RR423212

RQ1.1: Initial pharmacological therapy for the management of type 2 diabetes.

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Research Question

For different population subgroups, which individual and/or combinations of pharmacological therapies are most clinically and cost effective as initial treatment for the management of type 2 diabetes.

Data

For each outcome, analyses were run on the full dataset and in two subgroups: i) a subset including only study arms where the dose reflected current clinical practice in the NHS (for excluded doses, see section NHS subset – excluded doses); ii) a subset excluding studies trialling treatments versus insulin, since it was felt that these studies were conducted in the population with more-severe disease.

Methods

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

The analysis of change in HbA1c followed code that used a Normal likelihood with an identity link function to estimate mean change in % HbA1c, with treatment effects assumed to be additive on the % HbA1c scale. 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 (Dias 2011).

The analysis of change in body weight (in kg) followed code that used a Normal likelihood with a log link function to estimate mean change in weight, with treatment effects assumed to be proportional on the kg scale. Models were run using TSD code TSD2-5 (Normal id, Dias 2011), 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. Where baseline weight was not reported for any study arm but mean baseline BMI was reported, baseline weight for each study arm was imputed from a linear regression of weight on BMI from studies reporting both metrics (Figure 1).

Within this model of weight change (Normal likelihood, log link), 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 standard error around the change from baseline, which is somewhat conservative (Balk et al. 2012, Daly et al. 2021).

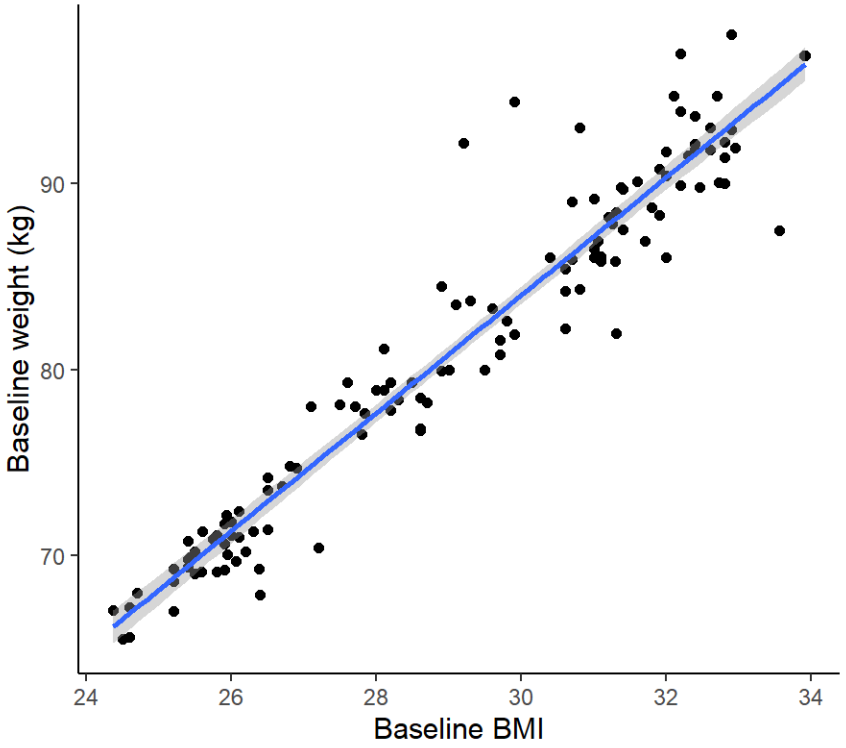

Figure 1. Linear regression of mean baseline weight on mean baseline BMI for all study arms reporting both metrics. The fitted linear model is shown by a solid blue line.

Model selection

Total residual deviance, posterior mean residual deviance, pD and DIC values were calculated within WinBUGS, 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.

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.

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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.

Change in glycaemic control: % HbA1c

NMAs for change in % HbA1c included 39 treatments of 18 classes, with results drawn from 107 studies (Figure 1).

Model fit

Moderate between-study variation in treatment effects was noted in this dataset, with the random-effects model preferred over the NMA modelling a single fixed (or common) treatment effect for each treatment comparison without interstudy variation (Table 1). Between-study standard deviation (SD) in the base-case model was 0.45 (95% CrI 0.40, 0.51), which is relatively high on the % HbA1c scale.

Clinical effectiveness relative to placebo

All treatments were effective in reducing % HbA1c relative to placebo (Figure 5). DPP4-inhibitors, in combination with metformin, SGLT-2 inhibitors in combination with metformin, and pioglitazone in combination with DPP-4 inhibitors were more effective than the treatments used individually (Figure 5). There was wide uncertainty around the effect estimate for the combination of glimepiride with metformin, with the credible interval including the probability of no difference in HbA1c relative to those receiving placebo (Figure 5).

Clinical effectiveness: active-active comparisons

There was clear evidence that metformin was effective in reducing % HbA1c relative to linagliptin, saxagliptin and vildagliptin (Table 2). There was evidence that tirzepatide and five treatment combinations – dapagliflozin with metformin, empagliflozin with metformin, linagliptin with metformin, pioglitazone with sitagliptin and sitagliptin with metformin – were effective in reducing % HbA1c relative to metformin alone. There were an additional 136 comparisons between active treatments where there was evidence to support a difference in the extent of HbA1c reduction (Appendix file 'RQ1.1_HbA1c_vsMetformin', tab Treatment Direct Effects). In general, smaller reductions in HbA1c were estimated in those receiving DPP4 inhibitors alone than in those receiving treatments of other classes and those receiving DPP4-inhibitors in combination with metformin.

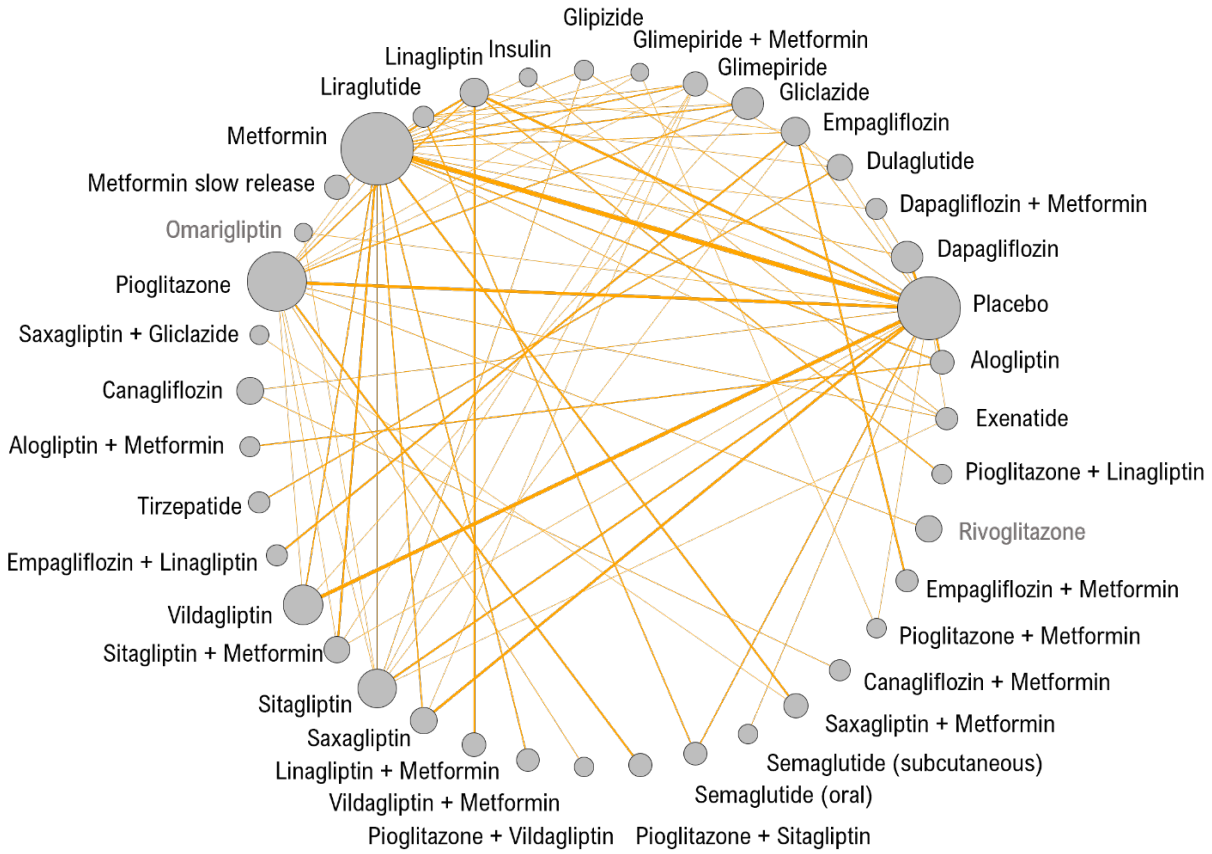

Figure 2. Network of evidence for change in % HbA1c on initial treatment in the population of people with type 2 diabetes. Circular points show interventions, with the size proportional to the number of participants receiving the intervention. Gold edges show treatment comparisons with RCT evidence, with the thickness of the edge proportional to the number of studies making the treatment comparison. Treatments shown in grey were included within the network of evidence but were not considered to be part of the decision set for initial treatment.

Change in % HbA1c: Global inconsistency check

Sensitivity of the NMA estimates to the consistency assumption was assessed by comparing the residual deviance of each study arm under the NMA (consistency) and UME (inconsistency) models. There was no improvement in model fit under the UME model (Table 1), though there was a reduction in the between-study SD from 0.45 (95% CrI 0.40, 0.51) to 0.38 (95% CrI 0.33, 0.44), suggesting that some inconsistency in direct and indirect trial evidence may be modelled as heterogeneity in the RE NMA.

Four study arms from three studies were flagged as inconsistent with evidence from the network (Figure 5): the third arm of Henry 2014, the fourth arm of Miyazaki 2002 and both arms of Camerini-Davalos 1988.

Camerini-Davalos 1988 reported particularly high final % HbA1c levels, suggesting possible differences in the study population or clinical practice. Final HbA1c levels were the highest reported in the dataset,

reporting means of 14 units % HbA1c in the placebo arm and 10.2 units % HbA1c on the glipizide arm. Final values in all other studies did not exceed 10 units % HbA1c.

Miyazaki 2002 was a dose-finding study trialling four doses of pioglitazone against placebo, within which the arm with the highest dose (45mg) was found to have relatively high deviance within the model. Henry 2014 was a seven-armed dose-finding study trialling three doses of pioglitazone and three doses of pioglitazone with sitagliptin against sitagliptin alone, within which the arm with a moderate dose of pioglitazone alone (30 mg) was found to have relatively high deviance within the model. This is consistent with the poor fit resulting from inclusion of several arms trialling different doses within the same study and an observed dose-response relationship that was not explicitly modelled. Other studies trialling pioglitazone at 30mg and 45mg did not show poor fit and the treatment effect can be interpreted as reflecting the estimated effect of a clinically appropriate dose of pioglitazone (between 7.5mg and 45mg) on % HbA1c.

Sensitivity analysis 1: restricting the dataset to doses used in UK clinical practice (NHS subset)

NMAs included 100 of the possible 107 studies (Figure 2). In the case of most treatments, treatment effect estimates for change in % HbA1c were very similar between the full model and the scenario analysis excluding doses not reflective of clinical practice in the UK (Figure 4). However, in the case of glipizide, there was a substantial increase in uncertainty of the treatment effect estimated from the restricted dataset. In the restricted dataset, doses of glipizide greater than 20mg daily were excluded: this excluded one study arm where the reported dose was 30mg; and one study arm where the reported dose was 20-40mg daily. The treatment effect estimated for glipizide in the base-case analysis (full dataset) reflects the treatment effect associated with a wide range of doses, including those higher than used in UK clinical practice. There was also a small increase in uncertainty in the treatment effect of linagliptin with metformin estimated from the restricted dataset, though there was no substantial movement in the mean treatment effect or conclusions of the combination treatment's efficacy relative to placebo.

The between-study SD was 0.46 units % HbA1c (95% CrI 0.42, 0.55), very similar to that estimated in the full dataset of 0.45 (95% CrI 0.40, 0.51) (Table 1).

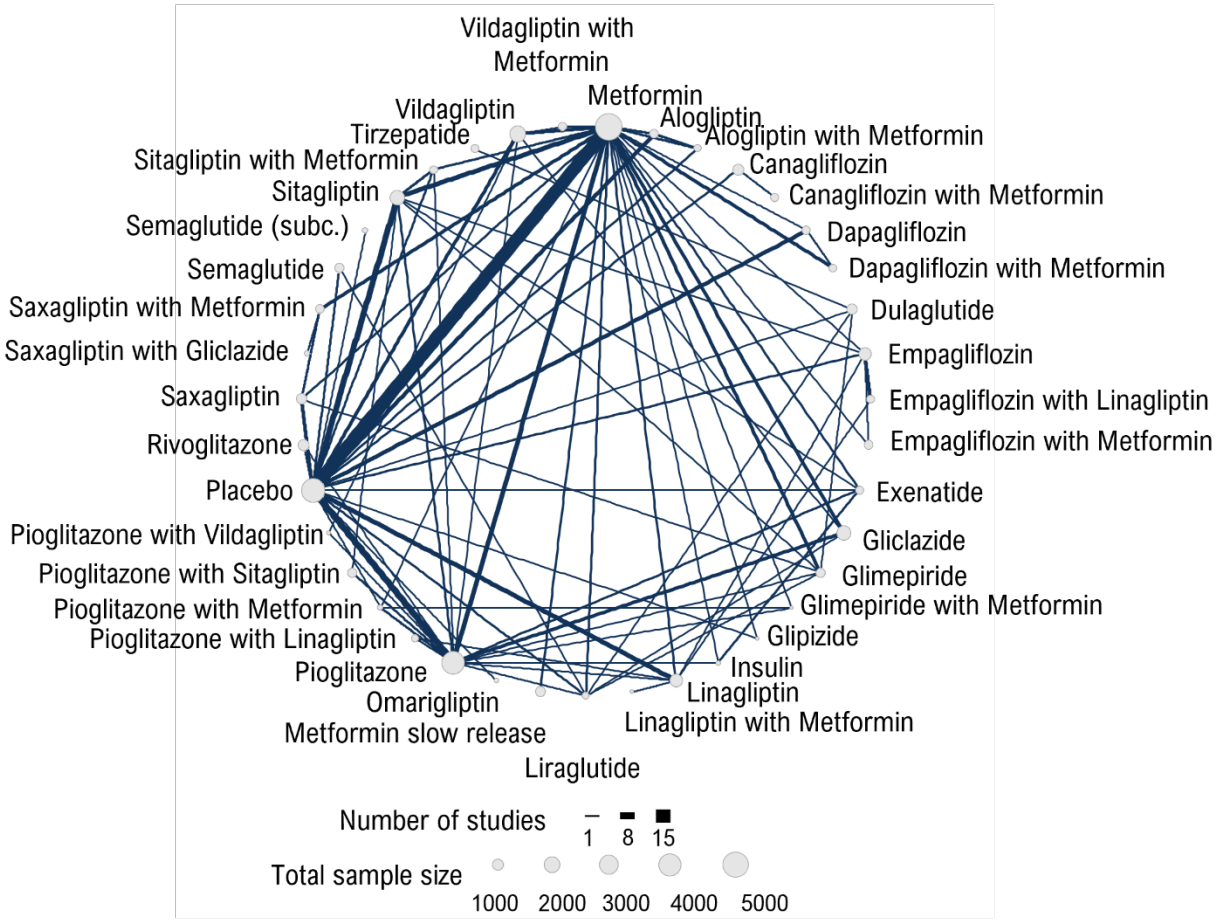

Figure 3. Network of evidence for change in % HbA1c on initial treatment in the population of people with type 2 diabetes (NHS subset: studies with doses reflecting current clinical practice).

Sensitivity analysis 2: excluding studies including insulin from analysis

NMAs included 104 of the possible 107 studies (Figure 3). Treatment effect estimates for change in % HbA1c were very similar between the full model and the scenario analysis excluding studies that included an insulin arm (Figure 4). Between-study SD was identical to that estimated in the full dataset (Table 1). Together these suggest there is little effect on treatment effect estimates of excluding studies including an insulin arm, where it was considered that there was a risk of the patient population experiencing more-severe disease.

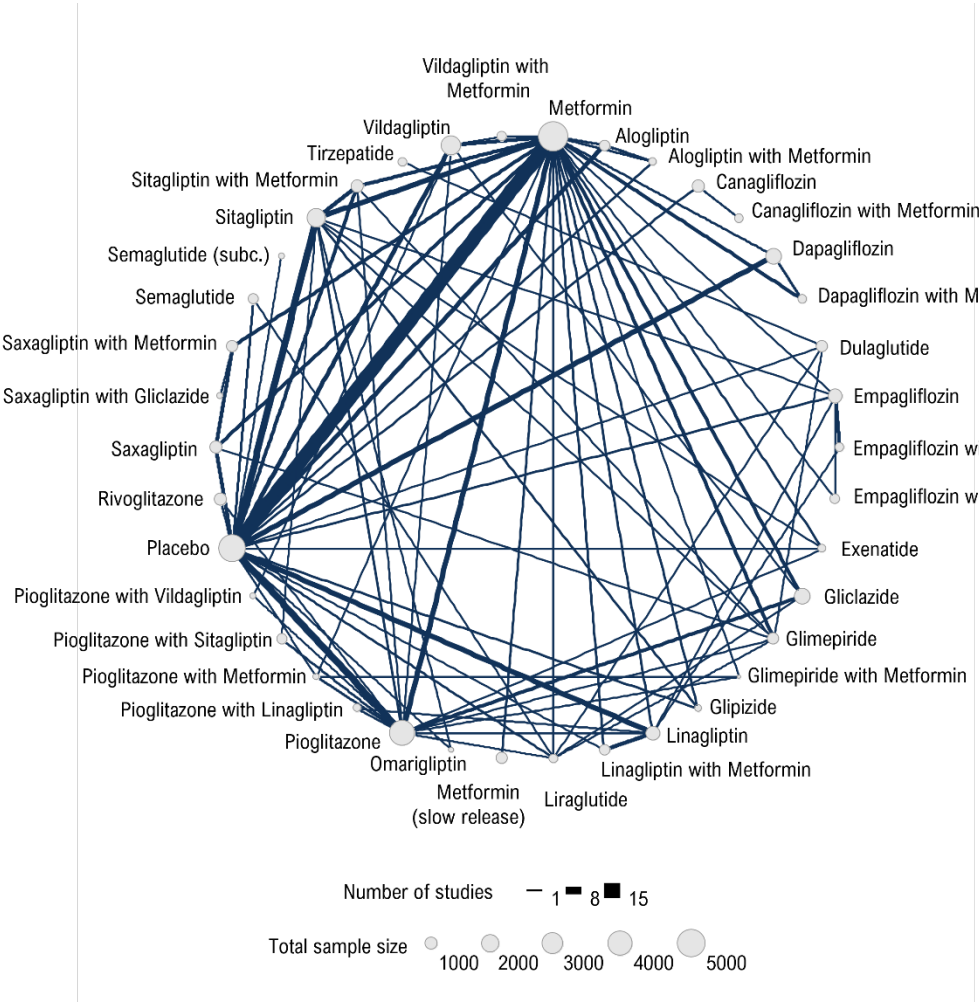

Figure 4. Network of evidence for change in % HbA1c on initial treatment in the population of people with type 2 diabetes (excluding studies trialling insulin).

Table 1. Model fit statistics, analysis of change in % HbA1c (RQ1.1).

Model effect structure	Model fit Total residual deviance[1]	Model fit Posterior mean residual deviance	Number of effective parameters (pD)	DIC (penalised deviance[1])	Between-study SD median, (95% CrI)
Main analysis, 327 datapoints from 107 studies					
Fixed, NMA	2048.0	1110.2	168.0	1278.2	-
Random, NMA	353.0	-585.3	320.6	-264.7	0.45 (0.40, 0.51)
Fixed, UME	1780.0	841.4	198.9	1040.4	-
Random, UME	358.4	-579.8	322.4	-257.4	0.38 (0.33, 0.44)
NHS subset, 293 datapoints from 100 studies					
Random, NMA	303.2	-533.6	285.9	-247.7	0.46 (0.42, 0.55)
Random, UME	307.3	-529.6	287.8	-241.8	0.41 (0.35, 0.48)
Insulin excluded, 320 datapoints from 104 studies					
Random, NMA	345.7	-575.0	314.0	-261.0	0.45 (0.40, 0.51)
Random, UME	351.3	-569.4	315.6	-253.7	0.38 (0.33, 0.44)

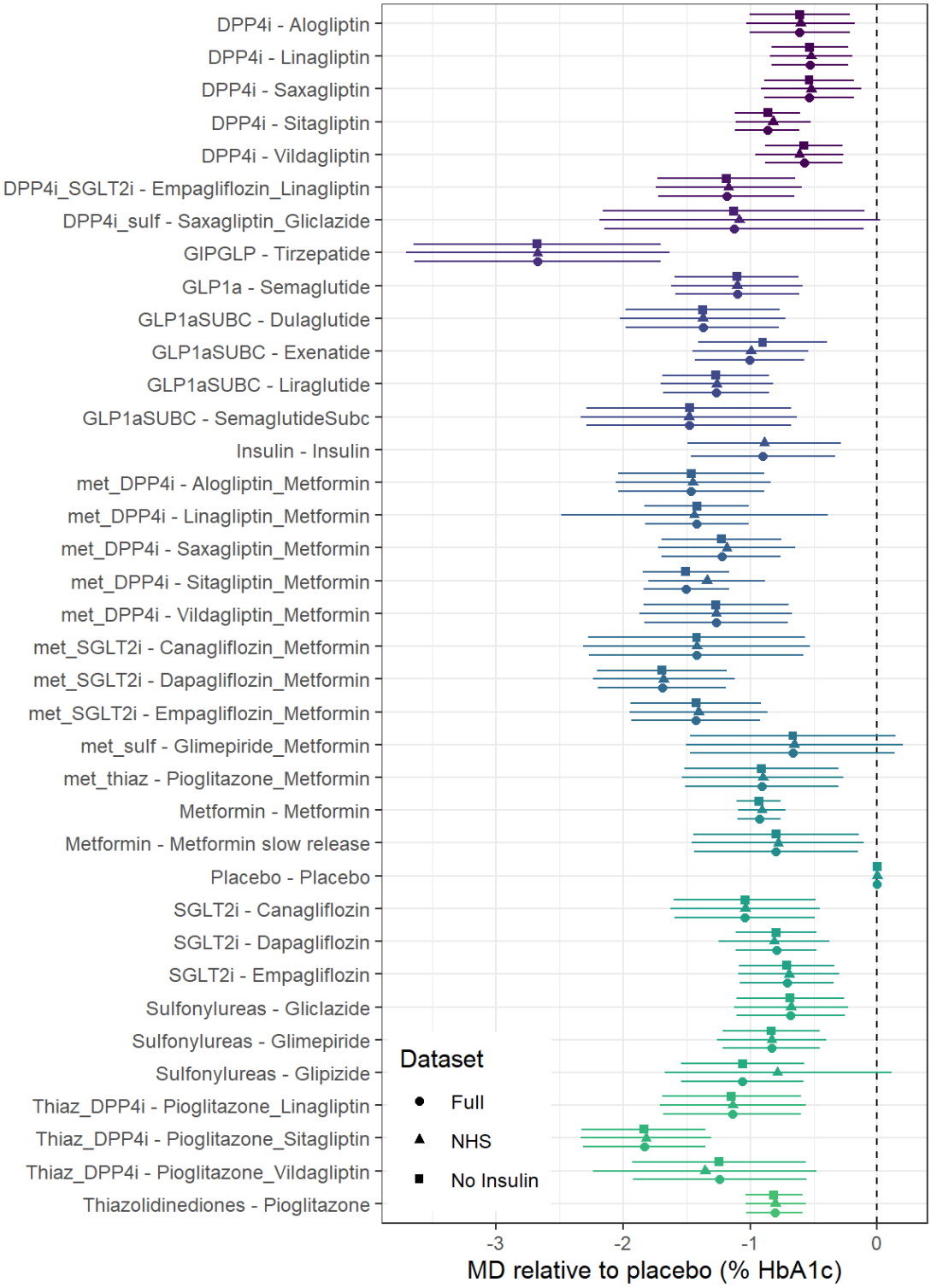

Figure 5. Mean difference in % HbA1c relative to placebo (mean and 95% CrI) for the full dataset (filled circles) and two data subsets: NHS (triangular points) and the dataset with insulin studies excluded (No Insulin).

Table 2. Treatment effects as mean differences in units of % HbA1c relative to i) metformin and ii) placebo. All measures expressed as mean value with 95% credible interval.

Class	Treatment	Mean difference in % HbA1c vs metformin Mean (95% CrI)	Mean difference in % HbA1c vs placebo Mean (95% CrI)
Metformin	Metformin	*Reference*	-0.93 (-1.10, -0.76)
	Metformin slow release	0.13 (-0.49, 0.76)	-0.80 (-1.44, -0.15)
Placebo	Placebo	0.93 (0.76, 1.10)	*Reference*
DPP4-inhibitor	Alogliptin	0.32 (-0.08, 0.72)	-0.61 (-1.00, -0.22)
	Linagliptin	0.40 (0.09, 0.71)	-0.53 (-0.83, -0.23)
	Omarigliptin	0.10 (-0.70, 0.90)	-0.83 (-1.62, -0.04)
	Saxagliptin	0.39 (0.04, 0.74)	-0.54 (-0.89, -0.18)
	Sitagliptin	0.07 (-0.19, 0.33)	-0.86 (-1.12, -0.61)
	Vildagliptin	0.35 (0.04, 0.67)	-0.58 (-0.88, -0.27)
DPP4-inhibitor with metformin	Alogliptin with Metformin	-0.53 (-1.10, 0.04)	-1.46 (-2.04, -0.89)
	Linagliptin with Metformin	-0.49 (-0.89, -0.09)	-1.42 (-1.83, -1.01)
	Saxagliptin with Metformin	-0.30 (-0.75, 0.16)	-1.23 (-1.70, -0.76)
	Sitagliptin with Metformin	-0.57 (-0.91, -0.24)	-1.50 (-1.84, -1.17)
	Vildagliptin with Metformin	-0.34 (-0.88, 0.21)	-1.27 (-1.83, -0.70)
SGLT2i with DPP4i	Empagliflozin with Linagliptin	-0.26 (-0.80, 0.28)	-1.19 (-1.72, -0.65)
DPP4i with sulfonylurea	Saxagliptin with Gliclazide	-0.20 (-1.21, 0.82)	-1.13 (-2.15, -0.11)
SGLT2-inhibitor	Canagliflozin	-0.11 (-0.69, 0.47)	-1.04 (-1.59, -0.49)
	Dapagliflozin	0.13 (-0.20, 0.47)	-0.80 (-1.11, -0.48)
	Empagliflozin	0.22 (-0.16, 0.59)	-0.71 (-1.08, -0.34)

SGLT2-inhibitor with metformin	Canagliflozin with Metformin	-0.49 (-1.36, 0.37)	-1.42 (-2.27, -0.58)
	Dapagliflozin with Metformin	-0.76 (-1.26, -0.27)	-1.69 (-2.20, -1.19)
	Empagliflozin with Metformin	-0.50 (-0.99, 0.00)	-1.43 (-1.94, -0.92)
GLP1 agonists	Dulaglutide	-0.44 (-1.06, 0.16)	-1.37 (-1.98, -0.77)
	Exenatide	-0.08 (-0.51, 0.35)	-1.01 (-1.44, -0.58)
	Liraglutide	-0.34 (-0.76, 0.09)	-1.27 (-1.69, -0.85)
	Semaglutide (oral)	-0.17 (-0.68, 0.34)	-1.10 (-1.59, -0.61)
	Semaglutide (subcutaneous)	-0.55 (-1.38, 0.27)	-1.48 (-2.29, -0.68)
GIPGLP	Tirzepatide	-1.74 (-2.72, -0.77)	-2.67 (-3.64, -1.70)
Sulfonylureas	Gliclazide	0.25 (-0.17, 0.67)	-0.68 (-1.10, -0.26)
	Glimepiride	0.10 (-0.28, 0.47)	-0.83 (-1.21, -0.45)
	Glipizide	-0.13 (-0.62, 0.35)	-1.06 (-1.55, -0.58)
Sulfonylurea with metformin	Glimepiride with Metformin	0.27 (-0.54, 1.07)	-0.66 (-1.47, 0.14)
Thiazolidinedione	Pioglitazone	0.12 (-0.11, 0.35)	-0.81 (-1.03, -0.59)
	Rivoglitazone	0.17 (-0.48, 0.83)	-0.76 (-1.40, -0.11)
Thiazolidinedione combination	Pioglitazone with Linagliptin	-0.21 (-0.76, 0.34)	-1.14 (-1.68, -0.60)
	Pioglitazone with Sitagliptin	-0.90 (-1.39, -0.42)	-1.83 (-2.32, -1.35)
	Pioglitazone with Vildagliptin	-0.31 (-1.00, 0.38)	-1.24 (-1.92, -0.55)
	Pioglitazone with Metformin	0.02 (-0.58, 0.63)	-0.91 (-1.51, -0.31)
Insulin	Insulin	0.03 (-0.53, 0.59)	-0.90 (-1.47, -0.33)

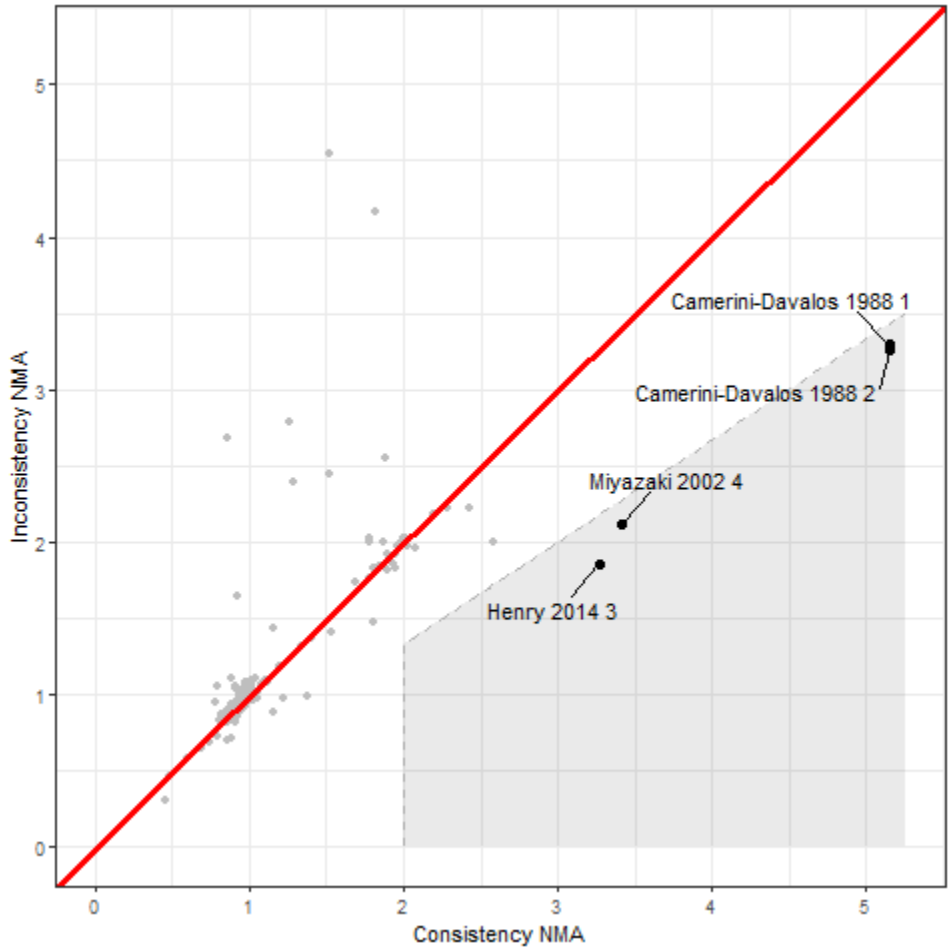

Figure 6. Residual deviance for each study arm in the analysis of HbA1c change during initial treatment for T2DM under the NMA (consistency) and UME (inconsistency) models. Study arms are labelled where the posterior mean residual deviance was higher in the model requiring consistency than in the model without this assumption.

Change in body weight

NMAs included 34 treatments of 14 classes, with results drawn from 68 studies (Figure 6). Nine studies were dropped from the original dataset of 76 studies because they did not report one or several of the following: mean weight change per arm, SD or SE of mean weight change, or at least one of baseline weight or BMI. The full list of included studies is available in the Appendix file RQ1.1 Weight vs Metformin (Data tab, column BN).

Model fit

The RE model, which estimates treatment effects as a distribution described by the between-study SD, was preferred over the FE model. The between-study SD was large on the modelling scale (Table 3): for example, the relative treatment effect for canagliflozin was -0.037 (95% CrI: -0.054, -0.019) on the log-ratio of mean scale, which corresponds to a ratio of weight at follow-up of 0.96 relative to placebo (95% CrI: 0.95, 0.98), whilst the between-study SD was 0.012 (95% CrI 0.010, 0.015).

Clinical effectiveness relative to placebo

There was strong evidence to support a reduction in weight compared to placebo for treatment with tirzepatide (Table 4) and the SGLT2-inhibitors canagliflozin, dapagliflozin and empagliflozin, both alone and in combination with metformin. There was strong evidence of an increase in body weight relative to the change in weight seen on placebo for insulin and for pioglitazone, both alone and in combination with the DPP4-inhibitors vildagliptin, linagliptin and sitagliptin. There was clear evidence of an increase in body weight relative to placebo on treatment with several DPP4-inhibitors, linagliptin, saxagliptin, sitagliptin and vildagliptin, as well as the sulfonylureas gliclazide and glipizide. There was weaker evidence of an increase in body weight relative to the change in weight seen on placebo for glimepiride and alogliptin. Metformin and slow-acting metformin showed similar action to each other and showed no evidence of either a reduction or increase in weight relative to placebo (Figure 9). There was strong evidence of a reduction in body weight on treatment with subcutaneous semaglutide when compared to placebo, and weaker evidence of a reduction in body weight (relative to placebo) on treatment with exenatide, liraglutide and oral semaglutide.

Clinical effectiveness: active-active comparisons

Treatment with tirzepatide saw the largest mean estimated reduction in weight, and there was clear evidence for a greater reduction in weight on tirzepatide than on the three represented sulfonylureas (gliclazide, glimepiride, glipizide); metformin (type-unspecified and slow-release); insulin; pioglitazone alone and in combination with linagliptin, sitagliptin, or vildagliptin; all represented DPP4-inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin), both alone and in combination with metformin; as well as dulaglutide, exenatide, liraglutide and dapagliflozin. For full treatment comparisons, see Appendix file RQ1.1 – Weight vs Metformin, tab Treatment Direct Effects.

Both canagliflozin and canagliflozin with metformin showed similar effectiveness, with clear evidence of reduction in weight on canagliflozin (with and without metformin) relative to the three represented sulfonylureas (gliclazide, glimepiride, glipizide); metformin (type-unspecified and slow-release); insulin; pioglitazone alone and in combination with linagliptin, sitagliptin, or

vildagliptin; all represented DPP4-inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin), both alone and in combination with metformin; exenatide and dapagliflozin.

With relatively large and precisely estimated treatment effects, there was evidence that treatment with subcutaneous semaglutide, empagliflozin, dapagliflozin and dapagliflozin with metformin resulted in greater reductions in body weight than treatment with 17 treatments estimated to have smaller reductions in weight: gliclazide, glipizide, alogliptin, linagliptin (with and without metformin), metformin alone, pioglitazone (alone and with linagliptin, sitagliptin or vildagliptin); saxagliptin, sitagliptin (with and without metformin) and vildagliptin (with and without metformin) (Appendix file RQ1.1 – Weight vs Metformin, tab Treatment Direct Effects).

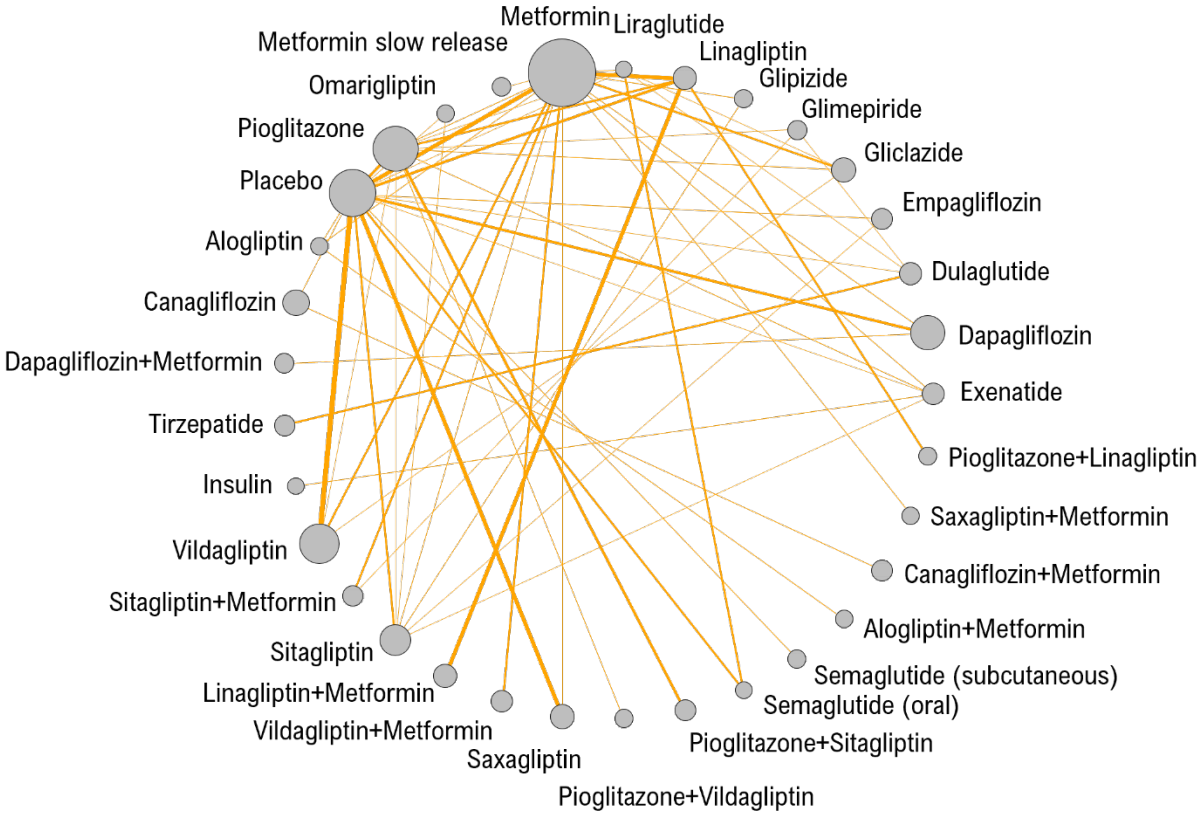

Figure 7. Network of evidence for change in body weight on initial treatment in the population of people with type 2 diabetes. Circular points show interventions, with the size proportional to the number of participants receiving the intervention. Gold edges show treatment comparisons with RCT evidence, with the thickness of the edge proportional to the number of studies making the treatment comparison.

Change in body weight: Global inconsistency check

Sensitivity of the NMA estimates to the consistency assumption was assessed by comparing the residual deviance of each study arm under the NMA (consistency) and UME (inconsistency) random-effect models. Study arms from Inagaki 2022 (3 and 4) and Zhang 2020A (1 and 2) were identified as inconsistent in the RE models. Additionally, between-study SD dropped slightly between NMA and UME models, suggesting a small reduction in between-study differences when the consistency assumption is relaxed and indirect estimates are no longer forced to be consistent with direct estimates.

Inagaki 2022 was a four-armed study trialling three doses of tirzepatide against dulaglutide. In this case, the two study arms reporting the larger (10.7kg reduction, SE=0.4) and smaller (5.8kg reduction, SE=0.4) changes in weight had higher deviance, whilst the study arm reporting a 8.5kg reduction (SE=0.4) fitted well in the NMA model. This is a consequence of the model not explicitly modelling drug dose and, since tirzepatide is on a spur of the network, these estimates may indicate heterogeneity in treatment effect estimates due to dose, rather than inconsistency. The impact of this may be localised to tirzepatide (and any comparisons with it) since this study is on a spur of the network.

Zhang 2020A was a two-armed study trialling pioglitazone against liraglutide in a small number of participants (30 per arm). The authors reported a large mean reduction in weight for those on the liraglutide arm (CFB = -10.1kg, SE=9.5kg), and a small mean increase in weight for those on the pioglitazone arm (CFB=1.1kg, SE=9.5kg). Given the small number of participants, both reported CFBs had large standard errors. This means that these study arms had less weight in the model, and appeared to fit poorly: the dataset also contained other, more precise, estimates of the treatment effects of liraglutide and pioglitazone from larger studies.

Sensitivity analysis 1: restricting the dataset to doses used in UK clinical practice

NMAs included 63 of the possible 68 studies (Figure 7). Treatment effect estimates for weight change were very similar between the full model and the scenario analysis excluding doses not reflective of clinical practice in the UK (Figure 10). The between-study standard deviation was identical to that estimated in the full dataset (Table 3).

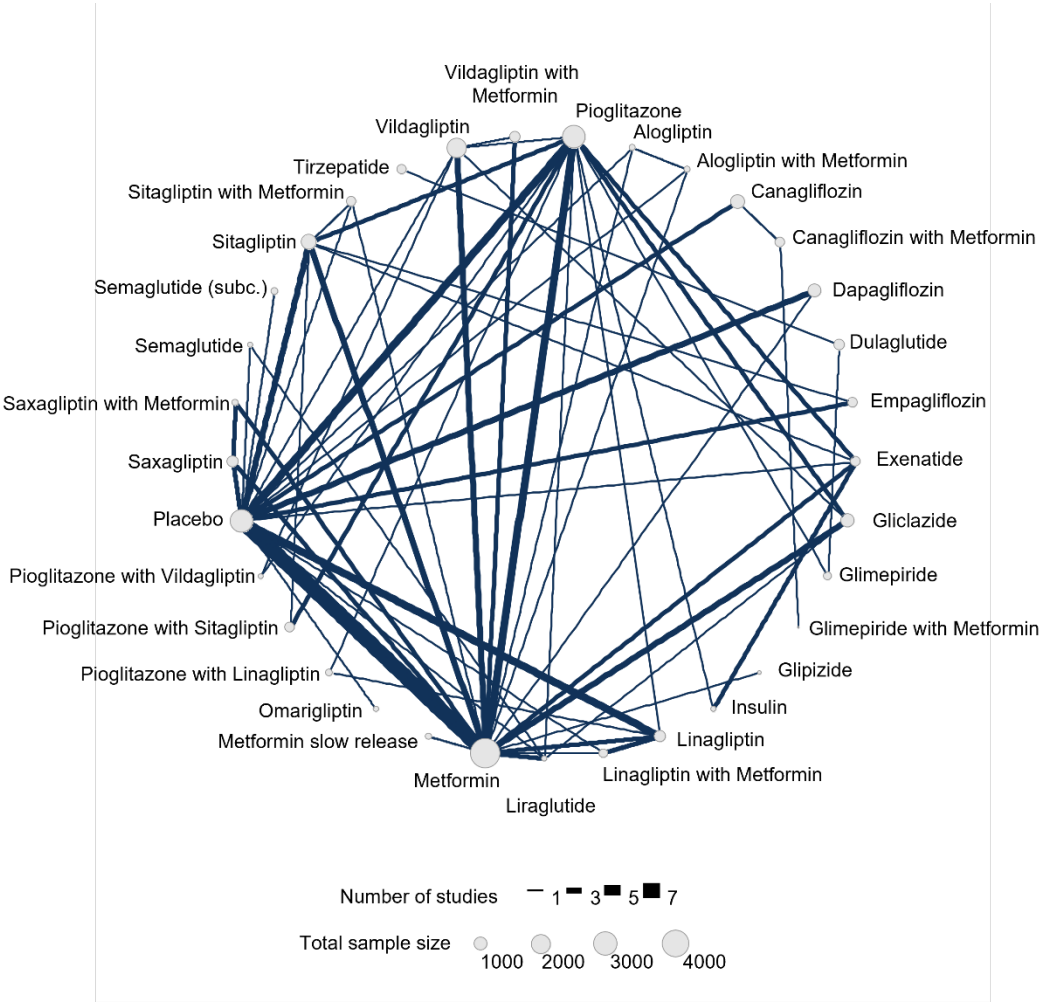

Figure 8. Network of evidence for change in body weight on initial treatment in the population of people with type 2 diabetes (subset of studies with doses reflecting current clinical practice).

Sensitivity analysis 2: excluding studies including insulin from analysis

NMAs included 66 of the possible 68 studies (Figure 8). Treatment effect estimates for weight change were very similar between the full model and the scenario analysis excluding studies that included an insulin arm (Figure 10). The between-study standard deviation – a measure of heterogeneity – was identical to that estimated in the full dataset (Table 3). Together these suggest there is little effect on treatment effect estimates of excluding studies including an insulin arm, where it was considered that there was a risk of the patient population experiencing more-severe disease.

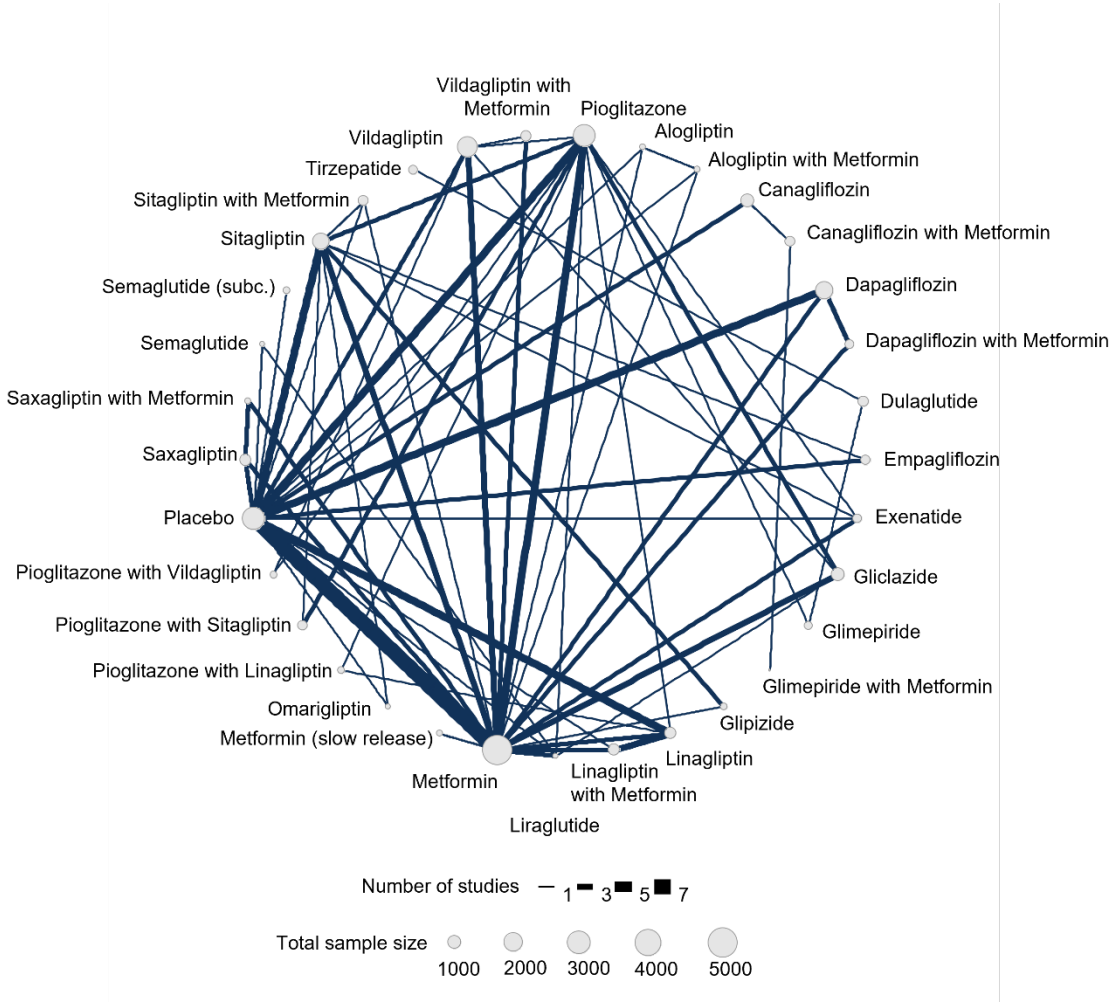

Figure 9. Network of evidence for change in body weight on initial treatment in the population of people with type 2 diabetes (excluding studies trialling insulin).

Table 3. Model fit statistics, analysis of weight change (RQ1.1).

NMA effect structure	Model fit Total residual deviance[1]	Model fit Posterior mean residual deviance	Number of effective parameters (pD)	DIC (penalised deviance[1])	Between-study SD median, (95% CrI)
Main, *235 datapoints from 68 studies*					
Fixed, NMA	2022.0	2063.2	124.0	2187.2	-
Random, NMA	234.9	276.2	203.7	479.8	0.012 (0.010, 0.015)
Fixed, UME	1952.0	1992.7	142.0	2134.7	-
Random, UME	226.3	267.4	209.8	477.2	0.010 (0.009, 0.013)
NHS subset, 205 datapoints from 63 studies					
Fixed, NMA	762.8	813.2	115.1	928.3	-
Random, NMA	207.5	258.1	177.4	435.4	0.012 (0.010, 0.015)
Fixed, UME	651.3	701.6	133.0	834.5	-
Random, UME	198.9	249.3	183.5	432.8	0.010 (0.008, 0.013)
Insulin excluded, 230 datapoints from 66 studies					
Fixed, NMA	2010.0	2044.3	119.0	2163.3	-
Random, NMA	226.0	260.2	197.5	457.6	0.012 (0.010, 0.015)
Fixed, UME	1944.0	1978.8	136.0	2114.7	-
Random, UME	219.4	253.6	203.4	457.0	0.010 (0.009, 0.013)

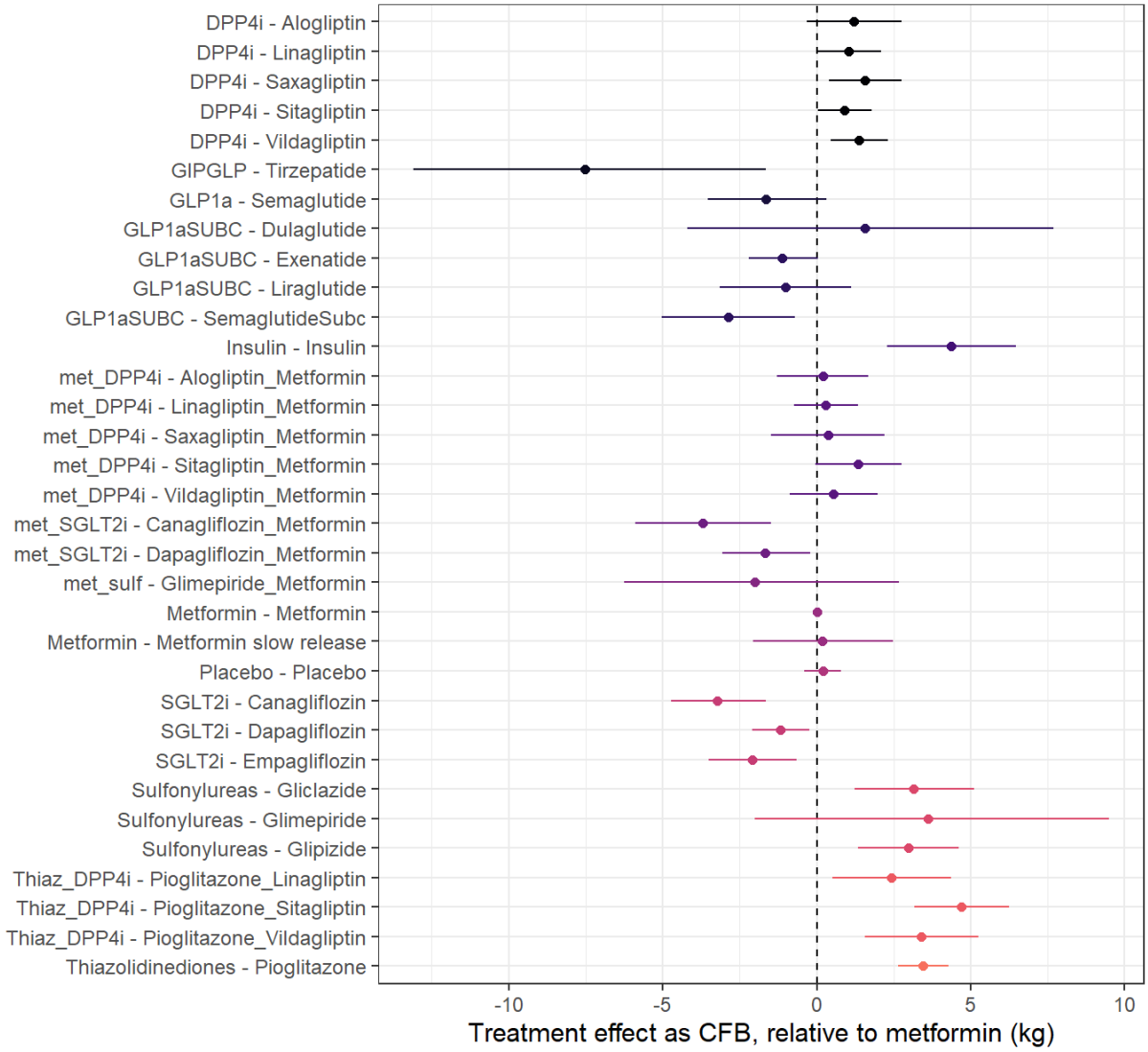

Figure 10. Treatment effect on weight change in kg, modelling treatment effect as a proportional measure. CFB is calculated given a baseline weight of 90kg and a CFB on metformin of -2.64kg.

Table 4. Treatment ranks and treatment effects as i) ratios ii) expressed in kg, given a representative CFB and final weight from the metformin arm of Roden 2005. All measures expressed as median value with 95% credible interval.

Treatment	**Treatment effect as ratio vs metformin[1]**	**Treatment effect as ratio vs placebo**	**Treatment effect as CFB (kg)**	**Treatment effect as Final weight (kg)**	**Rank**
Metformin	Reference	0.99 (0.97, 1.00)	Representative: -2.64	Representative: 89.7	14 (11, 18)
Metformin slow release	1.00 (0.98, 1.03)	1.00 (0.97, 1.03)	-2.5 (-4.7, -0.2)	89.9 (87.6, 92.2)	15 (6, 27)
Placebo	1.00 (1.00, 1.01)	Reference	-2.4 (-3.0, -1.9)	89.9 (89.3, 90.5)	15 (12, 20)
Alogliptin	1.01 (1.00, 1.03)	1.01 (0.99, 1.03)	-1.4 (-3.0, 0.1)	90.9 (89.4, 92.5)	22 (13, 28)
Linagliptin	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	-1.6 (-2.6, -0.5)	90.7 (89.7, 91.8)	21 (15, 27)
Omarigliptin	1.01 (0.99, 1.04)	1.01 (0.99, 1.03)	-1.6 (-3.5, 0.5)	90.8 (88.8, 92.9)	21 (10, 29)
Saxagliptin	1.02 (1.00, 1.03)	1.02 (1.00, 1.03)	-1.1 (-2.2, 0.1)	91.3 (90.1, 92.5)	24 (17, 29)
Sitagliptin	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	-1.7 (-2.6, -0.9)	90.6 (89.7, 91.5)	20 (15, 25)
Vildagliptin	1.02 (1.01, 1.03)	1.01 (1.00, 1.02)	-1.3 (-2.2, -0.3)	91.1 (90.2, 92.0)	23 (17, 27)
Alogliptin with Metformin	1.00 (0.99, 1.02)	1.00 (0.98, 1.02)	-2.4 (-3.9, -1.0)	89.9 (88.4, 91.4)	16 (9, 25)
Linagliptin with Metformin	1.00 (0.99, 1.02)	1.00 (0.99, 1.01)	-2.4 (-3.4, -1.3)	90.0 (89.0, 91.0)	16 (11, 23)
Saxagliptin with Metformin	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	-2.3 (-4.1, -0.4)	90.1 (88.2, 91.9)	17 (8, 26)
Sitagliptin with Metformin	1.02 (1.00, 1.03)	1.01 (1.00, 1.03)	-1.3 (-2.7, 0.1)	91.0 (89.7, 92.5)	23 (14, 28)
Vildagliptin with Metformin	1.01 (0.99, 1.02)	1.00 (0.99, 1.02)	-2.1 (-3.5, -0.7)	90.3 (88.8, 91.7)	18 (10, 26)

[1] Where ratio interval is below one, the mean body weight at follow-up on treatment will be lower than that on metformin. Where the ratio interval is above one, the mean body weight at follow-up on treatment will be higher than that on metformin.

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Canagliflozin	0.96 (0.95, 0.98)	0.96 (0.95, 0.98)	-5.9 (-7.4, -4.3)	86.5 (85.0, 88.0)	4 (2, 7)
Dapagliflozin	0.99 (0.98, 1.00)	0.98 (0.98, 0.99)	-3.8 (-4.7, -2.9)	88.5 (87.6, 89.5)	9 (6, 13)
Empagliflozin	0.98 (0.96, 0.99)	0.97 (0.96, 0.99)	-4.7 (-6.1, -3.3)	87.6 (86.2, 89.1)	6 (3, 11)
Canagliflozin with Metformin	0.96 (0.93, 0.98)	0.96 (0.93, 0.98)	-6.3 (-8.5, -4.1)	86.0 (83.8, 88.2)	3 (1, 8)
Dapagliflozin with Metformin	0.98 (0.97, 1.00)	0.98 (0.96, 1.00)	-4.3 (-5.7, -2.9)	88.0 (86.7, 89.5)	7 (3, 13)
Dulaglutide	1.02 (0.95, 1.09)	1.02 (0.95, 1.08)	-1.1 (-6.8, 5.1)	91.3 (85.5, 97.4)	24 (2, 33)
Exenatide	0.99 (0.98, 1.00)	0.99 (0.97, 1.00)	-3.8 (-4.9, -2.6)	88.6 (87.5, 89.7)	10 (5, 14)
Liraglutide	0.99 (0.97, 1.01)	0.99 (0.96, 1.01)	-3.7 (-5.8, -1.5)	88.7 (86.6, 90.8)	10 (4, 21)
Semaglutide (oral)	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)	-4.3 (-6.2, -2.3)	88.1 (86.2, 90.0)	8 (3, 16)
Semaglutide (subcutaneous)	0.97 (0.94, 0.99)	0.97 (0.94, 0.99)	-5.5 (-7.7, -3.3)	86.8 (84.7, 89.0)	4 (1, 11)
Tirzepatide	0.92 (0.85, 0.98)	0.91 (0.85, 0.98)	-10.2 (-15.7, -4.3)	82.2 (76.6, 88.0)	1 (1, 7)
Gliclazide	1.04 (1.01, 1.06)	1.03 (1.01, 1.06)	0.5 (-1.4, 2.5)	92.8 (90.9, 94.8)	29 (23, 34)
Glimepiride	1.04 (0.98, 1.11)	1.04 (0.98, 1.10)	1.0 (-4.6, 6.9)	93.3 (87.7, 99.2)	31 (7, 34)
Glipizide	1.03 (1.02, 1.05)	1.03 (1.01, 1.05)	0.3 (-1.3, 2.0)	92.7 (91.0, 94.3)	29 (23, 33)
Glimepiride with Metformin	0.98 (0.93, 1.03)	0.98 (0.93, 1.03)	-4.7 (-8.9, 0.0)	87.7 (83.5, 92.4)	6 (1, 27)
Pioglitazone	1.04 (1.03, 1.05)	1.04 (1.03, 1.05)	0.8 (0.0, 1.6)	93.2 (92.4, 94.0)	30 (27, 33)
Pioglitazone with Linagliptin	1.03 (1.01, 1.05)	1.03 (1.00, 1.05)	-0.2 (-2.1, 1.7)	92.1 (90.2, 94.1)	27 (18, 32)
Pioglitazone with Sitagliptin	1.05 (1.04, 1.07)	1.05 (1.03, 1.07)	2.1 (0.5, 3.6)	94.4 (92.9, 96.0)	33 (30, 34)
Pioglitazone with Vildagliptin	1.04 (1.02, 1.06)	1.04 (1.02, 1.06)	0.8 (-1.1, 2.6)	93.1 (91.3, 95.0)	30 (24, 34)

Insulin	1.05 (1.03, 1.07)	1.05 (1.02, 1.07)	1.7 (-0.4, 3.8)	94.1 (92.0, 96.2)	32 (27, 34)

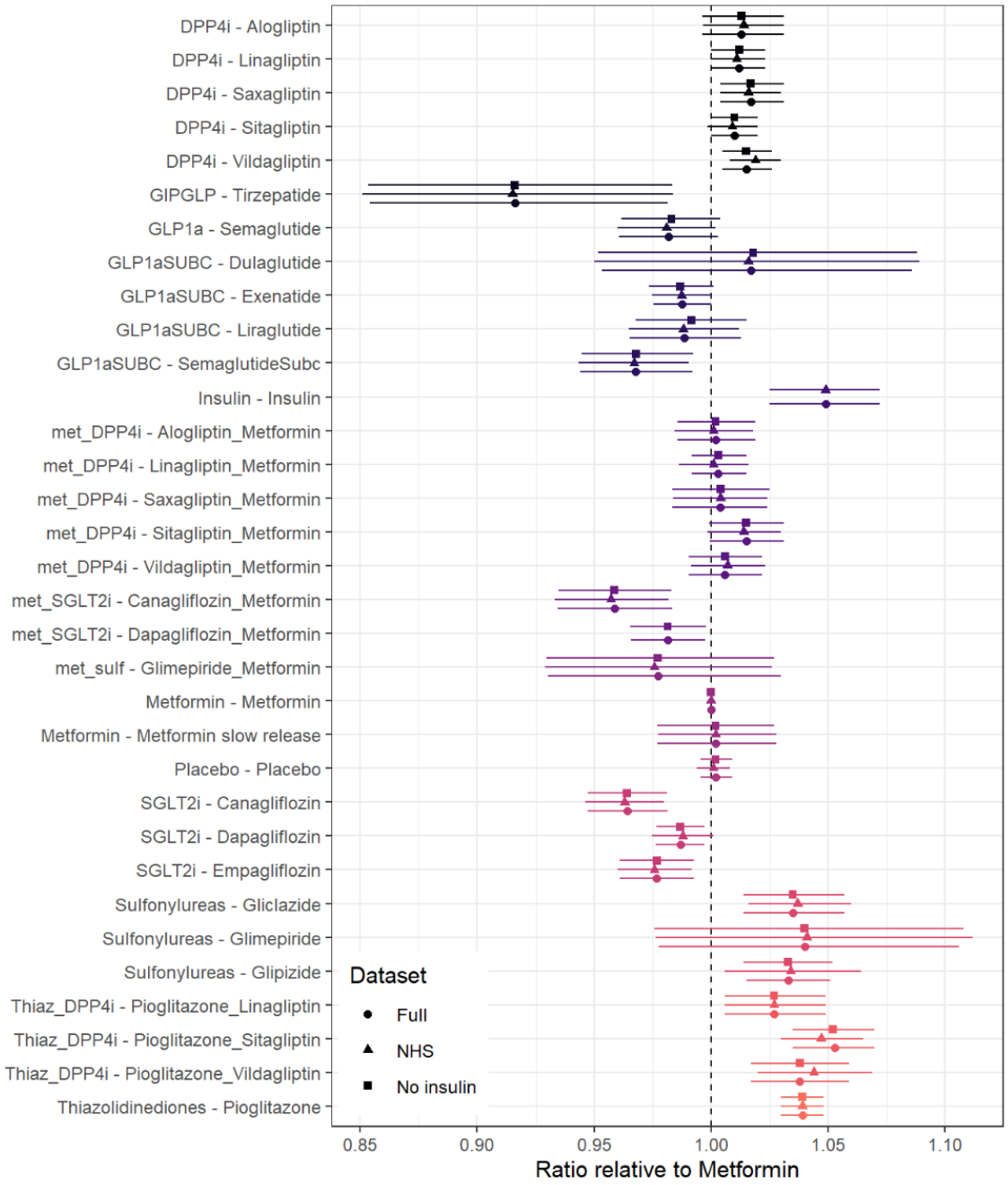

Figure 11. Treatment effect on weight change, expressed as a ratio relative to metformin as estimated from the full dataset (circular points); the subset of trial arms delivering doses reflecting clinical practice in the NHS (triangular points); and the dataset having excluded studies which trialled active treatments against insulin (square points). Colour of line is related to treatment class, for ease of viewing.

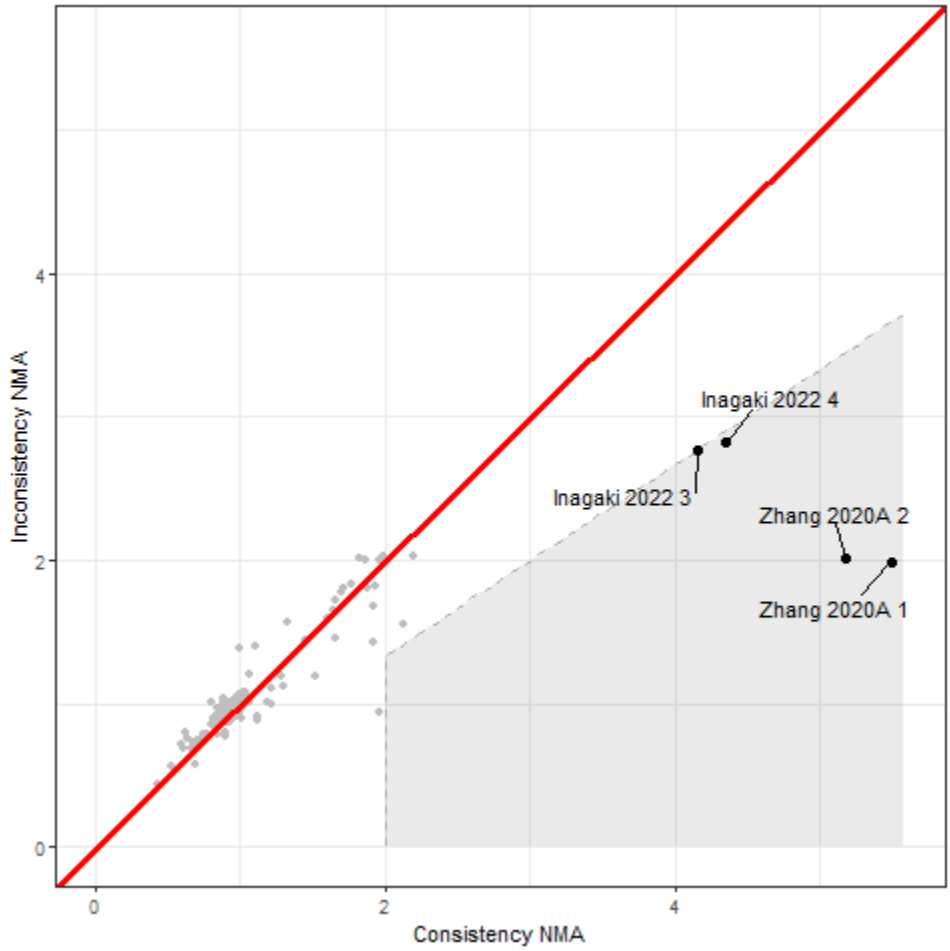

Figure 12. Residual deviance for each study arm in the analysis of weight change during initial treatment for T2DM under the NMA (consistency) and UME (inconsistency) models. Arms from Inagaki 2022 and Zhang 2020A were identified as inconsistent.

NHS subset – excluded doses

Following discussion with the committee, doses that were not expected to reflect current clinical practice were excluded from the dataset.

The results of these analyses are presented as a sensitivity analysis in sections headed 'Sensitivity analysis 1: restricting the dataset to doses used in UK clinical practice (NHS subset)'.

- Saxagliptin, less than 5mg daily or 10mg
- Dapagliflozin, 1mg, 2.5mg, 5mg daily
- Glimepiride, greater than 8mg daily
- Glipizide, greater than 20mg daily
- Pioglitazone, 7.5mg daily
- Vildagliptin, 50mg once daily
- Sitagliptin, doses other than 100mg daily
- Alogliptin, total daily dose of less than 25mg
- Exenatide, less than 0.1 micrograms daily
- Linagliptin, less than 5mg daily

References

- Balk EM, Earley A, Patel K, Trikalinos TA, Dahabreh IJ. Empirical assessment of within-arm correlation imputation in trials of continuous outcomes. Rockville: Agency for Healthcare Research and Quality; 2012.

- 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.

- Dias S, Welton N, Sutton A, Ades A. 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 https://www.sheffield.ac.uk/nice-dsu/tsds

- Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence Synthesis for Decision Making 4: Inconsistency in Networks of Evidence Based on Randomized Controlled Trials. Medical Decision Making 2013 33:641-656

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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).
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
# 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 (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
    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
treat k is best
            prob[h,k] <- equals(rk[k],h)              # prob k is h-th best
```

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```
      }
}

# 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
```

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).
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
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

# 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
    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 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
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 with relative effect modelled on the log scale (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;
#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
# 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
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,0.001)           # 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.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)
      }
  }

### 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
      armn[i,k] <- n[i,k]

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

# Outcome measure: change from baseline (requires baseline)
            yc[i,k] <- CFB_mean[i,k]
            phiB[i,k] <- base_mean[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
            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 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)
      for (k in 1:na[i]) {    ##  LOOP THROUGH ARMS

      armn[i,k] <- n[i,k]

# SE and variances at baseline and follow-up
            base_se[i,k] <- base_sd[i,k]/sqrt(armn[i,k])
            base_var[i,k] <- pow(base_se[i,k],2)
            f_se[i,k] <- f_sd[i,k]/sqrt(armn[i,k])
            f_var[i,k] <- pow(f_se[i,k],2)
            prec[i,k] <- pow(0.5,-2) # not used in estimation for these rows

# Outcome measure: baseline and post-treatment means standardised by study SD
```

```
            yp[i,k,1] <- base_mean[i,k]
            yp[i,k,2] <- f_mean[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, 0.0001)

## 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]  * f_se[i,k] )
      sigma[i, k, 2, 1]  <- ( corr * base_se[i,k]  *f_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)
            res[i, k, j] <- yp[i, k, j] - phiPP[i, k, j]
            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

      armn[i,k] <- n[i,k]

# SE
            f_se[i,k] <- f_sd[i,k]/sqrt(armn[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(0,5)     # 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
      best[k] <- equals(rk[k],1)    ## probability that treat k 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]
            }
      }

### dummy variables so that same dataset may be used for all models
dum[1] <- class[1,1]
dum[2] <- corr + pp[1] + t[1,1]
dum[3] <- base_sd[1,1] + f_sd[1,1]
```

```
}                                       # *** 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).
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
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
    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, 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).
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
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,0.001)           # 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 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
## 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
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
    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
```

END