RR423212

RQ 1.2 – Subsequent pharmacological therapy for the management of type 2 diabetes.

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August 2024

Research Question

This analysis focused on subsequent therapies for management of type 2 diabetes. In this context, study participants would be receiving the trialled treatments against a background of initial management, which could include treatments included in the subsequent treatment set. Study populations varied in their existing treatments and in the use of rescue therapies.

Definition of population

These analyses focus on people with type 2 diabetes mellitus (T2D) at high cardiovascular risk (or mixed/unclear cardiovascular risk) with no other comorbidities.

This category of high cardiovascular risk includes risk of the following events: ischaemic stroke; transient ischaemic attack; coronary heart disease, including myocardial infarction and angina; peripheral arterial disease and coronary and non-coronary revascularisation procedures. Studies in people at risk of cardiovascular disease (with and without T2D) were not included in the evidence, including where a T2D subgroup was reported.

Methods

Network meta-analyses (NMAs) were conducted in WinBUGS, version 1.4.3, using standard and adapted TSD codes.

Normal likelihood with identity link function for estimation of mean change, additive treatment effects

Used for the analysis of change in % HbA1c, and adapted in the analysis of change in % HbA1c with meta-regression on mean-centred baseline % HbA1c.

Models were run using TSD code TSD2-8 (Normal shared), which estimates treatment effects jointly, updated to allow for direct use of mean differences reported in different formats: as arm- or contrast-level change-from-baseline (CFB) and arm- or contrast-level mean value at follow-up.

Normal likelihood with log link function for estimation of mean change, proportional treatment effects

This model was used for the analysis of change in weight (kg). Models were run using TSD code TSD2-5 (Normal id), updated to allow for direct use of mean differences reported in different formats: as CFB or mean value at follow-up. In this model, studies not reporting baseline values and studies reporting contrast-level estimates were excluded from the dataset for analysis.

Within this model, it was necessary to assume correlation between baseline and follow-up measures to combine relative effects from studies reporting the change from baseline and studies reporting relative effects as baseline and follow-up values. A value of 0.5 was used for the correlation to calculate the SE around the change from baseline, which is somewhat conservative (Balk et al. 2012, Daly et al. 2021).

Model selection

The choice of whether to proceed with the NMA with fixed-effect (FE) or random-effects (RE) structure on the treatment differences was made by first considering the network structure, then by comparing model fit statistics between the two models, taking into account the size and precision of the between-study variation estimated under the RE model. Where DIC in the FE and RE models differed by >3 units, the model with the lower DIC was chosen. Where DIC values in FE and RE models were within 2 units, the FE model was selected provided that total residual deviance was similar to the number of data points and either the median of between-study SD was low or between-study SD was poorly estimated from the data (skewed distribution and a large uncertainty interval). There were no cases where differences in FE DIC and RE DIC were within 2 units and the between-study SD was both high and precisely estimated.

Total residual deviance, posterior mean residual deviance, pD and DIC values were calculated within WinBUGS (version 1.4.3), using TSD standard code for calculation of the total residual deviance and the inbuilt tool for calculation of posterior mean residual deviance (Dbar), pD and DIC.

Assessing inconsistency with Unrelated Mean Effect models

NMA assumes that the included studies are similar in terms of factors that might interact with the intervention effects (effect modifiers). So, the relative effect of intervention B vs intervention A would be expected to be similar in all of the studies (if they had included A and B interventions). We can assess this assumption by measuring statistical heterogeneity, and also by checking if the direct and indirect estimates are in agreement when there are loops of evidence in the network. To determine if there is evidence of inconsistency, the selected consistency model (fixed or random effects) was compared to an “inconsistency”, or unrelated mean effects (UME), model (Dias 2013). The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. We further explored inconsistency using dev-dev plots, which can highlight individual studies that are contributing to inconsistency. These study arms appear in the area shaded grey in the included dev-dev plots.

Population at risk of CVD: Change in HbA1c

Model fit

The main analysis included 337 studies of 36 treatments (Figure 1). The random-effect (RE) NMA model was preferred on model fit (Table 1), with moderate heterogeneity noted in treatment effects: 0.25 units % HbA1c (95% credible interval: 0.23, 0.28). The analysis including regression on baseline HbA1c included 310 studies of 35 treatments. Whilst there was no improvement in model fit when introducing the meta-regression term (Table 1), the coefficient for baseline severity was entirely negative, supporting the hypothesis that, as baseline % HbA1c increases, there is an additional reduction in % HbA1c associated with treatment.

Clinical effectiveness relative to placebo

Under both models, there was clear evidence that all treatments were more effective than placebo in reducing mean % HbA1c (Figure 2). Where treatments of two classes were given in combination, there was a trend that the estimated treatment effect was greater, though more uncertain, than the effect of either of the individual treatments trialled separately.

Clinical effectiveness: active-active comparisons

Tirzepatide, subcutaneous semaglutide and the insulin combinations IDegLira and IGlarLixi were ranked highly (Table 2), with central estimates suggesting large reductions in % HbA1c estimated with relatively low uncertainty (Figure 2).

Tirzepatide showed greater reductions in % HbA1c than the represented sulfonylureas (gliclazide, glimepiride and glipizide), five DPP4-inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin, alone and in combination with metformin) and the SGLT2-inhibitors (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin as well as the combinations dapagliflozin + saxagliptin, empagliflozin + linagliptin and ertugliflozin + sitagliptin). It also showed greater reductions in % HbA1c than all GLP1 receptor agonists (dulaglutide, exenatide, liraglutide, lixisenatide and both oral and subcutaneous semaglutide) as well as insulin, IDegLira, metformin and pioglitazone (both alone and in combination with either alogliptin or metformin).

Subcutaneous semaglutide showed greater reductions in % HbA1c than the represented sulfonylureas (gliclazide, glimepiride and glipizide), five DPP4-inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin, alone and in combination with metformin) and the SGLT2-inhibitors (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin as well as the combination dapagliflozin + saxagliptin). It also showed greater reductions in % HbA1c than the other GLP1 receptor agonists (dulaglutide, exenatide, liraglutide, lixisenatide and oral semaglutide) as well as insulin, metformin and pioglitazone.

The insulin combination treatment IDegLira showed greater reductions in % HbA1c than the represented sulfonylureas (gliclazide, glimepiride and glipizide), five DPP4-inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin) and four SGLT2-inhibitors (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin). It also showed greater reductions in % HbA1c than four GLP1 receptor agonists (dulaglutide, exenatide, liraglutide and lixisenatide), pioglitazone, metformin and insulin.

The insulin combination treatment IGlarLixi showed greater reductions in % HbA1c than the represented sulfonylureas (gliclazide, glimepiride and glipizide), five DPP4-inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin) and four SGLT2-inhibitors (canagliflozin,

dapagliflozin, empagliflozin and ertugliflozin). It also showed greater reductions in % HbA1c than three GLP1 receptor agonists (exenatide, liraglutide and lixisenatide), pioglitazone, metformin and insulin.

For a complete list of active-active comparisons, please see the 'Treatment Direct Effects' tabs in RQ1.2 results files pop 5 HbA1c and pop 5 HbA1c with meta-regression.

Global inconsistency in NMA of change in % HbA1c

Three study arms were flagged as having relatively high deviance in the NMA model, which enforces consistency in relative effects (Figure 3). The same study arms – the oral semaglutide arm of Yabe 2020 and two tirzepatide arms of Frias 2018 - were identified by the main (Figure 3, panel a) and meta-regression (Figure 3, panel b) models. Frias 2018 trialled four doses of tirzepatide against dulaglutide and placebo, whilst Yabe 2020 trialled three doses of oral semaglutide against dulaglutide. Since dose was not modelled in these NMAs, studies that explored different doses of the same treatment would be constrained to estimate a single relative effect, leading to poor fit for some study arms. A sensitivity analysis was conducted within which only the treatment arm best reflecting clinical practice was modelled and other arms trialling the same treatment were excluded. Treatment effects for tirzepatide and oral semaglutide were very similar (Table 4) but model fit improved, indicating that the potential inconsistency associated with these arms could be ascribed to dose, rather than unexplained conflict between direct and indirect evidence in the network.

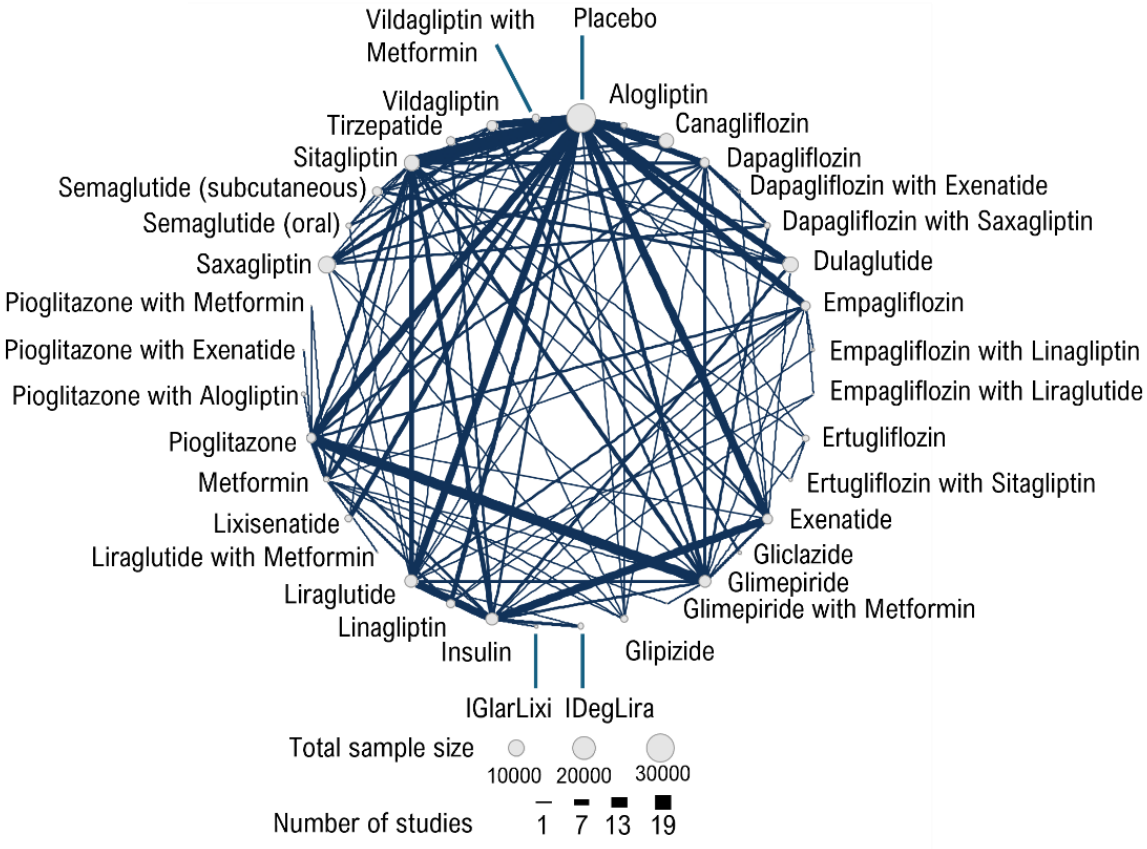

Figure 1. Network of evidence for change in HbA1c, in the population of people with type 2 diabetes at high risk of cardiovascular disease. Circular points show interventions, with the size proportional to the number of participants receiving the intervention. Blue edges show treatment comparisons with

RCT evidence, with the thickness of the edge proportional to the number of studies making the treatment comparison.

Table 1. Model fit statistics for network meta-analysis (NMA) model of change in % HbA1c in the subpopulation of people with diabetes at high risk of CVD. This is given for the full dataset, and for the subset of studies reporting baseline HbA1c with and without regression on baseline HbA1c.

[1] DIC = posterior mean residual deviance + pD; Lower values are preferred for model fit.

Model effect structure	Meta-regression on baseline HbA1c β median (95% CrI)	Model fit Total residual deviance[1]	Model fit Posterior mean residual deviance[1]	Number of effective parameters (pD)	DIC (penalised deviance[1])	Between-study SD Median (95% CrI)
Full dataset, *711 datapoints from 337 studies*						
Fixed, NMA	-	3517.0	1873.1	273.9	2147.0	-
Random, NMA	-	671.5	-970.4	566.1	-404.3	0.25 (0.23, 0.28)
Random, UME	-	672.9	-970.0	589.2	-380.8	0.25 (0.23, 0.28)
Only studies reporting baseline, *654 datapoints from 310 studies*						
Random, NMA	-	624.2	-916.4	522.9	-393.5	0.25 (0.23, 0.28)
Random, NMA	-0.093 (-0.182, -0.006)	622.1	-917.9	522.5	-395.4	0.25 (0.23, 0.28)
Random, UME	-0.099 (-0.192, -0.007)	622.0	-918.6	543.7	-374.9	0.25 (0.22, 0.28)

Table 2. Change in HbA1c relative to placebo for all 35 active treatments in the network, full dataset, random-effects structure on treatment effects. Where effect estimates are uncertain or many treatments have a similar effect, ranks will overlap and be less easy to interpret.

Class	Treatment	Mean change, % HbA1c Median (95% CrI)	Rank Median (95% CrI)
Placebo	Placebo	*Reference*	36 (36, 36)
DPP4i	Alogliptin	-0.56 (-0.81, -0.31)	30 (18, 35)
	Linagliptin	-0.54 (-0.67, -0.41)	31 (23, 35)
	Saxagliptin	-0.53 (-0.66, -0.39)	31 (24, 35)
	Sitagliptin	-0.64 (-0.72, -0.56)	25 (21, 30)
	Vildagliptin	-0.66 (-0.77, -0.54)	24 (19, 31)
DPP4i with metformin	Vildagliptin with Metformin	-0.69 (-1.20, -0.17)	22 (8, 35)
GIPGLP	Tirzepatide	-1.68 (-1.88, -1.48)	1 (1, 4)
GLP with metformin	Liraglutide with Metformin	-1.35 (-1.95, -0.73)	5 (1, 20)
GLP-1RA	Dulaglutide	-0.98 (-1.10, -0.86)	14 (10, 17)
	Exenatide	-0.80 (-0.90, -0.69)	18 (15, 22)
	Liraglutide	-0.89 (-0.99, -0.80)	16 (12, 19)
	Lixisenatide	-0.51 (-0.67, -0.35)	32 (23, 35)
	Semaglutide (oral)	-1.06 (-1.26, -0.86)	11 (6, 17)
	Semaglutide (subcutaneous)	-1.30 (-1.46, -1.14)	6 (3, 10)
Insulin mix	IDegLira	-1.23 (-1.43, -1.04)	7 (3, 12)
	IGlarLixi	-1.35 (-1.72, -0.96)	5 (1, 14)
Insulin	Insulin	-0.74 (-0.85, -0.64)	20 (17, 25)
Metformin	Metformin	-0.54 (-0.68, -0.41)	31 (23, 35)
SGLT2i with DPP4	Dapagliflozin with Saxagliptin	-1.01 (-1.21, -0.79)	13 (7, 18)
	Empagliflozin with Linagliptin	-1.12 (-1.48, -0.78)	10 (3, 19)
	Ertugliflozin with Sitagliptin	-1.13 (-1.51, -0.74)	10 (3, 20)
SGLT2i	Canagliflozin	-0.68 (-0.84, -0.53)	23 (17, 32)
	Dapagliflozin	-0.63 (-0.75, -0.51)	26 (19, 32)
	Empagliflozin	-0.71 (-0.82, -0.59)	21 (17, 28)
	Ertugliflozin	-0.62 (-0.89, -0.35)	26 (16, 35)
SGLT2i with GLP-1RA	Dapagliflozin with Exenatide	-1.24 (-1.75, -0.72)	7 (1, 20)
	Empagliflozin with Liraglutide	-1.33 (-1.85, -0.82)	5 (1, 17)
SU	Gliclazide	-0.68 (-0.96, -0.39)	23 (14, 35)
	Glimepiride	-0.59 (-0.69, -0.49)	28 (22, 33)
	Glipizide	-0.41 (-0.64, -0.19)	34 (26, 35)
SU with metformin	Glimepiride with Metformin	-1.25 (-1.83, -0.66)	7 (1, 24)
TZD	Pioglitazone	-0.64 (-0.74, -0.54)	25 (20, 31)
TZD with DPP4i	Pioglitazone with Alogliptin	-1.14 (-1.59, -0.68)	10 (2, 22)
TZD with GLP-1RA	Pioglitazone with Exenatide	-1.13 (-1.72, -0.54)	10 (1, 31)
TZD with metformin	Pioglitazone with Metformin	-0.94 (-1.47, -0.43)	14 (3, 34)

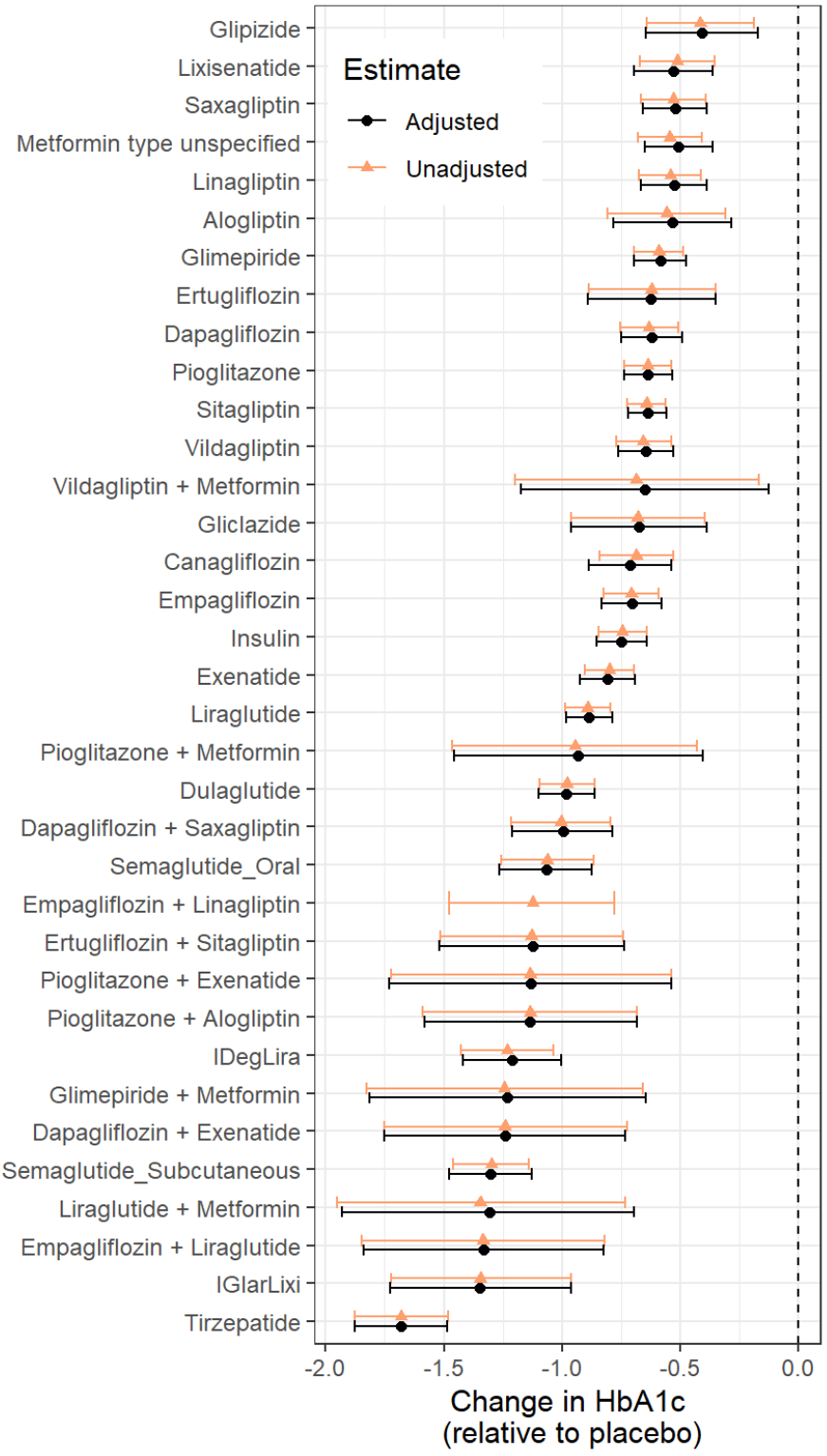

Figure 2. Change in % HbA1c in the population with diabetes and at high risk of CVD. Median treatment effects (with 95% CrI) are given for unadjusted estimates (orange triangles) from the model without meta-regression and from the adjusted model (black circles) including meta-regression given baseline % HbA1c of 8.15.

Table 3. Change in HbA1c relative to placebo for all 34 active treatments in the network from the meta-regression model at different levels of baseline HbA1c.

Class	Treatment	Change in HbA1c, adjusted estimates Median (95% CrI)		
		Baseline HbA1c = 7	Baseline HbA1c = 8.15	Baseline HbA1c = 12
Placebo	Placebo	Reference	Reference	Reference
DPP4i	Alogliptin	-0.42 (-0.70, -0.14)	-0.53 (-0.78, -0.28)	-0.89 (-1.29, -0.50)
	Linagliptin	-0.42 (-0.59, -0.24)	-0.52 (-0.67, -0.38)	-0.88 (-1.25, -0.52)
	Saxagliptin	-0.41 (-0.59, -0.24)	-0.52 (-0.66, -0.38)	-0.88 (-1.24, -0.52)
	Sitagliptin	-0.53 (-0.67, -0.39)	-0.64 (-0.72, -0.56)	-0.99 (-1.34, -0.66)
	Vildagliptin	-0.54 (-0.70, -0.38)	-0.64 (-0.76, -0.53)	-1.00 (-1.36, -0.66)
DPP4i with metformin	Vildagliptin with Metformin	-0.54 (-1.09, 0.00)[1]	-0.65 (-1.17, -0.13)	-1.01 (-1.62, -0.39)
GIPGLP	Tirzepatide	-1.58 (-1.79, -1.35)	-1.68 (-1.88, -1.48)	-2.04 (-2.43, -1.65)
GLP with metformin	Liraglutide + Metformin	-1.20 (-1.84, -0.58)	-1.30 (-1.93, -0.70)	-1.67 (-2.35, -0.98)
GLP-1RA	Dulaglutide	-0.87 (-1.03, -0.72)	-0.98 (-1.10, -0.86)	-1.34 (-1.70, -0.99)
	Exenatide	-0.70 (-0.86, -0.54)	-0.81 (-0.92, -0.69)	-1.17 (-1.51, -0.82)
	Liraglutide	-0.78 (-0.92, -0.63)	-0.88 (-0.98, -0.79)	-1.24 (-1.59, -0.91)
	Lixisenatide	-0.42 (-0.61, -0.23)	-0.53 (-0.69, -0.36)	-0.89 (-1.27, -0.51)
	Semaglutide (Oral)	-0.96 (-1.18, -0.74)	-1.07 (-1.26, -0.87)	-1.42 (-1.82, -1.04)
	Semaglutide (Subcutaneous)	-1.20 (-1.40, -0.99)	-1.30 (-1.48, -1.13)	-1.66 (-2.05, -1.28)
Ins with mix	IDegLira	-1.10 (-1.33, -0.87)	-1.21 (-1.42, -1.00)	-1.57 (-1.96, -1.17)
	IGlarLixi	-1.24 (-1.64, -0.84)	-1.35 (-1.73, -0.96)	-1.71 (-2.22, -1.19)
Insulin	Insulin	-0.64 (-0.79, -0.49)	-0.75 (-0.85, -0.64)	-1.11 (-1.46, -0.76)
Metformin	Metformin	-0.40 (-0.58, -0.21)	-0.51 (-0.65, -0.36)	-0.87 (-1.23, -0.52)
SGLT2 with DPP4	Dapagliflozin with Saxagliptin	-0.89 (-1.12, -0.65)	-1.00 (-1.21, -0.79)	-1.35 (-1.76, -0.95)

[1] The upper bound for the treatment effect of Vildagliptin with metformin was 0.0002

	Ertugliflozin with Sitagliptin	-1.02 (-1.42, -0.61)	-1.12 (-1.52, -0.74)	-1.48 (-2.00, -0.97)
SGLT-2i	Canagliflozin	-0.61 (-0.80, -0.40)	-0.71 (-0.89, -0.54)	-1.07 (-1.46, -0.69)
	Dapagliflozin	-0.51 (-0.67, -0.35)	-0.62 (-0.75, -0.49)	-0.98 (-1.35, -0.62)
	Empagliflozin	-0.60 (-0.76, -0.43)	-0.70 (-0.83, -0.58)	-1.06 (-1.43, -0.71)
	Ertugliflozin	-0.51 (-0.80, -0.22)	-0.62 (-0.89, -0.35)	-0.98 (-1.41, -0.56)
SGLT-2i with GLP-1RA	Dapagliflozin with Exenatide	-1.13 (-1.65, -0.61)	-1.24 (-1.75, -0.73)	-1.60 (-2.21, -0.99)
	Empagliflozin with Liraglutide	-1.22 (-1.75, -0.70)	-1.33 (-1.84, -0.82)	-1.69 (-2.30, -1.07)
SU	Gliclazide	-0.57 (-0.88, -0.26)	-0.67 (-0.96, -0.39)	-1.03 (-1.48, -0.59)
	Glimepiride	-0.48 (-0.63, -0.32)	-0.58 (-0.69, -0.47)	-0.94 (-1.29, -0.60)
	Glipizide	-0.30 (-0.57, -0.04)	-0.41 (-0.64, -0.17)	-0.77 (-1.17, -0.37)
SU with metformin	Glimepiride with Metformin	-1.12 (-1.71, -0.53)	-1.23 (-1.81, -0.65)	-1.59 (-2.27, -0.91)
TZD	Pioglitazone	-0.53 (-0.67, -0.38)	-0.64 (-0.74, -0.53)	-0.99 (-1.35, -0.65)
TZD with DPP4i	Pioglitazone with Alogliptin	-1.03 (-1.49, -0.56)	-1.13 (-1.58, -0.68)	-1.50 (-2.06, -0.93)
TZD with GLP-1RA	Pioglitazone with Exenatide	-1.02 (-1.63, -0.41)	-1.13 (-1.73, -0.54)	-1.49 (-2.17, -0.83)
TZD with metformin	Pioglitazone with Metformin	-0.82 (-1.36, -0.28)	-0.93 (-1.46, -0.40)	-1.29 (-1.91, -0.68)

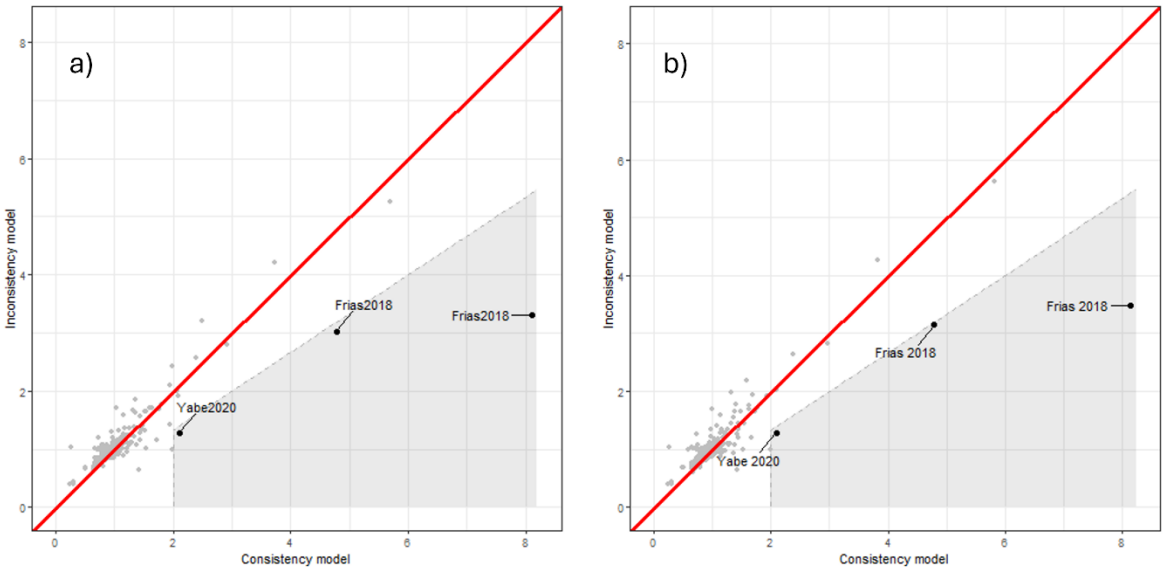

Figure 3. Plots showing model fit of individual study arms under the consistency (NMA) and inconsistency (UME) models for a) the main analysis of change in % HbA1c and b) the analysis of change in % HbA1c with meta-regression on baseline HbA1c. Study arms where fit was poor in the NMA and improved under UME (points in the grey shaded area) are labelled.

Both Frias 2018 and Yabe 2020 were dose-finding studies within which multiple arms trialled the same treatment at different doses, and report a dose-response relationship in % HbA1c change. In type-2 diabetes, starting dose may not be meaningful because treatments are titrated until the desired outcome is reached, therefore it was felt that modelling dose would not reflect clinical practice. Therefore, the protocol for base-case models in this guideline specified that dose should not be modelled explicitly. However, where there was a dose-response, study arms that trialled very high or low doses and report more extreme treatment effects will fit poorly in models that ignore dose.

A sensitivity analysis was conducted within which the committee recommended the dose most representative of clinical practice, and arms trialling other doses of the treatment were dropped. For Frias 2018, which trialled tirzepatide, the 10mg dose weekly was retained and arms trialling doses of 1mg, 5mg and 15mg were dropped. For Yabe 2020, which trialled oral semaglutide, the 7mg dose weekly was retained and arms trialling doses of 3mg and 14mg were dropped.

With this done, treatment effects for tirzepatide and oral semaglutide are virtually unchanged (Table 4), the high residual deviance noted for these studies disappeared and there is a small reduction in the between-study SD.

Table 4. Impact of dropping arms with high/low doses from two dose-finding studies, Frias 2018 and Yabe 2020.

Model	Treatment effect, mean difference in % HbA1c *Median (95% CrI)*		Posterior mean residual deviance for study		Between-study SD *Median (95% CrI)*
	Tirzepatide	Semaglutide (oral)	Frias 2018	Yabe 2020	
Base-case	-1.68 (-1.88, -1.48)	-1.06 (-1.26, -0.86)	16.6 (6 arms)	5.3 (4 arms)	0.25 (0.23, 0.28)
Sensitivity analysis	-1.73 (-1.93, -1.53)	-1.08 (-1.27, -0.89)	2.8 (3 arms)	1.8 (2 arms)	0.24 (0.22, 0.27)

RR423212

Population at risk of CVD: Change in HbA1c

Update following quality assurance: January 2025

External QA of the NMA work for the guideline in December 2024 identified an error in the WinBUGS code used for the specification of the covariance matrix in models with a Normal likelihood and identity link that included contrast-level data for trials with more than two arms. These models were used only in the analysis of change in % HbA1c in the population at risk of CVD.

Refitting these models identified several errors and inconsistencies in the data that have also been corrected, including reordering of study arms, which resulted in contrast-level differences being recorded in the wrong direction; studies reporting change in HbA1c in unit of mmol/ml that had been inappropriately excluded because of inconsistencies in the units reporting of baseline and follow-up values; and isolated errors in treatment codes or study inclusion/exclusion.

The previous analysis included 337 studies of 36 treatments, the random-effect (RE) NMA model was preferred on model fit and there was moderate heterogeneity (variation in studies reporting the same treatment comparison): 0.25 units % HbA1c (95% credible interval [CrI]: 0.23, 0.28).

The updated analysis included 344 studies of 36 treatments, the RE NMA model was again preferred on the basis of model fit (Table 5) and the estimate of between-study SD was very similar to the previous estimate: 0.25 units % HbA1c (95% CrI: 0.23, 0.27).

Treatment effect estimates from the updated analysis were overlapping and very similar to those from the version of analyses previously shared.

Model fit

The main analysis included 344 studies of 36 treatments (Figure 4): 102 studies reported treatment differences as contrasts between arms, 242 reported treatment differences as arm-level summaries. The random-effect (RE) NMA model was preferred on model fit (Table 5), with moderate heterogeneity noted in treatment effects: 0.25 units % HbA1c (95% credible interval: 0.23, 0.27).

The analysis including a regression on baseline HbA1c. This model fitted a common effect across all active treatments to include the impact of baseline severity of treatment effect. The dataset included 316 studies (94 contrast-level, 222 arm-level summaries) of 35 treatments. Whilst there was no meaningful improvement in model fit when introducing the meta-regression term (Table 5), the coefficient for baseline severity was entirely negative, supporting the hypothesis that, as baseline % HbA1c increases, there is an additional reduction in % HbA1c associated with treatment.

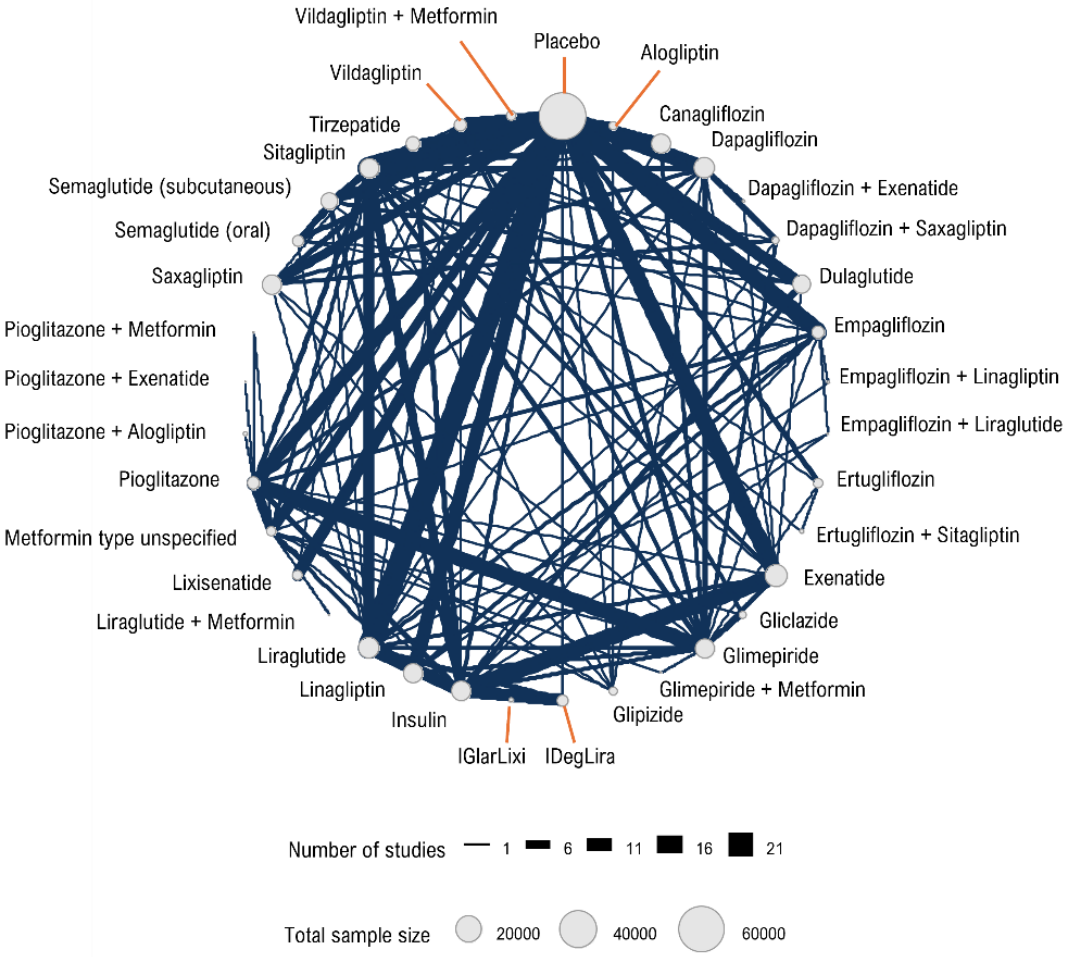

Figure 4. Network of evidence for change in HbA1c, in the population of people with type 2 diabetes at high risk of cardiovascular disease. Circular points show interventions, with the size proportional to the number of participants receiving the intervention. Blue edges show treatment comparisons with RCT evidence, with the thickness of the edge proportional to the number of studies making the treatment comparison.

Table 5. Model fit statistics for network meta-analysis (NMA) model of change in % HbA1c in the subpopulation of people with diabetes at high risk of CVD. This is given for the full dataset, and for the subset of studies reporting baseline HbA1c with and without regression on baseline HbA1c.
[1] DIC = posterior mean residual deviance + pD; Lower values are preferred for model fit.

Model effect structure	Meta-regression on baseline HbA1c (common across all active treatments) β posterior median (95% CrI)	Model fit Total residual deviance[1]	Model fit Posterior mean residual deviance[1]	Number of effective parameters (pD)	DIC (penalised deviance[1])	Between-study SD Posterior median (95% CrI)
Full dataset, *722 datapoints from 344 studies*						
Fixed, NMA	-	3921.0	1791.7	277.0	2068.7	-
Random, NMA	-	735.1	-1393.8	611.6	-782.1	0.25 (0.23, 0.27)
Random, UME	-	742.4	-1386.3	636.1	-750.2	0.25 (0.22, 0.27)
Only studies reporting baseline, *662 datapoints from 316 studies*						
Random, NMA	-	676.1	-1239.8	558.6	-681.2	0.25 (0.22, 0.27)
Random, NMA MR	-0.081 ($-0.169, -2.36\times10^{-4}$)	674.8	-1241.0	558.8	-682.2	0.25 (0.22, 0.27)
Random, UME MR	-0.072 (-0.159, 0.013)	681.7	-1233.8	581.0	-652.8	0.25 (0.22, 0.27)

Clinical effectiveness relative to placebo

Under both models, there was clear evidence that all treatments were more effective than placebo in reducing mean % HbA1c (Figure 5). Where treatments of two classes were given in combination, there was a trend that the estimated treatment effect was greater, though more uncertain, than the effect of either of the individual treatments trialled separately.

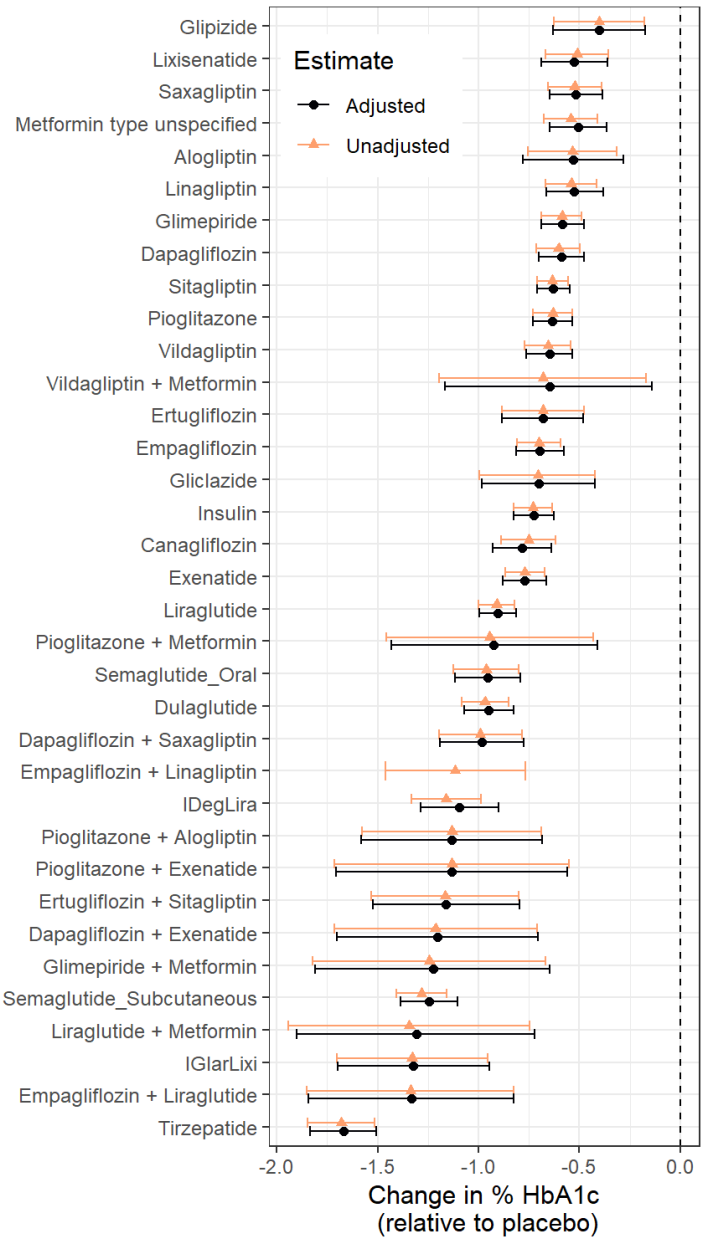

Figure 5. Change in % HbA1c in the population with diabetes and at high risk of CVD. Posterior median treatment effects (with 95% CrI) are given for unadjusted estimates (orange triangles) from the model without meta-regression and from the adjusted model (black circles) including meta-regression given baseline % HbA1c of 8.1.

Clinical effectiveness: active-active comparisons

Tirzepatide, subcutaneous semaglutide and the insulin combinations IDegLira and IGlarLixi were ranked highly (Table 6), with central estimates suggesting large reductions in % HbA1c estimated with relatively low uncertainty (Figure 5).

Tirzepatide showed greater reductions in % HbA1c than the represented sulfonylureas (gliclazide, glimepiride and glipizide), five DPP4-inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin, alone and in combination with metformin) and the SGLT2-inhibitors (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin as well as the combinations dapagliflozin + saxagliptin, ertugliflozin + sitagliptin and empagliflozin + linagliptin). It also showed greater reductions in % HbA1c than all GLP1 receptor agonists (dulaglutide, exenatide, liraglutide, lixisenatide and both oral and subcutaneous semaglutide) as well as insulin, IDegLira, metformin and pioglitazone alone.

Subcutaneous semaglutide showed greater reductions in % HbA1c than oral semaglutide, the represented sulfonylureas (gliclazide, glimepiride and glipizide), five DPP4-inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin, alone and in combination with metformin) and the SGLT2-inhibitors (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin). It also showed greater reductions in % HbA1c than other GLP1 receptor agonists (exenatide, liraglutide and lixisenatide) as well as insulin, metformin and pioglitazone.

The insulin combination treatment IDegLira showed greater reductions in % HbA1c than the represented sulfonylureas (gliclazide, glimepiride and glipizide), five DPP4-inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin) and four SGLT2-inhibitors (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin). It also showed greater reductions in % HbA1c than four GLP1 receptor agonists (dulaglutide, exenatide, liraglutide and lixisenatide), pioglitazone, metformin and insulin.

The insulin combination treatment IGlarLixi showed greater reductions in % HbA1c than the represented sulfonylureas (gliclazide, glimepiride and glipizide), five DPP4-inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin) and four SGLT2-inhibitors (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin). It also showed greater reductions in % HbA1c than three GLP1 receptor agonists (exenatide, liraglutide and lixisenatide), pioglitazone, metformin and insulin.

For a complete list of active-active comparisons, please see the 'Treatment Direct Effects' tabs in RQ1.2 results files: "Population 5 - HbA1c v10" and "Population 5 - HbA1c with meta-regression v10".

Table 6. Change in HbA1c relative to placebo for all 35 active treatments in the network, full dataset, random-effects structure on treatment effects. Where effect estimates are uncertain or many treatments have a similar effect, ranks will overlap and be less easy to interpret.

Class	Treatment	Mean change, % HbA1c Posterior median (95% CrI)	Rank Posterior median (95% CrI)
Placebo	Placebo	*Reference*	36 (36, 36)
DPP4i	Alogliptin	-0.53 (-0.76, -0.32)	31 (20, 35)
	Linagliptin	-0.54 (-0.67, -0.42)	31 (24, 35)
	Saxagliptin	-0.52 (-0.66, -0.39)	32 (24, 35)
	Sitagliptin	-0.63 (-0.71, -0.56)	26 (21, 30)
	Vildagliptin	-0.66 (-0.77, -0.54)	24 (19, 31)
DPP4i with metformin	Vildagliptin with Metformin	-0.68 (-1.20, -0.17)	23 (8, 35)
GIPGLP	Tirzepatide	-1.68 (-1.85, -1.51)	1 (1, 3)
GLP with metformin	Liraglutide with Metformin	-1.34 (-1.94, -0.75)	5 (1, 20)
GLP-1RA	Dulaglutide	-0.97 (-1.08, -0.85)	13 (9, 17)
	Exenatide	-0.77 (-0.87, -0.67)	19 (16, 23)
	Liraglutide	-0.91 (-1.00, -0.82)	15 (12, 18)
	Lixisenatide	-0.51 (-0.67, -0.36)	32 (23, 35)
	Semaglutide (oral)	-0.96 (-1.12, -0.80)	14 (9, 18)
	Semaglutide (subcutaneous)	-1.28 (-1.41, -1.16)	6 (3, 10)
Insulin mix	IDegLira	-1.16 (-1.33, -0.99)	9 (4, 13)
	IGlarLixi	-1.33 (-1.70, -0.96)	5 (1, 14)
Insulin	Insulin	-0.73 (-0.83, -0.63)	21 (17, 26)
Metformin	Metformin	-0.54 (-0.68, -0.41)	31 (24, 35)
SGLT2i with DPP4	Dapagliflozin with Saxagliptin	-0.99 (-1.20, -0.78)	13 (7, 18)
	Empagliflozin with Linagliptin	-1.11 (-1.46, -0.77)	10 (3, 19)
	Ertugliflozin with Sitagliptin	-1.16 (-1.53, -0.80)	9 (2, 18)
SGLT2i	Canagliflozin	-0.75 (-0.89, -0.62)	20 (16, 27)
	Dapagliflozin	-0.60 (-0.71, -0.50)	28 (21, 33)
	Empagliflozin	-0.70 (-0.81, -0.59)	22 (18, 28)
	Ertugliflozin	-0.68 (-0.88, -0.48)	23 (16, 33)
SGLT2i with GLP-1RA	Dapagliflozin with Exenatide	-1.21 (-1.71, -0.71)	7 (1, 21)
	Empagliflozin with Liraglutide	-1.34 (-1.85, -0.83)	5 (1, 17)
SU	Gliclazide	-0.71 (-0.99, -0.42)	22 (13, 34)
	Glimepiride	-0.59 (-0.69, -0.49)	29 (23, 33)
	Glipizide	-0.40 (-0.63, -0.18)	35 (26, 35)
SU with metformin	Glimepiride with Metformin	-1.24 (-1.82, -0.67)	7 (1, 23)

TZD	Pioglitazone	-0.63 (-0.73, -0.54)	26 (21, 31)
TZD with DPP4i	Pioglitazone with Alogliptin	-1.13 (-1.58, -0.69)	9 (2, 22)
TZD with GLP-1RA	Pioglitazone with Exenatide	-1.13 (-1.71, -0.55)	9 (1, 30)
TZD with metformin	Pioglitazone with Metformin	-0.94 (-1.46, -0.43)	14 (3, 34)

Global inconsistency in NMA of change in % HbA1c

Three study arms were flagged as having relatively high deviance in the NMA model, which enforces consistency in relative effects (Figure 6). The same study arms – the oral semaglutide arm of Yabe 2020 and two tirzepatide arms of Frias 2018 - were identified by the main (Figure 6, panel a) and meta-regression (Figure 6, panel b) models. Frias 2018 trialled four doses of tirzepatide against dulaglutide and placebo, whilst Yabe 2020 trialled three doses of oral semaglutide against dulaglutide. Since dose was not modelled in these NMAs, studies that explored different doses of the same treatment would be constrained to estimate a single relative effect, leading to poor fit for some study arms.

A sensitivity analysis was conducted within which only the treatment arm best reflecting clinical practice was modelled and other arms trialling the same treatment were excluded. Treatment effects for tirzepatide and oral semaglutide were very similar (Table 7) but model fit improved, indicating that the potential inconsistency associated with these arms could be ascribed to dose, rather than unexplained conflict between direct and indirect evidence in the network.

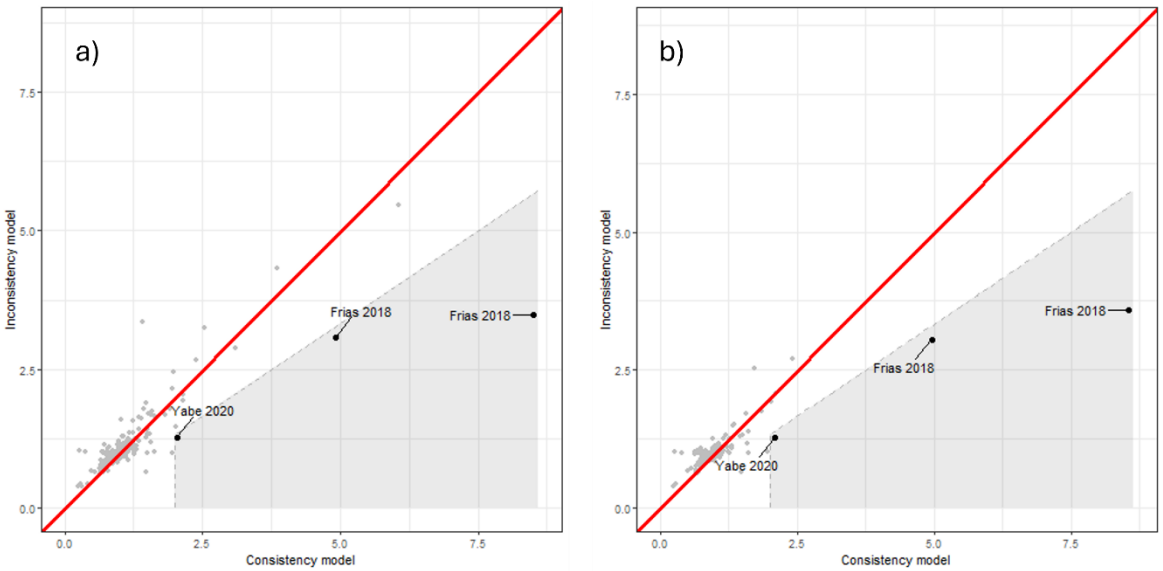

Figure 6. Plots showing model fit of individual study arms under the consistency (NMA) and inconsistency (UME) models for a) the main analysis of change in % HbA1c and b) the analysis of change in % HbA1c with meta-regression on baseline HbA1c. Study arms where fit was poor in the NMA and improved under UME (points in the grey shaded area) are labelled.

Both Frias 2018 and Yabe 2020 were dose-finding studies within which multiple arms trialled the same treatment at different doses, and report a dose-response relationship in % HbA1c change. In type 2 diabetes, starting dose may not be meaningful because treatments are titrated until the desired outcome is reached, therefore it was felt that modelling dose would not reflect clinical practice. For this reason, the protocol for base-case models in this guideline specified that dose should not be modelled explicitly. However, where there was a dose-response, study arms that trialled very high or low doses and report more extreme treatment effects will fit poorly in models that ignore dose.

A sensitivity analysis was conducted within which the committee recommended the dose most representative of clinical practice, and arms trialling other doses of the treatment were dropped. For

Frias 2018, which trialled tirzepatide, the 10mg dose weekly was retained and arms trialling doses of 1mg, 5mg and 15mg were dropped. For Yabe 2020, which trialled oral semaglutide, the 7mg dose weekly was retained and arms trialling doses of 3mg and 14mg were dropped.

With this done, treatment effects for tirzepatide and oral semaglutide are within the same range as previously estimated (Table 7) and the high residual deviance noted for these studies disappeared.

Table 7. Impact of dropping arms with high/low doses from two dose-finding studies, Frias 2018 and Yabe 2020.

Model	Treatment effect, mean difference in % HbA1c *Posterior median (95% CrI)*		Posterior mean residual deviance for study		Between-study SD *Posterior median (95% CrI)*
	Tirzepatide	Semaglutide (oral)	Frias 2018	Yabe 2020	
Base-case	-1.68 (-1.85, -1.52)	-0.96 (-1.12, -0.80)	17.2 (6 arms)	5.3 (4 arms)	0.25 (0.23, 0.27)
Sensitivity analysis	-1.74 (-1.91, -1.58)	-0.97 (-1.13, -0.81)	4.7 (3 arms)	1.8 (2 arms)	0.24 (0.22, 0.26)

Population at risk of CVD: Change in weight

The main analysis included 174 studies of 31 treatments (Figure 7).

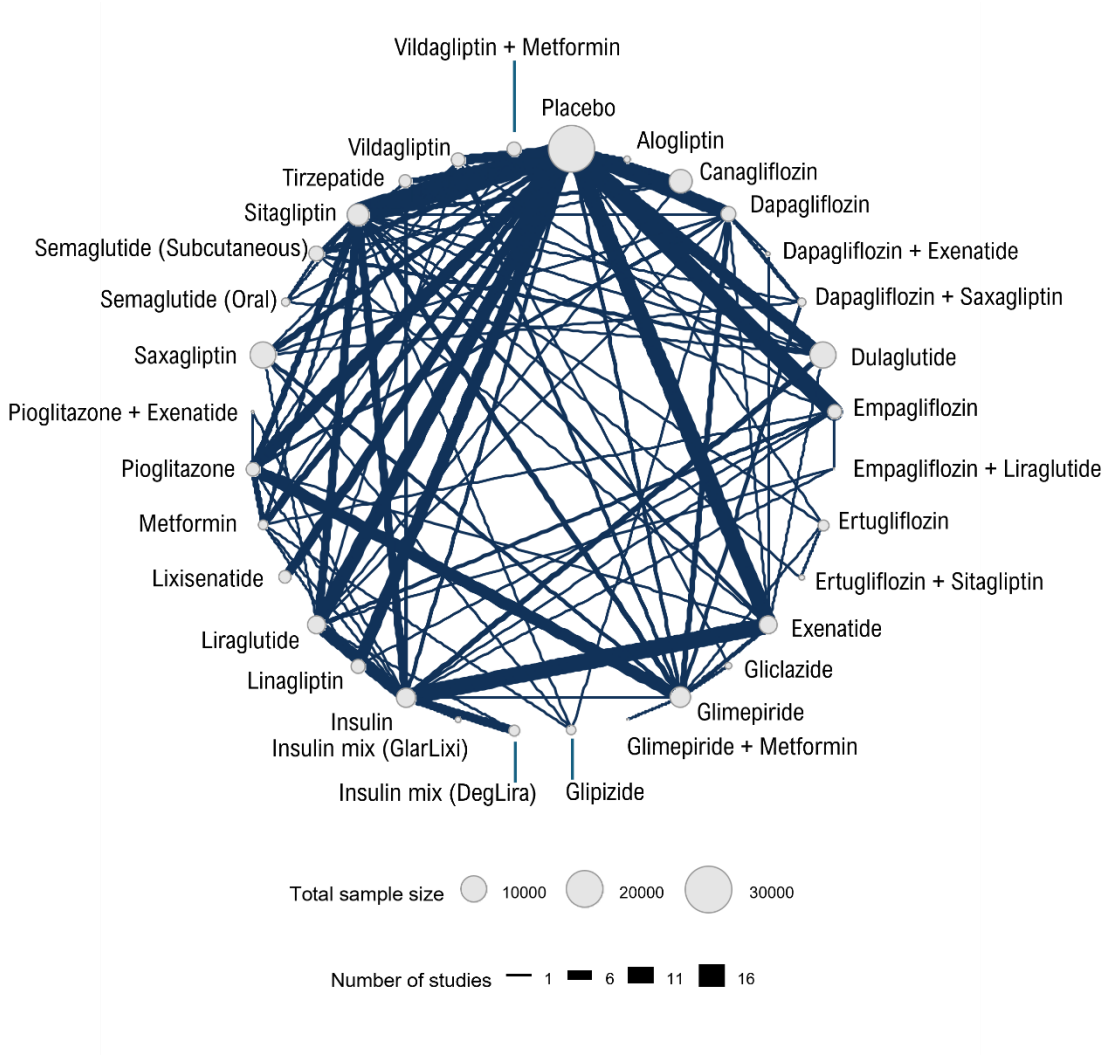

Figure 7. Network of evidence for change in weight in the population with type-2 diabetes at risk of CVD.

Model fit

There was high variability between studies making the same treatment comparisons in this dataset, with the between-study standard deviation (Table 8) being larger than some of the estimated treatment effects on the log-ratio scale. The fixed-effect model fitted extremely poorly, reflecting the high heterogeneity in this outcome. The random-effect model fitted well, as expected given that the between-study standard deviation (SD) was relatively large on the modelling scale: treatment differences were modelled as the log ratio of means.

Table 8. Model fit statistics for network meta-analysis model of proportional change in weight (kg). [1]Lower values for model fit and DIC preferred.

Model effect structure	Model fit Total residual deviance[1]	Model fit Posterior mean residual deviance[1]	Number of effective parameters (pD)	DIC (penalised deviance[1])	Between-study SD median, (95% CrI)
Weight as proportional change in kg *Included only studies reporting baseline weight, 494 datapoints from 174 studies*					
Fixed, NMA	2005.0	2247.7	275.0	2522.6	-
Random, NMA	489.4	732.2	438.1	1170.3	0.015 (0.014, 0.018)
Random, UME	500.0	742.8	442.8	1185.6	0.013 (0.011, 0.015)

Clinical effectiveness relative to placebo

Four single treatments – glipizide, insulin, glimepiride and pioglitazone – were found to be associated with a smaller weight loss than for participants on placebo arms (Table 9).

Ten single treatments and three combination treatments were associated with reduction in weight, relative to placebo. These were dulaglutide, exenatide, liraglutide, semaglutide (both oral and subcutaneous), tirzepatide, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, dapagliflozin with saxagliptin, ertugliflozin with sitagliptin and dapagliflozin with exenatide (Figure 8). There was clear evidence that the DPP4 inhibitors alogliptin, linagliptin, sitagliptin, saxagliptin and vildagliptin had weight-neutral effects, relative to placebo. There was weaker, more uncertain evidence for a reduction in weight, relative to the weight change seen on placebo, for lixisenatide and the treatment combinations pioglitazone with exenatide, empagliflozin with liraglutide and vildagliptin with metformin.

Clinical effectiveness: active-active comparisons

Tirzepatide and semaglutide by both oral and subcutaneous routes all showed effectiveness (reduction in body weight) relative to all five DPP4-inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin), the three sulfonylureas represented in the network (gliclazide, glimepiride and glipizide), insulin alone and in combination as IDegLira and IGlarLixi, metformin and pioglitazone alone. Tirzepatide also showed greater reductions in body weight when compared to all GLP1 receptor agonists (dulaglutide, exenatide, liraglutide, lixisenatide and both oral and subcutaneous semaglutide), whilst subcutaneous semaglutide showed greater reductions than four GLP1 receptor agonists (dulaglutide, exenatide, liraglutide and lixisenatide), and oral semaglutide to three GLP1 receptor agonists (dulaglutide, exenatide and lixisenatide).

For a complete list of active-active comparisons, please see the 'Treatment Direct Effects' tabs in RQ1.2 results files pop 5 weight.

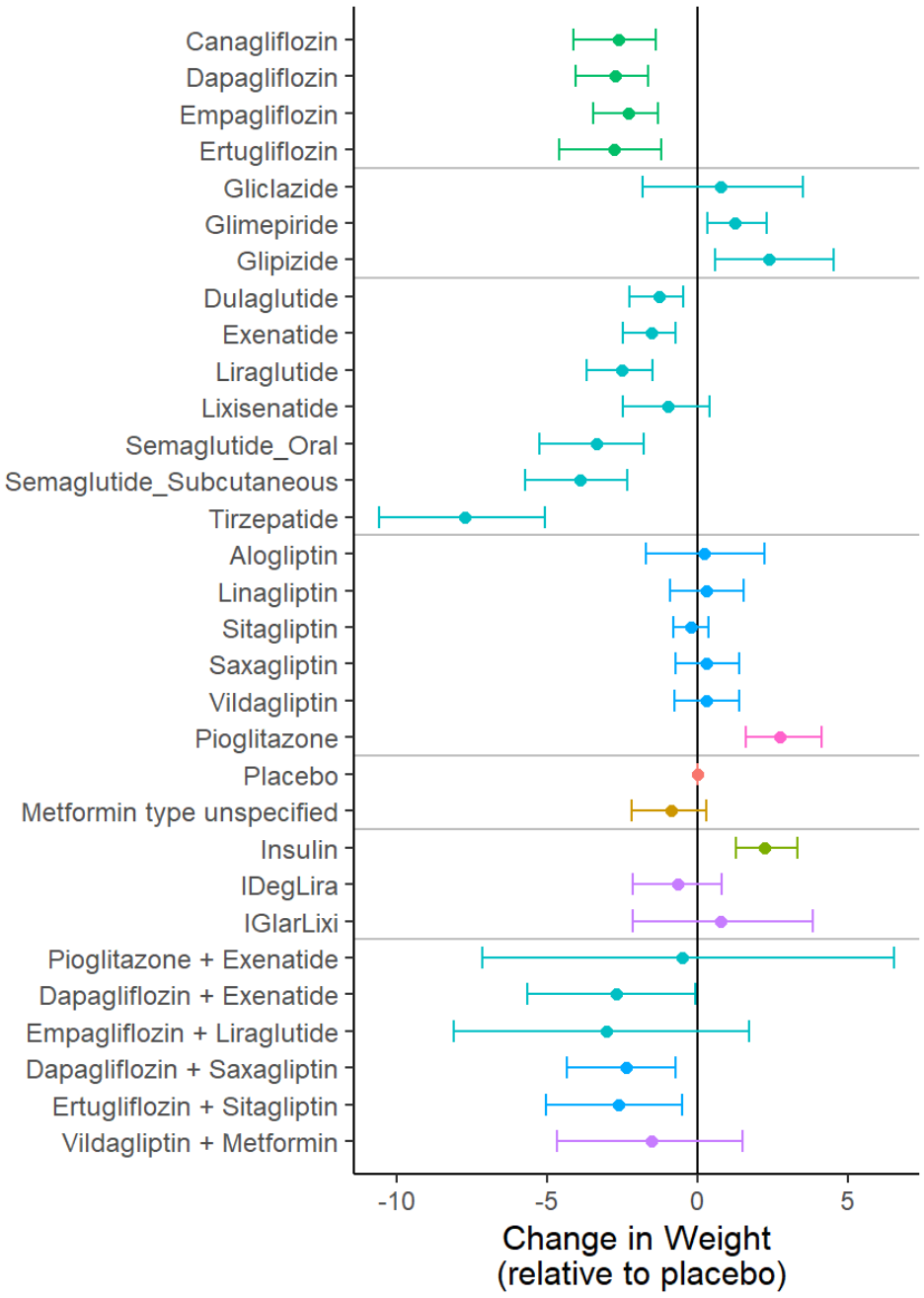

Figure 8. Change in body weight in kg, relative to placebo, for the subpopulation of people with diabetes at high risk of CVD. Colour and horizontal grey lines have been added to assist in discriminating between different treatments.

Table 9. Predicted weights at follow-up for all 30 active treatments in the network. This was a proportional model, therefore treatment-specific final weights are given at two representative weights (60kg and 90kg) as well as the treatment effect as a ratio relative to placebo.

Class	Treatment	Final weight on Placebo arm=60kg Median (95% CrI)	Final weight on Placebo arm=90kg Median (95% CrI)	Ratio Median (95% CrI)
DPP4i	Alogliptin	60.14 (58.87, 61.43)	90.21 (88.31, 92.14)	1.002 (0.981, 1.024)
	Linagliptin	60.18 (59.39, 60.98)	90.27 (89.09, 91.48)	1.003 (0.99, 1.016)
	Saxagliptin	60.19 (59.52, 60.87)	90.29 (89.28, 91.31)	1.003 (0.992, 1.015)
	Sitagliptin	59.86 (59.48, 60.23)	89.78 (89.22, 90.35)	0.998 (0.991, 1.004)
	Vildagliptin	60.19 (59.49, 60.89)	90.28 (89.24, 91.33)	1.003 (0.992, 1.015)
DPP4i with metformin	Vildagliptin with Metformin	58.98 (57.04, 60.99)	88.47 (85.56, 91.48)	0.983 (0.951, 1.016)
GIPGLP	Tirzepatide	54.85 (54.14, 55.58)	82.28 (81.21, 83.37)	0.914 (0.902, 0.926)
GLP-1RA	Dulaglutide	59.14 (58.62, 59.66)	88.70 (87.92, 89.48)	0.986 (0.977, 0.994)
	Exenatide	58.98 (58.50, 59.46)	88.47 (87.74, 89.20)	0.983 (0.975, 0.991)
	Liraglutide	58.33 (57.86, 58.80)	87.50 (86.79, 88.20)	0.972 (0.964, 0.980)
	Lixisenatide	59.34 (58.44, 60.26)	89.01 (87.66, 90.40)	0.989 (0.974, 1.004)
	Semaglutide (Oral)	57.75 (56.87, 58.64)	86.63 (85.31, 87.96)	0.963 (0.948, 0.977)
	Semaglutide (Subcutaneous)	57.40 (56.67, 58.14)	86.10 (85.01, 87.21)	0.957 (0.945, 0.969)
Insulin	Insulin	61.47 (60.99, 61.96)	92.21 (91.48, 92.94)	1.025 (1.016, 1.033)
Insulin mix	IDegLira	59.57 (58.62, 60.51)	89.35 (87.93, 90.77)	0.993 (0.977, 1.009)
	IGlarLixi	60.50 (58.58, 62.46)	90.75 (87.86, 93.70)	1.008 (0.976, 1.041)
Metformin	Metformin	59.41 (58.62, 60.20)	89.11 (87.93, 90.31)	0.990 (0.977, 1.003)
SGLT-2i with DPP4	Dapagliflozin with Saxagliptin	58.41 (57.35, 59.48)	87.62 (86.02, 89.22)	0.974 (0.956, 0.991)
	Ertugliflozin with Sitagliptin	58.26 (56.89, 59.64)	87.38 (85.34, 89.46)	0.971 (0.948, 0.994)
SGLT-2i	Canagliflozin	58.24 (57.54, 58.95)	87.36 (86.31, 88.43)	0.971 (0.959, 0.983)
	Dapagliflozin	58.17 (57.64, 58.71)	87.26 (86.46, 88.07)	0.970 (0.961, 0.979)

	Empagliflozin	58.47 (57.96, 58.99)	87.71 (86.94, 88.48)	0.975 (0.966, 0.983)
	Ertugliflozin	58.16 (57.22, 59.12)	87.24 (85.83, 88.69)	0.969 (0.954, 0.985)
SGLT-2i with GLP-1RA	Dapagliflozin with Exenatide	58.19 (56.49, 59.95)	87.29 (84.73, 89.92)	0.970 (0.942, 0.999)
	Empagliflozin with Liraglutide	57.96 (54.91, 61.16)	86.94 (82.36, 91.74)	0.966 (0.915, 1.019)
SU	Gliclazide	60.49 (58.80, 62.24)	90.74 (88.20, 93.36)	1.008 (0.980, 1.037)
	Glimepiride	60.81 (60.23, 61.41)	91.22 (90.34, 92.11)	1.014 (1.004, 1.023)
	Glipizide	61.59 (60.40, 62.78)	92.38 (90.60, 94.18)	1.026 (1.007, 1.046)
TZD	Pioglitazone	61.82 (61.23, 62.42)	92.74 (91.85, 93.63)	1.030 (1.021, 1.040)
TZD with GLP-1RA	Pioglitazone with Exenatide	59.59 (55.38, 64.23)	89.39 (83.07, 96.34)	0.993 (0.923, 1.070)

Global inconsistency in NMA of proportional change in weight

No study arms were noted to show relatively improved fit in the model where the consistency assumption was relaxed. Several study arms fitted poorly under both the NMA (consistency) and unrelated-mean effects models (Figure 9), with deviances as high as 11. Some study arms fitted more poorly in the UME model, which may be related to the smaller between-study SD restricting heterogeneity in this model. In particular, arms three and five of Frias 2018 (both tirzepatide, in this multi-arm dose-finding study) fitted extremely poorly under both NMA and UME models. This is likely to be due to a similar impact of lumping together different doses that was observed in the NMA for change in HbA1c (Global inconsistency in NMA of change in % HbA1c).

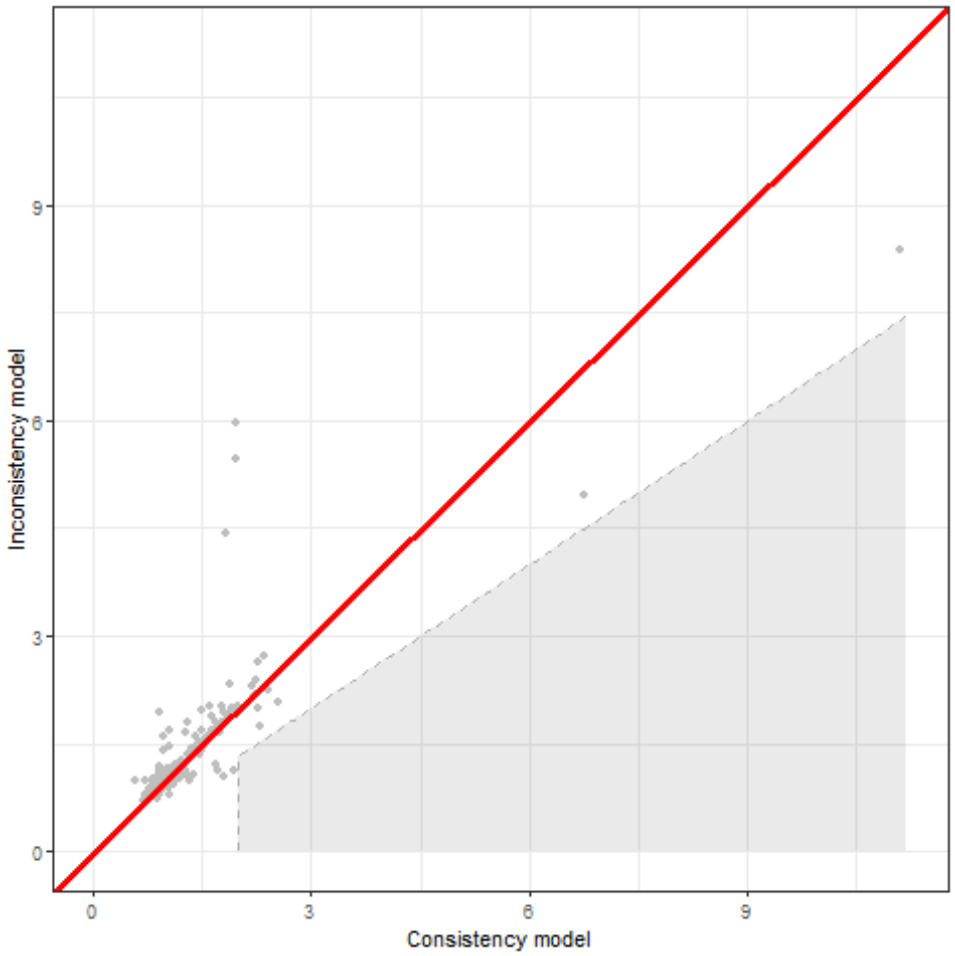

Figure 9. Model fit of individual study arms under different modelling assumptions: the consistency (NMA) and inconsistency (UME) models for proportional weight change in the subpopulation of people with diabetes at high risk of CVD. There were no points in the grey area; no evidence that study arms were inconsistent with evidence from the rest of the network.

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- Daly C, Welton, S.J., Dias, S., Anwer,S., Ades, A.E. Meta-Analysis of Continuous Outcomes. Guideline Methodology Document 2: NICE Guidelines Technical Support Unit 2021.
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WinBUGS code

Based on TSD2: Normal likelihood, identity link, additive FE treatment effects

```
#This code is part of
#Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
#NICE DSU Technical Support Document 2: A Generalised Linear Modelling
#Framework for Pairwise and Network Meta-Analysis of Randomised Controlled
Trials. 2011;
http://www.nicedsu.org.uk).
is used whether in its standard form or adapted.

## This is adapted for the T2D medicines update

# Normal likelihood, identity link
# Arm and Trial-level data (treatment differences)
# FIXED effects model for multi-arm trials
# Added code to accept CFB, baseline-final and final values

model{                                  # *** PROGRAM STARTS
for(i in 1:ns.a){                       # LOOP THROUGH STUDIES WITH ARM DATA
    mu[i] ~ dnorm(0,.0001)              # vague priors for all trial
baselines
    for (k in 1:na[i]) {                #  LOOP THROUGH ARMS
        delta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]  # FE
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
  }

### SECTION A - estimation specific to studies reporting CFB
for(i in cb[1]:cb[2]){                 #   LOOP THROUGH STUDIES (CFB)
      for (k in 1:na[i]) {                #  LOOP THROUGH ARMS

# SE and precision for CFB
            CFB_se[i,k] <- se[i,k]
            prec[i,k] <- pow(CFB_se[i,k],-2)      ## precision

# Outcome measure: change from baseline (requires baseline)
            yc[i,k] <- y[i,k]
            phi[i,k] <- delta[i,k]

# Likelihood: univariate Normal
            yc[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for CFB means
       dev[i,k] <- (yc[i,k]-phi[i, k])*(yc[i,k]-phi[i, k])*prec[i,k]
      }           # END ARM LOOP
}   # END STUDY LOOP FOR CFB DATA


### SECTION C - estimation specific to studies reporting follow-up values
for(i in pt[1]:pt[2]){  ##   LOOP THROUGH STUDIES (follow-up data)
      for (k in 1:na[i]) {              ##  LOOP THROUGH ARMS
```

```
RR423212
# SE
            f_se[i,k] <- se[i,k]
            prec[i,k] <- pow(f_se[i,k],-2)   ## precision

# Outcome measure: post-treatment mean
            ypt[i,k] <- y[i,k]
            phi[i,k] <- delta[i,k]

# Likelihood: univariate Normal
            ypt[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for post-treatment mean
        dev[i,k] <- (ypt[i,k]-phi[i, k])*(ypt[i,k]-phi[i, k])*prec[i,k]
      }           # END ARM LOOP

}     ## END STUDY LOOP (follow-up data)


for(i in 1:ns2) {                    # LOOP THROUGH 2-ARM CONTRAST STUDIES
    md[i,2] ~ dnorm(delta[(i+ns.a),2],prec.c[i,2]) # normal likel. 2-arm
trials
    resdev[(i+ns.a)] <- (md[i,2]-delta[(i+ns.a),2])*(md[i,2]-
delta[(i+ns.a),2])*prec.c[i,2]
  }
for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM CONTRAST
STUDIES
        for (j in 1:2) {
            Sigma[i,j,k] <- V[i]*(1-equals(j,k)) +
prec.c[i,k+1]*equals(j,k)
      }
    Omega[i,1:2,1:2] <- inverse(Sigma[i,,])  #Precision matrix
# normal likelihood for 3-arm trials
    md[i,2:3] ~ dmnorm(delta[(i+ns.a),2:3],Omega[i,1:2,1:2] )

#Deviance contribution for trial i
    for(k in 1:2) {  # multiply vector & matrix
        ydiff[i,k]<- md[i,(k+1)] - delta[(i+ns.a),(k+1)]
        z[i,k]<- inprod2(Omega[i,k,1:2], ydiff[i,1:2])
              }
    resdev[(i+ns.a)]<- inprod2(ydiff[i,1:2], z[i,1:2])
  }

for(i in (ns2+ns3+1):ns.t) {        # LOOP THROUGH FOUR-ARM CONTRAST
STUDIES
        for (j in 1:3) {
            Sigma2[i,j,k] <- V[i]*(1-equals(j,k)) +
prec.c[i,k+1]*equals(j,k)
      }
    Omega2[i,1:3,1:3] <- inverse(Sigma2[i,,])  #Precision matrix
# normal likelihood for 4-arm trials
    md[i,2:na.c[i]] ~ dmnorm(delta[(i+ns.a),2:4],Omega2[i,1:3,1:3] )

#Deviance contribution for trial i
    for(k in 1:3) {  # multiply vector & matrix
```

```
        ydiff[i,k]<- md[i,(k+1)] - delta[(i+ns.a),(k+1)]
        z[i,k]<- inprod2(Omega2[i,k,1:3], ydiff[i,1:3])
              }
    resdev[(i+ns.a)]<- inprod2(ydiff[i,1:3], z[i,1:3])
  }
for(i in 1:ns.t){                  #   LOOP THROUGH ALL CONTRAST STUDIES
    delta[(i+ns.a),1] <- 0   # treatment effect is zero for control arm
    for (k in 2:na.c[i]) {             #  LOOP THROUGH ARMS
        var.c[i,k] <- pow(se.c[i,k],2)   # calculate variances
        prec.c[i,k] <- 1/var.c[i,k]      # set precisions
        delta[(i+ns.a),k] <-  d[t.c[i,k]] - d[t.c[i,1]]
      }
#bse[i,1] <- base_sd[i,1] / sqrt(n.c[i,1])
V[i] <- pow(base_sd[i,1],2)
  }

# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA, precA)
seA <- sdA/sqrt(n_A)    ## SE
precA <- pow(seA,-2)   ## precision

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

## NO class effect
d[1]<-0       # treatment effect is zero for reference treatment / class

# vague priors for treatment effects within class
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
sd ~ dunif(0,sdUpper)     # vague prior for between-trial SD
totresdev <- sum(resdev[])            #Total Residual Deviance

# rank interventions
for (k in 1:nt) {
   # rk[k] <- nt+1-rank(d[],k)             # assumes positive diffs
are  good
are  good
that treat k is best
            prob[h,k] <- equals(rk[k],h)              # prob k is h-th
best
}

# MDs for all possible pair-wise comparisons - trts
for (c in 1:(nt-1)) {
      for (k in (c+1):nt) {
       diff[c,k] <- d[k] - d[c]
  }
}

#Stop unused variables causing error message
```

```
RR423212
dv[1] <- n[1,1]
dv[2] <- base_m[1,1] + base_sd[51,1] + base_n[1,1]
dv[3] <- n.c[1,1]
dv[4] <- base_m.c[1,1] + base_sd.c[1,2] + base_n.c[1,2]

}                                       # *** PROGRAM ENDS
```

Based on TSD2: Normal likelihood, identity link, additive RE treatment effects

```
#This code is part of
#Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
#NICE DSU Technical Support Document 2: A Generalised Linear Modelling
#Framework for Pairwise and Network Meta-Analysis of Randomised Controlled
Trials. 2011;
http://www.nicedsu.org.uk).
is used whether in its standard form or adapted.

## This is adapted for the T2D medicines update

# Normal likelihood, identity link
# Arm and Trial-level data (treatment differences)
# RANDOM effects model for multi-arm trials
# Added code to accept CFB, baseline-final and final values (DONE)
# Altered the Norm_diff section to explicitly model 4-armed trials

model{                                  # *** PROGRAM STARTS
for(i in 1:ns.a){                       # LOOP THROUGH STUDIES WITH ARM DATA
    w.a[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
arm
    mu[i] ~ dnorm(0,.0001)              # vague priors for all trial
baselines
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {                # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(MD[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
        MD[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw.a[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w.a[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw.a[i,k] <- sum(w.a[i,1:k-1])/(k-1)
      }
  }
### SECTION A - estimation specific to studies reporting CFB
for(i in cb[1]:cb[2]){                #   LOOP THROUGH STUDIES (CFB)
      for (k in 1:na[i]) {              #  LOOP THROUGH ARMS
```

RR423212

```
# SE and precision for CFB
            CFB_se[i,k] <- se[i,k]
            prec[i,k] <- pow(CFB_se[i,k],-2)      ## precision

# Outcome measure: change from baseline (requires baseline)
            yc[i,k] <- y[i,k]
            phi[i,k] <- theta[i,k]

# Likelihood: univariate Normal
            yc[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for CFB means
       dev[i,k] <- (yc[i,k]-phi[i, k])*(yc[i,k]-phi[i, k])*prec[i,k]
      }           # END ARM LOOP
}   # END STUDY LOOP FOR CFB DATA


### SECTION C - estimation specific to studies reporting follow-up values
for(i in pt[1]:pt[2]){  ##   LOOP THROUGH STUDIES (follow-up data)
      for (k in 1:na[i]) {             ##  LOOP THROUGH ARMS
# SE
            f_se[i,k] <- se[i,k]
            prec[i,k] <- pow(f_se[i,k],-2)   ## precision

# Outcome measure: post-treatment mean
            ypt[i,k] <- y[i,k]
            phi[i,k] <- theta[i,k]

# Likelihood: univariate Normal
            ypt[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for post-treatment mean
        dev[i,k] <- (ypt[i,k]-phi[i, k])*(ypt[i,k]-phi[i, k])*prec[i,k]
      }           # END ARM LOOP

}     ## END STUDY LOOP (follow-up data)


for(i in 1:ns2) {                    # LOOP THROUGH 2-ARM CONTRAST STUDIES
    md[i,2] ~ dnorm(delta[(i+ns.a),2],prec.c[i,2]) # normal likel. 2-arm
trials
    resdev[(i+ns.a)] <- (md[i,2]-delta[(i+ns.a),2])*(md[i,2]-
delta[(i+ns.a),2])*prec.c[i,2]
  }
for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM CONTRAST
STUDIES
        for (j in 1:2) {
            Sigma[i,j,k] <- V[i]*(1-equals(j,k)) +
prec.c[i,k+1]*equals(j,k)
      }
    Omega[i,1:2,1:2] <- inverse(Sigma[i,,])  #Precision matrix
# normal likelihood for 3-arm trials
    md[i,2:3] ~ dmnorm(delta[(i+ns.a),2:3],Omega[i,1:2,1:2] )
```

RR423212

```
#Deviance contribution for trial i
    for(k in 1:2) {  # multiply vector & matrix
        ydiff[i,k]<- md[i,(k+1)] - delta[(i+ns.a),(k+1)]
        z[i,k]<- inprod2(Omega[i,k,1:2], ydiff[i,1:2])
              }
    resdev[(i+ns.a)]<- inprod2(ydiff[i,1:2], z[i,1:2])
  }

for(i in (ns2+ns3+1):ns.t) {        # LOOP THROUGH FOUR-ARM CONTRAST
STUDIES
        for (j in 1:3) {
            Sigma2[i,j,k] <- V[i]*(1-equals(j,k)) +
prec.c[i,k+1]*equals(j,k)
      }
    Omega2[i,1:3,1:3] <- inverse(Sigma2[i,,])  #Precision matrix
# normal likelihood for 4-arm trials
    md[i,2:na.c[i]] ~ dmnorm(delta[(i+ns.a),2:4],Omega2[i,1:3,1:3] )

#Deviance contribution for trial i
    for(k in 1:3) {  # multiply vector & matrix
        ydiff[i,k]<- md[i,(k+1)] - delta[(i+ns.a),(k+1)]
        z[i,k]<- inprod2(Omega2[i,k,1:3], ydiff[i,1:3])
              }
    resdev[(i+ns.a)]<- inprod2(ydiff[i,1:3], z[i,1:3])
  }
for(i in 1:ns.t){                   #   LOOP THROUGH ALL CONTRAST STUDIES
    w.c[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
arm
        var.c[i,k] <- pow(se.c[i,k],2)   # calculate variances
        prec.c[i,k] <- 1/var.c[i,k]      # set precisions
# trial-specific LOR distributions
        delta[i+ns.a,k] ~ dnorm(MD[i+ns.a,k],taud.c[i,k])
# mean of LOR distributions, with multi-arm trial correction
        MD[i+ns.a,k] <-  d[t.c[i,k]] - d[t.c[i,1]] + sw.c[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud.c[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w.c[i,k] <- (delta[i+ns.a,k] - d[t.c[i,k]] + d[t.c[i,1]])
# cumulative adjustment for multi-arm trials
        sw.c[i,k] <- sum(w.c[i,1:k-1])/(k-1)


      }
#bse[i,1] <- base_sd[i,1] / sqrt(n.c[i,1])
V[i] <- pow(base_sd.c[i,1],2)
  }

# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA, precA)
seA <- sdA/sqrt(n_A)    ## SE
precA <- pow(seA,-2)   ## precision
```

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

## NO class effect
d[1]<-0       # treatment effect is zero for reference treatment / class

# vague priors for treatment effects within class
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
sd ~ dunif(0,sdUpper)     # vague prior for between-trial SD
totresdev <- sum(resdev[])            #Total Residual Deviance

# rank interventions
for (k in 1:nt) {
   # rk[k] <- nt+1-rank(d[],k)             # assumes positive diffs
are  good
are  good
that treat k is best
            prob[h,k] <- equals(rk[k],h)              # prob k is h-th
best
}

# MDs for all possible pair-wise comparisons - trts
for (c in 1:(nt-1)) {
      for (k in (c+1):nt) {
       diff[c,k] <- d[k] - d[c]
  }
}

#Stop unused variables causing error message

dv[1] <- n[1,1] + baseA[1]  ## baseA appears in mr coding
dv[2] <- base_m[1,1] + base_sd[51,1] + base_n[1,1]
dv[3] <- n.c[1,1]
dv[4] <- base_m.c[1,1] + base_sd.c[1,2] + base_n.c[1,2]

}                                     # *** PROGRAM ENDS
```

Based on TSD2: Normal likelihood, additive RE treatment effects with meta-regression on baseline severity (baseline % HbA1c)

```
#This code is part of
#Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling
#Framework for Pairwise and Network Meta-Analysis of Randomised Controlled
Trials. 2011;
http://www.nicedsu.org.uk).
is used whether in its standard form or adapted.

## This is adapted for the T2D medicines update
## This version has a single beta
```

```
RR423212
# Normal likelihood, identity link
# Arm and Trial-level data (treatment differences)
# RANDOM effects model for multi-arm trials
# Added code to accept CFB and final values (DONE)
# Altered the Norm_diff section to explicitly model 4-armed trials (DONE)
# Added MR term for baseline HbA1c
# this uses the centred pooled mean at baseline

model{                                  # *** PROGRAM STARTS
for(i in 1:ns.a){                       # LOOP THROUGH STUDIES WITH ARM DATA
    w.a[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
arm
    mu[i] ~ dnorm(0,.0001)              # vague priors for all trial
baselines
# model for linear predictor
            #  theta[i,k] <- mu[i] + delta[i,k]
            theta[i,k] <- mu[i] + delta[i,k] + (beta[t[i,k]]-beta[t[i,1]])
* base_c[i]
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {                # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(MD[i,k],taud[i,k])
# mean of distributions, with multi-arm trial correction
        MD[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw.a[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w.a[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw.a[i,k] <- sum(w.a[i,1:k-1])/(k-1)
      }
  }
### SECTION A - estimation specific to studies reporting CFB
for(i in cb[1]:cb[2]){              #   LOOP THROUGH STUDIES (CFB)
      for (k in 1:na[i]) {             #  LOOP THROUGH ARMS

# SE and precision for CFB
            CFB_se[i,k] <- se[i,k]
            prec[i,k] <- pow(CFB_se[i,k],-2)      ## precision

# Outcome measure: change from baseline (requires baseline)
            yc[i,k] <- y[i,k]
            phi[i,k] <- theta[i,k]

# Likelihood: univariate Normal
            yc[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for CFB means
       dev[i,k] <- (yc[i,k]-phi[i, k])*(yc[i,k]-phi[i, k])*prec[i,k]
      }           # END ARM LOOP
}   # END STUDY LOOP FOR CFB DATA
```

```
### SECTION C - estimation specific to studies reporting follow-up values
for(i in pt[1]:pt[2]){  ##   LOOP THROUGH STUDIES (follow-up data)
      for (k in 1:na[i]) {             ##  LOOP THROUGH ARMS
# SE
            f_se[i,k] <- se[i,k]
            prec[i,k] <- pow(f_se[i,k],-2)   ## precision

# Outcome measure: post-treatment mean
            ypt[i,k] <- y[i,k]
            phi[i,k] <- theta[i,k]

# Likelihood: univariate Normal
            ypt[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for post-treatment mean
        dev[i,k] <- (ypt[i,k]-phi[i, k])*(ypt[i,k]-phi[i, k])*prec[i,k]
      }           # END ARM LOOP

}     ## END STUDY LOOP (follow-up data)


for(i in 1:ns2) {                    # LOOP THROUGH 2-ARM CONTRAST STUDIES
    md[i,2] ~ dnorm(theta[(i+ns.a),2],prec.c[i,2]) # normal likel. 2-arm
trials
    resdev[(i+ns.a)] <- (md[i,2]-theta[(i+ns.a),2])*(md[i,2]-
theta[(i+ns.a),2])*prec.c[i,2]
  }
for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM CONTRAST
STUDIES
        for (j in 1:2) {
            Sigma[i,j,k] <- V[i]*(1-equals(j,k)) +
prec.c[i,k+1]*equals(j,k)
      }
    Omega[i,1:2,1:2] <- inverse(Sigma[i,,])  #Precision matrix
# normal likelihood for 3-arm trials
    md[i,2:3] ~ dmnorm(theta[(i+ns.a),2:3],Omega[i,1:2,1:2] )

#Deviance contribution for trial i
    for(k in 1:2) {  # multiply vector & matrix
        ydiff[i,k]<- md[i,(k+1)] - theta[(i+ns.a),(k+1)]
        z[i,k]<- inprod2(Omega[i,k,1:2], ydiff[i,1:2])
              }
    resdev[(i+ns.a)]<- inprod2(ydiff[i,1:2], z[i,1:2])
  }

for(i in (ns2+ns3+1):ns.t) {        # LOOP THROUGH FOUR-ARM CONTRAST
STUDIES
        for (j in 1:3) {
            Sigma2[i,j,k] <- V[i]*(1-equals(j,k)) +
prec.c[i,k+1]*equals(j,k)
      }
    Omega2[i,1:3,1:3] <- inverse(Sigma2[i,,])  #Precision matrix
# normal likelihood for 4-arm trials
```

```
    md[i,2:na.c[i]] ~ dmnorm(theta[(i+ns.a),2:4],Omega2[i,1:3,1:3] )

#Deviance contribution for trial i
    for(k in 1:3) {  # multiply vector & matrix
        ydiff[i,k]<- md[i,(k+1)] - theta[(i+ns.a),(k+1)]
        z[i,k]<- inprod2(Omega2[i,k,1:3], ydiff[i,1:3])
              }
    resdev[(i+ns.a)]<- inprod2(ydiff[i,1:3], z[i,1:3])
  }
for(i in 1:ns.t){                  #   LOOP THROUGH ALL CONTRAST STUDIES
    w.c[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
arm
        var.c[i,k] <- pow(se.c[i,k],2)   # calculate variances
        prec.c[i,k] <- 1/var.c[i,k]      # set precisions
# trial-specific LOR distributions
        delta[i+ns.a,k] ~ dnorm(MD[i+ns.a,k],taud.c[i,k])
# mean of distributions, with regression and multi-arm trial correction
            theta[i+ns.a,k] <- delta[i+ns.a,k] + (beta[t.c[i,k]]-
beta[t.c[i,1]]) * base_c[i+ns.a]

        MD[i+ns.a,k] <-  d[t.c[i,k]] - d[t.c[i,1]] + sw.c[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud.c[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w.c[i,k] <- (delta[i+ns.a,k] - d[t.c[i,k]] + d[t.c[i,1]])
# cumulative adjustment for multi-arm trials
        sw.c[i,k] <- sum(w.c[i,1:k-1])/(k-1)
      }
V[i] <- pow(base_sd.c[i,1],2)
  }

# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA, precA)
seA <- sdA/sqrt(n_A)    ## SE
precA <- pow(seA,-2)   ## precision

for (j in 1:3) {
for (k in 1:nt) {
      T[k,j] <- A + d[k] + (baseA[j]-centSev)*B
      dbeta[k,j] <- d[k] + (baseA[j]-centSev)*B
      }
}
## NO class effect
d[1]<-0       # treatment effect is zero for reference treatment / class

# vague priors for treatment effects within class
## common covariate effect (B) multiplied by whether t was active

for (k in 2:nt){
      d[k] ~ dnorm(0,.0001)
      beta[k] <- B
```

```
RR423212
      }
beta[1] <- 0      ## effect of baseline severity is zero for placebo arms
B ~ dnorm(0, 0.001)           # vague prior for meta-regression
coefficient
severity, for centring
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
sd ~ dunif(0,sdUpper)     # vague prior for between-trial SD
totresdev <- sum(resdev[])            #Total Residual Deviance

for(i in 1:ns.a+ns.t){
      b_mean[i] <- pooledM[i]
      w_sev[i] <- b_mean[i]*sn[i]         ## weighting baseline by study
size
      }

## SECTION 8 - Calculate pooled mean for arm studies, length=ns.a
for(i in 1:ns.a) {       # LOOP THROUGH STUDIES
      for(k in 1: na[i]) {    # LOOP THROUGH ARMS
            pm.step1[i,k] <- ( (n[i,k] - 1) * pow(base_sd[i,k], 2) )
            pm.step2[i,k] <- ( base_m[i,k] * n[i,k] )
      }
      SD_pooled[i] <- sqrt( sum(pm.step1[i, 1:na[i]]) / (sn[i] - na[i]) )
      pooledM[i] <- sum(pm.step2[i, 1:na[i]]  ) / sn[i]
      sn[i] <- sum(n[i,1:na[i]])
}           ## END LOOP (pooled means)

## SECTION 8 - Calculate pooled mean for contrast studies, length=ns.t
for(i in 1:ns.t) {       # LOOP THROUGH STUDIES
      for(k in 1: na.c[i]) {  # LOOP THROUGH ARMS
            pm.step1c[i,k] <- ( (n.c[i,k] - 1) * pow(base_sd.c[i,k], 2) )
            pm.step2c[i,k] <- ( base_m.c[i,k] * n.c[i,k] )
      }
      SD_pooledc[i] <- sqrt( sum(pm.step1c[i, 1:na.c[i]]) / (sn[i+ns.a] -
na.c[i]) )
      sn[i+ns.a] <- sum(n.c[i,1: na.c[i]])
}           ## END LOOP (pooled means)




# rank interventions
for (k in 1:nt) {
   # rk[k] <- nt+1-rank(d[],k)             # assumes positive diffs
are  good
are  good
that treat k is best
            prob[h,k] <- equals(rk[k],h)              # prob k is h-th
best
}

# MDs for all possible pair-wise comparisons - trts
for (c in 1:(nt-1)) {
      for (k in (c+1):nt) {
       diff[c,k] <- d[k] - d[c]
```

```
RR423212
  }
}

#Stop unused variables causing error message

dv[1] <- n[1,1]
dv[2] <- base_m[1,1] + base_sd[51,1] + base_n[1,1]
dv[3] <- n.c[1,1]
dv[4] <- base_m.c[1,1] + base_sd.c[1,2] + base_n.c[1,2]

}                                    # *** PROGRAM ENDS
```

Based on TSD2: Normal likelihood, log link, proportional RE treatment effects

```
#This code is part of
#Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling
#Framework for Pairwise and Network Meta-Analysis of Randomised Controlled
Trials. 2011;
http://www.nicedsu.org.uk).
is used whether in its standard form or adapted.

## This is adapted for the T2D medicines update

# Normal likelihood, identity link
# Random effects model for multi-arm trials
# Added code to accept CFB, baseline-final and final values (DONE)


model{                                # *** PROGRAM STARTS
for(i in 1:ns){                     # LOOP THROUGH STUDIES WITH ARM DATA
    w.a[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
arm
    mu[i] ~ dnorm(0,0.001)           # vague priors for all trial
baselines
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud.a[i,k])
# mean of LOR distributions, with multi-arm trial correction
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw.a[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud.a[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w.a[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw.a[i,k] <- sum(w.a[i,1:k-1])/(k-1)
```

```
RR423212
      }
  }

### SECTION A - estimation specific to studies reporting CFB
for(i in cb[1]:cb[2]){              #   LOOP THROUGH STUDIES (CFB)
      for (k in 1:na[i]) {             #  LOOP THROUGH ARMS

# SE and precision for CFB
            #CFB_se[i,k] <- sqrt(n[i,k]) * SD[i,k]
            prec[i,k] <- pow(se[i,k],-2)

# Outcome measure: change from baseline (requires baseline)
            #yc[i,k] <- y[i,k]
            phiB[i,k] <- base_m[i,k]
            phi[i,k] <- phiF[i,k] - phiB[i,k]
       ## CFB
            log(phiF[i,k]) <- log(phiB[i,k]) + theta[i,k]                ##
Follow-up
# Likelihood: univariate Normal
            y[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for CFB means
       dev[i,k] <- (y[i,k]-phi[i, k])*(y[i,k]-phi[i, k])*prec[i,k]
      }           # END ARM LOOP
}   # END STUDY LOOP FOR CFB DATA

### SECTION B - estimation specific to studies reporting baseline and
follow-up values
for(i in pp[1]:pp[2] ) {            ##   LOOP THROUGH STUDIES (baseline
and follow-up)

# SE and variances at baseline and follow-up
            base_se[i,k] <- base_sd[i,k]/sqrt(base_n[i,k])
            base_var[i,k] <- pow(base_se[i,k],2)
            #f_se[i,k] <- SD[i,k]/sqrt(n[i,k])
            f_var[i,k] <- pow(se[i,k],2)
            prec[i,k] <- 1/f_var[i,k]

# Outcome measure: baseline and post-treatment means
            yp[i,k,1] <- base_m[i,k]
            yp[i,k,2] <- y[i,k]
            phiPP[i,k,1] <- exp( basephi[i,k] )
            log(phiPP[i,k,2]) <- ( basephi[i,k] + theta[i,k] )
            basephi[i,k] ~ dnorm(0, 0.01)

## Likelihood: bivariate Normal
            yp[i,k,1:2] ~ dmnorm(phiPP[i,k,1:2], sigmaInv[i, k, 1:2, 1:2])

# Precision matrix for mvnorm
      sigma[i, k, 1, 1] <- base_var[i,k]
```

```
      sigma[i, k, 1, 2] <- ( corr * base_se[i,k]  * se[i,k] )
      sigma[i, k, 2, 1]  <- ( corr * base_se[i,k]  * se[i,k] )
      sigma[i, k, 2, 2]  <- f_var[i,k]
      sigmaInv[i, k, 1:2, 1:2] <- inverse(sigma[i, k, 1:2, 1:2])

# Deviance: Mahalanobis distance for trial i (baseline and follow-up data)
           for (j in 1:2) {        ## n of dimensions of mvnorm (i.e.
bivariate)
           temp[i, k, j] <- inprod(sigmaInv[i, k, j, 1:2], res[i, k,
1:2])
       Msq[i,k] <- inprod(res[i, k, 1:2], temp[i, k, 1:2])
       M[i,k] <- sqrt(Msq[i,k])
      dev[i,k] <- Msq[i,k]
      } ## END ARM LOOP

}   ## END STUDY LOOP (baseline and follow-up data)

### SECTION C - estimation specific to studies reporting follow-up values
#for(i in pt[1]:pt[2]){ ##   LOOP THROUGH STUDIES (follow-up data)
#     for (k in 1:na[i]) {             ##  LOOP THROUGH ARMS
#
# SE
#           f_se[i,k] <- f_sd[i,k]/sqrt(n[i,k])       ## SE
#           prec[i,k] <- pow(f_se[i,k],-2)   ## precision

# Outcome measure: post-treatment mean
#           ypt[i,k] <- f_mean[i,k]
#           log(phi[i,k]) <- theta[i,k]

# Likelihood: univariate Normal
#           ypt[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for post-treatment mean
  #      dev[i,k] <- (ypt[i,k]-phi[i, k])*(ypt[i,k]-phi[i, k])*prec[i,k]
    #  }          # END ARM LOOP

#}    ## END STUDY LOOP (follow-up data)


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

## NO class effect
d[1]<-0       # treatment effect is zero for reference treatment / class
dExp[1] <- 1

# vague priors for treatment effects within class
for (k in 2:nt){  d[k] ~ dnorm(0,.0001)
                                                    dExp[k] <- exp(d[k])
}
```

```
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
sd ~ dunif(0,sdUpper)     # vague prior for between-trial SD

# Calculate all relative treatment differences, array [nt-1, nt]
for (c in 1:(nt-1)) {  #
    for (k in (c+1):nt)  {    diff[c,k] <- T[k,1] - T[c,1]
      ratiodiff[c,k] <- exp(d[k] - d[c])       # on ratio scale
      }
  }

# Ranking on relative scale, length=nt
for (k in 1:nt) {
      rk[k] <- rank(d[],k)    ## assumes events are "bad" / negative d
values are good
is best
      for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } ## probability that
treat k is h-th best
 }

for (k in 1:nt) {
## treatment effect as difference between CFB on treatment k and reference
treatment (metformin)
      T[k,1] <- T[k,2] - (A[2] - A[1])

      ## Absolute effect treatment k is absolute effect on treatment 1
multiplied by RoM for treatment k
      T[k,2] <- A[2] * exp(d[k])

      for (j in 1:2){
                  MD[k,j] <- T[k,j] - T[1,j]
                  RoM[k,j] <- T[k,j] / T[1,j]
            }

      kg[k] <- MD[k,1]
      finalkg90[k] <- (90*dExp[k])
      finalkg60[k] <- (60*dExp[k])
      }

### dummy variables so that same dataset may be used for all models
dv[1] <- n[1,1]
dv[2] <- base_sd[1,1] + base_n[1,1]
A[1] ~ dnorm(meanCFB, precCFB)
precCFB <- pow(sdA[1], -2)
A[2] ~ dnorm(meanF, precF)
precF <- pow(sdA[2], -2)


}                                       # *** PROGRAM ENDS
```

Based on TSD4: Normal likelihood, identity link, RE, UME

```
#This code is part of
#Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling
#Framework for Pairwise and Network Meta-Analysis of Randomised Controlled
Trials. 2011;
http://www.nicedsu.org.uk).
is used whether in its standard form or adapted.

## This is adapted for the T2D medicines update

# Normal likelihood, identity link
# Arm and Trial-level data (treatment differences)
# RANDOM effects model for multi-arm trials
# Added code to accept CFB, baseline-final and final values (DONE)
# Altered the Norm_diff section to explictly model 4-armed trials

model{                                  # *** PROGRAM STARTS
for(i in 1:ns.a){                       # LOOP THROUGH STUDIES WITH ARM DATA
    w.a[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
arm
    mu[i] ~ dnorm(0,.0001)              # vague priors for all trial
baselines
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {                # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(d[t[i,1],t[i,k]],tau)

      }
  }
### SECTION A - estimation specific to studies reporting CFB
for(i in cb[1]:cb[2]){                 #   LOOP THROUGH STUDIES (CFB)
      for (k in 1:na[i]) {                #  LOOP THROUGH ARMS

# SE and precision for CFB
            CFB_se[i,k] <- se[i,k]
            prec[i,k] <- pow(CFB_se[i,k],-2)      ## precision

# Outcome measure: change from baseline (requires baseline)
            yc[i,k] <- y[i,k]
            phi[i,k] <- theta[i,k]

# Likelihood: univariate Normal
            yc[i,k] ~ dnorm(phi[i,k], prec[i,k])
```

```
# Deviance: contribution for CFB means
       dev[i,k] <- (yc[i,k]-phi[i, k])*(yc[i,k]-phi[i, k])*prec[i,k]
      }           # END ARM LOOP
}   # END STUDY LOOP FOR CFB DATA


### SECTION C - estimation specific to studies reporting follow-up values
for(i in pt[1]:pt[2]){  ##   LOOP THROUGH STUDIES (follow-up data)
      for (k in 1:na[i]) {             ##  LOOP THROUGH ARMS
# SE
            f_se[i,k] <- se[i,k]
            prec[i,k] <- pow(f_se[i,k],-2)   ## precision

# Outcome measure: post-treatment mean
            ypt[i,k] <- y[i,k]
            phi[i,k] <- theta[i,k]

# Likelihood: univariate Normal
            ypt[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for post-treatment mean
        dev[i,k] <- (ypt[i,k]-phi[i, k])*(ypt[i,k]-phi[i, k])*prec[i,k]
      }           # END ARM LOOP

}     ## END STUDY LOOP (follow-up data)


for(i in 1:ns2) {                    # LOOP THROUGH 2-ARM CONTRAST STUDIES
    md[i,2] ~ dnorm(delta[(i+ns.a),2],prec.c[i,2]) # normal likel. 2-arm
trials
    resdev[(i+ns.a)] <- (md[i,2]-delta[(i+ns.a),2])*(md[i,2]-
delta[(i+ns.a),2])*prec.c[i,2]
  }
for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM CONTRAST
STUDIES
        for (j in 1:2) {
            Sigma[i,j,k] <- V[i]*(1-equals(j,k)) +
prec.c[i,k+1]*equals(j,k)
      }
    Omega[i,1:2,1:2] <- inverse(Sigma[i,,])  #Precision matrix
# normal likelihood for 3-arm trials
    md[i,2:3] ~ dmnorm(delta[(i+ns.a),2:3],Omega[i,1:2,1:2] )

#Deviance contribution for trial i
    for(k in 1:2) {  # multiply vector & matrix
        ydiff[i,k]<- md[i,(k+1)] - delta[(i+ns.a),(k+1)]
        z[i,k]<- inprod2(Omega[i,k,1:2], ydiff[i,1:2])
              }
    resdev[(i+ns.a)]<- inprod2(ydiff[i,1:2], z[i,1:2])
  }
```

```
for(i in (ns2+ns3+1):ns.t) {        # LOOP THROUGH FOUR-ARM CONTRAST
STUDIES
    for (k in 1:3) {    # set variance-covariance matrix
        for (j in 1:3) {
            Sigma2[i,j,k] <- V[i]*(1-equals(j,k)) +
prec.c[i,k+1]*equals(j,k)
      }
    Omega2[i,1:3,1:3] <- inverse(Sigma2[i,,])  #Precision matrix
# normal likelihood for 4-arm trials
    md[i,2:na.c[i]] ~ dmnorm(delta[(i+ns.a),2:4],Omega2[i,1:3,1:3] )

#Deviance contribution for trial i
    for(k in 1:3) {  # multiply vector & matrix
        ydiff[i,k]<- md[i,(k+1)] - delta[(i+ns.a),(k+1)]
        z[i,k]<- inprod2(Omega2[i,k,1:3], ydiff[i,1:3])
              }
    resdev[(i+ns.a)]<- inprod2(ydiff[i,1:3], z[i,1:3])
  }
for(i in 1:ns.t){                   #   LOOP THROUGH ALL CONTRAST STUDIES
    w.c[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.c[i]) {             #  LOOP THROUGH ARMS
        var.c[i,k] <- pow(se.c[i,k],2)   # calculate variances
        prec.c[i,k] <- 1/var.c[i,k]      # set precisions
# trial-specific LOR distributions
        delta[i+ns.a,k] ~ dnorm(d[t.c[i,1],t.c[i,k]],tau)
      }
#bse[i,1] <- base_sd[i,1] / sqrt(n.c[i,1])
V[i] <- pow(base_sd.c[i,1],2)
  }

# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA, precA)
seA <- sdA/sqrt(n_A)    ## SE
precA <- pow(seA,-2)   ## precision

# vague priors for treatment effects within class
## common covariate effect (B) multiplied by whether t was active
# treatment effect is zero for control arm
for (c in 1:nt) {       d[c,c] <- 0 }
# vague priors for treatment effects
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
    for (k in (c+1):nt)  {
                d[c,k] ~ dnorm(0,.0001)
                d[k,c] <- -d[c,k]
                diff[c,k] <- d[c,k]
```

```
                    }
  }

tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
sd ~ dunif(0,sdUpper)     # vague prior for between-trial SD
totresdev <- sum(resdev[])            #Total Residual Deviance


#Stop unused variables causing error message

dv[1] <- n[1,1]
dv[2] <- base_m[1,1] + base_sd[51,1] + base_n[1,1]
dv[3] <- n.c[1,1]
dv[4] <- base_m.c[1,1] + base_sd.c[1,2] + base_n.c[1,2]

}                                     # *** PROGRAM ENDS
```

Based on TSD4: Normal likelihood, identity link, RE with meta-regression, UME

```
#This code is part of

#Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.

# NICE DSU Technical Support Document 2: A Generalised Linear Modelling

#Framework for Pairwise and Network Meta-Analysis of Randomised Controlled
Trials. 2011;

#last updated September 2016 (available #from http://www.nicedsu.org.uk).

#This work should be cited whenever the code is used whether in its
standard form or adapted.


## This is adapted for the T2D medicines update

## This version has a single beta


# Normal likelihood, identity link

# Arm and Trial-level data (treatment differences)

# RANDOM effects model for multi-arm trials

# Added code to accept CFB and final values (DONE)

# Altered the Norm_diff section to explictly model 4-armed trials (DONE)

# Added MR term for baseline HbA1c

# this uses the centred pooled mean at baseline
```

```
model{                                  # *** PROGRAM STARTS
for(i in 1:ns.a){                       # LOOP THROUGH STUDIES WITH ARM DATA
    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[i]) {             #  LOOP THROUGH ARMS
# model for linear predictor
            #  theta[i,k] <- mu[i] + delta[i,k]
            theta[i,k] <- mu[i] + delta[i,k] + (beta[t[i,k]]-beta[t[i,1]])
* base_c[i]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific mean difference random effects distribution
        delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)


      }
  }
### SECTION A - estimation specific to studies reporting CFB
for(i in cb[1]:cb[2]){              #   LOOP THROUGH STUDIES (CFB)
      for (k in 1:na[i]) {             #  LOOP THROUGH ARMS


# SE and precision for CFB
            CFB_se[i,k] <- se[i,k]
            prec[i,k] <- pow(CFB_se[i,k],-2)      ## precision


# Outcome measure: change from baseline (requires baseline)
            yc[i,k] <- y[i,k]
            phi[i,k] <- theta[i,k]
```

```
# Likelihood: univariate Normal
            yc[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for CFB means
       dev[i,k] <- (yc[i,k]-phi[i, k])*(yc[i,k]-phi[i, k])*prec[i,k]
      }           # END ARM LOOP
}   # END STUDY LOOP FOR CFB DATA


### SECTION C - estimation specific to studies reporting follow-up values
for(i in pt[1]:pt[2]){  ##   LOOP THROUGH STUDIES (follow-up data)
      for (k in 1:na[i]) {             ##  LOOP THROUGH ARMS
# SE
            f_se[i,k] <- se[i,k]
            prec[i,k] <- pow(f_se[i,k],-2)   ## precision

# Outcome measure: post-treatment mean
            ypt[i,k] <- y[i,k]
            phi[i,k] <- theta[i,k]

# Likelihood: univariate Normal
            ypt[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for post-treatment mean
        dev[i,k] <- (ypt[i,k]-phi[i, k])*(ypt[i,k]-phi[i, k])*prec[i,k]
      }           # END ARM LOOP

}     ## END STUDY LOOP (follow-up data)


for(i in 1:ns2) {                   # LOOP THROUGH 2-ARM CONTRAST STUDIES
```

```
    md[i,2] ~ dnorm(theta[(i+ns.a),2],prec.c[i,2]) # normal likel. 2-arm
trials

#Deviance contribution for trial i (2-armed trials)

    resdev[(i+ns.a)] <- (md[i,2]-theta[(i+ns.a),2])*(md[i,2]-
theta[(i+ns.a),2])*prec.c[i,2]

  }

for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM CONTRAST
STUDIES

    for (k in 1:2) {    # set variance-covariance matrix

        for (j in 1:2) {

            Sigma[i,j,k] <- V[i]*(1-equals(j,k)) +
prec.c[i,k+1]*equals(j,k)

          }

      }

    Omega[i,1:2,1:2] <- inverse(Sigma[i,,])  #Precision matrix

# normal likelihood for 3-arm trials

    md[i,2:3] ~ dmnorm(theta[(i+ns.a),2:3],Omega[i,1:2,1:2] )


#Deviance contribution for trial i

    for(k in 1:2) {  # multiply vector & matrix

        ydiff[i,k]<- md[i,(k+1)] - theta[(i+ns.a),(k+1)]

        z[i,k]<- inprod2(Omega[i,k,1:2], ydiff[i,1:2])

              }

    resdev[(i+ns.a)]<- inprod2(ydiff[i,1:2], z[i,1:2])

  }


for(i in (ns2+ns3+1):ns.t) {        # LOOP THROUGH FOUR-ARM CONTRAST
STUDIES

    for (k in 1:3) {    # set variance-covariance matrix

        for (j in 1:3) {

            Sigma2[i,j,k] <- V[i]*(1-equals(j,k)) +
prec.c[i,k+1]*equals(j,k)

          }

      }
```

```
    Omega2[i,1:3,1:3] <- inverse(Sigma2[i,,])  #Precision matrix
# normal likelihood for 4-arm trials
    md[i,2:na.c[i]] ~ dmnorm(theta[(i+ns.a),2:4],Omega2[i,1:3,1:3] )

#Deviance contribution for trial i
    for(k in 1:3) {  # multiply vector & matrix
        ydiff[i,k]<- md[i,(k+1)] - theta[(i+ns.a),(k+1)]
        z[i,k]<- inprod2(Omega2[i,k,1:3], ydiff[i,1:3])
              }
    resdev[(i+ns.a)]<- inprod2(ydiff[i,1:3], z[i,1:3])
  }
for(i in 1:ns.t){                  #   LOOP THROUGH ALL CONTRAST STUDIES
    w.c[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.c[i]) {             #  LOOP THROUGH ARMS
        var.c[i,k] <- pow(se.c[i,k],2)   # calculate variances
        prec.c[i,k] <- 1/var.c[i,k]      # set precisions
# trial-specific LOR distributions
        delta[i+ns.a,k] ~ dnorm(d[t.c[i,1],t.c[i,k]],taud.c[i,k])
# mean of distributions, with regression and multi-arm trial correction
            theta[i+ns.a,k] <- delta[i+ns.a,k] + (beta[t.c[i,k]]-
beta[t.c[i,1]]) * base_c[i+ns.a]

# precision of LOR distributions (with multi-arm trial correction)
        taud.c[i,k] <- tau *2*(k-1)/k
      }
V[i] <- pow(base_sd.c[i,1],2)
  }

# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
```

```
# with precision (1/variance) precA
A ~ dnorm(meanA, precA)
seA <- sdA/sqrt(n_A)    ## SE
precA <- pow(seA,-2)   ## precision

for (j in 1:3) {
for (k in 1:nt) {
      T[k,j] <- A + d[k,1] + (baseA[j]-centSev)*B
      dbeta[k,j] <- d[k,1] + (baseA[j]-centSev)*B
      }
}

# vague priors for treatment effects within class
## common covariate effect (B) multiplied by whether t was active
# treatment effect is zero for control arm
for (c in 1:nt) {       d[c,c] <- 0 }
# vague priors for treatment effects
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
    for (k in (c+1):nt)  {
                d[c,k] ~ dnorm(0,.0001)
                d[k,c] <- -d[c,k]
                diff[c,k] <- d[c,k]
                }
  }

for (k in 2:nt){
      beta[k] <- B
      }
beta[1] <- 0      ## effect of baseline severity is zero for placebo arms
B ~ dnorm(0, 0.001)           # vague prior for meta-regression
coefficient
```

```
centSev <- sum(w_sev[])/sum(sn[])   ## mean of baseline severity, for
centring


tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)

sd ~ dunif(0,5)     # vague prior for between-trial SD

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


for(i in 1:ns.a+ns.t){

      b_mean[i] <- pooledM[i]

      w_sev[i] <- b_mean[i]*sn[i]         ## weighting baseline by study
size

      base_c[i] <- b_mean[i] - centSev    ## centring baseline by mean

      }


## SECTION 8 - Calculate pooled mean for arm studies, length=ns.a

for(i in 1:ns.a) {       # LOOP THROUGH STUDIES

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

            pm.step1[i,k] <- ( (n[i,k] - 1) * pow(base_sd[i,k], 2) )

            pm.step2[i,k] <- ( base_m[i,k] * n[i,k] )

      }

      SD_pooled[i] <- sqrt( sum(pm.step1[i, 1:na[i]]) / (sn[i] - na[i]) )

      pooledM[i] <- sum(pm.step2[i, 1:na[i]]  ) / sn[i]

      sn[i] <- sum(n[i,1:na[i]])

}           ## END LOOP (pooled means)


## SECTION 8 - Calculate pooled mean for contrast studies, length=ns.t

for(i in 1:ns.t) {       # LOOP THROUGH STUDIES

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

            pm.step1c[i,k] <- ( (n.c[i,k] - 1) * pow(base_sd.c[i,k], 2) )

            pm.step2c[i,k] <- ( base_m.c[i,k] * n.c[i,k] )

      }

      SD_pooledc[i] <- sqrt( sum(pm.step1c[i, 1:na.c[i]]) / (sn[i+ns.a] -
na.c[i]) )
```

```
      pooledM[i+ns.a] <- sum(pm.step2c[i, 1:na.c[i]]  ) / sn[i+ns.a]

      sn[i+ns.a] <- sum(n.c[i,1: na.c[i]])

}           ## END LOOP (pooled means)



#Stop unused variables causing error message


dv[1] <- n[1,1]

dv[2] <- base_m[1,1] + base_sd[51,1] + base_n[1,1]

dv[3] <- n.c[1,1] +sdUpper

dv[4] <- base_m.c[1,1] + base_sd.c[1,2] + base_n.c[1,2]


}                                       # *** PROGRAM ENDS
```

Based on TSD4: Normal likelihood, log link, RE, UME

```
#This code is part of
#Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling
#Framework for Pairwise and Network Meta-Analysis of Randomised Controlled
Trials. 2011;
http://www.nicedsu.org.uk).
is used whether in its standard form or adapted.

## This is adapted for the T2D medicines update

# Normal likelihood, identity link
# Random effects model for multi-arm trials
# Added code to accept CFB, baseline-final and final values (DONE)


model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                       # LOOP THROUGH STUDIES WITH ARM DATA
    w.a[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
arm
    mu[i] ~ dnorm(0,0.001)            # vague priors for all trial
baselines
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
```

```
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific mean difference random effects distribution
        delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
      }
  }

### SECTION A - estimation specific to studies reporting CFB
for(i in cb[1]:cb[2]){              #   LOOP THROUGH STUDIES (CFB)
      for (k in 1:na[i]) {             #  LOOP THROUGH ARMS

# SE and precision for CFB
            #CFB_se[i,k] <- sqrt(n[i,k]) * SD[i,k]
            prec[i,k] <- pow(se[i,k],-2)

# Outcome measure: change from baseline (requires baseline)
            #yc[i,k] <- y[i,k]
            phiB[i,k] <- base_m[i,k]
            phi[i,k] <- phiF[i,k] - phiB[i,k]
       ## CFB
            log(phiF[i,k]) <- log(phiB[i,k]) + theta[i,k]                ##
Follow-up
# Likelihood: univariate Normal
            y[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for CFB means
       dev[i,k] <- (y[i,k]-phi[i, k])*(y[i,k]-phi[i, k])*prec[i,k]
      }           # END ARM LOOP
}   # END STUDY LOOP FOR CFB DATA

### SECTION B - estimation specific to studies reporting baseline and
follow-up values
for(i in pp[1]:pp[2] ) {            ##   LOOP THROUGH STUDIES (baseline
and follow-up)

# SE and variances at baseline and follow-up
            base_se[i,k] <- base_sd[i,k]/sqrt(base_n[i,k])
            base_var[i,k] <- pow(base_se[i,k],2)
            #f_se[i,k] <- SD[i,k]/sqrt(n[i,k])
            f_var[i,k] <- pow(se[i,k],2)
            prec[i,k] <- 1/f_var[i,k]

# Outcome measure: baseline and post-treatment means
            yp[i,k,1] <- base_m[i,k]
            yp[i,k,2] <- y[i,k]
            phiPP[i,k,1] <- exp( basephi[i,k] )
            log(phiPP[i,k,2]) <- ( basephi[i,k] + theta[i,k] )
            basephi[i,k] ~ dnorm(0, 0.01)

## Likelihood: bivariate Normal
            yp[i,k,1:2] ~ dmnorm(phiPP[i,k,1:2], sigmaInv[i, k, 1:2, 1:2])
```

```
# Precision matrix for mvnorm
      sigma[i, k, 1, 1] <- base_var[i,k]
      sigma[i, k, 1, 2] <- ( corr * base_se[i,k]  * se[i,k] )
      sigma[i, k, 2, 1]  <- ( corr * base_se[i,k]  * se[i,k] )
      sigma[i, k, 2, 2]  <- f_var[i,k]
      sigmaInv[i, k, 1:2, 1:2] <- inverse(sigma[i, k, 1:2, 1:2])

# Deviance: Mahalanobis distance for trial i (baseline and follow-up data)
            for (j in 1:2) {        ## n of dimensions of mvnorm (i.e.
bivariate)
            temp[i, k, j] <- inprod(sigmaInv[i, k, j, 1:2], res[i, k,
1:2])
       Msq[i,k] <- inprod(res[i, k, 1:2], temp[i, k, 1:2])
       M[i,k] <- sqrt(Msq[i,k])
      dev[i,k] <- Msq[i,k]
      } ## END ARM LOOP

}   ## END STUDY LOOP (baseline and follow-up data)

### SECTION C - estimation specific to studies reporting follow-up values
#for(i in pt[1]:pt[2]){ ##   LOOP THROUGH STUDIES (follow-up data)
#     for (k in 1:na[i]) {             ##  LOOP THROUGH ARMS
#
# SE
#           f_se[i,k] <- f_sd[i,k]/sqrt(n[i,k])       ## SE
#           prec[i,k] <- pow(f_se[i,k],-2)   ## precision

# Outcome measure: post-treatment mean
#           ypt[i,k] <- f_mean[i,k]
#           log(phi[i,k]) <- theta[i,k]

# Likelihood: univariate Normal
#           ypt[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for post-treatment mean
  #      dev[i,k] <- (ypt[i,k]-phi[i, k])*(ypt[i,k]-phi[i, k])*prec[i,k]
    #  }          # END ARM LOOP

#}    ## END STUDY LOOP (follow-up data)


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

## NO class effect

# treatment effect is zero for control arm
for (c in 1:nt) {       d[c,c] <- 0 }
# vague priors for treatment effects
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
```

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```
    for (k in (c+1):nt)  {
                  d[c,k] ~ dnorm(0,.0001)
                  d[k,c] <- -d[c,k]
                  ratio[c,k] <- exp(d[c,k])
                  }
  }

tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
sd ~ dunif(0,sdUpper)     # vague prior for between-trial SD


### dummy variables so that same dataset may be used for all models
dv[1] <- n[1,1]
dv[2] <- base_sd[1,1] + base_n[1,1]
A[1] ~ dnorm(meanCFB, precCFB)
precCFB <- pow(sdA[1], -2)
A[2] ~ dnorm(meanF, precF)
precF <- pow(sdA[2], -2)


}                                        # *** PROGRAM ENDS
```

Update following quality assurance: NMA model for change in HbA1c: base-case

```
#This code is part of Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011;
# last updated September 2016 (available #from http://www.nicedsu.org.uk).
# This work should be cited whenever the code is used whether in its standard form or adapted.

## This is adapted for the T2D medicines update
## Arm and Trial-level data (treatment differences)
## RANDOM effects model for multi-arm trials
## Added code to accept CFB, baseline-final and final values
## Altered the Norm_diff section to explicitly model 4-armed trials

model{                  # *** PROGRAM STARTS
for(i in 1:ns.a){          # LOOP THROUGH STUDIES WITH ARM DATA
   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[i]) {          #  LOOP THROUGH ARMS
      theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
    }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {          # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(MD[i,k],taud[i,k])
```

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```
# mean of LOR distributions, with multi-arm trial correction
      MD[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw.a[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w.a[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw.a[i,k] <- sum(w.a[i,1:k-1])/(k-1)
    }
  }
### SECTION A - estimation specific to studies reporting CFB
for(i in cb[1]:cb[2]){                          #   LOOP THROUGH STUDIES (CFB)
          for (k in 1:na[i]) {          #  LOOP THROUGH ARMS

# SE and precision for CFB
                    CFB_se[i,k] <- se[i,k]
                    prec[i,k] <- pow(CFB_se[i,k],-2)    ## precision

# Outcome measure: change from baseline (requires baseline)
                    yc[i,k] <- y[i,k]
                    phi[i,k] <- theta[i,k]

# Likelihood: univariate Normal
                    yc[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for CFB means
     dev[i,k] <- (yc[i,k]-phi[i, k])*(yc[i,k]-phi[i, k])*prec[i,k]
    }               # END ARM LOOP
}  # END STUDY LOOP FOR CFB DATA


### SECTION C - estimation specific to studies reporting follow-up values
for(i in pt[1]:pt[2]){       ##   LOOP THROUGH STUDIES (follow-up data)
          for (k in 1:na[i]) {          ##  LOOP THROUGH ARMS
# SE
                    f_se[i,k] <- se[i,k]
                    prec[i,k] <- pow(f_se[i,k],-2)   ## precision

# Outcome measure: post-treatment mean
                    ypt[i,k] <- y[i,k]
                    phi[i,k] <- theta[i,k]

# Likelihood: univariate Normal
                    ypt[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for post-treatment mean
      dev[i,k] <- (ypt[i,k]-phi[i, k])*(ypt[i,k]-phi[i, k])*prec[i,k]
    }               # END ARM LOOP

}          ## END STUDY LOOP (follow-up data)
```

```
for(i in 1:ns2) {                # LOOP THROUGH 2-ARM CONTRAST STUDIES
   md[i,2] ~ dnorm(delta[(i+ns.a),2],prec.c[i,2]) # normal likel. 2-arm trials
#Deviance contribution for trial i (2-armed trials)
   resdev[(i+ns.a)] <- (md[i,2]-delta[(i+ns.a),2])*(md[i,2]-delta[(i+ns.a),2])*prec.c[i,2]
 }
for(i in (ns2+1):(ns2+ns3)) {       # LOOP THROUGH THREE-ARM CONTRAST STUDIES
           V[i] <- pow(refarm_se[i],2) # variance of reference arm (arm 1)

   for (k in 1:2) {    # set variance-covariance matrix
      for (j in 1:2) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var.c[i,k+1]*equals(j,k)
       }
    }
   Omega[i,1:2,1:2] <- inverse(Sigma[i,1:2,1:2])  #Precision matrix
# normal likelihood for 3-arm trials
   md[i,2:3] ~ dmnorm(delta[(i+ns.a),2:3],Omega[i,1:2,1:2] )

#Deviance contribution for trial i
   for(k in 1:2) {  # multiply vector & matrix
      ydiff[i,k]<- md[i,(k+1)] - delta[(i+ns.a),(k+1)]
      z[i,k]<- inprod2(Omega[i,k,1:2], ydiff[i,1:2])
                     }
   resdev[(i+ns.a)]<- inprod2(ydiff[i,1:2], z[i,1:2])
 }

for(i in (ns2+ns3+1):ns.t) {       # LOOP THROUGH FOUR-ARM CONTRAST STUDIES
           V[i] <- pow(refarm_se[i],2) # variance of reference arm (arm 1)

   for (k in 1:3) {    # set variance-covariance matrix
      for (j in 1:3) {
         Sigma2[i,j,k] <- V[i]*(1-equals(j,k)) + var.c[i,k+1]*equals(j,k)
       }
    }
   Omega2[i,1:3,1:3] <- inverse(Sigma2[i,,])  #Precision matrix
# normal likelihood for 4-arm trials
   md[i,2:na.c[i]] ~ dmnorm(delta[(i+ns.a),2:4],Omega2[i,1:3,1:3] )

#Deviance contribution for trial i
   for(k in 1:3) {  # multiply vector & matrix
      ydiff[i,k]<- md[i,(k+1)] - delta[(i+ns.a),(k+1)]
      z[i,k]<- inprod2(Omega2[i,k,1:3], ydiff[i,1:3])
                     }
   resdev[(i+ns.a)]<- inprod2(ydiff[i,1:3], z[i,1:3])
 }
for(i in 1:ns.t){              #   LOOP THROUGH ALL CONTRAST STUDIES
   w.c[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.c[i]) {          #  LOOP THROUGH ARMS
      var.c[i,k] <- pow(se.c[i,k],2)   # calculate variances
```

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```
      prec.c[i,k] <- 1/var.c[i,k]     # set precisions
# trial-specific LOR distributions
      delta[i+ns.a,k] ~ dnorm(MD[i+ns.a,k],taud.c[i,k])
# mean of LOR distributions, with multi-arm trial correction
      MD[i+ns.a,k] <-  d[t.c[i,k]] - d[t.c[i,1]] + sw.c[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud.c[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w.c[i,k] <- (delta[i+ns.a,k] - d[t.c[i,k]] + d[t.c[i,1]])
# cumulative adjustment for multi-arm trials
      sw.c[i,k] <- sum(w.c[i,1:k-1])/(k-1)
    }
 }

# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA, precA)
seA <- sdA/sqrt(n_A)     ## SE
precA <- pow(seA,-2)   ## precision

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

## NO class effect
d[1]<-0      # treatment effect is zero for reference treatment / class

# vague priors for treatment effects within class
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
sd ~ dunif(0,sdUpper)     # vague prior for between-trial SD
totresdev <- sum(resdev[])          #Total Residual Deviance

# rank interventions
for (k in 1:nt) {
  # rk[k] <- nt+1-rank(d[],k)          # assumes positive diffs are "good"
  rk[k] <- rank(d[],k)              # assumes negative diffs are "good"
  best[k] <- equals(rk[k],1)       #calculate probability that treat k is best
  for (h in 1:nt) {
                    prob[h,k] <- equals(rk[k],h)                    # prob k is h-th best
          }
}

# MDs for all possible pair-wise comparisons - trts
for (c in 1:(nt-1)) {
          for (k in (c+1):nt) {
     diff[c,k] <- d[k] - d[c]
 }
}

#Stop unused variables causing error message
```

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```
dv[1] <- n[1,1] #+ baseA[1]  ## baseA appears in mr coding
dv[2] <- base_m[1,1] + base_sd[51,1] + base_n[1,1]
dv[3] <- n.c[1,1]
dv[4] <- base_m.c[1,1] + base_sd.c[1,2] + base_n.c[1,2]

}                              # *** PROGRAM ENDS
```

Update following quality assurance: NMA model for change in HbA1c: meta-regression on mean-centred baseline severity (common effect for all active treatments)

```
#This code is part of
#Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling
#Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011;
#last updated September 2016 (available #from http://www.nicedsu.org.uk).
#This work should be cited whenever the code is used whether in its standard form or adapted.

## This is adapted for the T2D medicines update
## Normal likelihood, identity link
## Arm and Trial-level data (treatment differences)
## RANDOM effects model for multi-arm trials
## Added code to accept CFB and final values
## Altered the Norm_diff section to explictly model 4-armed trials
## Added MR term for baseline HbA1c
## this uses the centred pooled mean at baseline

model{                          # *** PROGRAM STARTS
for(i in 1:ns.a){               # LOOP THROUGH STUDIES WITH ARM DATA
   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[i]) {           #  LOOP THROUGH ARMS
# model for linear predictor with meta-regression term
                    #  theta[i,k] <- mu[i] + delta[i,k]  # linear regression for standard NMA
                    theta[i,k] <- mu[i] + delta[i,k] + (beta[t[i,k]]-beta[t[i,1]]) * base_c[i]
    }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {           # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(MD[i,k],taud[i,k])
# mean of distributions, with multi-arm trial correction
      MD[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw.a[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w.a[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw.a[i,k] <- sum(w.a[i,1:k-1])/(k-1)
    }
 }
### SECTION A - estimation specific to studies reporting CFB
for(i in cb[1]:cb[2]){                          #   LOOP THROUGH STUDIES (CFB)
          for (k in 1:na[i]) {           #  LOOP THROUGH ARMS

# SE and precision for CFB
                    CFB_se[i,k] <- se[i,k]
                    prec[i,k] <- pow(CFB_se[i,k],-2)    ## precision
```

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```
# Outcome measure: change from baseline (requires baseline)
                    yc[i,k] <- y[i,k]
                    phi[i,k] <- theta[i,k]

# Likelihood: univariate Normal
                    yc[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for CFB means
     dev[i,k] <- (yc[i,k]-phi[i, k])*(yc[i,k]-phi[i, k])*prec[i,k]
    }               # END ARM LOOP
}  # END STUDY LOOP FOR CFB DATA


### SECTION C - estimation specific to studies reporting follow-up values
for(i in pt[1]:pt[2]){       ##   LOOP THROUGH STUDIES (follow-up data)
          for (k in 1:na[i]) {          ##  LOOP THROUGH ARMS
# SE
                    f_se[i,k] <- se[i,k]
                    prec[i,k] <- pow(f_se[i,k],-2)   ## precision

# Outcome measure: post-treatment mean
                    ypt[i,k] <- y[i,k]
                    phi[i,k] <- theta[i,k]

# Likelihood: univariate Normal
                    ypt[i,k] ~ dnorm(phi[i,k], prec[i,k])

# Deviance: contribution for post-treatment mean
      dev[i,k] <- (ypt[i,k]-phi[i, k])*(ypt[i,k]-phi[i, k])*prec[i,k]
    }               # END ARM LOOP

}          ## END STUDY LOOP (follow-up data)


for(i in 1:ns2) {               # LOOP THROUGH 2-ARM CONTRAST STUDIES
   md[i,2] ~ dnorm(theta[(i+ns.a),2],prec.c[i,2]) # normal likel. 2-arm trials
#Deviance contribution for trial i (2-armed trials)
   resdev[(i+ns.a)] <- (md[i,2]-theta[(i+ns.a),2])*(md[i,2]-theta[(i+ns.a),2])*prec.c[i,2]
 }
for(i in (ns2+1):(ns2+ns3)) {       # LOOP THROUGH THREE-ARM CONTRAST STUDIES
          V[i] <- pow(refarm_se[i],2)
   for (k in 1:2) {    # set variance-covariance matrix
      for (j in 1:2) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var.c[i,k+1]*equals(j,k)
       }
    }
   Omega[i,1:2,1:2] <- inverse(Sigma[i,,])  #Precision matrix
# normal likelihood for 3-arm trials
   md[i,2:3] ~ dmnorm(theta[(i+ns.a),2:3],Omega[i,1:2,1:2] )

#Deviance contribution for trial i
```

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```
   for(k in 1:2) {  # multiply vector & matrix
      ydiff[i,k]<- md[i,(k+1)] - theta[(i+ns.a),(k+1)]
      z[i,k]<- inprod2(Omega[i,k,1:2], ydiff[i,1:2])
                        }
   resdev[(i+ns.a)]<- inprod2(ydiff[i,1:2], z[i,1:2])
  }

for(i in (ns2+ns3+1):ns.t) {       # LOOP THROUGH FOUR-ARM CONTRAST STUDIES
            V[i] <- pow(refarm_se[i],2)
   for (k in 1:3) {    # set variance-covariance matrix
      for (j in 1:3) {
         Sigma2[i,j,k] <- V[i]*(1-equals(j,k)) + var.c[i,k+1]*equals(j,k)
        }
     }
   Omega2[i,1:3,1:3] <- inverse(Sigma2[i,,])  #Precision matrix
# normal likelihood for 4-arm trials
   md[i,2:na.c[i]] ~ dmnorm(theta[(i+ns.a),2:4],Omega2[i,1:3,1:3] )

#Deviance contribution for trial i
   for(k in 1:3) {  # multiply vector & matrix
      ydiff[i,k]<- md[i,(k+1)] - theta[(i+ns.a),(k+1)]
      z[i,k]<- inprod2(Omega2[i,k,1:3], ydiff[i,1:3])
                        }
   resdev[(i+ns.a)]<- inprod2(ydiff[i,1:3], z[i,1:3])
  }
for(i in 1:ns.t){                #   LOOP THROUGH ALL CONTRAST STUDIES
   w.c[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.c[i]) {           #  LOOP THROUGH ARMS
      var.c[i,k] <- pow(se.c[i,k],2)   # calculate variances
      prec.c[i,k] <- 1/var.c[i,k]      # set precisions
# trial-specific LOR distributions
      delta[i+ns.a,k] ~ dnorm(MD[i+ns.a,k],taud.c[i,k])
# mean of distributions, with regression and multi-arm trial correction
                  theta[i+ns.a,k] <- delta[i+ns.a,k] + (beta[t.c[i,k]]-beta[t.c[i,1]]) * base_c[i+ns.a]

      MD[i+ns.a,k] <-  d[t.c[i,k]] - d[t.c[i,1]] + sw.c[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud.c[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w.c[i,k] <- (delta[i+ns.a,k] - d[t.c[i,k]] + d[t.c[i,1]])
# cumulative adjustment for multi-arm trials
      sw.c[i,k] <- sum(w.c[i,1:k-1])/(k-1)
     }
  }

# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA, precA)
seA <- sdA/sqrt(n_A)      ## SE
```

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precA <- pow(seA,-2)   ## precision

for (j in 1:3) {
for (k in 1:nt) {
        T[k,j] <- A + d[k] + (baseA[j]-centSev)*B
        dbeta[k,j] <- d[k] + (baseA[j]-centSev)*B
        }
}
## NO class effect
d[1]<-0      # treatment effect is zero for reference treatment / class

# vague priors for treatment effects within class
## common covariate effect (B) multiplied by whether t was active

for (k in 2:nt){
        d[k] ~ dnorm(0,.0001)
        beta[k] <- B
        }
beta[1] <- 0       ## effect of baseline severity is zero for placebo arms
B ~ dnorm(0, 0.001)                 # vague prior for meta-regression coefficient
centSev <- sum(w_sev[])/sum(sn[])        ## mean of baseline severity, for centring

tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
sd ~ dunif(0,sdUpper)     # vague prior for between-trial SD
totresdev <- sum(resdev[])          #Total Residual Deviance

for(i in 1:ns.a+ns.t){
        b_mean[i] <- pooledM[i]
        w_sev[i] <- b_mean[i]*sn[i]                  ## weighting baseline by study size
        base_c[i] <- b_mean[i] - centSev## centring baseline by mean
        }

## SECTION 8 - Calculate pooled mean for arm studies, length=ns.a
for(i in 1:ns.a) {  # LOOP THROUGH STUDIES
        for(k in 1: na[i]) {          # LOOP THROUGH ARMS
                pm.step1[i,k] <- ( (n[i,k] - 1) * pow(base_sd[i,k], 2) )
                pm.step2[i,k] <- ( base_m[i,k] * n[i,k] )
        }
        SD_pooled[i] <- sqrt( sum(pm.step1[i, 1:na[i]]) / (sn[i] - na[i]) )
        pooledM[i] <- sum(pm.step2[i, 1:na[i]]  ) / sn[i]
        sn[i] <- sum(n[i,1:na[i]])
}                   ## END LOOP (pooled means)

## SECTION 8 - Calculate pooled mean for contrast studies, length=ns.t
for(i in 1:ns.t) {   # LOOP THROUGH STUDIES
        for(k in 1: na.c[i]) {        # LOOP THROUGH ARMS
                pm.step1c[i,k] <- ( (n.c[i,k] - 1) * pow(base_sd.c[i,k], 2) )
                pm.step2c[i,k] <- ( base_m.c[i,k] * n.c[i,k] )
        }
        SD_pooledc[i] <- sqrt( sum(pm.step1c[i, 1:na.c[i]]) / (sn[i+ns.a] - na.c[i]) )
        pooledM[i+ns.a] <- sum(pm.step2c[i, 1:na.c[i]]  ) / sn[i+ns.a]
```

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        sn[i+ns.a] <- sum(n.c[i,1: na.c[i]])
}                   ## END LOOP (pooled means)

# rank interventions
for (k in 1:nt) {
  # rk[k] <- nt+1-rank(d[],k)          # assumes positive diffs are  good
  rk[k] <- rank(d[],k)              # assumes negative diffs are  good
  best[k] <- equals(rk[k],1)       #calculate probability that treat k is best
  for (h in 1:nt) {
                    prob[h,k] <- equals(rk[k],h)                    # prob k is h-th best
        }
}

# MDs for all possible pair-wise comparisons - trts
for (c in 1:(nt-1)) {
        for (k in (c+1):nt) {
     diff[c,k] <- d[k] - d[c]
 }
}

#Stop unused variables causing error message
dv[1] <- n[1,1]
dv[2] <- base_m[1,1] + base_sd[51,1] + base_n[1,1]
dv[3] <- n.c[1,1]
dv[4] <- base_m.c[1,1] + base_sd.c[1,2] + base_n.c[1,2]

}                           # *** PROGRAM ENDS
```

END