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SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Empagliflozin combination therapy for treating type 2 diabetes [ID 641]

Dear [redacted]

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have now had an opportunity to take a look at the submission by Boehringer Ingelheim and Lilly UK received on 23 April. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm on 3 June**. Two versions of this written response should be submitted; one with any academic/commercial in confidence information clearly marked and one from which this information is removed. You may feel that some of the technical questions relating to the economic model could be answered more efficiently via a teleconference rather than in writing. If this is the case, please contact [redacted] by 5pm on 23 May so that a teleconference can be arranged within the appropriate time period.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

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If you have any further queries on the technical issues raised in this letter then please contact [redacted]. Any procedural questions should be addressed to Bijal Joshi, Project Manager, in the first instance.

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

A1. **PRIORITY.** The four key trials (counting EMPA-REG 1245-23 as two trials, one in dual therapy, one in triple, with the other two being EMPA-REG BASAL and EMPA-REG MD) report mean change in HbA1c. Please provide for each of the four trials, the proportions of patients achieving the following HbA1c targets: 6.5% or less (the NICE CG 87 target); 7.0% or less (to cater for a situation wherein NICE relax the current target during the current guideline revision): and 7.5% or less (based on the NICE "switching point").
It would be useful to have these data by baseline HbA1c, by completing the following table.

	% achieving HbA1c levels, by 24 weeks, of		
	6.5% or less	7.0% or less	7.5% or less
EMPA-REG MET			
Baseline HbA1c			
<8.0%			
8.0-8.9%			
9.0 and over			
All baseline A1Cs			
EMPA-REG METSU			
Baseline HbA1c			
<8.0%			
8.0-8.9%			
9.0% and over			
All baseline A1cs			
BASAL			
Baseline HbA1c			
<8.0%			
8.0-8.9%			
9.0% and over			
All baseline A1cs			

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MDI			
Baseline HbA1c			
<8.0%			
8.0-8.9%			
9.0% and over			
All baseline A1cs			

A2. For convenience and clarity in the NMA diagrams, please identify trials for each line, rather than just number of RCTs – using name of first author. For example, in figure 28, replace "5" in the line connecting sitagliptin with metformin with the names of first authors of the five RCTs.

A3. Since the NMAs have been done to inform the cost effectiveness model, and since the MS specifies the cost effectiveness is done to compare sitagliptin v. canagliflozin, v dapagliflozin v empagliflozin, please clarify why studies of additional gliptins (linagliptin, saxagliptin, alogliptin) have been included in the NMA shown in Figures 28 etc. We note that vidagliptin studies appear in the NMA shown in Figures 28, but are missing from the NMA in figure 29.

A4. **PRIORITY**. The NMA diagram in Figure 28 has a single study comparing Met versus Met + SU; please confirm that this is Charpentier et al 2001 (ref 56). Please comment on why this particular study was chosen, from amongst the many studies of Met vs Met + SU.

A5. **PRIORITY**. We note that the figures given for the Charpentier study in Table 29 of the manufacturer's submission (MS) are not the same as those in the paper by Charpentier et al. For example for the Met + SU arm;

	MS	Paper
Mean age	58.8	56.8
Male %	41	59
Baseline HbA1c	7.6	6.4
Weight	90.8	81

Please check and correct the figures. We have not yet checked data from any of the other trials in the NMA, so we don't know if there are other errors.

A6. For completeness. The intervention "Placebo" does not appear in any of the NMA diagrams (Figs 28 to 32). Please confirm that the trials where only one drug is mentioned, they are used in combination with metformin.

A7. LOCF. The MS has no information regarding the amount of missing data; in particular please specify separately for each of the two sub-studies of 1245.23, the proportion of

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observations at week 24 that were carried forward from week 18 for HbA1c in each of the intervention groups (i.e. placebo, Empa10 and Empa25), and similarly for other outcomes listed in tables 17 and 18 of MS.

A8. The value of the EXTEND study (1245.31, monotherapy) is for safety data. However Table 20 provides no information on adverse events, in particular for UTI or GTI. Across studies considered in section 6.92 there appears to be a consistent excess of AEs belonging to BICMO "genital infection" category in empagliflozin interventions relative to all others. Section 6.10.1 acknowledges this excess but states "these were generally of mild or moderate intensity". Please provide any data supporting this.

A9. **PRIORITY**. It is difficult to relate the individual studies listed in Table 29 to the 5 NMA diagrams in Figures 28 to 32. Please provide separate tables for the studies included in each of the NMAs illustrated in Figure 28 and in Figure 29.

A10. Table 31 appears to present only comparative results from the NMAs. Please present absolute results for each intervention, as some appear to have been used in the economic model. Please clarify which sets of NMA results derive from which NMAs shown in Figures 28 and 29.

A11. The intervention "Placebo" does not appear in any of the NMA diagrams (Figs 28 to 32) in any form. The large NMA depicted in Figure 28 therefore appears to have assumed equivalence of the following treatments: [a] Met = Met +Placebo; [b] Met + SU = Met + SU + Placebo. Please clarify and justify this assumption. The identification of intervention and comparator in the list of studies in Table 29 is inconsistent with regard to the inclusion of "placebo". For example: ERG are familiar with the study of Bolinder in which Met was administered with placebo but in Table 29 it appears the comparator was only Met. Please supply full details of intervention and comparator for all studies in Table 29.

Section B: Clarification on cost-effectiveness data

B1. The MS considers models submitted to NICE for canagliflozin and dapagliflozin as well as the submitted empagliflozin model. While the relative differences between different treatments are consistent across these models there are large differences in the lifetime accumulated QALYs for interventions according to model. Thus the Empagliflozin model generates QALYs in the range 6.9 to 7.5, whereas the Canagliflozin model generates QALYs in the range 8.9 to 9, and the Dapagliflozin model QALYs in the range 11.2 to 12.6. These differences have not been commented upon in the MS. Please clarify.

B2. **PRIORITY.** Please clarify table 59, page 253, reproduced below, for hypoglycaemia, non-severe (dual therapy) and how this relates to model inputs? Where does the figure of 0.018 come from, and is it a rate rather than a probability? Is that the rate per annum on metformin alone?

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In the second half of the table below, the figures look like relative risks – have the tables been labelled the wrong way round? Please explain how the RR of 3.33 was derived, and why the figures for the comparators are all 1.5.

Hypoglycaemia – non severe (prob.)	
Baseline risk	0.018
Met + Sitagliptin	0.5
Met + Empagliflozin 10mg	4.17
Met + Empagliflozin 25mg	2.87
Met + Canagliflozin 100mg	2.27
Met + Canagliflozin 300mg	1.38
Met + Dapagliflozin	1.38
Hypoglycaemia – non severe (number)	
Met + Sitagliptin	1.5
Met + Empagliflozin 10mg	3.33
Met + Empagliflozin 25mg	1.5
Met + Canagliflozin 100mg	1.5
Met + Canagliflozin 300mg	1.5
Met + Dapagliflozin	1.5

B3. **PRIORITY**. Earlier in Table 59, a baseline figure for HbA1c change of a reduction of 0.05% is given. Where does that come from? Is it the reduction on metformin and placebo? It appears that in the model, the baseline figure has been added to the reductions on active drugs, whereas a placebo-adjusted figure would subtract the reduction on placebo, as done in para 2 of page 113. This appears to happen with most baseline figures in the modelling, which will exaggerate the effects. For example, if a reduction in HbA1c is 0.05% on placebo, and 0.6% on empagliflozin, adding the former gives an empagliflozin value of 0.65% where correctly subtracting it gives a value of 0.55%. Please check and re-run the model with correct effect sizes.

B4. **PRIORITY.** Please explain table 59 for dual therapy UTIs and how this relates to model inputs? Again, the figures in the top half of the section below, described as RRs, look more like absolute values (rates per time period) and the figures in the bottom half, though described as numbers, look more like relative risks. Please clarify, and explain why the figures for empagliflozin 25 and both canagliflozin doses are 1. Why should the RR be higher for the lower dose of empagliflozin?

UTIs (RR)	
Baseline risk	0.03
Met + Sitagliptin 100mg	0.87

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Met + Empagliflozin 10mg	1.15
Met + Empagliflozin 25mg	1.09
Met + Canagliflozin 100mg	1.15
Met + Canagliflozin 300mg	1.09
Met + Dapagliflozin 10mg	2.21
UTIs (number)	
Met + Sitagliptin 100mg	1
Met + Empagliflozin 10mg	1.41
Met + Empagliflozin 25mg	1
Met + Canagliflozin 100mg	1
Met + Canagliflozin 300mg	1
Met + Dapagliflozin 10mg	1

B5. **PRIORITY.** Please explain the figures in table 59 for non-severe hypoglycaemia and how they relate to model inputs? The figures in the model appear different.

Baseline risk (Met +SU)	0.083
Met + SU + Sitagliptin	1.62
Met + SU + Empagliflozin 10mg	1.68
Met + SU + Empagliflozin 25mg	1.29
Met + SU + Canagliflozin 100mg	2.27
Met + SU + Canagliflozin 300mg	2.76
Baseline risk (Met + Pio)	0.01
Met + Pioglitazone + Sitagliptin	2.29
Met + Pioglitazone + Empagliflozin 10mg	0.62
Met + Pioglitazone + Empagliflozin 25mg	1.49
Met + Pioglitazone + Canagliflozin 100mg	0.1
Met + Pioglitazone + Canagliflozin 300mg	0.11

B6. **PRIORITY**. Please explain why the figures in table 59 for Triple therapy BMI/weight change differ from those in the model.

BMI/weight change (change from baseline) kg	
Baseline (Met + SU)	-0.49
Met + SU + Sitagliptin	0.97
Baseline (Met + TZD)	0.907

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Met + Pioglitazone + Sitagliptin	0.20

B7. **PRIORITY**. Please check the values in table 59, insulin combination – BMI/ weight change, and the values in the model? For example, we think the 0.21 for insulin + sitagliptin may be wrong.

BMI/weight change		
Baseline risk (insulin)	0.323	NMA
Insulin + Sitagliptin 100mg	0.21	
Insulin + Empagliflozin 10mg	-1.36	
Insulin + Empagliflozin 25mg	-1.78	
Insulin + Canagliflozin 100mg	-1.85	
Insulin + Canagliflozin 300mg	-2.33	
Insulin + Dapagliflozin 10mg	-1.43	
Insulin add-on	0.5	Khunti K et al 2013 (99)

B8. **PRIORITY**. Please explain how the figures in table 59 for insulin combination and non-severe hypoglycaemia are derived, and how they relate to model inputs?

Hypoglycaemia – non severe	
Baseline risk (Insulin)	0.241
Insulin + Sitagliptin 100mg	0.97
Insulin + Empagliflozin 10mg	1.06
Insulin + Empagliflozin 25mg	1.07
Insulin + Canagliflozin 100mg	1.44
Insulin + Canagliflozin 300mg	1.4
Insulin + Dapagliflozin 10mg	1.02

B9. **PRIORITY**. We are puzzled by some of the effects of changing the relative inputs. For example, changing the absolute inputs for HbA1c level for Met + Empag from 0.65 to 0.10, changes the mean QALY from 7.424 to 7.343. Should we not expect a bigger change? Also, changing HbA1c level for Met + Empag from 0.65 to 0.45 did not change the mean QALY. Why does such a big change in absolute effect not affect the mean QALYS?

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B10. With regard to the model inputs, where have the covariances within the variance-covariance matrices of the risk equations been drawn from; e.g. cell BP49 of the *Baseline_Parameters* worksheet?

B11. **PRIORITY** With regard to the model structure, it is not immediately clear how many treatment changes, in terms of moving onto the next line of therapy due to treatment failure (rather than switching treatment at the same line of therapy), occur within the model. Please outline:

- For 2nd line therapies what a typical sequence of treatments would be as the patient changes treatment due to hitting the HBA1c threshold.
- For 3rd line therapies what a typical sequence of treatments would be as the patient changes treatment due to hitting the HBA1c threshold.

B12. **PRIORITY** "*The frequency of events was based on the methods used in the UKPDS Outcomes Model*." Please outline how this is aligned with the values of cells BT24:BW28 of the *Model_Scope* worksheet, what the function of these cells is and where this appears in the VBA of the model.

B13**.** Please clarify if the QALY decrements associated with UKPDS68 events are assumed to be cumulative; i.e. a patient having experienced two events has the sum of their disutilities applied?

B14. Please clarify if the disutility for weight gain only applies to weight gain. Or does it also apply to weight loss when it would result in a QALY gain?

Please provide a separate response to each of the following questions on model implementation (B15–B17), even if this involves some repetition.

B15. **PRIORITY** Please outline how to run the model deterministically; i.e. without any 2nd order sampling. When cell H22 of the *Run_Model* worksheet reads "*No*" does this reliably indicate when the model is being run deterministically?

B16. **PRIORITY** It appears that the model results reported in the submission are all based upon probabilistic modelling; i.e. sampling of 2nd order uncertainty of parameter values. How do these results compare with running the model "deterministically"; i.e. without sampling of 2nd order uncertainty of parameter values?

B17. **PRIORITY** The model can be set to run with cells AJ28, AJ31, AJ34, AJ37, AJ40, AJ42, AJ45 and AJ48 of the *Model_Scope* worksheet being "No", cell BA15:BB15 of the *Model_Scope* worksheet being 1 and the number of patients in cell BA14:BB14 of the *Model_Scope* worksheet being 10,000. Further setting the comparison to 3rd line empagliflozin 10mg versus canagliflozin 100mg and running the model, the results for the 10,000 patients simulated can be outputted to the *Graph_CE* worksheet. Within this, it appears that columns N:Q contain the total costs and QALYs by arm, this interpretation

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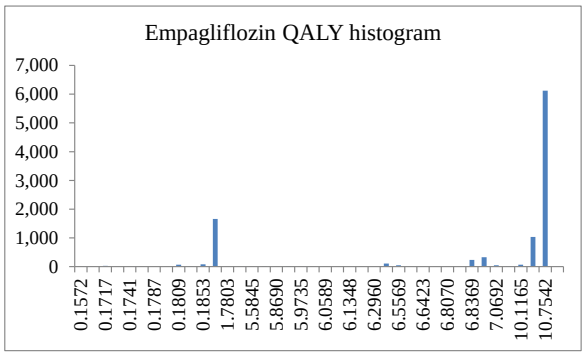
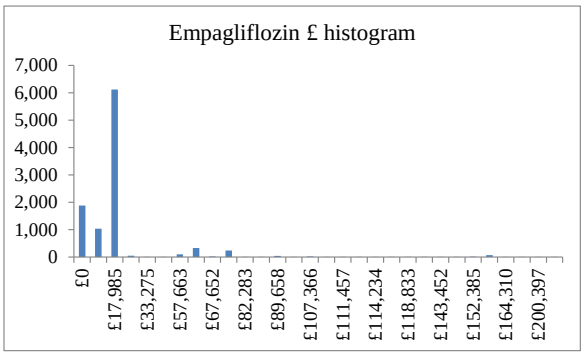
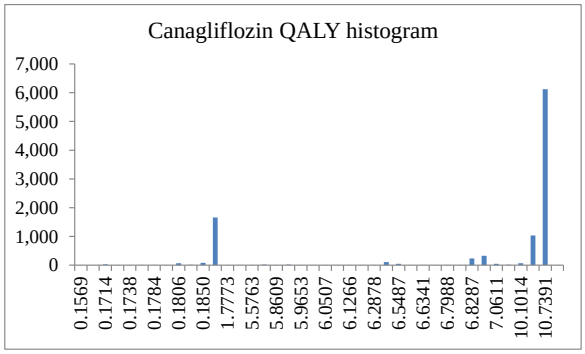
cross checking with the net values reported in columns C:F. The means of the values in columns C:F also cross check with the values reported in cells O13 and O53 of the *Results* worksheet. Concentrating upon the values reported in columns N:Q of the *Graph_CE* worksheet it can be noted that of the 10,000 patients simulated:

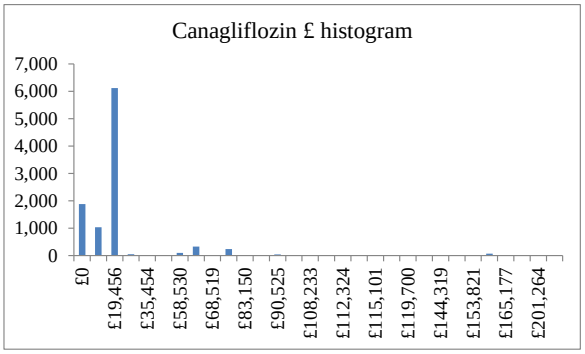
- In column N there are 40 distinct values for empagliflozin QALYs, with 1,886/10,000 accruing less than 1.8 QALYs
- In column O there are 30 distinct values for empagliflozin £s, with 1,886/10,000 having £0
- In column P there are 40 distinct values for canagliflozin QALYs, with 1,886/10,000 accruing less than 1.8 QALYs
- In column Q there are 30 distinct values for canagliflozin £s, with 1,886/10,000 having £0

The histograms for these are provided below.









Please provide:

- An explanation of why there are so few distinct values for the total QALYs and total Costs for each arm reported in columns N:Q of the *Graph_CE* worksheet.
- An account of what interpretation should be placed upon the 1,886 patients who appear to be simulated as accruing less than 1.8 QALYs within column N and column P of the *Graph_CE* worksheet.
- An account of what interpretation should be placed upon the 1,886 patients who appear to be simulated as having £0 total costs within column O and column Q of the *Graph_CE* worksheet.

B18. The submission notes that "*In total, 60,000 simulations were conducted, considering a sample of 30,000 patients per treatment arm (300 samples of 100 patients each). These values were chosen as this was the maximum number of simulations Excel can manage.*"

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The maximum number of patients of 30,000 was apparently the limiting factor.

- How should the 300 samples be interpreted. Is this the number of PSA loops undertaken for the assessment of 2nd order uncertainty?
- How should the 100 patients be interpreted. Is this the number of patients with different patient characteristics at baseline due to the sampling of patient characteristics? And is each patient only run once through the model for a given arm (two arms being compared) and PSA iteration?

B19. **PRIORITY** For a given set of parameter values it seems unlikely that the patient level model will have converged after having run only 100 patients through the model. To what extent has this been explored during model development?

B20. **PRIORITY** Why was it not possible to develop the model along the following lines:

- Sample the 2nd order uncertainty to derive parameter values for a PSA iteration
- Simulate 10,000 patients for each arm using the parameter values for that PSA iteration as sampled above
- Store the resulting mean net cost and mean net QALY for this PSA iteration
- Discard the results for the individual 10,000 patients simulated for this PSA iteration
- Repeat the above four bullets 5,000 times to yield 5,000 PSA iterations

The remaining questions in this section relate to visual basic programming in the model.

B21. Within the VBA the *CEM_running* value is set equal to 1 in the *CEM_Computation_1* module. For the model as submitted is the *CEM_running* value ever not equal to 1. If so, where does this occur in the VBA and why? What is the distinction between CEM and BIM?

B22. Within the *first_steps_effect_diabetes* procedure there is the calculation of the HbA1c as:
*Mat_Current_HbA1c(2) = ((100 *Mat_Current_HbA1c(1)-7.09)+ MatHbA1cStep(1))/100+7.09 / 100*
The ERG is having some difficulty identifying where *MatHbA1cStep(1)* is calculated or inputted as a parameter value. It would be much appreciated if this could be clarified.

B23. The calculation of the probability of a UKPDS Table 2 event happening within a six month cycle within the *first_steps_effects_diabetes* procedure seems slightly peculiar. Rather than calculate the cumulative hazard for the start of cycle (e.g. t = 12.0, with the weibull exp(.).t^γ) and the end of cycle (e.g. t=12.5) it appears to calculate the cumulative hazard for the start of cycle (t = 12.0) and the cumulative hazard for one year later (t=13.0) and then average these to get the cumulative hazard for the end of the cycle (t=12.5). Is there any particular reason for adopting the form chosen, given that it is a more convoluted implementation and gives slightly different values?

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B24. The ERG is also having some difficulty understanding the logic of the following condition that appears repeatedly in the *higher_steps_effects_diabetes* procedure calculations of the probabilities of a UKPDS Table 2 event:
*If MatTx_Current(index_cycle + 1) < 10 * MatTx_Current(index_cycle - 1*) Then
Please provide an intuitive account of this condition, the reason for multiplying by 10 and the effect of the condition.

B25. Please clarify the modelling of the event fatality of equation 8 of the UKPDS 68 within the *first_steps_effects_diabetes* procedure and the comment "*needs to adjust for the year the firt (sic) event happened, so for MI and stroke we know whether the event happened the previous year*". If an event happened in the previous year equation 8 does not apply as it only applies to the first event of either MI, CHF, stroke, amputation or renal failure. Please provide an account of what these adjustments are and why they are necessary.

B26. The adjustment *MatEventDeath_ln_Age_event(1) = Log(MatEventDeath_Age_Event(1) + 52.59) - Log(52.59)*
This does not appear to be in line with Table 1 of the UKPDS 68. Please provide an explanation for this adjustment.

B27. **PRIORITY** It is not immediately clear whether the model treats equations 8, 9 and 10 of the UKPDS as being mutually exclusive; i.e. only one can apply in any one cycle (and any one year). Are these treated as being mutually exclusive, or can more than one apply in a given cycle?

B28. **PRIORITY** Please clarify how the model applies the half of the year of event costs and the QoL values to the first two 6 month cycles of an event, and thereafter applies half the year subsequent to event costs and the QoL values to all subsequent cycles. It would be much appreciated if an outline of where and how the VBA calculates this.

B29. Within the procedure *GenerateRandomValuesPat* please why is it necessary for *RandomMatrix2* to be dynamic, due to the variable *patient_run* which changes with each patient simulated being a determinant of *RandomMatrixRows2*.

B30. Within the procedures *First_Steps_Effects_Diabetes* and *Higher_ Steps_Effects_Diabetes* it appears that the procedures work through the risks of events sequentially rather than randomising the order of the assessment of these. The submission suggests that these are evaluated in random order. Please outline how within the visual basic the order in which the evaluation of events is randomised.

B31. **PRIORITY** Within the procedures *First_Steps_Effects_Diabetes* and *Higher_ Steps_Effects_Diabetes* the visual basic code for adverse event deaths, immediately following the comment *'Adverse events death*, may not be required. Please confirm if this can be safely deleted from the visual basic without affecting the running or outputs of the model, and if it cannot be safely deleted please outline why.

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B32. The visual basic notes that *we want to have sum_weight_end - sum_weight start for the two next cycles. Call this difference b. Then weight half is equal to 1/3 a + 1/3 b in order to obtain linear change in H(t+1) - H(t) and to obtain correct estimates.* The ERG is having difficulty understanding the logic behind this calculation and would much appreciate some further explanation of it.

B33. **PRIORITY** Within the procedure *Higher_ Steps_Effects_Diabetes* the calculation of whether an event happens appears to be dependent upon the condition *If Mat_Update_RiskEqs(index_cycle + 1) = 1 Then*; i.e. if the cycle is the first half of a year or not. The calculation of whether an event happens appears to be then based upon a six monthly probability. But it is unclear how or where the calculation of whether an event happens in the second half of a year occurs; i.e. when Mat_Update_RiskEqs(index_cycle + 1) = 0. If the probability of an event happening in the second half of the year is by default zero, it would seem that the calculation of the probability of an event happening in the first half of the year should be based upon the annual risk rather than the six monthly risk. Please provide an explanation for this, including if relevant where in the visual basic the calculation of whether an event happens in the second half of a year occurs.

B34. Similarly to the above question, the *MatEventDeath_Prob(1) = 1 - sqrt_one_minus_prob_year* appears to be the six monthly probability of an event related death. The model should presumably apply this probability for two consecutive cycles given that the UKPDS 68 calculates annual probabilities. Please identify where and how in the VBA this occurs.

B35. **PRIORITY** There are a number of variables within the excel front end that are hidden that feed global variables into the VBA, for example *MatAE_CV_Spec(5)*. These hidden variables run throughout the VBA code. Please provide a list of these hidden variables identified by their excel location, also identified by their variable name within the VBA, what their default value should be for the correct running of the model and what is the logic of the default values.

Section C: Textual clarifications and additional points

C1. The committee are provided with black and white printed versions of graphs. Printed in black and white the lines in the CEAC figures are poorly reproduced. In particular please supply versions of Figures 36 and 37 that print in black and white with all lines distinguishable and clearly labelled with regard to their intervention, and similarly for Figures 34 and 35.

C2. Please check the title of figure 16, which includes OLS.

C3. Titles to Figures 18 to 21 contain the abbreviation OC. Please define.

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C4. Please confirm that the terms second line and third line (as used in Tables 29, 31 etc.) refer to “dual therapy” and “triple therapy”. We prefer to use dual and triple, because “second-line” could encompass substitution as well as addition.