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

February 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
John Petrie	General		The overall approach seems sensible and is comprehensively described. Owing to gaps in the evidence however an outcome may be that it is necessary to commission new primary research rather than rely entirely on synthesizing existing primary and secondary research.	2	Thank you for your comment; if research gaps identified, will be discussed in Discussion section of Rapid REA Report.
Torstein Baade Rø	Table 1-1	10	"Science" (typing mistake)	3	Changed, thank you.
Torstein Baade Rø	7	104-106	"…on other technologies" and Table 2-1: Very general terms, unspecific	2	Thank you, this is standard text used in all EUnetHTA Project plan template so could not be changed.
Torstein Baade Rø	7	110	REA – abbreviation not explained first time mentioned	3	Changed, thank you.
Torstein Baade Rø	7	113	The terms "adjunctive" and "non-adjunctive" – in reality this may not be dichotomized but a scale of recommendations as to whether the sensor value should be/need to be controlled or not, but a very important point for use – in reality adjunctive systems will probably be phased out quite rapidly.	2	Thank you, this part was revised.

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Torstein Baade Rø	7	117	The objectives of the project are very important, and term effective could be better defined (cost-effective? Time-effective? treatment-effective? etc). I realize that this is elaborated on in the PICO-table and that it may not be necessary to define the terms more fully in this section.	2	Thank you.
Torstein Baade Rø	7	122-	This paragraph is well written and really captures the essence of why this assessment is warranted, in my opinion.		Thank you very much.
Torstein Baade Rø	8-9		Project approach and method as well as Litterature search strategy are state-of-the-art and I like the fact that you also involve patients via focus group interviews and patient organisations.		Thank you very much.
John Petrie	8	136	When collating and assessing existing systematic reviews, those with individual patient-level data should be favored as of higher quality rather than those using mean values.	1	Thank you; if we identify the report as a SR and MA of individual participant data we will consider it for use in our assessment.
John Petrie	11	148	Although it may be worthwhile including "Integrated sensor-augmented pump therapy (SAPT) vs MDII + CGM" and "Integrated sensor-augmented pump therapy (SAPT) vs MDII + SMBG" for completeness, "integrated systems" trials have often used non-integrated systems as the comparator. Superiority in that comparison suggests superiority to MDII + SMBG as well.	1	Thank you; we re-write this section.
John Petrie	7	109	"CGM and FGMs" should read "CGM and FGM systems"	3	Correction was done accordingly, thank you.
Torstein Baade Rø	10	Table 2-4	I think fasting plasma glucose is of limited value as an outcome when the population is restricted to insulin-using patients. HbA1c covers this better and fasting glucose values give no additional information to HbA1c. This also applies for Table 2-5 "Outcomes".	2	Thank you, we agree and deleted it.
Torstein Baade Rø	11	Comparison, Table 2-5	Applies to third section, "For patients on insulin pump therapy….": In my opinion you are comparing CSII vs. MDII here, and not CGM/FGM vs. SMBG, because the differences in outcome between a CSII-group and a MDII-group can often be explained by pump vs. pen and not CGM/FGM vs. SMGB. Thus, you are comparing something else than your purpose/aim, i.e. your outcomes may be due to pump therapy and not sensor use. The comparison between SAPT and CSII+CGM is relevant, although not very clinically interesting.	1	Thank you, we re-write this section.

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Torstein Baade Rø	11	Outcomes, Table 2-5	The clinical validity may be related to more than Device Accuracy. Consider failure rate, usability, functionality, need for calibrations etc.	2	Thank you; the outcomes are revised in the final version of the Project plan.
Torstein Baade Rø	11	Outcomes, Table 2-5	You could consider defining QoL, fear of hypoglycemia and hypoglycemia awareness, at least restricting them to validated measurement methods.	2	Hypoglycemia awareness is explained now in the new section – Abbreviations and Glossary. Hypoglycemia fear will be connected with a valid and reliable measure of hypoglycemia fear – Hypoglycemia Fear Survey II (HFS-II), thank you.
Torstein Baade Rø	19	3 Social	CGM/FGMs are now relatively small and easy to hide under clothes so I don't see this potential for stigmatization. If so, it is the alarm (sound) and not visibility that is the problem.	2	Thank you; this section was re-written as: "*Questions related to patients' perspectives and perception as well as expectations to the technology could be important. This covers whether any positive or negative issues arise as a consequence of using the technology (i.e., worries, satisfaction, stigmatisation, social status…).A new technology allows patients to return to the workplace, but since the technology can be seen or alarm sound can be heard by co-workers, it may lead to visibility and hearing."*

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MANUFACTURER

Comments were received from:

Name	
Fleur Levrat-Guillen, Abbott Diabetes Care	Factual accuracy check
Donald Rentoul, Dexcom, Inc.	Factual accuracy check
Medtronic	Factual accuracy check

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**
Dexcom Inc.			We have reviewed the draft project plan regarding Dexcom products and are happy with the content. We have no amendments to suggest.		Thank you!
Medtronic		General	Compatible not to be used as synonymous of integrated	1	Thank you, we agree.

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Abbott Diabetes Care	3	66	FreeStyle Libre system provides real-time numerical and graphical information about the current glucose level, glucose trends, and the direction/rate of change of glucose We would use the same description for both types of CGM; only differentiator are the rt-alarms We are quite surprised about your decision to not include FreeStyle Libre in the class of CGM. This seems counterintuitive to us given: -the unique code used by Global Medical Device Nomenclature to identify CMG and FreeStyle Libre (class of sensor measuring glucose in the interstitial fluid) - all products have different features but they all measure glucose in the interstitial fluid and they all present data with a current value, a trend and historical graphs - this notion of class is supported by recent medical guidelines published in December 2017 (ATTD consensus) - and finally, given the short life cycle in device innovation it is not practical to distinguish these products as the review will be irrelevant shortly		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy. ***For clarity and transparency we gave an explanation below:*** In the current literature different definitions for CGM and FGM are used: Flash glucose monitoring is sometimes regarded as a separate entity from CGM. Alternatively, flash glucose monitoring can be regarded as a special case or subset of CGM. (Rodbard D. Continuous Glucose Monitoring: A Review of Recent Studies Demonstrating Improved Glycemic Outcomes. Diabetes Technology & Therapeutics. Volume 19, Supplement 3, S-25, 2017.) In the recently published article (Danne et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40:1631–40.) continuous glucose monitoring (CGM) was divided in real-time use (rtCGM) or intermittently viewed (iCGM) – also known as "flash" monitoring… **Because of data written above, we used definitions according Instruction for Use documents – "Indication for use" sections, and listed them as flash glucose monitoring (FGM) system and continuous glucose monitoring (CGM) systems.**

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Abbott Diabetes Care	3	70	Depending on studies MARD could be median or mean average relative difference By ˚ definition˝ normally it is only mean		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy.
Medtronic		80,81	Please add within the SAP section sensor-integrated to be differentiated from sensor compatible	1	Thank you; changes were made accordingly.
Abbott Diabetes Care	8	178-179	Continuous glucose monitoring (including CGM real-time and i-CGM)		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy. See above.
Abbott Diabetes Care	8	185	Continuous glucose monitoring (including CGM real-time and i-CGM)		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy. See above.
Abbott Diabetes Care	8	189-190	Continuous glucose monitoring (including CGM real-time and i-CGM)		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy. See above.
Abbott Diabetes Care	9	194	Relevant in patients on insulin who require frequent adherence to SMBG		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy.

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Abbott Diabetes Care	11	214 Intervention	Continuous glucose monitoring (including CGM real-time and i-CGM)		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy. See above.
Abbott Diabetes Care	12	Comparison	<u>Patients on multiple daily insulin injection (MDII)</u> MDI + Stand-alone CGM vs MDI +SMBG MDI + CGM1 vs. MDI + CGM2 <u>Patients on insulin pump therapy (CSII)</u> CSII + Stand-alone CGM vs CSII + SMBG CSII + Stand-alone CGM vs CSII + Stand-alone CGM CSII + Stand-alone CGM vs sensor-augmented (enabled) CSII CSII + SMBG vs sensor-augmented (enabled) CSII		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy. See above.
Abbott Diabetes Care	12	Outcomes	Clarke error grid → Parkes Error Grid (consensus Error Grid)		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy.
Abbott Diabetes Care	12	Outcomes	Clinical utility: Add : - % of data collected - glucose variability		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy.
Abbott Diabetes Care	13	Subgroup analysis	Abbott suggests to distinguish adults over 65 and under 65 (working generation). With older persons: aim to reduce hypo in night. Different goal setting. Hb1Ac not that important.		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy.

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Abbott Diabetes Care	13	Study design	Effectiveness: prospective real life studies are important data to show the generalization of RCTs results in real life and should therefore be taken into account. We also would like to add non-controlled, single arm studies / data		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy.

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Medtronic	15	Table at line 230 **MiniMed Paradigm Veo® system, compatible with Guardian 2 Link transmitter and Enlite Sensor, Medtronic** **MiniMed 640G® system, compatible with MiniLink® transmitter and Enlite Sensor, Medtronic**	Medtronic pumps are not "compatible" with Enlite and the transmitter, they are an integrated system. The use of the word "compatible" does only apply to the other pumps and sensors, where the values of CGM are just displayed, whereas Medtronic pumps as of today are the only one on the market that are adjusting insulin delivery based on the CGM values. The Medtronic MiniMed family of devices that automate insulin delivery is collectively referred to as **sensor-integrated systems** with SmartGuard™ technology. In that regard, it is important to recognize that sensor-integrated pumps act in response to the CGM sensor data, whereas a sensor compatible pump merely displays CGM sensor data and does not take action. Display of sensor data is necessary but not sufficient for a system to be called sensor integrated. Please refer to the file that has been shared for correct terminology regarding Medtronic products, rewording has been suggested below. Product transmitter's names have been erroneously associated to different models of pumps. The name of the transmitter that is integrated with Veo and 640G pumps are provided below as per IFU. **Rewording:** **Paradigm Veo® system, integrated with MiniLink® transmitter and Enlite Glucose Sensor,Medtronic** **MiniMed 640G® system, integrated with Guardian 2 Link transmitter and Enlite Glucose Sensor, Medtronic**	1	Thank you; changes were made accordingly.

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Abbott Diabetes Care	22	354	Ethical: the question "CGMs could be superior in quality of life, but due the high costs not all patients who need it can receive it" should be addressed		The manufacturer was asked to check factual accuracy of the draft project plan. We believe this comment is not related to a factual inaccuracy.

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