Input from external experts and manufacturers on **2nd draft assessment**
"Custom-made or customisable 3D printed implants and cutting guides versus non-3D printed standard implants and cutting guides for improving outcome in patients undergoing knee, maxillofacial, or cranial surgery"

(Project ID: OTCA11)

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Content

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[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 "Custom-made or customisable 3D printed implants and cutting guides versus non-3D printed standard implants and cutting guides for improving outcome in patients undergoing knee, maxillofacial, or cranial surgery"

April 2019

EXTERNAL EXPERTS

Comments were received from:

Name	Affiliation
Prof. Dr. Constantinus Politis, MD, DDS, MM, MHA, PhD	Full Professor & Chairperson Oral & Maxillofacial Surgery University Hospitals Leuven, Leuven, Belgium UZ Leuven, Leuven, Belgium
Dirk Leonhardt	Chief Dental Technician Aarhus University, Department of Dentistry and Oral Health, Aarhus, Denmark

Comment from *Insert your name, title and affiliation*	**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**
Dirk Leonhardt	General		After having read the whole assessment on 3D printed implants, I can tell that I have no comments at all to the document. It has been very interesting reading and a kind of eye opener regarding 3d-print in relation to surgery and in my daily work too.		Thank you.
Summary					
Constantinus Politis		P.13, line 293	According to table 0.1 the quality of evidence varies from very low to moderate and not low	2	Thank you for noticing. We have now changed this in the Summary.
Description and technical characteristics of the technology					
Constantinus Politis, UZL		P.28	Table 3.3: 3D Systems and 3Dsystems (last row) are the same company so please remove the last row.	1	We will correct it accordingly.

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			3D systems recently purchased "Layerwise, Leuven, Belgium" and the company focuses on 3D metal printing. Consider adding the company as it is related to the topic		
Constantinus Politis, UZL			Table 3.3 could benefit from a recent Spanish company called "Avinent": www.avinent.com The company added a new medical section production for customized implants	2	We will add it.
Constantinus Politis, UZL			Consider adding "Layerwise" to Table 3.4	2	We will add it.
Health problem and current use					
Constantinus Politis, UZL		P.34, question A0011	How much should be how frequent are the 3D printed….	3	The question A0011 has now been reworded.
Constantinus Politis, UZL		P.39, question A0011	How much should be how frequent are the 3D printed….	3	Same as above.
Clinical effectiveness					
Constantinus Politis, UZL	General	Section: "Morbidity", page 42 to 46	The focus was on knee and the different types of assessment with no mention of similar assessments/measurements for cranial nor for maxillofacial. Please add or clarify	1	In the introduction under 4.2. it is added that: ' Not all patient groups are represented under a specific outcome, since some outcomes relate to particular patient groups e.g. the outcome 'number of outliers' which only include results from knee patients.'

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Constantinus Politis, UZL	General	Section: "Changes in sensory function"	Please clarify why was the study of Al-Ahmad et al. 2013 (p.73) included while it has nothing to do with the recent question and the focus of oral cancer/mandible reconstruction. Therefore, I suggest to remove the study from the table and the paragraph (p.48) as it is irrelevant.	1	When describing the health problem, oral cancer is mentioned as one of the main reasons for using 3D technology in mandible reconstruction. However, this does not exclude other clinical conditions.
Discussion					
Constantinus Politis, UZL		P. 54, line 1312	Please rephrase the sentence, it is not clear	3	We agree that this sentence is unclear and have now rephrased it. Thank you.
Constantinus Politis, UZL	General		It has to be stressed in the discussion on updating the methods of evaluation and assessment to be three dimensional instead of 2D. with the availability of CT and MRI scans and the recent developments in CAD software along with papers suggesting different methods to assess in 3D, there is no excuse not to update the evaluation methods to 3D and stressing the validation of these methods for more reliable and accurate results.	1	We agree and have added your point of view to the discussion under Need for research/ evidence gaps with the following: "In addition, there need to be a focus on evaluation methods for 3D print technologies. The availability of CT and MRI and the recent developments in CAD software provide possibilities for updating the evaluation methods for 3D printing technologies and thereby strengthen methods for more reliable and accurate results".
Appendix					

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MANUFACTURERS

Comments were received from:

Name	
Johnson & Johnson	Factual accuracy check
Materialise	Factual accuracy check
Raomed	Factual accuracy check

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Materialise	11 13	266 307	It is inaccurate to state that manufacturers of custom-made medical devices do not need to apply any CE marking to their product. Article 4, section 2 of the Medical Devices Directive (reference below) explicitly states that these devices shall not bear the CE marking. This means it's legally impossible, rather than not needed.	2	We will correct this accordingly to better reflect the state of the art.
Materialise	11	270-273	It is factually incorrect that it is difficult to point out the producer. It is factually incorrect that the legal situation on custom-made devices is unclear due to missing legal regulations. On the contrary, custom-made devices are regulated and require a statement by their MANUFACTURER, in accordance with Annex VIII of the Medical Devices Directive (articles 4 and 11 jo. Annex VIII, Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (OJ L 169, 12.7.1993, p. 1))	2	We have tried to clarify what was meant with the text by rephrasing it: On the other hand, the legal situation on custom-made or customisable 3D printed implants and cutting guides is unclear due to missing legal regulations. Manufactures statement is devoted to single or short series production of medical devices. In the case of 3D printers, a large production is an option, and the current regulation does not take this issue in to account. Although principles of liability are applicable to 3D printed implants and cutting guides, this does not cover the case of large productions.
Materialise	14	329	Please note that the outcomes included in the „scope" described here, are not aligned with the outcomes included in the results of the report.	2	Outcomes have been aligned, and as stated under 2.7. In addition any

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					relevant deviations from the project plan have been commented.
Materialise	25	558	Inaccuracy: The guides used in the study published by Ayoub, 2014 are polyamide instead of acryl and are produced by laser sintering.	2	We have corrected that the guides are polyamide and produced by laser sintering.
Johnson and Johnson	27		**TruMatch** is not consistently spelled in the report. All TruMatch products (including Materialise TruMatch CMF and TruMatch knee) should be spelled **TruMatch** according to the IFU of the CE-Mark or the FDA clearance.	3	Thank you for noticing. We have now spelled TruMatch correct in the report.
Johnson and Johnson	27		Please note that **only TruMatch Devices are Patient Specific Instruments**. **Sigma Total Knee Implants and Attune Total Knee Implants are not customized**. The TruMatch™ Patient Specific Instruments are intended for use with Sigma Total Knee Implants and Attune Total Knee Implants and their cleared indications for use. In order to avoid misinterpretation **please change to TruMatch cutting guides, for use with standard Total Knee Arthroplasty (i.e. non-customised) implants (Sigma & Attune)** instead of *TruMatch 3.0 SYSTEM: Cutting guides/Patient specific instruments. SIGMA Total Knee Implants, ATTUNE Total Knee System*	1	We have now changed to: "TruMatch cutting guides, for use with standard Total Knee Arthroplasty (i.e. non-customised) implants (Sigma & Attune)" according to your suggestion.
Raomed	27	Table 3.3.	Relevant products"are stated as "Raomed implants".	2	We have now corrected this according to your suggestion.

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			We suggest: "Custom-made implants and custom-made surgical guides for cranio-maxillofacial surgery and ortopaedic traumatology surgery."		
Materialise	27	Materialise entry in the table	Typo: the correct name of the device referenced is TRUMATCH	3	Thank you. We have now corrected the name.
Materialise	27	Materialise entry in the table	Website: please accurately link to our portfolio. Since both knee guides and CMF implants are considered, and we are active in both, please link the following two sites: https://www.materialise.com/en/medical/patient-specific-guides/patient-specific-knee-guides and https://www.materialise.com/en/medical/patient-specific-cranio-maxillofacial-implants	2	We have linked the two sites you suggested in Table 3.3.

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Materialise	30	Materialise entry in the table	Inaccuracy: Materialise is not a *socio de DePuySynthes*. (Remnant from Spanish language text?) Materialise is the legal manufacturer of a number of CMF devices that are distributed by DePuy Synthes. In line 1 of the Materialise entry, please mention TRUMATCH as a cranial product range, and separately also as a maxillo-facial product range. Guides AND Prostheses are correctly marked. The material for the prosthesis is TITANIUM (please omit the word porous). Guides come in titanium and polyamide variants. In line 2 of the Materialise entry, you can add that the material for our knee guides is Polyamide. We have several products for which we are the legal manufacturer, but it is OK to leave the product names blank since all of them are exclusively sold via other medical devices companies.	2	We have now removed socio de DePuySynthes from Materialise and made corrections according to your suggestions.
Johnson and Johnson	30		**Table 3.4**. *Finceramica (part of Johnson$ Johnson).* **Please note that Johnson$ Johnson should be spelled Johnson & Johnson.** Please note that Finceramica is not a part of Johnson and Johnson. Custombone is no longer distributed by Johnson and Johnson since 2018. **Please remove *(part of Johnson$ Johnson).***	1	We have corrected this to: "Johnson & Johnson".

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Johnson and Johnson	30		**Table 3.4**. ATTUNE, SIGMA, SROM, LCS **Please note that only TruMatch Devices are Patient Specific Instruments**. **Sigma Total Knee Implants and Attune Total Knee Implants are not customized**. The TruMatch™ Patient Specific Instruments are intended for use with Sigma Total Knee Implants and Attune Total Knee Implants and their cleared indications for use. In order to avoid misinterpretation - **please change to TruMatch cutting guides, for use with standard Total Knee Arthroplasty (i.e. non-customised) implants (Sigma & Attune)** - **and please remove SROM, LCS as they are not included in the Instructions for Use.**	1	Thank you for clarifying this. We have changed it to: "TruMatch cutting guides, for use with standard Total Knee Arthroplasty (i.e. non-customised) implants (Sigma & Attune)" and removed "SROM, LCS".
Johnson and Johnson	30		**Table 3.4**. The TruMatch™ Patient Specific Instruments are intended for use with Sigma Total Knee Implants and Attune Total Knee Implants and their cleared indications for use. **Please add a cross in the guide's column.**	1	Done.
Johnson	30		**Table 3.4**. *Materialise ***socio de DePuySynthes (Johnson&Johnson)*	1	To avoid misinterpretation we have

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and Johnson			Johnson and Johnson has a distribution agreement with Materialise **only for the TruMatch CMF products.** - **Please specify Materialise (manufacturer) and Johnson & Johnson Medical (DePuySynthes) distributor for TruMatch CMF products** - **Please remove the mention of knee as not part of the agreement when Johnson & Johnson Medical (DePuySynthes) is mentioned with Materialise.**		now specified it to: "Materialise (manufacturer) and Johnson & Johnson Medical (DePuySynthes) distributor for TruMatch CMF products" and removed the mention of knee when Johnson & Johnson Medical (DePuySynthes) is mentioned with Materialise.
Johnson and Johnson	30		**Table 3.4**. *Materialise ***socio de DePuySynthes (Johnson&Johnson) craneo-maxilo* **Please change to craniomaxillofacial,**	3	Done.
Raomed	31	Table 3.4.	The materials stated for both cranial and maxillofacial guides and prosthesis are incomplete, and there is an error with a material: "PEC" instead of "PEEK". We suggest: For **cranial** guides and prosthesis: Material 1: Titanium; Material 2: PEEK; Material 3: PMMA, Polyamide. For **maxillofacial** guides and prosthesis: Material 1: Titanium; Material 2: PEEK; Material 3: Cr-Co-Mo, UHMWPE, PMMA, Polyamide	2	We agree and have now changed this according to your suggestions.

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Materialise	31	606 ff	We feel that the paragraph in lines 606 until 611 is subjective and unsubstantiated. Plenty of commercial solutions for 3D printed implants and guides are cleared in several markets worldwide, with clearly identified and documented clinical evidence. Outside of the EU, we refer to Materialise's Health Canada License no 100870 for CMF implants, License no 101810, 101811, 102363 for knee guides as an easily referenced example of registered and reviewed patient-specific devices. This is an example of just one jurisdiction with just one manufacturer, whereas dozens more examples are available. References can be checked via https://health-products.canada.ca/mdall-limh/prepareSearch-preparerRecherche.do?type=active And https://health-products.canada.ca/mdall-limh/information.do?companyId_idCompanie=134641&lang=eng In line with current legislation, Materialise also maintains clinical evaluation reports which are, as part of our ISO 13485 certification, subject to audit and oversight.	1	There is no documented clear evidence in the case of most of the solutions retrieved as it occurs in other medical devices. One thing is receiving the license and the other being prepared to be accepted by systems with no further clinical studies of the comparison against standard of care and this is lacking in most of the cases.
Materialise	31	607	Inaccuracy: since Materialise is the legal manufacturer of certain TRUMATCH implants commercialized by Johnson and Johnson, for which MATERIALISE has received FDA clearance through the 510k procedure, please list Materialise together with Johnson & Johnson at this point of the document. Reference: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K170272.pdf	2	We will include this in the specifications.

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			Please specify this applies to TRUMATCH CMF.		
Raomed	32	639-640	The question [B0009] regards the **use** of 3D printed implants and cutting guides. However, the wording of the paragraph relates more to the **production** of the implants and cutting guides. We suggest to replace "the equipment used to produce" with "the equipment required to use"	3	We have now replaced this with: "the equipment used to produce" with "the equipment required to use".
Materialise	32	644 ff	We feel that the paragraph in lines 644-659 is inaccurate. It is meanwhile an established fact that a 3D printer in itself only constitutes a medical device is claims of diagnostic or therapeutic purpose are made by the manufacturer of the printer. This is very rare. A 3D printer typically is no more a medical device than a milling machine is. The text also ignores the fact that, despite the peculiar regime for custom-made devices in the EU, regulatory control including post-market surveillance, is in place via the Competent Authorities of the member states. Absence of scientific literature doesn't mean there is no evidence of safety, as manufactures even of custom-made devices are required to report on incidents and maintain post-market surveillance. Line 649: again, CE marking is not possible, rather than not needed. Line 651: please either list all manufacturers, including Materialise, which have received CE marks or 510k clearances, or none.	1	We have now rephrased this according to your comment. Please see page 33 line 643 to 650. We have changed the text and written that custom-made devices shall not bear the CE mark. As it is not that important which platforms that have received the CE mark, we have deleted Johnson & Johnson. The point we want to make is that the implants and cutting guides shall not bear the CE mark.
Materialise	33	661	In our opinion, it is not appropriate to draw general conclusions on reimbursement like mentioned in this paragraph.	1	We agree and have changed the

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			- Reimbursement is country dependent is it is impossible to draw general conclusions that are valid in all markets. - While in certain cases reimbursement based on a case-by-case basis is one option, this is not generally applied. The way that custom made implants are reimbursed will depend on the funding system that applies in the country and the hospital. - There examples where there is reimbursement specifically for custom made implants or guides and where the decision to have this product reimbursed is made on clinical evidence. - It is not clear what is meant by „holistic platform".		section to: "In some cases, the 3D printed devices are reimbursed at a case-by-case level, but the way that 3D printed implants and cutting guides are reimbursed will depend on the funding system that applies in different countries and the hospitals. There are examples where there is reimbursement specifically for custom made implants or cutting guides and where the decision to have this product reimbursed is made on clinical evidence".
Materialise	50	1198	The scope and relevance of the results for knee guides vs. Implants is unclear. Line 1198 mentions *„In these short-term studies, there were no additional complications associated with 3D printed implants and cutting guides",* however, it was previously stated in table 3.2 that there were no references found for knee guides. We suggest to be clarify in the results whether the data apply to guides or implants.	1	Table 3.2 has been adjusted in relation to whether the studies related to guides or implants

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			Also in the discussion, conclusions are drawn for guides and implants while there are no references available specifically for guides.		
Materialise	51	1374	It is also unclear how „minor differences"are defined and how a statistically significant difference can be minor. In line 1374 (discussion) it is stated that *„In patients undergoing knee surgery, only minor differences in operating time are shown, however, differences were statistically significant, favouring 3D surgery patients compared with standard instrumentation. Estimates range from 4.4 to 10.7 minutes*" Also line 1067 mentions „a minor significant difference".	2	We distinguish between statistical and clinical significance, where the latter represent an assessment of the results in relation to the magnitude of the results. This is common practice when analysing data to appraise if a difference is large enough to be of practical importance to patients and healthcare providers.
Materialise	57	1436	Inacurracy: the results are not correctly reflected in the discussion. Line 1436 mentions *„A minor difference was found in ischemic time in mandibular reconstruction with a decrease in the 3D print group with individual surgical guides."* While in the results in line 1079, the data from Ayoub were used to show *„ischemic time (which comprises time from dissection of the transplant until perfusion is restored); with a significant difference in favour of 3D print group with 96.1 min vs. 122.9 min (p<0.005)*". Also here it is unclear how a „minor difference" is defined and how a minor difference relates to a statistically significant difference.	1	We have rephrased the first sentence that now states : "a difference was…".

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