in 1:(na[i]-1)) {  
      # set variance-covariance matrix
      Sigma[i,j,k] <-(V[i]*(1-equals(j,k))+var[i,k+1]*equals(j,k))
    }
    Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,..])  
    #Precision matrix
    # multivariate normal likelihood for 3-arm trials
    y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[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[i,(k+1)] - delta[i,(k+1)]
      z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
    }
    resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
  }
  for(i in 1:(ns2+ns3)){  
    # LOOP THROUGH ALL STUDIES
    for (k in 2:na[i]) {  
      # LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)  
      # calculate variances
      prec[i,k] <- 1/var[i,k]  
      # set precisions
      delta[i,k] <- d[t[i,k]] - d[t[i,1]]
    }
    resdev[i] <- sum(dev[i,2:na[i]])  
    # summed residual deviance contribution for this trial
  }
  totresdev <- sum(resdev[])  
  #Total Residual Deviance
  d[1]<-0  
  # treatment effect is zero for reference treatment
  for (k in 2:nt){  
    d[k] ~ dnorm(0.,0.0001)  
    # vague priors for treatment effects
  }
  # *** PROGRAM ENDS

  # Initial Values
  #chain 1
  list(d=c(NA, 0.0,0.0,0))
  #chain 2
  list(d=c(NA, -1,-3,-1,1))
  #chain 3
  list(d=c(NA, 2,2,2,2))
}
```

Results

Results (based on 3 chains: 100,000 iterations after a burn-in of 50,000) are presented in Table A9 and are the same as the results obtained using the model in Example 5.

EXAMPLE 8. Parkinson’s shared parameters (mixed treatment difference and arm-level data)

To illustrate a meta-analysis with a shared parameter model we will assume that the data available for the Parkinson’s example were the mean off-time reduction for patients in each
arm of the trial for the first three trials, but only the differences between the intervention and control arms (and their standard errors) were available for the remaining trials (Table A8).

Random and fixed effects models were fitted. The code below consists of a combination of the code used in Example 5, for the arm-level data, and the code used in Example 7, for the trial level data.

Program 8(a): Normal likelihood, identity link, shared parameter model, Random Effects (Parkinson’s shared parameters)

```r
# Normal likelihood, identity link, Arm and Trial-level data (treatment differences)
# Random effects model for multi-arm trials
model{  
  for (i in 1:ns.a) {  
    w.a[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
  for (k in 1:na.a[i]) {  
    var.a[i,k] <- pow(se.a[i,k],2)  
    # calculate variances
    prec.a[i,k] <- 1/var.a[i,k]  
    # set precisions
    y.a[i,k] ~ dnorm(theta[i,k],prec.a[i,k])  
    # normal likelihood
    theta[i,k] <- mu[i] + delta[i,k]  
    # model for linear predictor
    dev[i,k] <- (y.a[i,k]-theta[i,k])*prec.a[i,k]  
    # Deviance contribution
  }
  resdev[i] <- sum(dev[i,1:na.a[i]])  
  # summed residual deviance contribution for this trial
  for (k in 1:na.a[i]) {  
    delta[i,k] ~ dnorm(md[i,k],taud.a[i,k])  
    # trial-specific LOR distributions
  }
  for (i in 1:ns.t){  
    w[i,1] <- 0  
    # adjustment for multi-arm trials is zero for control arm
    delta[i+ns.a,1] <- 0  
    # treatment effect is zero for control arm
    for (k in 2:na[i]) {  
      var[i,k] <- pow(se[i,k],2)  
      # calculate variances
      prec[i,k] <- 1/var[i,k]  
      # set precisions
      y[i,k] ~ dnorm(delta[i+ns.a,k],prec[i,k])  
      # normal likelihood
      dev[i+ns.a,k] <- (y[i,k]-delta[i+ns.a,k])*prec[i,k]  
      # Deviance contribution
    }
    resdev[i+ns.a] <- sum(dev[i+ns.a,2:na[i]])  
    # summed residual deviance contribution for this trial
  }
  for (k in 2:nt){  
    d[k] ~ 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 = (1/between-trial variance)
}
```

# *** PROGRAM ENDS
Additional code to monitor all treatment contrasts, rank treatments and obtain absolute treatment effects can be added as before.

The data structure for this code consists of three parts. First, a list giving the number of studies with arm-level information, \( ns.a \), the number of studies with trial-level information, \( ns.t \), and the number of treatments, \( nt \). Two sections of column format data follow: one with the arm-level data, with the structure described for program 5(a), and another with the trial-level data and the same structure described for program 7(a). All three data components need to be loaded into WinBUGS for the program to run. Note that, because two separate sets of data are being read into WinBUGS, the variable names referring to the arm-level data have the added suffix .a, to distinguish them from the trial-level data.

```
# Data (Parkinson’s example: Arm and Trial-level data)
list(ns.a=3, ns.t=4, nt=5)

# Arm-level data
t.a[,1] t.a[,2] y.a[,1] y.a[,2] y.a[,3] se.a[,1] se.a[,2] se.a[,3] na.a[]
1 3 NA -1.22 -1.53 NA 0.504 0.439 NA 2 # 1
1 2 NA -0.7 -2.4 NA 0.282 0.258 NA 2 # 2
1 2 4 -0.3 -2.6 -1.2 0.505 0.510 0.478 3 # 3

# Trial-level data
t[,1] t[,2] y[,2] se[,2] na[]
3 4 -0.35 0.441941738 2 # 4
3 4 0.55 0.555114559 2 # 5
4 5 -0.3 0.274276316 2 # 6
4 5 -0.3 0.320087245 2 # 7

# Initial Values
# Initial values for delta can be generated by WinBUGS.
#chain 1
list(d=c(NA, 0,0,0,0), sd=1, mu=c(0, 0, 0))
#chain 2
list(d=c(NA, -1,-3,-1,1), sd=4, mu=c(-3,-3,-3))
#chain 3
list(d=c(NA, 2,2,2,2), sd=2, mu=c(-3, 5, -1))
```

The parameters to monitor are the same as in Example 5.

**Program 8(b): Normal likelihood, identity link, shared parameter model, Fixed Effects**

(Parkinson’s shared parameters)

```
# Normal likelihood, identity link, Arm and Trial-level data (treatment differences)
# Fixed effects model
model{
  for(i in 1:ns.a) {
    mu[i] ~ dnorm(0,0001)
  }
  for (k in 1:ns.t) {
    # *** PROGRAM STARTS
    # LOOP THROUGH STUDIES WITH ARM DATA
    # LOOP THROUGH ARMS
  }
  # *** PROGRAM ENDS
  # LOOP THROUGH ARMS
```

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```
var.a[i,k] <- pow(se.a[i,k],2)  # calculate variances
prec.a[i,k] <- 1/var.a[i,k]    # set precisions
y.a[i,k] ~ dnorm(theta[i,k],prec.a[i,k])  # normal likelihood
theta[i,k] <- mu[i] + d[t.a[i,k] - d[t.a[i,1]]   # model for linear predictor
dev[i,k] <- (y.a[i,k]-theta[i,k])*(y.a[i,k]-theta[i,k])*prec.a[i,k]  # Deviance contribution
}
resdev[i] <- sum(dev[i,1:na.a[i]])  # summed residual deviance contribution for this trial
for(i in 1:ns.t){  # LOOP THROUGH STUDIES WITH TRIAL DATA
  for (k in 2:na[i]) {  #  LOOP THROUGH ARMS
    var[i,k] <- pow(se[i,k],2)  # calculate variances
    prec[i,k] <- 1/var[i,k]    # set precisions
    y[i,k] ~ dnorm(theta[i+ns.a,k],prec[i,k])  # normal likelihood
    theta[i+ns.a,k] <- d[t[i,k]] - d[t[i,1]]  # model for linear predictor
    dev[i+ns.a,k] <- (y[i,k]-theta[i+ns.a,k])* (y[i,k]-theta[i+ns.a,k])*prec[i,k]  # Deviance contribution
  }
  resdev[i+ns.a] <- sum(dev[i+ns.a,2:na[i]])  # summed residual deviance contribution for this trial
}
totresdev <- sum(resdev[])  #Total Residual Deviance
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }  # vague priors for treatment effects
```

**Results**

Results (based on 3 chains: 100,000 iterations after a burn-in of 20,000 and 50,000 for the FE and Re models, respectively) are presented in Table A9 and are the same as the results obtained using the model in Example 5.

**References**


