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

“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 project plan "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"

August 2018

EXTERNAL EXPERTS

Comments were received from:

Name	Affiliation
Prof. Dr. Constantius 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	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
Dirk Leonhardt	General		After close reading of the Project Outline material you have sent to me, I can only conclude that I don´t have any comments to make. In my humble opinion the plan covers all of the aspects that I can think of which could be relevant for the new technology compared to the conventional.		Thank you.
Constantius Politis	8	105-107	The research question is the wrong question in maxillo-facial surgery. Whether one creates a MANUAL waefer or a PRINTED waefer is not the only issue. In maxillofacial surgery ALL waefers (manual and printed) are patient-specific and NEVER standard. As such the research question cannot apply to maxillo-facial surgery. The difference between the manual workflow and the digital 3D-workflow with the end-result being a 3D-printed waefer is the accuracy and quality of the planning compared. This at least in orthognathic surgery.	1	We think that it is a very good point you make here and we have modified the research question. The research question and text below have been adjusted to emphasize that it's possible to adjust/customize conventional/standard solutions as well not using 3D-print.The text in green is new:

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					Research question: This rapid assessment addresses the research question whether 3D printed custom-made or customisable implants and cutting guides used in patients undergoing knee, maxillofacial, or cranial surgery are more effective and/or safer than usual care using standard/conventional medical devices or other solutions. In the text below the research question, we have also added some text: In theory, the main advantage of 3D printing compared to conventional/established solutions is the extended opportunities to adjust the device to each patient's characteristics while conventional solutions provide standard sizes or fewer options to customize the device to the patient's characteristic. Thus, it is highly relevant to identify and describe the current use of 3D printed custom-made or customisable implants and cutting guides used in patients undergoing knee, maxillofacial,

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					or cranial surgery and to assess the effectiveness and safety of this technology.
Constantius Politis	8		Further, thanks to cutting guides allowing to avoid the nerve, procedures have become possible which were impossible before due to the major risk to sever the inferior alveolar nerve (trigeminal nerve). The research question cannot be applied to this development. The same applies in oncological resections of the mandible and the maxilla, where 3D-planning, cutting guides were non-existing and cannot be compared with any 'commercial solution'.	1	Assessing new medical devices this issue is often relevant – new treatment procedures allowing for interventions not possible before. Revising the research question and comparing 3D-print to usual care is likely to accommodate this issue.
Constantius Politis	8		It will be very important to REDEFINE the research question in order to include the maxillo-facial field. Or one needs to choose NOT to include the maxillo-facial field and limit the existing research question to the orthopaedic field.	1	We find that in the adjustments made the maxillo-facial field now can be included in this report. If relevant please suggest any further amendments to the text to support this.

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August 2018

MANUFACTURERS

Comments were received from:

Name	
Johnson & Johnson	Factual accuracy check
Materialise	Factual accuracy check

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Materialise	general		We would like to challenge the scope of the project with respect to the impact of 3D printing technologies on EFF and SAF domains. 3D printing technologies do not hold intrinsic promise to improve safety or effectiveness of medical devices. Patient-specific medical devices manufactured using subtractive techniques (such as CNC milling machines) have been introduced on the market years before the commercial introduction of 3D printed devices. Similarly, some standard medical devices are today produced using 3D printing technologies. 3D printing have however enabled the expansion of applications of patient-specific devices by lowering the cost of these applications or by enabling the production of novel designs. Still many patient-specific devices rely on other technologies to be manufactured. Considering these facts, our guess is that the real intent of the project aims at evaluating the safety and effectiveness of custom-made devices in general which have benefited from 3D printing technologies. We suggest to change the scope of the project accordingly.	1	We agree that these are important considerations and we will describe these in the background and introduction in the assessment report. We also understand that custom-made devices can be produced using various technics. In this assessment however, the aim is to assess the devices produced using 3D printing techniques and not custom-made devices as such. 3D printing is one way and a new way to produce these devices and therefore it needs an assessment on its own. When we

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					start to use a new production procedure or technology, like the ones incorporating 3D printing, we need to assess this technology on its own. One could make other health technology assessments comparing e.g. custom-made devices to standard devices or 3D printed custom-made devices with custom-made devices in general, but that would be a different assessment, although also relevant.
Materialise	general		A corollary to the previous comment is that the printing of the physical parts represents only a part of the systems that manufacturers are bringing to the market. Typically such systems consist of: a scanning protocol, an online platform that allows the clinician to send the imaging of his patient to the manufacturer and to track the progress of the case, a service that converts the imaging into virtual 3D models, a planning solution (in collaboration or not with clinical engineers), the design of the parts and the manufacturing of the parts. Reducing the value of the devices by the way parts are produced hides a more complex situation in which many other factors may have an even more important impact on SAF and EFF domains. The current document doesn't describe how other device characteristics will be dealt with.	1	Internal in the project group, we have discussed these issues about the organization and systems operating around the 3D printing of the devices a lot. We know that various systems are used and in the assessment report there are dedicated areas for describing the technology. In this part of the assessment report we will do our best to describe the differences on a general plan and referring to the systems we have identified in the literature and through feedback from manufactures. So as far as it is possible the systems will be described,

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			Reply from Materialise to author's answer: To clarify our position – these other components are an integral part of the guide or implant, for instance a patient-specific guide or implant can't exist without a planning software. We remain available if you need more information on the matter.		but only the implants and the cutting guides will be part of the comparison, being aware of other factors influencing the procedures. Author's answer on additional comment: As mentioned above, we are aware of the different systems used together with 3D printing. In the assessment we will describe the systems used in the different studies, if possible. If we, in our analysis, can detect a pattern, where one or more systems perform better then others, we will emphasise this.
Johnson & Johnson	8	109-112	"This rapid assessment addresses the research question whether 3D printed custom-made or customisable implants and cutting guides used in patients undergoing knee, maxillofacial, or cranial surgery are more effective and/or safer than usual care using standard/conventional medical devices or other solutions. " In some cases, 3D printing offers the opportunity to treat complex patient cases, with no alternative treatment because of the complexity. In these cases where there is no standard solutions available, comparison will be "no treatment" or "usual care."	1	We agree that "no treatment" and "usual care" in some cases will be the comparison. This is not a problem and we will clarify it in the project plan. We also understand that custom-made devices can be produced using various technics. In this assessment, however the aim is to assess the devices produced using 3D printing techniques.

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			Additionally, depending on individual patient needs patient specific treatment using computer assisted surgery and custom-made 3D printed or milled implants is commonly used in complex cranial or maxillofacial reconstruction procedures. These techniques offer an alternative to treatment with standard, mass produced implants, allowing to treat for a variety of reconstruction cases. The only difference in the two types of patient specific devices (3D printed and milled) is the manufacturing technique, whilst other procedural steps from pre-operative planning to implantation remain the same. Therefore we would like to include the milled implants in order to ensure that all relevant comparators will be assessed.		
Materialise	8	Section 1.2	The project segments the devices in 6 main categories (guides and implants in knee, maxillofacial and cranial surgery) in adult patients. This segmentation hides the multiplicity and heterogeneity of the covered applications and indications and which raises concerns with respect to the aggregation of data and the validity of the analysis. The value proposition of custom-made medical devices is not homogenous across the different applications. To illustrate the situation, here is an attempt at a non-exhaustive list of the covered applications as described in the document: - Primary total knee arthroplasty indicated for patients with: o Osteoarthritis o Rheumatoid arthritis o Post-traumatic arthritis o Extra-articular deformity	1	The assessment and results of 3D printed costume-made implants and cutting guides will not be reported in one analysis. We will divide the assessment in meaningful subgroups and make subgroup analysis when necessary and possible. According to TKA we see a possibility to conduct a unified analysis for at least osteoarthritis and rheumatoid arthritis and if possible make some meta analysis. The other indications are not mentioned often in the studies.

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			- Primary unicondylar knee arthroplasty indicated for patients with:
			  o Unicondylar osteoarthritis
			  o osteonecrosis
			- CMF
			  o applications:
			  ▪ Orthognathic surgery
			  ▪ Mandibular reconstruction
			  ▪ Maxilla reconstruction
			  ▪ Cranioplasty
			  ▪ Orbital reconstruction
			  ▪ Midface reconstruction
			  ▪ Mandilectomy
			  ▪ Maxillectomy
			  ▪ Mandibular distraction
			  ▪ Midfacial distraction
			  o Indications
			  ▪ Congenital deformation
			  ▪ Trauma
			  ▪ Cancer
			
			We request the project plan to be updated in order to describe how data aggregation will take place.
			
			Note: printed models and splints are not part of the scope of this project but
					For maxillofacial and cranial surgery, the patient groups are quite different and the studies small, so the assessment of these indications will be reported using a qualitative description of the study results.
					
					We have tried to clarify this in the project plan by including this text:
					
					For the "Clinical effectiveness (EFF)" and the "Safety (SAF)" domains statistical summary estimates of associations across studies will if possible be derived from random effects meta-analysis, based on thoughtful consideration to whether or not it is appropriate to combine the numerical results of the studies, concerning e.g. patient characteristics and the comparability of interventions and comparisons, furthermore anticipating clinical heterogeneity, with modeling allowing for differences in the association from study to study.

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			represent a significant part of custom-made devices in a number of applications.		
Materialise	9	Section 1.2.1	As it is often the case with innovative technologies, gaps still remain regarding clinical evidence. In many publications, investigators rely on surrogate outcomes to assess the effectiveness of the devices without critical appraisal of the validity of these outcomes. Although a consensus often exists regarding a given surrogate outcome (for instance the relationship between malalignment and implant survival) there is not enough evidence to precisely quantify the influence of the performance of the procedure and its clinical outcome. Another important factor that blurs the relationship between the performance of the device and the clinical outcome lies into the planning stage of the process. At the moment no golden standard or guidelines exist regarding the optimization of a planning. In the absence of golden standards or guidelines, surgeons assess their planning with respect to their knowledge and experience. These facts lead to a situation where a device could very well perform perfectly as intended by its manufacturer but where the clinical evidence would seem to dismiss the clinical added value. Hence it is we believe difficult to assess the EFF domain given the current clinical background/state of the art and we propose to put the focus of the project on the performance of the devices.	1	We agree that a thorough investigation of chosen outcomes is very important. In the assessment we will account for the outcomes presented in the report and we will also make clear if it is a surrogate outcome We are not really sure what is meant by "the performance of the device" in contrast to clinical outcomes. Is it some performance measures set by you as the manufacturer? In any case, the outcome measures normally included in a health technology assessment should reflect effects on a clinical, organizational or economic level. In a health technology assessment, you have to include the EFF domain to see if the new technology at least performs at the same level as the comparators and to make sure that there are no major side effects when

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			Reply from Materialise to author's answer: We understand performance according to the definition of ISO 14155: 2011 :"behavior of a medical device or response of the subject(s) to that medical device in relation to its intended use, when correctly applied to appropriate subjects". In essence the notion of performance relates to the ability of the device to perform as intended by its manufacturer while clinical effectiveness is concerned by the clinical impact of the technology. For instance, in that context the accuracy of a guide when performing a cut is a performance indicator – and may become a surrogate outcome - while a PROM is a clinical outcome indicator. We want to stress out the distinction between the two notions because publication authors are sometimes confused about the clinical effectiveness of some of our products, which relies heavily on the planning performed by the surgeon. We understand the need to include the EFF domain into the HTA and we are confident that the available data can demonstrate that the technology performs at least as good as comparators, but we believe there is also a potential to improve clinical effectiveness of the technology with the progress in the understanding of pathophysiology, treatment options and assessment methods. Reply from Materialise to author's answer: Thank you for your reaction. From our perspective, while we believe that an experience surgeon will be able to take a better advantage of the technology – which could translate in a better device performance – the experience of the		using the technology. We will of course make clear on what level of evidence the conclusions are drawn and point out evidence gaps. Author's answer on additional comment: Thank you for clarifying your comment. As we wrote above, we will include the performances measures if they are reported in the included studies. Generally in HTA's, focus is on clinical effectiveness and not so much on efficacy. It is of course almost always the case that clinical effectiveness is dependent on different aspects beside the assessed technology, but that is also the case for the comparator. In some technologies, it is relevant to discuss learning curves and implementation issues but we do not find it a crucial aspect with regard to 3D printed implants and surgical guides. Most studies account for these issues by using only experienced and qualified surgeons in the aspect of both the assessed and standard technology.

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			surgeon plays only a limited role in effectiveness because there is still much to learn about planning methods. As mentioned in another comment, planning methods are still a matter of discussion in many of the areas our products are used in. To make an analogy, if our devices were GPS navigation devices, the route description can be as accurate as can be, but if the address entered is wrong it will not lead you to your destination, no matter how familiar you are with the device.		
Johnson & Johnson	10	131	*"Inclusion: Human population, controlled clinical trial, observational study (cohort or case control but prospective), randomized controlled trial, systematic review, meta-analysis. "* We acknowledge that randomized clinical trials or systematic reviews are preferred, but difficult to achieve for rare diseases or complex anatomical cases, and where the comparator, such as standard implants, are not relevant. The use of a specific-patient implant may impact the design and the outcomes collection of the study. In some cases, lower evidence levels might suffice. The benefits of some 3D implants and surgical guides can be also supported by post-market surveillance registries for instance, not only from RCTs or comparative studies.	1	In the Technology, Safety and Current use domains other study designs will be included to answer the research questions. However, in the effectiveness domain we will only include the study designs mentioned in the inclusion criteria. In the effectiveness domain we need to move beyond generating hypothesizes. We will of course state clearly if we identify evidence gaps.
Materialise	12	Section 1.2.2	We would like the reviewers to be mindful regarding the assessment methods used to measure the performance of the devices. From experience we see investigators using a broad range of methodologies used, a number of these raising major concerns regarding their validity. A typical example is that measurements are often performed on inaccurate post-operative 2D	1	This is a good point and we will be aware of this issue. In many of the included studies it is also addressed by referring to intra-interobservator variability.

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			radiographs while the surgery was planned based on 3D CT-based models. Reply from Materialise to author's answer: Please note that inter-intraobserver variability is not enough to address the validity of the measurement methods. Authors often fail to include the influence of the imaging protocol. This is especially blatant in knee arthroplasty where limb rotation is known to have an effect on measurements, still publication authors warrant the precision of their measurements based solely on intra-interobserver variability (measured on a single set of radiographs)[1]. Another important point is that different methods don't necessarily measure the same endpoints.		Author's answer on additional comment: We agree that there might bee some issues with the various methods for measuring the effects of the implants and guides, but we can not change the methods used in the published studies. So the assessment will report on the outcome measures used in the studies. We will of course try to explain both the methods and the

[1] Here are some references to provide more context :

- Wu, P.-H., Zhang, Z.-Q., Gu, M.-H., Zhao, X.-Y., Kang, Y., Liao, W.-M., Fu, M., 2017. Radiographic Measurement of Femoral Lateral Bowing and Distal Femoral Condyle Resection Thickness: Variances and Effects on Total Knee Arthroplasty Planning. Chin Med J (Engl) 130, 2557–2562. https://doi.org/10.4103/0366-6999.217083
- Radtke, K., Becher, C., Noll, Y., Ostermeier, S., 2010. Effect of limb rotation on radiographic alignment in total knee arthroplasties. Arch Orthop Trauma Surg 130, 451–457. https://doi.org/10.1007/s00402-009-0999-1
- Ostermeier, S., Stukenborg-Colsman, C., Hurschler, C., Windhagen, H., 2009. Influence of Femoral Limb Rotation on Radiographic Alignment After Total Knee Arthroplasty. Orthopaedic Proceedings 91-B, 30–30.
- Cooke, T.D.V., Sled, E.A., 2009. Optimizing Limb Position for Measuring Knee Anatomical Axis Alignment from Standing Knee Radiographs. J Rheumatol 36, 472–477. https://doi.org/10.3899/jrheum.080732
- Hirschmann, M.T., Konala, P., Amsler, F., Iranpour, F., Friederich, N.F., Cobb, J.P., 2011. The position and orientation of total knee replacement components: a comparison of conventional radiographs, transverse 2D-CT slices and 3D-CT reconstruction. J Bone Joint Surg Br 93, 629–633. https://doi.org/10.1302/0301-620X.93B5.25893

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					outcomes reported in the assessment. Thanks for the references.
Materialise	12	Table 1.2-5	Regarding the Population: - Indications are wide ranging and are not tackled in the description, see comment on section 1.2 Regarding the Intervention: - Patient-specific guides exist in a range of designs, cutting guides representing only a minority of guides in the field of knee arthroplasty (Materialise manufactures a majority of drilling guides). We see no reason to limit the scope of the project to cutting guides only. - In maxillo-facial applications, especially on orthognathic surgery, patient-specific splints represent a substantial part of our custom-made devices, we propose to add them to the scope of the project - Anatomical models play a significant role in the proposed categories, we propose to add them to the scope of the project. Regarding the outcomes: - Accuracy of printed parts is typically not reported by authors and a weak indicator of EFF or SAF. We suggest to remove that outcome. Although often reported in the literature because it is believed to be a factor of success, Materialise considers limb alignment to be a weak indicator of device performance since 1/ ligament balancing is a typical part of knee arthroplasty procedures, a parameter over which guides have no control over; 2/ most guiding systems are based on imaging taken with the patient in supine position while leg alignment is typically measured in a load-bearing position. We	1	The list of indications in the project plan is not exhaustive; more indications will be included in the assessment if there is enough research to support it. Drilling guides and anatomic models are two different technologies compared to 3D printed implants and cutting guides and are not included since the focus is on 3D printed devices. We know that other technologies are used within this area but it is not the aim of this assessment to cover all technologies used but to focus on 3D printing. If the splints are 3D printed, costume-made and implanted in the body, we have considered them as implants and they should be included. We are not really sure what is meant by this bullet:

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			propose to remove this outcome and replace it with component position. Even if guides do not place the components as such, component position is a somewhat closer indicator of device performance. Reply from Materialise to author's answer : Please note that in the vast majority of cases are anatomical models provided together with the implants and/or guides. In our product portfolio, anatomical models and drilling guides are also 3D printed. If drilling guides are not part of the project scope then a big part of studies on TKA patient-specific guides will be excluded (the Zimmer Biomet Signature and PSI systems consist of mostly drilling guides). Please also consider the fact that depending on the application cutting guides include also holes for the purpose of drilling. Below is a picture of such a guide in a case of mandibular reconstruction[2].		"Accuracy of printed parts is typically not reported by authors and a weak indicator of EFF or SAF. We suggest to remove that outcome." According to position, this outcome is often not reported in the literature and we also see alignment as a more clinical relevant outcome. We will of course report position where if it is possible. Author's answer on additional comment: Thank you for clarifying the statement. After going through the literature we agree with you and we will remove accuracy from the outcome list. the search strategy did not exclude studies with anatomic models and/or drillimg guides if they also included 3D

[2] From Mascha, F., Winter, K., Pietzka, S., Heufelder, M., Schramm, A., Wilde, F., 2017. Accuracy of computer-assisted mandibular reconstructions using patient-specific implants in combination with CAD/CAM fabricated transfer keys. Journal of Cranio-Maxillofacial Surgery. https://doi.org/10.1016/j.jcms.2017.08.028

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			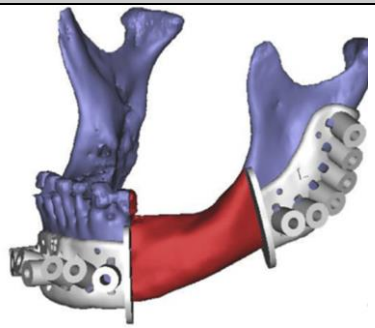 We mention drilling guides, anatomical models and splints because in reality a case will often benefit from the combination of different types of devices. Splints used in CMF surgery manufactured by Materialise are 3D printed but they are not implants, they are instruments used intra-operatively and then disposed of. Should they be included? By accuracy of printed parts we understand the geometrical accuracy of the part as compared to the 3D virtual model. This can be expressed for instance as an average of the distance between the surfaces of an optical scan of the printed part and the CAD model. While this is an important metric in our manufacturing process, it is typically not reported in the literature.		printed implants or surgical guides, but we do not include them, if they only deal with drilled guides og modells. If the splints are 3D printed, costume-made and implanted in the body, we have considered them as implants and they should be included. <u>Author's answer on additional comment</u>: The search strategy did not exclude studies with anatomic models and/or drillimg guides if they also included 3D printed implants or surgical guides, but we do not include them, if they only deal with drilled guides og modells. Splints used in CMF surgery should not be included. Thank you for clarifying the statement. After going through the literature we

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			We see leg alignement as a poor surrogate outcome for clinical effectiveness. It is still a hot topic of debate within the surgical community[3] and a poor predictor of clinical outcome. Reply from Materialise to author's answer : Thank you for clarifying this out. Please bear in mind that according to the number reported in the publication from Thienpont et al.[4], in 2012 TKA drilling guides manufactured by Materialise accounted for about half of the patient-specific 3D printed TKA guides used in Europe		agree with you and we will remove accuracy from the outcome list. We understand your point and we will look at the references you have provided so that we can nuance the discussion about outcome measures. Alignment will be reported in the assessment, since it is often reported in the included studies and it will be reported together with other relevant outcomes.

[3] Here are a few references to substantiate our position:

- Becker, R., Tandogan, R., Violante, B., 2016. Alignment in total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 24, 2393–2394. https://doi.org/10.1007/s00167-016-4247-2
- Vandekerckhove, P.-J., Lanting, B., Bellemans, J., Victor, J., MacDonald, S., 2016. The current role of coronal plane alignment in Total Knee Arthroplasty in a preoperative varus aligned population: an evidence based review. Acta orthopaedica Belgica 82, 129–142.
- Abdel, M.P., Ollivier, M., Parratte, S., Trousdale, R.T., Berry, D.J., Pagnano, M.W., 2018. Effect of Postoperative Mechanical Axis Alignment on Survival and Functional Outcomes of Modern Total Knee Arthroplasties with Cement: A Concise Follow-up at 20 Years*. JBJS 100, 472. https://doi.org/10.2106/JBJS.16.01587
- Rivière, C., Iranpour, F., Auvinet, E., Howell, S., Vendittoli, P.-A., Cobb, J., Parratte, S., 2017. Alignment options for total knee arthroplasty: A systematic review. Orthopaedics & Traumatology: Surgery & Research 103, 1047–1056. https://doi.org/10.1016/j.otsr.2017.07.010

[4] Thienpont, E., Bellemans, J., Delport, H., Van Overschelde, P., Stuyts, B., Brabants, K., Victor, J., 2013. Patient-specific instruments: industry's innovation with a surgeon's interest. Knee Surg. Sports Traumatol. Arthrosc. 21, 2227–2233. https://doi.org/10.1007/s00167-013-2626-5

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Johnson & Johnson	12	142	*Table 0-5: Project Scope: PICO (please see HTA Core Model® for rapid REA)* • ***Outcomes for patients undergoing knee arthroplasty*** : to add Patient satisfaction • ***Outcomes for patients undergoing maxillofacial surgery*****:** to add Patient satisfaction • ***Outcomes for patients undergoing cranial surgery*****:** to add Patient	1	We will include Patient Satisfaction as an outcome measure in the project plan. From what we know so fare, it is not reported very often in the studies, but it is a relevant outcome measure.

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			satisfaction		
Johnson & Johnson	18	207	*Table 0-1: Selected Assessment Elements* ***"Description and technical characteristics of technology*** ***What are 3D printed implants and cutting guides versus conventional implants and cutting guides?"*** In some cases, 3D printing offers the opportunity to treat complex patient cases, with no alternative treatment because of the complexity. In these cases where there is no standard solutions available, comparison will be "no treatment" or "usual care." Additionally, depending on individual patient needs patient specific treatment using computer assisted surgery and custom-made 3D printed or milled implants is commonly used in complex cranial or maxillofacial reconstruction procedures. These techniques offer an alternative to treatment with standard, mass produced implants, allowing to treat for a variety of reconstruction cases. The only difference in the two types of patient specific devices (3D printed and milled) is the manufacturing technique, whilst other procedural steps from pre-operative planning to implantation remain the same. Therefore we would like to include the milled implants in order to ensure that all relevant comparators will be assessed,	1	See the reply to comment one.
Johnson &	19	207	***"Health problem and current use of technology***	1	We agree and it is important to

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Johnson			*What is the target population in this assessment?* *How many people belong to the target population?"* The primary objective of 3D printing technology in medical devices was to address medical unmet needs by unlocking possibilities to treat complex cases with a fully customised device to the dimensions and the needs of the patient. Large cranial defects, complex anatomical reconstruction cases represent a challenge in the selected procedures as knee, maxillofacial, or cranial surgery. The intended goal is a perfect fit of the implant and a good aesthetic result (in particular for patients undergoing maxillofacial surgery). As a result, the surgical target population for 3D implants can be considered in some cases as a niche, and not as a replacement for standard implants in non-complex cases. Indeed, the nature of the niche and targeted unmet needs this technology serves is also reflected in the specialized regulatory process for 3D printed devices relative to standard implants. Please note, this needs to be taken into consideration in any comparative review that is undertaken, as comparing the use of 3D implants or guides in complex cases with standard implants used in routine cases would not be a like-for-like comparison.		describe this in the assessment. However, the assessment and results of 3D printed costume-made implants and cutting guides will not be reported in one analysis. We will divide the assessment in meaningful subgroups and make subgroup analyses when necessary and possible. We will only compare when it makes sense.
Johnson & Johnson	19	207	***Clinical effectiveness*** ***Research question(s) or reason for non-relevance of 'mandatory' elements*** For all the research questions Additionally, depending on individual patient needs patient specific treatment		See the reply to comment one.

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			using computer assisted surgery and custom-made 3D printed or milled implants is commonly used in complex cranial or maxillofacial reconstruction procedures. These techniques offer an alternative to treatment with standard, mass produced implants, allowing to treat for a variety of reconstruction cases. The only difference in the two types of patient specific devices (3D printed and milled) is the manufacturing technique, whilst other procedural steps from pre-operative planning to implantation remain the same. Therefore we would like to include the milled implants in order to ensure that all relevant comparators will be assessed,		
Johnson & Johnson	19	207	*NM Were patients satisfied with the use of 3D printed implants and cutting guides?* It might be M instead of NM	2	As described above, we will include patient satisfaction as an outcome.
Johnson & Johnson	19	207	***Safety*** *How safe is the use of 3D printed implants and cutting guides in relation to conventional implants and cutting guides?* When considering outcomes, the clinical outcomes related to durability and longevity of the implant are key in most of the considered treatment spaces, and so revision rates should be included to assess the outcomes of the product	1	We agree and we will include it explicitly as outcomes measures. However, the studies published in the area do not report long follow-up.
Johnson & Johnson	21	222	***2. Organisational*** *Does comparing the new technology to the defined, existing comparator(s)*	1	In the assessment, we will do our best to clarify the frame of reference for the

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			point to any differences that may be organisationally relevant? The comparators of interest should not be limited to <u>only</u> conventional/standard non-3D printed implants, or manual instrumentation. Assessing the performance and/or the management of the procedure in terms of accuracy and consistency in addition to the outcomes associated to the implant itself might be relevant. It might include the use of CT scan.		comparisons that we make. Some of the included studies are also trying to take this into account, when performing their analysis. But as you also are aware, it will of course never be a 100% similar comparison.
Johnson & Johnson	21	222	*1.* ***Legal*** ***"Requirements for market access*** *In the current EU-regulations the requirements for putting 3D-printed medical devices on the marked depends on their classification as a "standard", "customisable" or "custom-made" device"* There is a need of a clear terminology with the definitions of the following 3D printed custom-made implants 3D customisable implants 3D cutting guides (and surgical guides if different)	1	We will provide a clear definition in the assessment report.
Johnson & Johnson	21	222	"*According to the new EU-regulations stricter requirements for 3D-printed medical devices made in larger quantities will be imposed. "* Do you mean mass produced here?	2	We are not completely sure either what is meant by "made in large quantities" ☺ But we will look into the new regulation in more detail.
Johnson & Johnson	21	222	*"The new regulations took effect on May the 25th 2917"*	2	Noted.

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EUnetHTA JA3 WP4 - Other technologies

All comments and author´s replies on the 2nd draft project plan "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"

August 2018

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			To be replaced by The new regulations took effect on May the 25th 2017		

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