National Institute for Health and Care Excellence

Version 1.0 Consultation

Endometriosis: diagnosis and management

Appendix L

Clinical guideline

Network Meta-Analysis

19 January 2017

Draft for Consultation

Developed by the National Guidelines Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

NGA National Guideline Alliance
Part of RCOG

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

ISBN:

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L.1 Data Investigations

L.1.1 Comparison of univariate and multivariate models

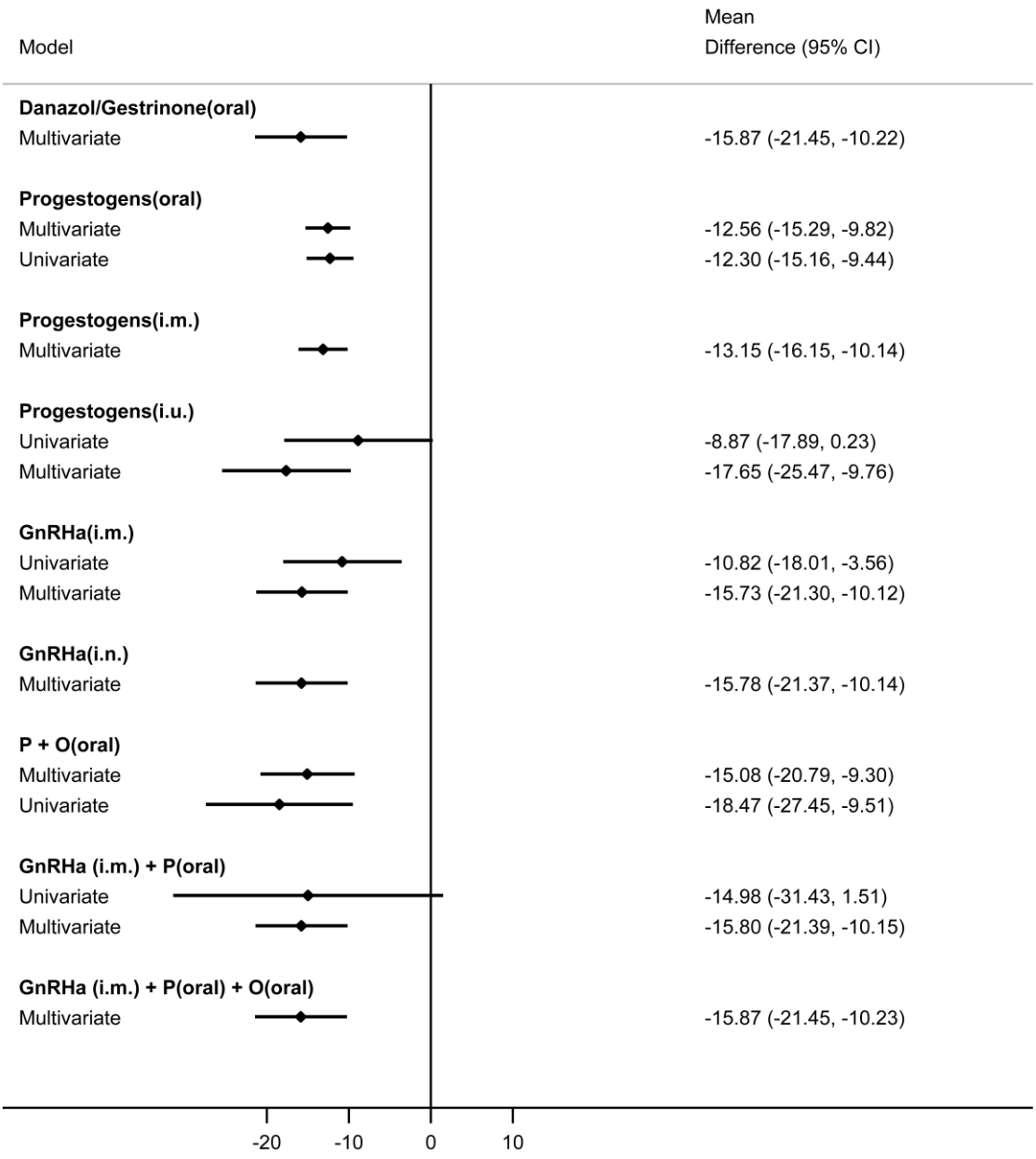
Results were broadly similar from the multivariate and univariate NMA where information was available for comparison (Table 1, Figure 1). The largest differences were for the progestogens (i.u.) and GnRHa (i.m) (less effective in the multivariate than in the univariate NMA). This is likely to be because GnRHa (i.m.) was found to be more effective for dysmenorrhea and non-menstrual pelvic pain compared to other treatments than using the VAS. Progestogens (i.u.) are linked to the network through GnRHa (i.m.) leading to it also having higher efficacy in the multivariate than univariate.

Table 1: Comparison of multivariate and univariate models for mean difference (MD) vs placebo for pain relief (VAS), probability of being in the best 3 treatments, probability of being in the 3 worst treatments, and the rank (95% CrI)

	Mean difference vs placebo		Prob of being in best 3 (%)		Prob of being in worst 3 (%)		Rank (95% CrI)	
Treatment	Multvar	Univar	Multvar	Univar	Multvar	Univar	Multvar	Univar
Placebo/ no treat	Reference	Reference	0.00%	0.00%	100.00%	99.99%	10 (10, 10)	6 (5, 6)
Danazol/ Gestrinone (oral)	-15.9 (-21.5,-10.2)	NA	52.61%	NA	1.35%	NA	3 (1, 7)	NA
Prog (oral)	-12.6 (-15.3,-9.8)	-12.3 (-15.2,-9.43)	10.41%	0.08%	84.50%	28.07%	9 (2, 9)	3 (1, 5)
Prog (i.m.)	-13.2 (-16.2,-10.1)	NA	16.15%	NA	72.39%	NA	8 (1, 9)	NA
Prog (i.u.)	-17.7 (-25.5,-9.8)	-8.87 (-17.9,0.26)	74.15%	85.10%	8.79%	78.57%	1 (1, 9)	5 (1, 6)
GnRHa (i.m.)	-15.7 (-21.3,-10.1)	-10.8 (-18.0,-3.57)	21.57%	84.49%	3.19%	57.39%	5 (2, 8)	4 (1, 5)
GnRHa (i.n.)	-15.8 (-21.4,-10.1)	NA	33.15%	NA	2.67%	NA	4 (1, 8)	NA
Prog(oral) + Oest(oral)	-15.1 (-20.8,-9.3)	-18.47 (-27.43,-9.49)	1.91%	95.87%	22.96%	4.94%	7 (4, 9)	1 (1, 4)
GnRHa(i.m.) + Prog(oral)	-15.8 (-21.4,-10.2)	-14.97 (-31.44,1.51)	37.52%	34.46%	2.78%	31.04%	4 (1, 8)	2 (1, 6)
GnRHa(i.m.) +Prog(oral) +Oest(oral)	-15.9 (-21.5,-10.2)	NA	52.53%	NA	1.36%	NA	3 (1, 7)	NA

(a) Results that are marked as "NA" could not be calculated from the univariate model, as Biberoglu and Behrman scales were used to inform these treatments.
(b) "Multvar" = Multivariate analysis, "Univar" = Univariate analysis
(c) For treatment name abbreviations see ***Error! Reference source not found.***

Figure 1: Forest plot for NMA results versus placebo for pain relief (VAS). Results are shown for univariate and multivariate (VAS, dysmenorrhea, non-menstrual pelvic pain) NMAs.



*Note: For treatment name abbreviations see **Error! Reference source not found.***

L.11.2 Imputation of missing standard deviations

Missing standard errors for continuous outcomes were calculated from standard deviations imputed using the method of Stevens et al. (2011). Deterministic values were used in the NMA, though a sensitivity analysis was conducted using the upper 95% CrI of the posterior distributions (Appendix L.3.2).

For pharmacological treatments for pain relief on the VAS, standard deviations were imputed for 4 of the 15 included studies. For one of these studies imputations were on the VAS and for three studies imputations were on the Biberoglu and Behrman subscales.

For pharmacological treatments for dyspareunia, standard deviations were imputed for three of the five included studies.

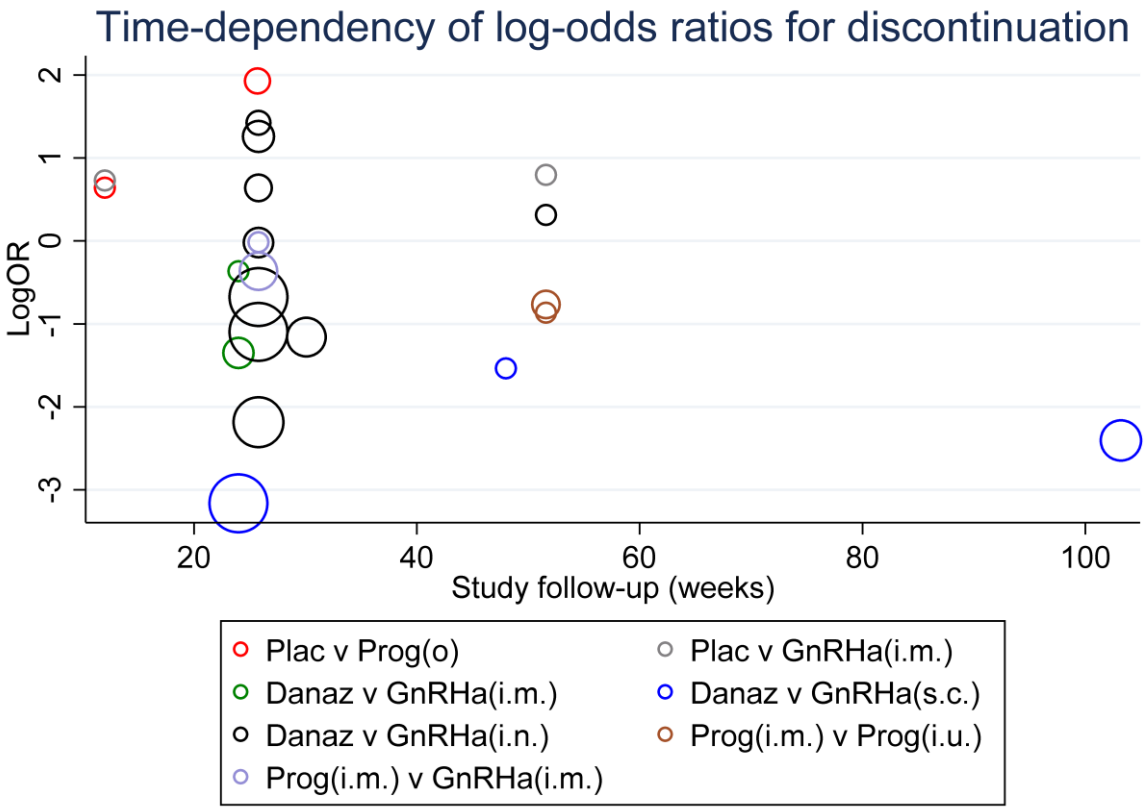
For surgical and combined surgical and hormonal treatments for pain relief on the VAS for two of the four included studies were imputed.

L.1.3 Assessment of impact of study follow-up

L.1.3.1 Pharmacological treatments for discontinuation due to adverse events

The network for discontinuation due to adverse events included studies in which relative effects for the same treatment comparison were reported at different follow-up times. Therefore this was the only outcome where the impact of study duration could be assessed. Though there was still relatively limited data to be able to investigate this in detail, there was no evidence of the relative treatment effects varying over time (Figure 2).

Figure 2: Bubble plot showing the relationship between study follow-up and relative treatment efficacy (log-odds ratios)

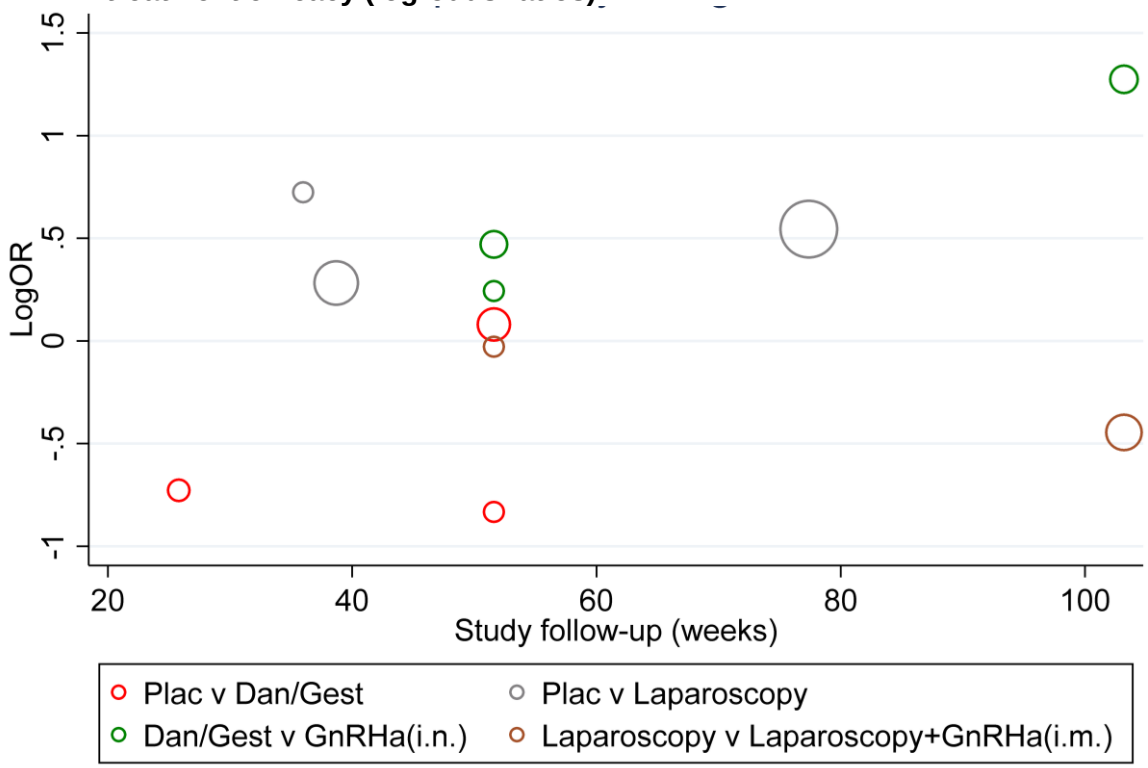


Note: The size of the bubbles is proportional to the standard error of the log-odds ratio (logOR), with larger bubbles indicating estimates with greater standard errors. Graph requires colour to discriminate different treatment comparisons. For treatment name abbreviations see ***Error! Reference source not found.****.*

L.1.3.2 Treatments to improve spontaneous pregnancy

Though there was relatively limited data to be able to investigate the impact of study follow-up in detail, there was no evidence of the relative treatment effects varying over time (Figure 3).

Figure 3: Bubble plot showing the relationship between study follow-up and relative treatment efficacy (log-odds ratios)



Note: The size of the bubbles is proportional to the standard error of the log-odds ratio (logOR), with larger bubbles indicating estimates with greater standard errors. Graph requires colour to discriminate different treatment comparisons. For treatment name abbreviations see Table 131 (section 12.1.2.3)

L.2 Model Fit Characteristics

Table 2: Model fit characteristics for pharmacological therapies for discontinuation of treatment due to adverse events

Model	Between-study standard deviation (95% CrI)	Residual deviance[b]	pD	DIC
Fixed effects	NA	105.3	47.7	354.7
Random effects	0.94 (0.45, 1.69)	78.5	59.4	339.6
Random effects with empirical prior[a]	0.70 (0.21, 1.30)	82.1	57.4	341.2
Random effects allowing for incoherence	0.47 (0.03, 1.50)	81.5	58.5	341.7

(a) Empirical prior from Turner et al (2012) – between-study variance followed a log-normal distribution with mean -3.23 and variance 3.53
(b) Compared to 77 data points
(c) "pD" = effective number of parameters, "DIC" = Deviance Information Criterion, "NA" = not applicable

Table 3: Model fit characteristics for pharmacological therapies for pain relief (VAS)

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD	DIC
Fixed effects	NA	41.07	NC	NC
Random effects	0.12 (0.01, 0.44)	41.96	NC	NC

(a) Compared to 32 data points
(b) pD and DIC could not be estimated for this model
(c) "pD" = effective number of parameters, "DIC" = Deviance Information Criterion, "NA" = not applicable, "NC" = not calculable

Table 4: Model fit characteristics for pharmacological therapies for dyspareunia

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD
Fixed effects	NA	8.13	7.92
Random effects	0.24 (0.01, 1.94)	9.67	9.35
Fixed effects allowing for incoherence	NA	7.17	8.19

(a) Compared to 10 data points
(b) DIC could not be estimated for this model due to the use of truncated prior distributions
(c) "pD" = effective number of parameters, "NA" = not applicable

Table 5: Model fit characteristics for surgical and combined surgical plus hormonal therapies for pain relief (VAS)

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD	DIC
Fixed effects	NA	8.94	8.84	70.9
Random effects	0.25 (0.12, 4.87)	8.97	8.86	70.9

(a) Compared to 9 data points
(b) "pD" = effective number of parameters, "DIC" = Deviance Information Criteria, "NA" = not applicable

Table 6: Model fit characteristics for treatments to improve spontaneous pregnancy

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD	DIC
Fixed effects	NA	30.0	26.3	184.9
Random effects	0.20 (0.01, 0.77)	30.5	27.8	186.9

Source/Note: Compared to 34 data points; pD: effective number of parameters; DIC: Deviance Information Criteria

L.3 Sensitivity Analysis

L.3.1 Exclusion of women with endometrioma

A sensitivity analysis was performed to assess the impact of excluding studies where the majority of women had endometrioma, as the Guideline Committee suspected these women may respond differently to treatment for pain relief.

However, only one study (Harada 2008) included a majority of women with endometrioma, and as this study connected the two Biberoglu and Behrman subscales included in the multivariate analysis (dysmenorrhea and non-menstrual pelvic pain) to the network, exclusion of it prevented estimation of treatment efficacy for danazol/gestrinone, GnRHa (i.n.), progestogens (i.m.) and GnRHa (i.m.) plus the pill.

Results excluding this study were therefore very similar to the univariate results shown in Appendix L.1.1. Results informed only by Biberoglu and Behrman subscales in the multivariate NMA should therefore be interpreted with some caution, as these treatment effects will be subject to the similarity in efficacy of the pill in women with and without endometrioma.

L.3.12 Use of upper 95% credible interval for imputing missing standard errors

To check the sensitivity of results to imputed standard errors, the upper 95% CrI for the posterior distribution of the imputed standard errors was used (calculated using the method of Stevens (2011)).

L.3.211 Pharmacological treatments for pain relief (VAS)

Table 7: Matrix of sensitivity results for the NMA of pain relief (VAS) using upper 95% CrIs of imputed standard errors

Placebo/no treatment	**-15.9 (-21.5,-10.2)**	**-12.6 (-15.3,-9.8)**	**-13.2 (-16.2,-10.1)**	**-17.7 (-25.5,-9.8)**	**-15.7 (-21.3,-10.1)**	**-15.8 (-21.4,-10.1)**	**-15.1 (-20.8,-9.3)**	**-15.8 (-21.4,-10.2)**	**-15.9 (-21.5,-10.2)**
-16 (-21.6,-10.1)	Danazol/ Gestrinone (oral)	3.3 (-2.1,8.7)	2.7 (-2.8,8.2)	-1.8 (-7.2,3.6)	0.1 (-0.5,0.8)	0.1 (-0.6,0.8)	0.8 (-0.1,1.6)	0.1 (-0.7,0.8)	0 (-0.7,0.7)
-12.6 (-15.4,-9.9)	3.3 (-2.3,8.8)	Progestogens (oral)	-0.6 (-1.8,0.6)	-5.1 (-12.8,2.7)	-3.2 (-8.5,2.2)	-3.2 (-8.6,2.2)	-2.5 (-8,3)	-3.3 (-8.6,2.2)	-3.3 (-8.7,2.1)
-13.2 (-16.2,-10.2)	2.7 (-3,8.3)	-0.6 (-1.8,0.7)	Progestogens (i.m.)	-4.5 (-12.4,3.4)	-2.6 (-8.1,2.9)	-2.6 (-8.2,2.9)	-1.9 (-7.6,3.7)	-2.7 (-8.2,2.9)	-2.7 (-8.3,2.8)
-17.6 (-25.3,-9.5)	-1.6 (-7.3,3.9)	-5 (-12.6,2.9)	-4.4 (-12.1,3.6)	Progestogens (i.u.)	1.9 (-3.4,7.3)	1.8 (-3.5,7.3)	2.5 (-2.8,8.1)	1.8 (-3.5,7.3)	1.8 (-3.6,7.2)
-15.8 (-21.4,-10)	0.2 (-0.6,0.9)	-3.2 (-8.6,2.4)	-2.6 (-8.1,3.2)	1.8 (-3.7,7.4)	GnRHa (i.m.)	0 (-0.7,0.6)	0.7 (-0.2,1.5)	-0.1 (-0.8,0.6)	-0.1 (-0.8,0.5)
-15.9 (-21.5,-10)	0.1 (-0.6,0.9)	-3.2 (-8.6,2.4)	-2.6 (-8.2,3.2)	1.8 (-3.7,7.5)	0 (-0.8,0.7)	GnRHa (i.n.)	0.7 (-0.2,1.5)	0 (-0.8,0.7)	-0.1 (-0.8,0.6)
-15.1 (-20.9,-9.1)	0.8 (-0.1,1.8)	-2.5 (-8,3.3)	-1.9 (-7.6,4)	2.5 (-3,8.2)	0.7 (-0.3,1.6)	0.7 (-0.3,1.6)	Prog(oral)+ Oest(oral)	-0.7 (-1.6,0.2)	-0.8 (-1.7,0.1)
-15.9 (-21.5,-10)	0.1 (-0.7,0.8)	-3.3 (-8.7,2.4)	-2.7 (-8.2,3.1)	1.7 (-3.8,7.4)	-0.1 (-0.8,0.7)	0 (-0.8,0.7)	-0.8 (-1.7,0.2)	GnRHa(i.m.)+ Prog(oral)	-0.1 (-0.8,0.6)
-16 (-21.6,-10.1)	0 (-0.8,0.8)	-3.3 (-8.8,2.3)	-2.7 (-8.3,3.1)	1.6 (-3.8,7.3)	-0.1 (-0.9,0.6)	-0.1 (-0.9,0.6)	-0.8 (-1.8,0.2)	-0.1 (-0.8,0.7)	GnRHa(i.m.)+ Prog(oral)+ Oest(oral)

(a) Mean differences and 95% credible intervals between the column-defined and row-defined treatments from the NMA with the upper 95% CrI of the SE posterior imputed (bottom left diagonal) and the original NMA with the median of the SE posterior imputed. Mean differences less than 0 favour the row-defined treatment. Numbers in bold, grey-shaded cells denote results where the 95% CrI credible intervals do not include 0. For treatment name abbreviations see Table 61 (section 11.1.3.2.3).

Table 8: Probabilities of being the best treatment and the rank (with 95% CrI) for each treatment, comparing the original imputation (using the median of the posterior for SE) and the upper 95% CrI of the posterior for SE

Treatment Class	Probability of being the best treatment (%)		Rank (95% CrI)	
	Median	Upper 95% CrI	Median	Upper 95% CrI
Placebo/no treatment	0.00%	0.00%	10 (10, 10)	10 (10, 10)
Danazol/Gestrinone (oral)	7.33%	8.93%	3 (1, 7)	3 (1, 7)
Progestogens (oral)	0.70%	0.80%	9 (2, 9)	9 (2, 9)
Progestogens (i.m.)	6.59%	7.10%	8 (1, 9)	8 (1, 9)
Progestogens (i.u.)	68.62%	66.51%	1 (1, 9)	1 (1, 9)
GnRHa (i.m.)	1.53%	1.62%	5 (2, 8)	5 (2, 8)
GnRHa (i.n.)	3.25%	2.97%	4 (1, 8)	5 (1, 8)
Prog (oral) + Oest (oral)	0.18%	0.24%	7 (4, 9)	7 (4, 9)
GnRHa (i.m.) + Prog (oral)	4.36%	4.56%	4 (1, 8)	4 (1, 8)

(a) For treatment name abbreviations see Table 61 (section 11.1.3.2.3)

L.3.252 Pharmacological treatments for pain relief – dyspareunia (Biberoglu and Behrman)

Table 9: Matrix of sensitivity results for the NMA of dyspareunia using upper 95% CrIs of imputed standard errors

Placebo/no treat	**-0.4 (-0.68, -0.11)**	**-0.22 (-0.41, -0.03)**	**-0.47 (-0.76, -0.19)**
-0.42 (-0.81, -0.04)	Danazol/Gestrinone	0.18 (-0.04, 0.39)	-0.08 (-0.22, 0.06)
-0.22 (-0.53, 0.09)	0.2 (-0.02, 0.43)	GnRHa (i.m.)	**-0.25 (-0.46, -0.04)**
-0.45 (-0.83, -0.06)	-0.03 (-0.24, 0.19)	**-0.23 (-0.45, 0.00)**	GnRHa (i.n.)

a) *Mean differences and 95% credible intervals between the column-defined and row-defined treatments from the NMA with the upper 95% CrI of the SE posterior imputed (bottom left diagonal) and the original NMA with the median of the SE posterior imputed. Mean differences less than 0 favour the row-defined treatment. Numbers in bold, grey-shaded cells denote results where the 95% CrI credible intervals do not include 0. For treatment name abbreviations see Table 61 (section 11.1.3.2.3)..*

Table 10: Probabilities of being the best treatment and the rank (with 95% CrI) for each treatment, comparing the original imputation (using the median of the posterior for SE) and the upper 95% CrI of the posterior for SE

Treatment Class	Probability of being the best treatment (%)		Rank (95% CrI)	
	Median	Upper 95% CrI	Median	Upper 95% CrI
Placebo/no treat	0.03%	0.58%	4 (4, 4)	4 (3, 4)
Danazol/Gestrinone	14.26%	40.34%	2 (1, 3)	2 (1, 3)
GnRHa (i.m.)	0.67%	0.65%	3 (2, 3)	3 (2, 4)
GnRHa (i.n.)	85.05%	58.43%	1 (1, 2)	1 (1, 2)

(a) For treatment name abbreviations see Table 61 (section 11.1.3.2.3)

L.3.2.13 Surgical and combined surgical and hormonal treatments for pain relief (VAS)

Table 11: Matrix of sensitivity results for the NMA of pain relief (VAS) using upper 95% CrIs of imputed standard errors

Diagnostic / no treatment	**-26.8 (-40.9, -12.7)**	**-54.0 (-80.5, -27.4)**	**-56.4 (-87.6, -25.4)**	**-50.7 (-68.6, -33.0)**	**-43.4 (-61.3, -25.6)**
-25.1 (-47.1,-3.1)	Laparoscopic surgery	**-27.2 (-49.8, -4.44)**	**-29.7 (-57.6, -1.83)**	**-23.9 (-35.0, -12.9)**	**-16.6 (-27.7, -5.53)**
-51.4 (-85.2,-17.7)	**-26.4 (-52.6,-0.02)**	Laparosc + Prog (o)	-2.54 (-35, 30.04)	3.25 (-16.7, 23.1)	10.6 (-12.1, 33.2)
-53.9 (-91.5,-16.7)	-28.9 (-59.8,2.99)	-2.57 (-35.0,30.0)	Laparosc + GnRH (i.m.)	5.75 (-19.9, 31.4)	13.1 (-14.9, 41)
-48.1 (-75.8,-20.4)	**-23.1 (-40.5,-5.75)**	3.28 (-16.7,23.2)	5.8 (-19.8,31.5)	Laparosc + Prog (o) + Oest (o)	7.32 (-3.79, 18.4)
-41.1 (-69.0,-13.3)	-16.0 (-33.5,1.48)	10.3 (-16.0,36.8)	12.9 (-18.1,43.9)	7.05 (-10.5,24.7)	Laparosc + P (o) + O (o) + CMH

Note: Mean differences and 95% credible intervals between the column-defined and row-defined treatments from the NMA with the upper 95% CrI of the SE posterior imputed (bottom left diagonal) and the original NMA with the median of the SE posterior imputed. Mean differences less than 0 favour the row-defined treatment. Numbers in bold, grey-shaded cells denote results where the 95% CrI credible intervals do not include 0. For treatment name *abbreviations see Table 117 (section 11.3.1.7.1)*.

Table 12: Probabilities of being the best treatment and the rank (with 95% CrI) for each treatment, comparing the original imputation (using the median of the posterior for SE) and the upper 95% CrI of the posterior for SE

	Probability of being the best treatment (%)		Rank (95% CrI)	
Treatment Class	**Median**	**Upper 95% CrI**	**Median**	**Upper 95% CrI**
Diagnostic/no treatment	0.00%	0.00%	6 (6, 6)	6 (6, 6)
Laparoscopic surgery	0.00%	0.03%	5 (4, 5)	5 (4, 5)
Laparosc + Prog (o)	36.60%	35.20%	2 (1, 4)	2 (1, 4)
Laparosc + GnRH (i.m.)	50.30%	49.04%	1 (1, 4)	2 (1, 5)
Laparosc + Prog (o) + Oest (o)	11.18%	9.67%	2 (1, 4)	3 (1, 4)
Laparosc + Prog (o) + Oest (o) + CMH	1.93%	6.05%	4 (2, 4)	4 (1, 5)

(c) For treatment name abbreviations see Table 117 (section 11.3.1.7.1)

L.4 Incoherence

L.4.1 Pharmacological treatments for discontinuation of treatment due to adverse events

Figure 4: Results of node-splitting to estimate direct and indirect contributions to NMA for discontinuation due to adverse events

Note: For treatment name abbreviations see Table 61 (section 11.1.3.2.3)

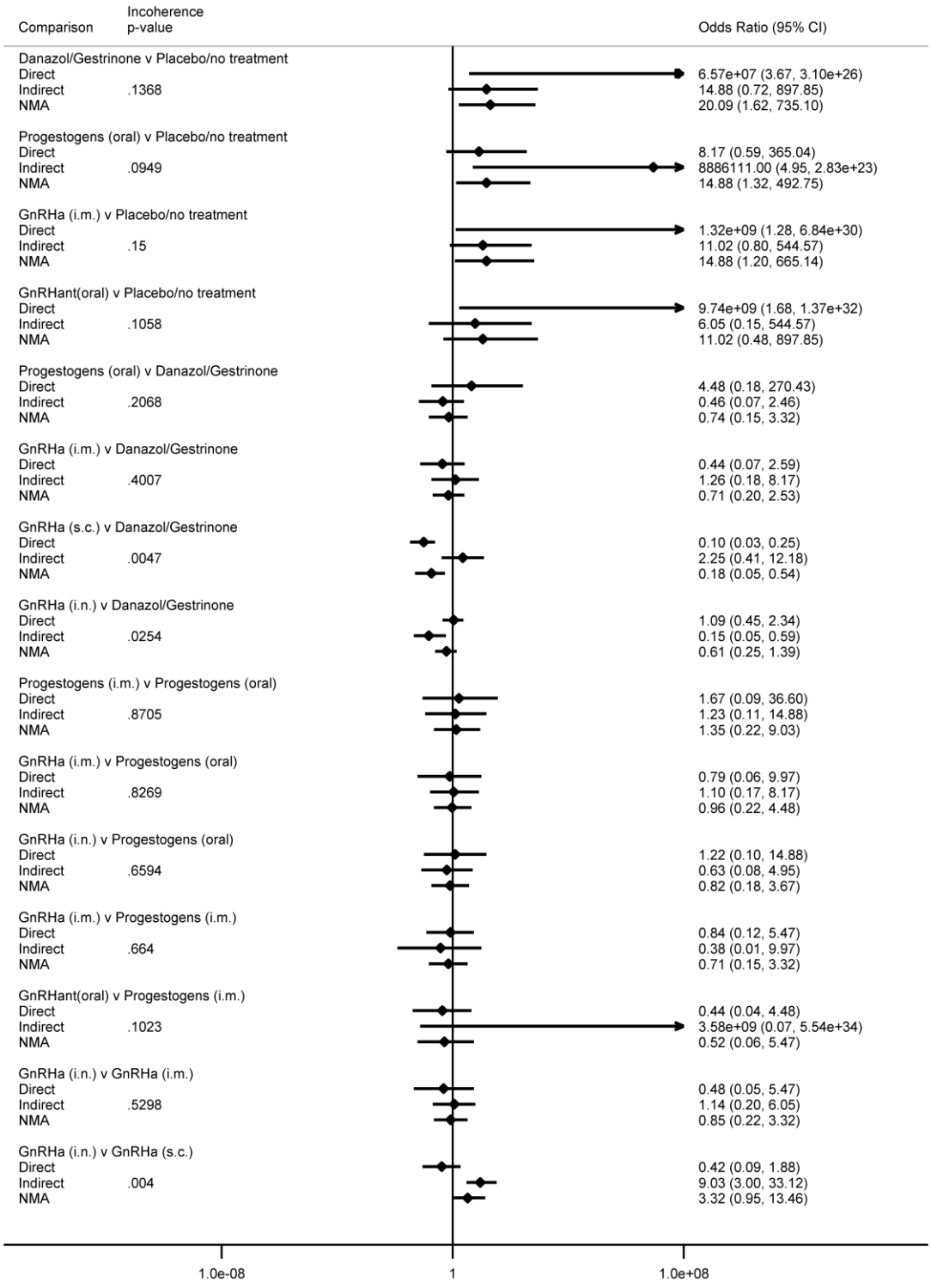
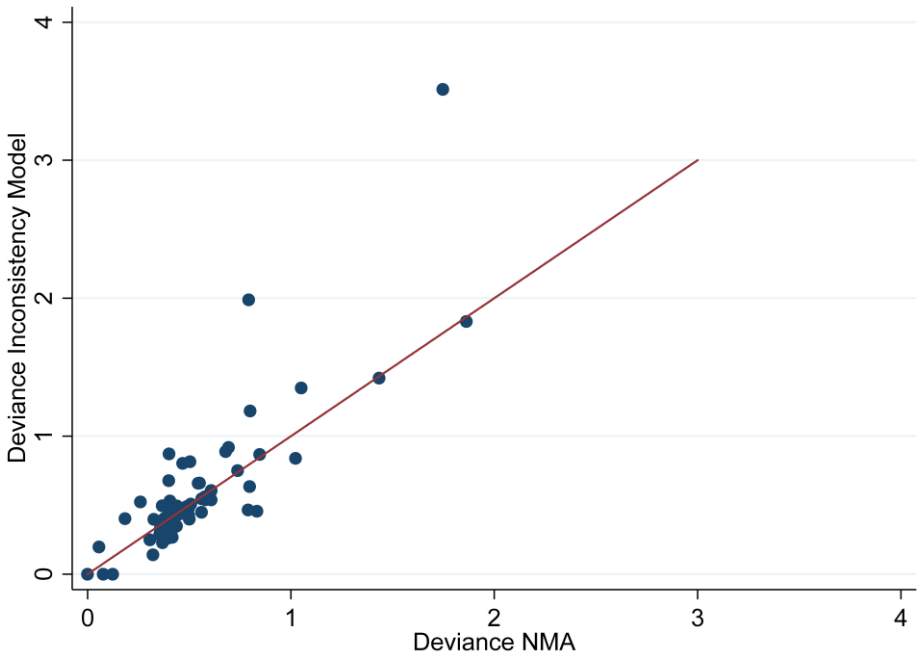


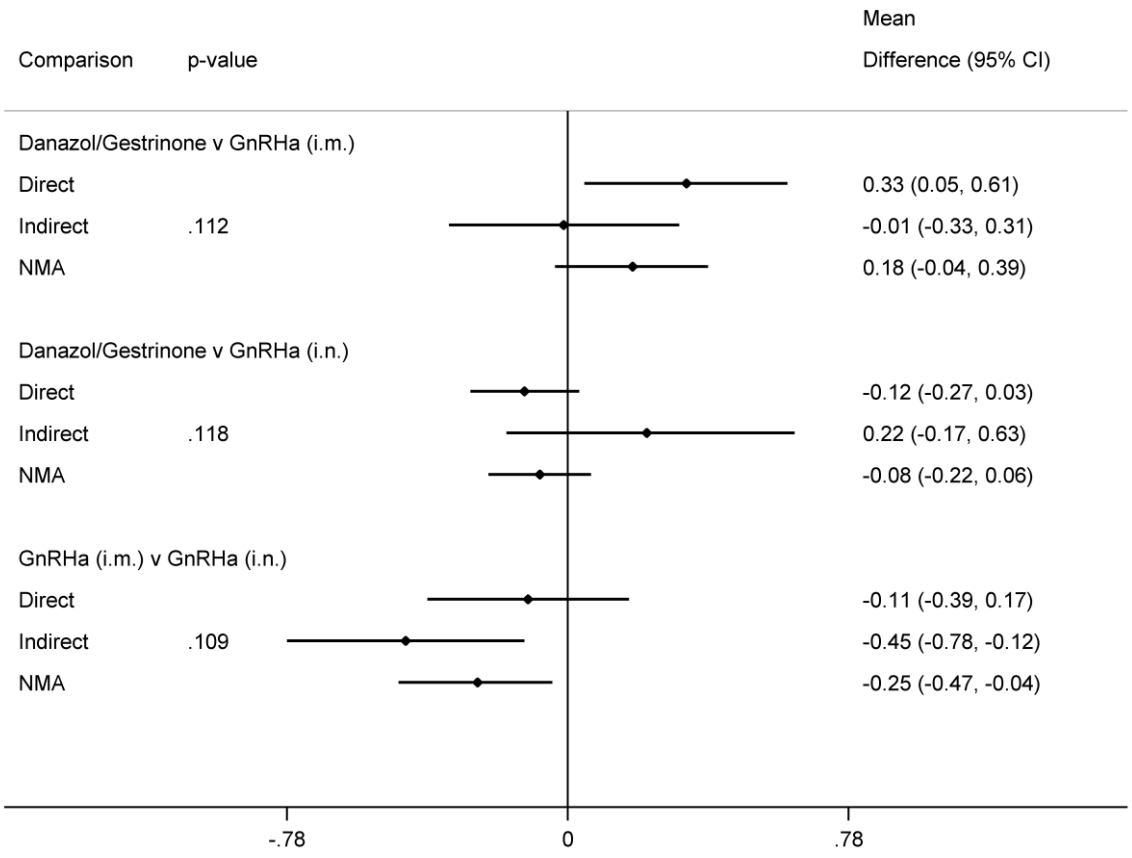
Figure 5: Residual deviances for direct comparisons from a pairwise (inconsistency) model and NMA model for discontinuation due to adverse



Note: Inconsistency can be expected to be present where residual deviances are substantially different between NMA and inconsistency (pairwise) models

L.4.12 Pharmacological treatments for pain relief – Dyspareunia

Figure 6: Results of node-splitting to estimate direct and indirect contributions to NMA for dyspareunia



Note: For treatment name abbreviations see Table 61 (section 11.1.3.2.3)

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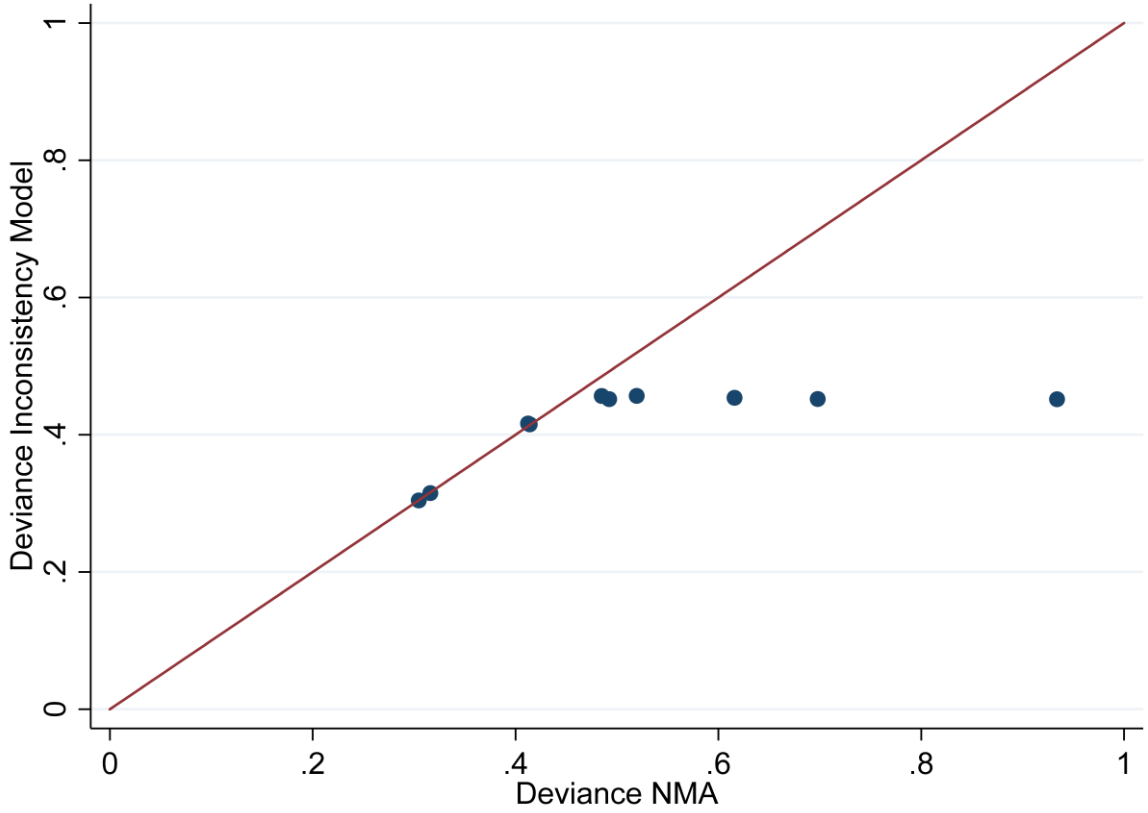
Figure 7: Residual deviances for direct comparisons from a pairwise (inconsistency) model and NMA model for dyspareunia



Note: Inconsistency can be expected to be present where residual deviances are substantially different between NMA and inconsistency (pairwise) models

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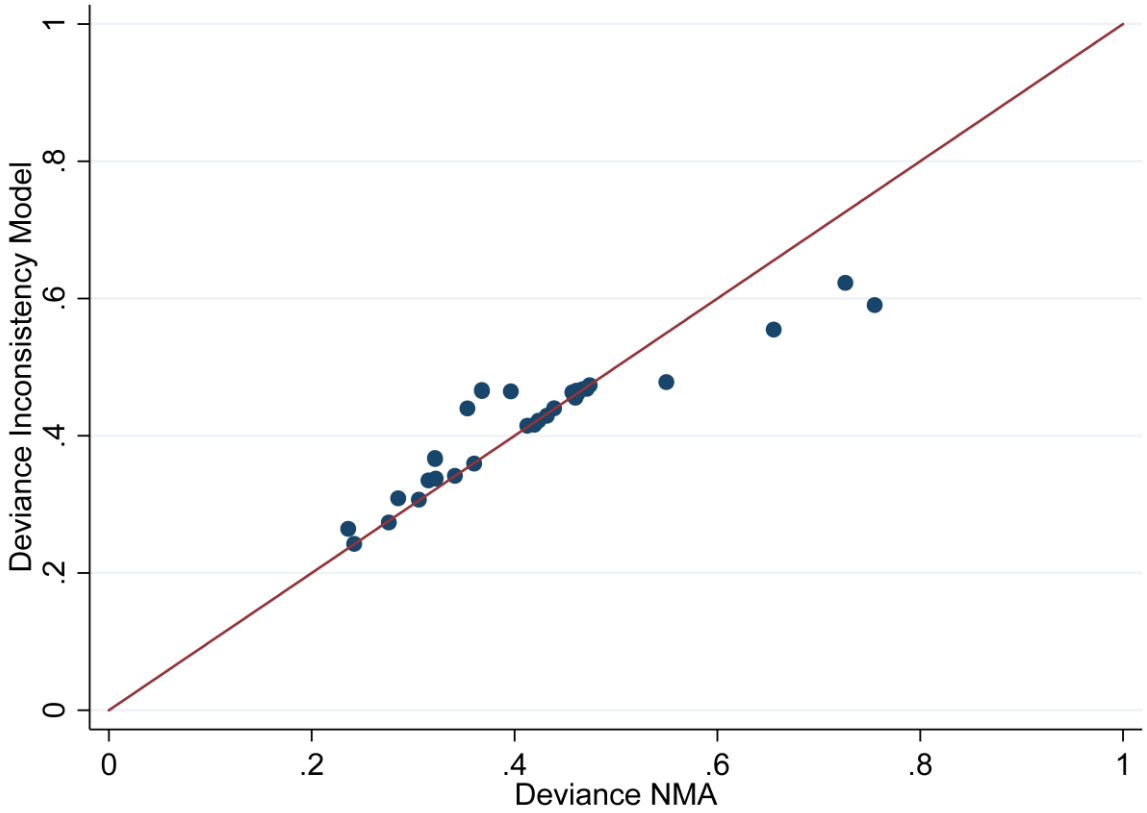
L.4.3 Treatments to improve spontaneous pregnancy

Figure 8: Residual deviances for direct comparisons from a pairwise (inconsistency) model and NMA model



Note: Inconsistency can be expected to be present where residual deviances are substantially different between NMA and inconsistency (pairwise) models

L.5 WinBUGS Sample Code

L.5.1 Multivariate NMA (normal likelihood, identity link)

```
# Normal likelihood, identity link
# Trial-level data given as single arms
# Fixed effects (class-level) model for multi-arm trials

model{                                  # *** PROGRAM STARTS
for(i in 1:N){

             # multivariate likelihood
                          y[i,1:3] ~ dmnorm(mean.y[study[i],arm[i],1:3],omega[i,,])
                          omega[i,1:3,1:3] <- inverse(cov.mat[i,,])# within-study
precision matrix

        #define elements of within-study covariance matrix
        cov.mat[i,1,1] <-  pow(se[i,1],2)
        cov.mat[i,2,2] <-  pow(se[i,2],2)
        cov.mat[i,3,3] <-  pow(se[i,3],2)
        cov.mat[i,1,2] <-  se[i,1]*se[i,2]*cor[1]
        cov.mat[i,1,3] <-  se[i,1]*se[i,3]*cor[2]
        cov.mat[i,2,3] <-  se[i,2]*se[i,3]*cor[3]
        cov.mat[i,2,1] <-  cov.mat[i,1,2]
```

```
        cov.mat[i,3,1] <-  cov.mat[i,1,3]
        cov.mat[i,3,2] <-  cov.mat[i,2,3]

    for(m in 1:no){
        se[i,m] ~ dnorm(0, prec.se[m])I(0,) # input missing standard errors
                        }

  }

    for(j in 1:ns){
        for(k in 1:NA[j]) {
            for(m in 1:no){
                 mean.y[j,k,m] <- mu[j,m] + (d[m,t[j,k]] - d[m,t[j,1]]) # define
study-specific treatment effects and consistency equations
            }
      }
   }

#Deviance contribution for each observation
for (i in 1:ns){
  for(m in 1:3){             # multiply vector & matrix
    ydiff[i,m] <- y[i,m] - mean.y[study[i],arm[i],m]
    z[i,m]<- inprod(omega[i,m,1:3], ydiff[i,1:3])
  }
  resdev[i]<- inprod(ydiff[i,1:3], z[i,1:3])
}

totresdev <- sum(resdev[])        #Total Residual Deviance

# Constraints
  d[1,1] <- 0
  d[2,1] <- 0
  d[3,1] <- 0


#Prior distributions and parameter to estimate
  sd.se~ dunif(0, 2)

   for(m in 1:no) {
      prec.se[m] <- pow(sd.se,-2)

             for(j in 1:ns){
         mu[j, m] ~ dnorm(0,0.0001)
      }
   }


# Borrowing information across outcomes
# Intervention effects and prior distributions
 for(k in 2: nt){
    for(m in 1:no) {
             meanD[m,k-1] <- alpha[k-1] + gamma[m]   #outcome and intervention
effects
             d[m,k] ~ dnorm(meanD[m,k-1], prec.btw)         #trt effects
      }
       }

  for(m in 1:1) {gamma[m] ~ dnorm(0, 0.001) } # More informed prior
  for(m in 2:3) {gamma[m] ~ dunif(-3, 3) }
  for(k in 1:(nt-1)) {alpha[k] ~ dnorm(0, 0.001) } # More informed prior
  prec.btw <- pow(sd.btw,-2)
  sd.btw ~ dunif(0, 2)


# all pairwise mean differences
for (c in 1:(nt-1)) {
             for (k in (c+1):nt)  {
                                      for (m in 1:no) {
                                  MD[m,c,k]<- d[m,k]-d[m,c]
                                  }
```

```
      }
  }


# all treatments to be used for ranking
for(k in 1:nt){
             for (m in 1:no) {dR[m,k] <- d[m,k] }
}


# ranking on relative scale
for (k in 1:ntR) {
             for (m in 1:no) {
#            rk[k]<- (ntR+1)-rank(dR[],k)     # events are "good"
             rk[m,k]<- rank(dR[m,],k)             # events are "bad"
             best[m,k] <- equals(rk[m,k],1)       # rank=1 is best
                          best3[m,k] <- (equals(rk[m,k],1)) + (equals(rk[m,k],2)) +
(equals(rk[m,k],3))
                          worst3[m,k] <- (equals(rk[m,k],ntR)) +
(equals(rk[m,k],ntR-1)) + (equals(rk[m,k],ntR-2))
#calculate probability that treat k is h-th best
             for (h in 1:nt) { prob[h,m,k] <- equals(rk[m,k],h) }
             }
       }



}                                    # *** PROGRAM ENDS
```

L.5.2 NMA for discontinuation of treatment due to adverse events (binomial likelihood, logit link)

```
# Binomial likelihood, logit link
# Trial-level data given as single arms
# Random effects model for multi-arm trials

model{                                  # *** PROGRAM STARTS
for(i in 1:ns) {        # LOOP THROUGH THREE-ARM STUDIES
             w[i,1] <- 0
             delta[i,1] <- 0
             mu[i] ~ dnorm(0,.0001)           # vague priors for all trial
baselines
    for (k in 1:na[i]) {             #  LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
# model for linear predictor
        logit(p[i,k]) <- mu[i] + delta[i,k]
        rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators

#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
            +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])

             for (k in 2:na[i]) {
                          delta[i,k] ~ dnorm(md[i,k],taud[i,k])
                          md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[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[])            #Total Residual Deviance

d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
```

```
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

sd ~ dunif(0,5)
tau <- pow(sd,-2)


# all pairwise mean differences
for (c in 1:(nt-1)) {
    for (k in (c+1):nt)  {
        OR[c,k]<- exp(d[k]-d[c])
      }
  }
# all treatments to be used for ranking
for(k in 1:nt){ dR[k] <- d[k] }
# ranking on relative scale
for (k in 1:ntR) {
#    rk[k]<- (ntR+1)-rank(dR[],k)     # events are "good"
    rk[k]<- rank(dR[],k)             # events are "bad"
    best[k] <- equals(rk[k],1)       # rank=1 is best
              best3[k] <- (equals(rk[k],1)) + (equals(rk[k],2)) + (equals(rk[k],3))
              worst3[k] <- (equals(rk[k],ntR)) + (equals(rk[k],ntR-1)) +
(equals(rk[k],ntR-2))
#calculate probability that treat k is h-th best
    for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
  }

}                                    # *** PROGRAM ENDS
```