Input from external experts and manufacturer on the **2nd draft assessment** "**Continuous glucose monitoring (CGM real-time) and flash glucose monitoring (FGM) as personal, standalone systems in patients with diabetes mellitus treated with insulin**"

(Project ID:OTJA08)

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Content

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

EUnetHTA JA3 WP4 - Other technologies
All comments and author´s replies on the 2nd draft assessment "Continuous glucose monitoring (CGM real-time) and flash glucose monitoring (FGM) as personal, standalone systems in patients with diabetes mellitus treated with insulin"

July 2018

EXTERNAL EXPERTS

Comments were received from:

Name	Affiliation
Professor John R Petrie, BSc MBChB PhD FRCP(Ed) FRCPSG	Institute of Cardiovascular and Medical Sciences BHF Glasgow, Scotland
Torstein Baade Rø MD, PhD	Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3	Author's reply
Summary					
John Petrie	General		Throughout there are missing "the"s and minor grammatical errors; will benefit from comprehensive final check from a native English speaker.	3	Thank you; the Medical editor, as well as English language lector will edit the final text.
John Petrie	10	183-195	The research question is buried in too many parentheses	3	Thank you; this is related to complexity of the research question.
Torstein Baade	11	246-	Already stated page 10	3	Thank you, text was revised.
Torstein Baade	14-15		When statistically significant differences are found, effect size should be stated.	2	Thank you; now statistically significant differences are better visible in Summary tables and figures.
Torstein Baade	General		The summary could be shortened, it is now 1/4 of main text, but reflects main text in an adequate manner.	2	Thank you; some revision was made.
Torstein Baade	28/general		Table & Figure numbering missing. Figure 1 both on page 28 and page 16.	3	Thank you; all table and figure numbering is presented in the final version.

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EUnetHTA JA3 WP4 - Other technologies

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Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3	Author's reply
Torstein Baade		656	"An update on excisting (…) (SRs) was not possible" – I guess could be substituted with "No previous SRs were found".	3	An update of existing systematic reviews (SRs) was not possible due to different scope of the assessment.
Description and technical characteristics of the technology					
Torstein Baade	66		Why is Medtronic 670G not included? No CE-mark? Not provided by Medtronic? Should be mentioned?	2	Not related to EU market.
John Petrie	Well-described				Thank you.
Torstein Baade	General		This section is adequate and I have no suggestions for revisions.		Thank you.
Health problem and current use					
John Petrie	Well-described				Thank you.
Torstein Baade	80	1851	Increased glucose production is an extremely rare cause of diabetes. Insulin resistance more common.	2	Text was revised, thank you.
Torstein Baade	81	Table 3	Arrows in row 1-5 don't make sense	3	Explanations were added now.
Torstein Baade	83	1951	180 mg/100 ml should read 180 mg/dL (10 mmol/L) to conform to the rest of the text.	2	Revised, thank you.
Torstein Baade	85	2017-	Severe hypoglycemia is usually regarded as an acute complication, even though it is usually caused by the treatment and not the disease.	2	Text added, thank you.
Torstein Baade	85	2022-	The references for prevalence of late complications are 20-30 years old – the prevalence has changed during the last decades	2	Revised, new data and references now added, thank you.
Torstein Baade	92	2291	PwD – unconventional abbreviation.	3	Full text written, thank you.
Clinical effectiveness					
John Petrie	General	2421	Some of the trials specified hypo rates as primary outcome (e.g. Heinemann et		Thank you; data on hypos are now better presented, descibed and

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			al) and showed a reduction in this – but this is a little lost with the focus on HbA1c. Could data on hypos be pooled?		discussed.
John Petrie	General		Perhaps in retrospect it was too early/ there was insufficient evidence to attempt to pool data formally.		Unfortunately, MA was not possible on majority of outcomes, as we described and explained the reasons behind.
Torstein Baade	99 + general		Regarding the quality rating of the RCTs. Its stated in the methodology section p. 30 that GRADE is used for assessing quality of RCTs. This is not my core field of expertise, but should GRADE be used for individual RCTs – shouldn't it be used only for SR/MAs? –anyway I think instead of pooling quality assessment for groups of trials like "moderate to very low" you should state your individual assessment of each trial for transparency for instance in the Tables (although I realize they are given in the appendices).	2	Pooling the data from different RCTs was not possible for majority of outcomes due to heterogeneity between populations, interventions and outcomes measures. All details related to GRADE on individual studies are written in Appendix 1. New text related to the GRADE approach and the purpose of this Rapid REA is added to Discussion section, to raise clarity and transparency of this report.
Torstein Baade	103	2519-	The inclusion criteriae/patients with IAH will tend to have low HbA1c values, and as this is not the primary endpoint in these trials, evaluating HbA1c changes is not releveant for these trials.	1	We slightly revised the text to address this issue, but all published results related to relevant outcomes for our assessment are presented here. Please see also answer below, thank you.
Torstein Baade	General (also summary)		It is important that primary endpoint(s) are clearly separated from secondary endpoints and observations. These three categories must be clearly separated in tables and text, and one must not draw conclusions from observations made in the studies as these may be biased due to the sample or inclusion criteria. Conclusions should mainly be drawn from primary outcome(s), but secondary outcomes may be included in the evaluations.	1	Thank you; in the EUnetHTA assessment, according the Project plan and EUnetHTA methodoligical guidelines, we are not separating primary and secondary outcomes as they are decribed in the primary studies; all published results related

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					to relevant outcomes for our assessment are presented according the relevant methodology and framework of the EUnetHTA Core Model for REA.
Torstein Baade	109 & general	2593	Again, it makes no sense to make a comparison of two RCTs ("opposite results were found") with completely different study populations and primary outcome. Bolinder has hypoglycemia as primary outcome, and inclusion with HbA1c <7.5% and you can't expect a reduction in HbA1c here, whereas Haak looks at reduction of HbA1c and not hypoglycemia. It is important that one does not look at other outcomes besides what the studies themselves state as primary and secondary outcomes. HbA1c is for instance NOT a relevant/important outcome in Bolinder, and is only included as observation, not outcome. The primary and secondary outcomes of each study should be more clearly stated in tables and text.	1	We revised wording in sentence you mentioned, thank you.We did not compare studies with different study populations or outcomes; we stated that MA was done only for one outcome, i.e. HbA1c change from baseline to the end of the study, pooling the data from two RCTs (DIAMOND and GOLD trials), due to heterogeneity between populations, interventions and outcomes measures.
Safety					
Torstein Baade			I have no suggestions for revisions in the safety sections. It is important that the patient perspective also is covered through the focus groups.		Thank you. Related to Patient involvement, due the fact that currently there is no standard operating procedures related to involvement of patients, we did our best and used two different methods for involving patients, one involving individual patients (two focus groups) and the second involving patient organisations (at EU and national level). Results from published qualitative studies were used in Discussion section.

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John Petrie	General	3031	Well-described		Thank you.
Appendix					
Torstein Baade			I have no suggestions for revisions in the appendices.		Thank you.
John Petrie	General		No comment		Thank you.

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part I: Methods				
1. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?	2x			
2. Are the quality appraisal tools appropriate? **Torstein Baade: Should be stated for individual studies. GRADE may not be appropriate for individual, small RCTs.**		2 x		
3. Is the type/presentation of evidence (e.g. Meta analysis, qualitative synthesis, GRADE) appropriate for this analysis? **Torstein Baade: The one 2-study MA is appropriate, I fail to see that any other pooling of studies is possible.**	x	x		
4. Is the risk of bias sufficiently assessed, both on study level and on an outcome level?	2x			
5. Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)? **Torstein Baade: As focus group interviews are used in the report, why not include qualitative studies in the assessment as well?**	x	x		
6. Are the types of studies to be included (randomised trials, quasi-randomised trials or other designs) described?	2x			
7. If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described? **Torstein Baade: Not relevant**				NA
8. Are appropriate methods of measuring each outcome and appropriate time points for measurement identified? **Torstein Baade: Primary and secondary outcomes for each study should be more clearly specified, and caution must be taken not to include for instance HbA1c as an outcome when for instance inclusion criteria is HbA1c <7,5%. Primary**	x	x		

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outcomes should be more weighted than secondary outcomes.				
Comments (John Petrie): As double-blind studies are not possible comparing two devices (or comparing one device with a different device), it seems that quality will always be by definition low. This should be acknowledged and discussed in 2.6 (page 29). Given the lack of data, should further attention have been paid to high quality observational data (e.g. reduced mortality with pumps in Sweden, Pubmed ID 26100640, better control in Austria Pubmed ID 29049584), particularly where patient reported outcomes are available.. **Answer author**: Thank you; we now explained the specific challenges related to assessment on medical devices in Discussion section. According the Project plan, observational studies should be included in Effectiveness domain only if relevant RCTs are not found. One observational study is mentioned in Discussion section, but the use of rtCGM was not analysed in it.				

9. Are details on sources of information and literature search strategies provided? **Torstein Baade: All ok.**					
Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
X	X	X	X	X	X
Comments: Yes (John Petrie)					

10. Information on basis for the assessment and interpretation of selected data and information:		
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?
X	X	X
Comments (John Petrie): Well described		

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	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part II: Results (See Domain Reports)				
Description and technical characteristics of the technology				
1. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	2x			
2. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	2x			
3. Are the supporting references current and do they provide an international picture of the problem?	2x			
Comments:				
Health problem and current use of the technology				
4. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?	x	X (see above)		
5. Are the supporting references current and do they provide an international picture of the problem?	x	X (see above)		
Comments:				
Safety and effectiveness				
6. Is the risk of bias clearly reported?	2x			
7. Is quality of data sufficiently evaluated?	2x			
8. Are both relative and absolute effect measures presented for each dichotomous outcome?	x			Not relevant
9. Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?	2x			
10. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented?				2NA
11. Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported?	x			Not relevant
12. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data?	2x			
13. In cases where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?	x			NA
14. Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered (if relevant)?				2NA
Comments:				
General				
15. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed	X	x		

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	Yes	Partly (please specify)	No (please specify)	Other (please specify)
and synthesised data still answer the question?				
16. Can the results be applied to the intended population?	2x			
17. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	2x			
Comments (John Petrie): In retrospect, perhaps too little evidence was available to embark on a formal evidence synthesis, but at least it is a starting point. This was particularly evident for patient-reported outcomes.				
Part III: Summary of Relative Effectiveness				
18. Does the summary present a balanced representation of the content of the report?	2x			
19. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	2x			
Comments:				
Part IV: Other Considerations				
20. Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)	2x			
Comments:				

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CONTRIBUTOR

Comments were received from:

Name	
David Jarrom, Senior Researcher, Health Technology Wales	Health Technology Wales, UK

Comment from	**Page number**	**Line/ section number**	**Comment and suggestion for rewording**	**Character of comment** • **'major'[a] =1** • **'minor'[b] = 2** • **'linguistic'[c] =3**	**Author's reply**
David Jarrom			Please see responses to the questions on Section I-IV below. No other general comments.		

	Yes	**Partly (please specify)**	**No (please specify)**	**Other (please specify)**
Part I: Methods				
1. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?	YES			
2. Are the quality appraisal tools appropriate?	YES			
3. Is the type/presentation of evidence (e.g. Meta analysis, qualitative synthesis, GRADE) appropriate for this analysis?	YES			
4. Is the risk of bias sufficiently assessed, both on study level and on an outcome level?	YES			
5. Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)?	YES			
6. Are the types of studies to be included (randomised trials, quasi-randomised trials or other designs) described?	YES			
7. If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described?				n/a

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	Yes	Partly (please specify)	No (please specify)	Other (please specify)
8. Are appropriate methods of measuring each outcome and appropriate time points for measurement identified?		YES – no explicit timings for outcome measurement are stated, but in practice longest follow up in each reported trial is used, which is a pragmatic approach.		
Comments:				

11. Are details on sources of information and literature search strategies provided?					
Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
YES	YES	YES	YES	YES	YES
Comments:					
12. Information on basis for the assessment and interpretation of selected data and information:					
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?		Method of data synthesis described?		
YES	Partially – see comments below		YES		
Comments David Jarrom, Senior Researcher, Health Technology Wales: In the GRADE Assessment (beginning Table A, page 533, line 4280), outcomes scored as both "serious" and "very serious" risk of bias have been assigned the same explanation (footnote A: "At least domain of RoB tool had high risk of bias in all studies"). It is assumed this should read "At least *one* domain of RoB tool had high risk of bias in all studies". If so:					

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1. It is not clear why some outcomes have been marked as "serious" and others as "very serious" using the same explanation.
2. Downgrading studies by two levels if *only* one domain of the RoB tool has high risk of bias seems at odds with the guidance in Section 5.2.1 of the GRADE Handbook. Consider providing separate justification for trials marked as "serious" and "very serious" RoB.

ANSWER AUTHOR: It should be read as: If one domain has high RoB, it is downgraded by one level (-1); if more domains are rated as high RoB or one domain rated as high and more other domains as unclear, it is downgraded by two levels (-2); please see the final version.

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Part II: Results (See Domain Reports)				
Description and technical characteristics of the technology				
21. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	YES			
22. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	YES			
23. Are the supporting references current and do they provide an international picture of the problem?	YES			
Comments:				
Health problem and current use of the technology				
24. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?	YES			
25. Are the supporting references current and do they provide an international picture of the problem?	YES			
Comments:				
Safety and effectiveness				
26. Is the risk of bias clearly reported?	YES			
27. Is quality of data sufficiently evaluated?		YES –see comments on GRADE ratings		
28. Are both relative and absolute effect measures presented for each dichotomous outcome?				Most data is

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				presented as continuous outcomes.
29. Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?	YES			
30. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented?	n/a			
31. Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported?	YES			
32. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data?				Narrative summary presented of safety outcomes.
33. In cases where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?				N/A
34. Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered (if relevant)?				N/A
Comments:				
General				
35. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	YES			
36. Can the results be applied to the intended population?		YES- evidence is lacking for some relevant groups, but this is clearly highlighted by the authors.		
37. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	YES			

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Comments:				
Part III: Summary of Relative Effectiveness				
38. Does the summary present a balanced representation of the content of the report?	YES			
39. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	YES			
Comments:				
Part IV: Other Considerations				
40. Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)	YES			
Comments:				

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MANUFACTURERS

Comments were received from:

Name	
Abbott Diabetes Care	Factual accuracy check
Dexcom, Inc.	Factual accuracy check
Medtronic	Factual accuracy check

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Description and technical characteristics of the technology					
Dexcom	Page 8	138	The line rtCGM: real-time CGM: provides real-time numerical and graphical information about the current glucose level, glucose trends, and the direction/rate of change of glucose. Should also include the provision of alarms and alerts at present thresholds.	1	Changed, thank you.
Medtronic	11	237	The correct brand name to the standalone CGM device from Medtronic is Guardian™ Connect, thanks for consistently using this brand name	1	Changed, thank you.
Dexcom	11	250	Comments that rt-CGM external monitors are worn like a pager. This should be changed to rt-CGM data can be viewed from an external receiver or smart device (Apple or Android).	1	Changed, thank you.
Dexcom	11	251	A person with diabetes will need to wear their rt-CGM device continuously to see the improvements. This was demonstrated by Lind et al (2017). To say rt-CGM systems could be used either intermittently or continuously will create confusion. Further to this it would be of value to examine the effect of when patients stopped using the CGM. Again, this data is available in the Lind et al (2017) paper.	1	Changed, thank you.
Dexcom	11	258	Comments that SMBG is one method to reduce hypoglycemia by "alerting"	1	Changed, thank you.

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			patients to modify their medications, diet, and physical activities. The term "alert" should not be used as that implies a proactive immediate action and in this context is inaccurate. SMBG is not proactive in the sense of this assessment.		
Dexcom	13	315	In the Methods section, input from patients and payor groups has been included. A potential omission is the involvement for the clinicians. This is obviously important, as relying upon RCTs (and patient and payors) diminishes the clinical importance, and can disadvantage newer technologies that may not yet have RCT done and published.	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy. For transparency reasons: clinitians are involved as external experts.
Dexcom	13	315	The assessment gives very little detail as to why the majority of the clinical studies have been given a low to very low grading with a high risk of bias. In the EUnetHTA therapeutic medical devices guidelines (2015) it is made clear that the guidelines on HTAs are mostly focused on medicinal products and not medical technology as such the Cochrane review may not be suited to medical devices. Due short life cycles and unavoidable differences in size, shape and administration, differences in study design should be expected. This issue regarding size, shape and administration is evident when blinding both the intervention and comparator. It would be very difficult to introduce blinding in to a study design when the intervention was rt-CGM and the comparator was SMBG. More consideration to this fact should be given and all studies included in the HTA must be given a rating that is in context to medical technology and the available clinical trials.	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy. For transparency reasons: further text is added in Discussion section to adress this issue.
Dexcom	14	365	Risk of bias should be put in to context and an explanation of why this is the case must be given.	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy. For transparency reasons: further text is added in Discussion section to

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					adress this issue.
Dexcom	14	380	HbA1c change is considered. In the case of Heinemann (2018), Reddy (2017), and Van Beers (2016) these studies included patients with impaired hypoglycaemia. As with IMPACT (2016) these studies were not designed to detect changes in HbA1c. Only studies where the primary outcome was changed in HbA1c should be include in this section. If not, the intended recipient may be unaware that some of the data with in this section may not be relevant. This should be the case for all sections as it would support both the validity and accuracy of the assessment. Page 16, line 469, figure 1 should be amended to reflect this.	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy. For transparency reasons: we slightly revised the text to address this issue, but all published results related to relevant outcomes for our assessment are presented here. In the EUnetHTA assessment, according the Project plan and EUnetHTA methodological guidelines, we are not separating primary and secondary outcomes as they are decribed in the primary studies; all published results related to relevant outcomes for our assessment are presented according the relevant methodology and framework of the EUnetHTA Core Model for REA.
Dexcom	15	430	This section should include the recently published Gold 3, O'lafsdottir et al (2018) as this would add to the body of evidence.	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy. For transparency reasons: further text is added in Discussion section to adress this issue.
Dexcom	22	544	The term "high cost" should be removed as cost is relative to the outcomes gained from the intervention. There has been no opportunity to communicate	1	The manufacturer was asked to check factual accuracy of the draft

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			budget impact or cost effectiveness with in the assessment.		assessment. We believe this comment is not related to a factual inaccuracy. For transparency reasons: this part is related to Patient involvement and answers.
Dexcom	22	582	This should be amended to read only rt-CGM devices under assessment are associated with reduction in HbA1c	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy.
Medtronic	22 156	539 3539 3550	Please use the term rtCGM consistently when referring to the real-time CGM, thus add real-time (rt) to the term CGM to avoid confusion. This should be checked for consistency also across the all document	1	Thank you, agree, with changes made.
Dexcom	31	733	Under the Intervention(s)/Control section for Beck 2017. It is factually correct to say G4 with 505 software, equivalent to G5 in EU.	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy. For transparency reasons: we used wording as written in published studies.
Medtroniic	37 to 380 43 (21) instances	3rd column	The mention of a Medtronic brand requires a superscripted TM i.e. Paradigm™ Veo Pump system MiniMed™ 640G system or MiniMed™ 640G pump Please refer to the respective brand consistently	1	Changed in consistent way, thank you.
Abbott	44	Table 1	The Dexcom G5® Mobile CGM System is designed to replace fingerstick blood glucose testing for diabetes treatment decisions. However, at the time that the GOLD and DIAMOND RCTs were conducted, this product was indicated for use as an adjunctive device to complement, not replace,	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy.

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			information obtained from standard home glucose monitoring devices. The A1c benefit associated with rt-CGM when compared with SMBG comes from a meta-analysis of 2 studies (GOLD & DIAMOND). At the time of the studies, the label for rt-CGM was adjunctive and the products were used as such in combination with SMBG. G5 now has a replacement claim and it is erroneous to extrapolate the findings from one use case (combination therapy) to another (monotherapy). As such, the document should clearly state that rt-CGMs vs SMBG with replacement claims do not have evidence relating to HbA1c.		
Medtronic	45		Various MMT numbers are referred in 17 instances: consider to remove these numbers since they are subject to change or add for each of the 17 instances the following footnote: these numbers are subject to change and may therefore no longer be valid for the mentioned device or system	1	The proposed footnote was added, thank you.
Dexcom	49	860	*"Most of the systems consist of a small needle which is inserted in the abdominal subcutaneous fat"* Due to SugarBEAT not being available in any European country or having a CE mark this should be amended to read. "*All currently available systems consist of a small needle which is inserted in the abdominal subcutaneous fat"*	1	Changed, thank you.
Dexcom	49	863	Not all rt-CGMs require figure stick calibration. This is not the case for the G6 the first factory calibrated rt-CGM.	1	Changed, thank you, related to newly approved G6 medical device.
Dexcom	49	866 & 867	These sentences must be amended to 3,6,7, or 10 day period for rt-CGM as this is factually correct.	1	Changed, thank you.
Dexcom	49	880	While external receivers are available for the G4, G5 and G6, the G5 and G6 can also be connected to a smart device that can be used as a receiver.	1	Changed, thank you.
Dexcom	52	979	This should be amended to read *"The optional receiver must be kept within 20 feet 980 (~600 cm) of the sensor and transmitter at all times for optimal performance."*	1	Not clear comment, we asked for clarification. Changed according to reply from Dexcom: *"The optional receiver must be kept*

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					within 20 feet (~600 cm) of the sensor and transmitter at all times for optimal performance."
Dexcom	54	1012	Contraindications to be added to section on Navigator 2	1	For consistency, contraindicatios were added when available from the IFU documents.
Dexcom	54	1056	Contraindications to be added to section on Guardian Connect	1	For consistency, contraindicatios were added when available from the IFU documents.
Dexcom	55	1017	Contraindications to be added to section on Enlite	1	For consistency, contraindicatios were added when available from the IFU documents.
Dexcom	59	1191	Contraindications to be added to section on SugarBEAT	1	The manufacturer of the medical device SugarBeat, Nemaura Medical Inc. informed us during the assessment that the 1st generation SugarBeat (which consists of a disposable adhesive skin-patch connected to a rechargeable transmitter, with an app displaying glucose readings) is not on the market, hence information on this device was deleted from TEC Domain text. The 2nd generation SugarBeat device does not yet have a CE-mark (expected to receive it later this year).
Dexcom	59	1222	Contraindications to be added to section on Libre	1	For consistency, contraindications were added when available from the IFU documents.
Dexcom	61	1298	Page 61, line 1298	1	As we stated in Deviations from the

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			Data from the FDA concurrence of Freestyle Libre readings and reference values (https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160030B.pdf) should be used to show the true picture of accuracy. The same should be communicated for all rt-CGMs under assessment: • G4 www.accessdata.fda.gov/cdrh_docs/pdf12/P120005S018b.pdf . • G5 Bailey TS, Chang A, J Diabetes Sci Technol. 2015;9(2):209-14. • G6 Wadwa RP, Laffel LM, Diabetes Technology & Therapeutics, 2018; DOI: 10.1089/dia.2018.0150		PP section, SR including accuracy studies was not performed, hence this assessment does not provide accuracy data related to medical devices under assessment.
Medtronic	64 349	1356 last line	When referring to the Soft sensor please add: this sensor is no longer on the market	2	Changed, thank you.
Medtronic	64 64 64 66	1326, 1336 1368 1418	when referring to 554: This pump system is no longer on the market	2	Changed, thank you.
Abbott	P.62	Table 3	FSN II is a non-adjunctive therapy	1	Thank you; corrected accordingly.
Medtronic	65	1391/2 1486/7	Add Trademark to Bolus Wizard™	1	Added, thank you.
Medtronic	66 67	1453/4 1487 1494/5	The 640G system comes with a compatible Bayer blood glucose meter: Please change to following sentence: The 640G system was compatible with Bayer blood glucose meter, now the system is compatible with Ascensia blood glucose meter	1	Changed, thank you.
Medtroinc	68	1513	Description of the 2nd algorithm is missing, add the following sentence: SmartGuard suspend before low automatically suspends insulin delivery when sensor glucose is predicted to fall below a predefined low limit	1	Changed, thank you.
Medtronic	73	1744	CE for Medtronic Guardian Connect is missing (as submitted from 16. July 2016)	1	Added, thank you.
Medtronic	73	1731	Add: predictive alerts for hypo- and hyperglycemia –	2	Added, thank you.
Abbott	P.75	Table 6	FSN II equipment has to be changed for the following: System Kit: FreeStyle Navigator receiver	2	Changed, thank you.

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			Transmitter Charging cable Wall charger Adapters Receiver skin <u>Sensor kit:</u> Sensor delivery unit Sensor insertor Sensor support mount		
Dexcom	78	1809	Amend to France nationally by HAS from June 2018	1	Changed, thank you.
Abbott	P.78	Line 1825-28	Reimbursed population mistakes + updates • France, Austria, Belgium, Luxembourg, Italy (depending on regions), UAE Qatar - Saudi Arabia, UK, Sweden, Switzerland, Denmark, Lebanon, - full reimbursement for T1 and T2 DM patients on insulin; • Portugal, Israel full reimbursement for T1 DM patients • Croatia reimbursement for T1 DM patients with hypoglycemia • Finland, Germany in individual payer contract, not nationwide; Spain in some regions, especially for pediatrics; Norway for pediatrics	1	Changed, thank you.
Abbott	P.73	Line 1723-24	In the US as per FDA and CMS (Medicare), G5 is not the only "therapeutic CGM". FreeStyle Libre also has the annoation of therapeutic CGM (FYI, FreeStyle Libre is considered a CGM in the United States).	1	As we reported, different definitions and/or category names are currently being used for rtCGM and FGM systems in the available published literature. FGM, for instance, may be described as a separate entity from

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					CGM between a traditional blood glucose meter and a continuous glucose monitoring (CGM) system, or as special case of CGM or subset of CGM or intermittently viewed CGM (iCGM) or "flash" CGM/(1, 2, 4, 6, 9). Authors have therefore decided to use definitions according their specific "Instruction for Use" documents – "Indication for use" sections, and thus are referring to them as flash glucose monitoring (FGM) system and real-time continuous glucose monitoring (rtCGM) systems.
Medtronic	78	1824	Remove yes Add Funding based on guideline recommendation.	2	Changed, thank you.
Dexcom	80	1831	Amend to Belgium full reimbursement is granted.	1	Changed, thank you.
Dexcom	95	2363	Include, in April 2018 guidance in the Netherlands has been updated that people with diabetes who have impaired hypo awareness are not eligible for reimbursement for Freestyle Libre and should be on rtCGM devices only.	1	Changed, thank you.
Dexcom	96	2369	It would be correct to say 300,000 according to HAS and CEPS		Not changed since number was indicated in Abbott submission file, thank you.
Dexcom	96	2403	Reasons for discontinuing FLASH needs to be added. Further to this reference 7 *(Diabetes Sci Technol. 2011 Jul 1;5(4):860-70. Real-life utilization of real-time continuous glucose monitoring: the complete picture.*	1	Text revised, thank you.

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			Ramchandani N1, Arya S, Ten S, Bhandari S.) should be removed as it focuses on out of date CGMs. The G4 had not been launched yet and this paper to communicate reasons for discontinuing CGM.		
Medtronic	125	2839	The Ly study (Ly T T, Nicholas A J, Retterath A, Mun Lim E, Davis A E and Jones W T. Effect of Sensor-Augmented Insulin Pump Therapy and Automated Insulin Suspension vs Standard Insulin Pump Therapy on Hypoglycemia in Patients With Type 1 Diabetes A Randomized Clinical Trial. JAMA. 2013; 310(12):1240-1247) has no standalone CGM group, the 2 compared therapies are: 1. Standalone pump therapy 2. Paradigm™ Veo system (SAP) with low glucose suspend feature on The study seems to have been included erroneously in this review.	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy. For transparency reasons: this study is included in relation to the published Project plan and comparators written in this document (PICO).
Dexcom	132	2937	Navigator 2 and Mauras (2012) should be removed from the assessment. The paper highlights 41% of subjects averaging 6 days a week of sensor wear. As it was published in 2012 and Navigator 2 was launched in 2014 the data is in respect to the original Navigator and as such is not reflective of current practice in any European health economy and should therefore be removed.	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy.
Dexcom	General Comment		While mentioning ketoacidosis under the "overview of the disease or health condition", hyperosmolar hyperglycemic nonketotic syndrome (HHNS) is not described and should be as it is an endpoint or an outcome reported in some of the studies listed later in the document; it is rare but very expensive event with high risk of mortality.	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy. For transparency reasons:Text was revised .
Medtronic	156	3529	We suggest removing wording *but not CSII* to align with conclusion on page 22: Based on narrative summary of high risk of bias studies and moderate to very low-quality results, rtCGM devices under assessment are associated with reduction in HbA1c;	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy.

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EUnetHTA JA3 WP4 - Other technologies

All comments and author´s replies on the 2nd draft assessment "Continuous glucose monitoring (CGM real-time) and flash glucose monitoring (FGM) as personal, standalone systems in patients with diabetes mellitus treated with insulin"

July 2018

Comment from	Page number	Line or section number	Comment and suggestion for rewording	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3	Author's reply
Health problem and current use					
Dexcom	80	1841	Impaired awareness of hypoglycemia (IAH) under" Health Problem" is not defined (yet its mentioned in the conclusions). It should be in list of abbreviations since its well-studied and reported 20-25% of Type 1 diabetes patients and 10% of Type 2 diabetes patients on insulin have IAH and are at greater risk of progressing to a hypoglycemic event. Van Beers et al 2016 reports results from (IN CONTROL): a randomized, open-label, crossover trial. The advantages of CGM is the ability to be alerted before the patient is progressing to a hypoglycemic event should be elaborated	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy. For transparency reasons: Text was revised to defined IAH.
Abbott	P.96	Line 2387-2404	Could you please specifiy that the Pubmed search on utilization aspect has been done on CGM only (not including Flash device). Abbott recommend that the pubmed search be conducted including terms describing FreeStyle Libre including Flash Glucose Monitoring.	1	Text revised, thank you.
Clinical effectiveness					
Abbott	general		During the PICO meeting in Vienna (held on the 2nd of February 2018) Abbott raised the methodological issues of the Reddy study which is the only pilot study with a head to head comparison of CGM with FreeStyle Libre. In this exploratory, small and short pilot study (only 40 people over a 8 weeks period), set up in a very specific population (hypoglycemia unaware T1 adult patients), the study design represented a potential source of bias: - Whereas the baseline data were recorded with a G4 sensor and a blinded receiver running the advanced '505' algorithm, data for the endpoint comparisons were recorded with different CGM devices (G5 sensor or FreeStyle Libre). - Different accuracy and performance data have been reported for these CGM devices. - Because of their different modes of calibration, these devices	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy.

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			inherently exhibit different sensitivities and specificities in the detection of biochemical hypoglycaemia. Whereas the G5 sensors require fingerstick calibrations by the user at least twice daily, the FreeStyle Libre system is factory-calibrated with no need for user calibrations. ➔ Accordingly, the applied study design disqualifies any comparisons regarding use of the tested CGM devices with respect to the assessment of any sensor-based outcomes, such as time below 3.3 mmol/l. ➔ By contrast, any outcome data that are not derived from the glucose sensor represent valid comparisons. In this respect, it is important to highlight that the authors did not identify any significant differences between the groups regarding episodes of severe hypoglycaemia within the 8 week intervention period, the overall Gold score from baseline to endpoint, HbA1c change from baseline to week 8, the Hypoglycaemia Fear Score II behavior sub-score and all Problem Areas in Diabetes questionnaire scores. These comments have been peer reviewed and published - Letter to Editor, Diabetic Medicine, A Seibold (document attached) Here you see a fundamental issue regarding the methodology of this study which should discredit any results being reported, discussed, and concluded upon in the current report draft without repeated mentioning of the study weaknesses On top of that, Abbott would like to highlight that at the origin, the study was planned as a pilot study. From a statistical point of view, ==> The Optimal Information Sizes (OIS) calculated based on the minimum		

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			differences expected are far from the sample size of the study: 40 participants (for the primary endpoint, change in time spent in hypoglycaemia (<3.3 mmol/L; 60 mg/dL) from baseline to endpoint with CGM vs. flash glucose monitoring, with a critical clinical change estimated at least at 20%, a sample of 2,493 patients is needed. This leads to imprecision and therefore to a lack of confidence in the results. ==> The sample size calculation is based in SD from the mean change from baseline but results are expressed in Median and Inter-Quartile Range (IQR). This introduce confusion in the interpretation of results. Although the justification is that the data are not normally distributed, this way of expressing results avoid the comparison of data with other studies. Therefore, due to discrepancies between planned way of reporting outcomes and finally reported, this pilot study reports outcomes poorly. Finally, Abbott would like to raise the late registration of the study on the clinicaltrials.gov. Website. Dexcom registered the study on clinicaltrial.gov on January 23, 2017, almost once the analysis of the study was complete (actual primary completion date is February 2017). Hence, Imperial college of London knew the results/ trend (small study). This brings up the ethical question of what would have happened if the study did not achieve its endpoint. As you can see the study has fundamental issues and biases that should discredit any results out of it being reported in the way it is reported in the draft . The Reddy study is quoted 50 times in the draft assessment without any mention of this methodological issues. The text throughout and in the conclusion section of the report should be modified to reflect what kind of study it is, and relate the patient target to the studied patient population of hypo unaware T1s. This would prevent misleading the reader and applying the findings to a broader population (ie. Lines 490-491)		

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Abbott	General		Abbott would like to raise the fact that in this draft assessment, a GRADE assessment has been done only for one question "Is the use of rt-CGM more effective and/or safer than using SMBG?" The table can be found from page 533. A summary of results of this assessment focusing on critical/important outcomes could be: • HbA1c (change from baseline) – *Critical* ➔ *Certainty: Moderate* • Time spent in normoglycemia – *Critical* ➔ *Certainty: Very Low* • Time spent in hypoglycemia – *Critical* ➔ *Certainty: Very Low* • Time spend in hyperglycemia – *Critical* ➔ *Certainty: Very Low* • QoL and user satisfaction - *Important* ➔ *Certainty: Very Low* As the global assessment is based on the lowest level of critical/important outcomes, the quality of evidence for the question rt-CGM vs SMBG should be **very low** meaning *"we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect".* The conclusion in different parts of this draft report does not appear to highlight this. Finally we would like to raise that there is no GRADE assessment of the question "Is the use of Flash more effective and/or safer than using SMBG?". This assessment therefore seems incomplete and the conclusion does not seems in harmony with the findings.		The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy. For transparency reasons: GRADE was added for FGM studies also.
Abbott	10	453	Although the research project was intended to be based on Flash vs. CGM vs. SMBG, the write is inconsistent in describing Flash and CGM as separate technologies. For example, in the summary of relative effectiveness section, Flash and CGM are often considered as a class when describing patient feedback. It would be more clear if the document tackles these products as separate for consistency.		The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy.
Abbott	143	3280	As demonstrated by patient testimonials, one of FreeStyle Libre's key		The manufacturer was asked to check

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			advantages vs. other CGMs is its ease of insertion and use. For example, patient comments on disadvantages of CGMs state "Most self-monitoring devices are quite easy to use, though the process of insertion for some can be somewhat complicated". Abbott suggest that it would be beneficial to payers across EU to be made aware of this information within the summary of relative effectiveness section of the document starting on page 10.		factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy.
Safety					
Abbott	General P154	Line 3504	"Majority of included studies reported AEs" Therefore why only FreeStyle Libre safety data are reported page 136 table X *Frequency and severity of local adverse event in RCTs*? We think it introduces a bias in the reading of this report	1	The manufacturer was asked to check factual accuracy of the draft assessment. We believe this comment is not related to a factual inaccuracy.
Medtronic	574	4855 Table A8: Regulatory status	CE mark missing for Guardian Connect (as submitted from 16. July 2016)	1	Added, thank you.
Medtronic	General		Reference not always visible through the document, many empty brackets (like this []) within the text, providing some challenges in reviewing the document	1	All references were added by EndNote in the final version.

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