Input from external experts and manufacturers on **2nd draft project plan:**

"The 24-hour blood pressure measurement device Mobil-O-Graph® with the built-in pulse wave velocity algorithm ARCSolver® to measure arterial stiffness for the optimization of hypertension treatment and assessment of cardiovascular risk"

(Project ID: OTCA24)

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA JA3 WP4 - other technologies, OTCA24
All comments and author´s replies on the 2nd draft project plan "The 24-hour blood pressure measurement device Mobil-O-Graph® with the built-in pulse wave velocity algorithm ARCSolver® to measure arterial stiffness for the optimization of hypertension treatment and assessment of cardiovascular risk"

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EXTERNAL EXPERTS

Comments were received from:

Name	Affiliation
MD, PhD Alfonso Bellia	Assistant Professor of Endocrinology, *University "Tor Vergata", Department of Systems Medicine,* Rome, Italy Associate Physician, Endocrinology and Diabetology Unit, Department of Medicine, *Fondazione Policlinico Tor Vergata (PTV),* Rome, Italy
dr. med. Thomas Schuh	*Krankenanstalt Rudolfstiftung*, Vienna, Austria

Comment from *Insert your name and organisation*	**Page number** *Insert 'general' if your comment relates to the whole document*	**Line/ section number**	**Comment and suggestion for rewording** *Please insert each new comment in a new row.*	**Character of comment** • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3 *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	**Author's reply**
Dr. Thomas Schuh	General	General	It may be that the evidence is lacking to assess the superiority in terms of safety and efficacy due to this being a relatively new technology and the cardiovascular events occurring over a longer time.	2	I agree, this is likely the case. This will be added to the discussion during the report.
Dr. Thomas	General	General	Would it be possible just to look at the software, or in the report, detail why		Yes, the software was looked at in

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Schuh			the software with the device was looked at rather than the software itself.	2	combination for 3 reasons. 1) Because not every device disclosed the software used, so it would be difficult to compare. 2) the device is studied in combination, there is no evidence in patients comparing just the algorithm 3) reimbursement is for the product with the algorithm, and not for the algorithm itself. This will be specified in the report.
Dr. Thomas Schuh	General		I suspect the use of this would probably not be in the GP sector but rather in internal medicine. I would expect them to have 3 to 5 devices at a time which they give to patients who experience syncopies so it is clear that their blood pressure is down, or someone who's blood pressure is really difficult to take care of.	2	Noted for the discussion section of the report.
Dr. Thomas Schuh	General		I suggest the wording be changed too high blood pressure instead of referring to diabetes only. Diabetes would be a subgroup in those with high blood pressure.	1	Changed accordingly.
Dr. Thomas Schuh	General	Table 2-6a and b	Up-to-date has further subgroups such as masked hypertension, etc.	2	All subgroups identified in the literature will be noted in the report. The fact that this may be a relevant subgroup will be noted in the discussion section of the report.
Dr. Thomas	General		Something that would be important for the SAF domain in terms of these		Added accordingly.

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Schuh			medical devices which collect and transmit data is what happens to the data, how is it stored. This should be considered in the SAF domain.	2	
Dr. Thomas Schuh	General		It would be important to mention whether the algorithm learns and in general touch upon this topic.	2	Will add to the report.
Alfonso Bellia – University of Rome "Tor Vergata"	General		In my opinion, a major issue with this project relates with identification of comparators in order to answer to the proposed research questions. It is reported that major scopes of the project are: 1) to assess efficacy of MOGARC device for use in diagnosis and monitoring of hypertension; 2) to assess efficacy of MOGARC device for assessment of cardiovascular risk. To do so, major comparators would be solely 24-hours blood pressure measurement systems currently approved (1) and cardiovascular risk equations currently used in routine practice (2), respectively. Conversely, choice of "**other commercially available non-invasive pulse wave analysis devices"** to be compared with MOGARC pulse wave analysis is probably not consistent with the aforementioned project scopes. This because the incremental prognostic value of pulse wave analysis (irrespective of the method used to assess it) to evaluate arterial stiffness vs conventional clinic BP measurement is not clearly demonstrated (Eur Heart J 2010;31:1865–1871). Accordingly, the use of PWV is not routinely recommended in either the management of hypertension or CV risk assessment (ESC guidelines, European Heart Journal 2018;39:3021–3104). Possible solution would be to consider the comparison of different methods	1	Thank you for this clear explanation and input. Major changes have been undertaken in the draft to address this comment. Please see the new draft. To summarize: Now there are 3 parts, 2 primary and 1 secondary question. 1) same 2) same 3) secondary: comparison with other PWA devices. See extra table for clarification. Two new options for title: The blood pressure measurement device Mobil-O-Graph® with the built-in pulse wave analysis algorithm ARCSolver® compared to: (1) standard 24-hour blood

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			to assess PWV (MOGARC vs other available devices) as second exploratory objective of the project, apart from major objectives as reported above. In my opinion, to avoid confusion and misinterpretation of results, this document would be reviewed (starting from the title), keeping in mind this concept.		pressure measurement for diagnosis and monitoring of arterial stiffness to optimize hypertension treatment, (2) cardiovascular risk equations to assess cardiovascular risk and (3) other pulse-wave velocity algorithms OR The 24-hour blood pressure measurement device Mobil-O-Graph® with the built-in pulse wave velocity algorithm ARCSolver® to measure arterial stiffness for the optimization of hypertension treatment and assessment of cardiovascular risk The information and references have been incorporated in the project plan.
Dr. Thomas Schuh	9	120	Atrial fibrillation is also a very important disease to mention as patients rarely show up with stroke but rather with afib	2	Added.
Dr. Thomas Schuh	10	Table 2.2	Should the superiority be considered or simply non-inferiority of the product compared to other products?	2	Both will be considered. Wording has been changed accordingly.

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Dr. Thomas Schuh	10	Table 2.2	I am not sure this technology would change the way patients are treated. For this reason will any outcomes be considered that are more broad?	2	The diagnosis, risk stratification and compliance will also be explored.
Dr. Thomas Schuh	10	Table 2.2	Adherence is one of the biggest issues in hypertensive patients and should be mentioned. A more exact diagnosis will not necessarily lead to improved care.	2	Adherence will also be explored. It is described on page 13.
Dr. Thomas Schuh	10	Table 2.2	The issue currently is not in the diagnosis of these but in the treatment, so the aims should try to focus on how this changes could change treatment.	2	Studies looking at treatment and diagnosis will be explored. Wording has been changed accordingly.
Dr. Thomas Schuh	10	Table 2.2	The focus should be on dropping the risk of cardiovascular disease	2	Wording has been changed accordingly.
Dr. Thomas Schuh	10	Table 2.2	The blood pressure day and night measurement and the "dips" are not a known main component or problem.	2	This might be a subgroup considered relevant by stakeholders.
Dr. Thomas Schuh	10	Table 2.2	The research aims would be better organized in a disease view--- primary and secondary prevention. The primary prevention focusing on all patients or those at risk and secondary on those who already have had a cardiovascular event.	2	Wording was changed accordingly and will be considered for organization of report.
Dr. Thomas Schuh	13	Table 2-6b	The risk scores may not be relevant to change--- as they are not really used in practice as such, but more as a guideline that one should know and keep in the back of their mind.	2	Noted, will be added to discussion in the report.
Alfonso Bellia – University	Page n. 13	Table 2-5(a) Line 155 "Population"	*Condition intended to diagnose/monitor*: "hypertension" instead of "hypertension via vascular aging"	2	Changed accordingly.

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of Rome "Tor Vergata"					
Alfonso Bellia – University of Rome "Tor Vergata"	Page n. 13	Table 2-5(a) Line 155 "Comparison"	*"Invasive Pulse wave analysis (PWA) is not a relevant comparator for the outpatient sector and will not be included as a comparator. Invasive PWA will be included only descriptively in the TEC domain."* As per current guidelines (European Heart Journal 2018;39:3021–3104), assessing PWA (both invasive and non-invasive) is not relevant in order to diagnose/monitor hypertension, irrespective of the setting (out- or inpatient). My suggestion is to delete this sentence.	2	Changed to *"Invasive Pulse wave analysis (PWA) will not be included as a comparator."* We need to make it clear that we are excluding any invasive PWA in the literature search.
Dr. Thomas Schuh	14	Table 2-6a and b	I suggest changing the outcomes to more hard endpoints. The current endpoints are a bit soft and difficult to quantify. Rather than does it reduce the risk, ask does it reduce cardiovascular death and stroke (disability).	2	Changed accordingly.
Dr. Thomas Schuh	14	Table 2-6a and b	An important subgroup may be those with kidney disease, for example for whom a deteriorating condition could indicate an opportunity for early dialysis rather than when the patient is really ill.	2	All subgroups identified in the literature will be noted in the report. The fact that this may be a relevant subgroup will be noted in the discussion section of the report.
Dr. Thomas Schuh	14	Table 2-6a and b	Two groups to exclude would be: Marfan's disease and Ehlers Danlos as these conditions are characterized by arteries which are built differently and not relevant for arterial stiffness measures.	2	Changed accordingly.

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Dr. Thomas Schuh	14	Table 2-6a and b	Another subgroup may be elderly patients. When their arterial stiffness rises, their cardio markers also rise (for example NT-proBNP) which can indicate aggravation of heart failure	2	All subgroups identified in the literature will be noted in the report. The fact that this may be a relevant subgroup will be noted in the discussion section of the report.
Alfonso Bellia – University of Rome "Tor Vergata"	Page n. 14	Table 2-6(b) Line 158 "Comparison"	*"Cardiovascular risk equations listed in a recently published study[1] comparing cardiovascular risk equations."* Looking at the references list, the quoted study (Wassertheurer S et al, J Hum Hypertens 2010;24:498-504) is just a validation study of the ARCSolver oscillometric method against the validated tonometric system (SphygmoCor), and does not report any cardiovascular risk equations. Better choice would be to clearly report the risk assessment systems to be compared with the selected intervention method. For instance, look at the SCORE system which estimates the 10-years risk of a first fatal atherosclerotic event in relation to a number of factors including blood pressure (available at: http://www.escardio.org/ Guidelines-&-Education/Practice-tools/CVD-prevention-toolbox/SC ORE-Risk-Charts).	1	This reference was a mistake and was corrected on a later version—apologies for that. The reference that it was supposed to be is: Betts MB, Milev S, Hoog M, Jung H, Milenković D, Qian Y, et al. Comparison of Recommendations and Use of Cardiovascular Risk Equations by Health Technology Assessment Agencies and Clinical Guidelines. Value in Health. 2019;22(2):210-9. We would like to use this for its HTA relevance. Upon looking at their list, they include SCORE for CVD.
Alfonso Bellia –	Page n. 14	Table 2-6(b) Line 158	*"Studies which suggest replacing blood pressure with pulse wave analysis or adding an element of pulse wave analysis will also be included."*		The reference has been incorporated in the document.

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University of Rome "Tor Vergata"		"Comparison"	Although additive value of pulse wave analysis beyond traditional cardiovascular risk assessment systems has been previously proposed (J Am Coll Cardiol 2014;63:636–646), its routine use is not recommended yet by current guidelines. For this reason, to avoid confusion and misinterpretation of results, I suggest to delete this sentence.	2	The sentence was taken out to avoid misunderstanding. I think it was poorly worded: what I meant is if PWV measured by MOGARC is compared to an entire risk equation or of it is considered as a replacement for one factor in a risk equation, the study will be included in both cases in the review. I do not expect to find such studies --- especially as this particular discussion is about PWA in general and not specific to MOGARC. Finally, while it is true that guidelines do not recommend this, we would like to build an overall picture of the landscape, especially based on manufacturer claims. We will be highlighting where there is evidence for or against, and where in insufficient evidence, but also where there are guidelines and especially conflicts between

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					manufacturer claims, guidelines, and/or evidence.

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MANUFACTURERS

Name	
IEM GmbH	Factual accuracy check

Note: The manufacturers had no comments on the 2nd draft project plan.

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