EUnetHTA Joint Action 3 2016-2020

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**

Project description and planning

DEFACTUM: Social & Health Service and Labour Market, Denmark

OSTEBA: Basque Office for Health Technology Assessment

This report is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

Version Log

Version number	Date	Modification	Reason for the modification
V1	08/03/2018		
V2	26/03/2018	Minor modifications and limitations to the PICO of the assessment.	Reflections from the author and comments from co-author and dedicated reviewers on the internal scoping e-meeting.
V3	17/05/2018	Minor modifications to the project plan after comments from dedicated reviewers, co-author, coordinator and WP4 Co-lead.	Comments from the mentioned partners gave rise to minor amendments to clarification on scope and inclusion criteria and the need to uniform language and concepts.
V4	29/06/2018	Minor reframing of the research question.	Comments from external experts.
V5	05/09/2018	Minor adjustments of outcome measures and other minor changes throughout the project plan.	Comments from manufacturers.

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1. PROJECT ORGANISATION

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	DEFACTUM - Social & Health Services and Labour Market (DEFACTUM)	Author	Denmark	Develop the first draft of EUnetHTA project plan, amend the draft if necessary. Perform the literature search. Carry out the assessment on CUR, EFF and SAF domains. Fill in checklist regarding potential "ethical, organizational, patient and social and legal aspects" of the HTA Core Model® for rapid REA. Send "draft versions" to reviewers and external experts, compile feedback from reviewers and perform changes according to reviewers' comments on CUR, EFF and SAF. Prepare final assessment and write a final summary of the assessment.
2.	Basque Office for Health Technology Assessment (OSTEBA)	Co-Author	Spain	Review draft of the project plan. Check and approve all steps (e.g. literature selection, data extraction, assessment of risk of bias). Carry out the assessment of the TEC domain. Perform changes according to reviewers' comments on the TEC domain. Review draft assessment, propose amendments where necessary and provide feedback on: information retrieval, sources and search terms for locating domain specific information, inclusion/exclusion criteria for studies or other information, in terms of content, methods and quality.
3.	Belgian Health Care Knowledge Center (KCE)	Dedicated Reviewer	Belgium	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts. Review methods, results, and

				conclusions based on the original studies included. Provide constructive comments in all the project phases.
4.	Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ)	Dedicated Reviewer	Croatia	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts. Review methods, results, and conclusions based on the original studies included. Provide constructive comments in all the project phases.
5.	National Institute of Pharmacy and Nutrition (NIPN)	Dedicated Reviewer	Hungary	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts. Review methods, results, and conclusions based on the original studies included. Provide constructive comments in all the project phases.
6.	Gesundheit Österreich (GÖG)	Dedicated Reviewer	Austria	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts. Review methods, results, and conclusions based on the original studies included. Provide constructive comments in all the project phases.
Contributors				
7.	Dirk Leonhardt	External expert	Denmark	Chief Technician at Department of Dentistry and Oral Health, at Aarhus University. Provides comments on the project plan and 2nd draft of the assessment.
8.	Constantinus Politis	External expert	Belgium	Full Professor & Chairperson Oral & Maxillofacial Surgery, at University Hospitals Leuven. Provides comments on the project plan and 2nd draft of the assessment.
9.	TBD	Medical Editor		
10.	Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ)	Project Manager	Croatia	Project management

1.2 Project stakeholders

Table 1-2: Project stakeholders[1]

Organisation	Role in the project
Anatomics	Manufacturer
Bespokemedical (Australia)	Manufacturer
Biomet (Denmark)	Manufacturer
CADskills BVBA (Belgium)	Manufacturer
Cerhum	Manufacturer
Cusmed	Manufacturer
Evonos	Manufacturer
Finceramica	Manufacturer
Fit-production	Manufacturer
Gsell	Manufacturer
Implantcast	Manufacturer
Johnson & Johnson Medical (DePuySynthes)	Manufacturer (have contributed with comments on scope and project plan and provided submission files)
Kelyniam	Manufacturer
KLS Martin	Manufacturer
Materialise	Manufacturer (have contributed with comments on scope and project plan and provided submission files)
Mathys Orthopaedics	Manufacturer
Medacta (Belgium)	Manufacturer
Medcad (Germany)	Manufacturer
Mimedis	Manufacturer
OssDsign	Manufacturer
Osteosymbionics	Manufacturer
Raomed	Manufacturer
ResMed	Manufacturer
Smith & Nephew	Manufacturer
Stryker	Manufacturer
3Dceram (Netherlands)	Manufacturer
3D-Side	Manufacturer
3D Systems	Manufacturer
Synimed	Manufacturer
Tecres	Manufacturer
Tissue Regeneration Systems	Manufacturer
Xilloc	Manufacturer
4webmedical	Manufacturer

[1] No comment beside certain manufacturer means that the manufacturer was contacted but did not respond or was not willing to participate in the assessment. Further information was not found via internet search.

1.3 Milestones and Deliverables

Table 1-3: Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**02/02/2018**	**19/04/2019**
Scoping phase	**02/02/2018**	**14/11/2018**
Identification of manufacturer(s) and external experts	02/02/2018	15/06/2018
Kick-off e-meeting with the assessment team	22/02/2018	
Scoping and development of draft Project Plan incl. preliminary PICO	26/02/2018	12/03/2018
Share the preliminary PICO with co-author for comments	12/03/2018	16/03/2018
Internal Scoping e-meeting with the assessment team	23/03/2018	
Consultation of draft Project Plan with dedicated reviewers	28/03/2018	10/04/2018
Contact with manufacturers	28/03/2018	
Send the preliminary PICO for comments and the request for the completion of the Submission file template to manufacturer(s)	20/06/2018	29/06/2018
Completion of Submission file template by manufacturer(s) and clarifying further questions concerning draft Submission file	29/06/2018	17/08/2018
Consultation of draft Project Plan with external experts and fact check by manufacturers	11/06/2018	25/06/2018
Amendment of draft Project Plan & final Project Plan available	09/11/2018	14/11/2018
Assessment phase	**14/11/2018**	**19/04/2019**
Writing first draft rapid assessment	14/11/2018	20/12/2018
Review by dedicated reviewer(s)	21/12/2018	11/01/2019
Writing second draft rapid assessment	14/01/2019	04/02/2019
Review by ≥ 2 external clinical experts and fact check by manufacturers	04/02/2019	18/02/2019
Writing third draft rapid assessment	18/02/2019	06/03/2019
Medical editing	07/03/2019	21/03/2019
Writing of fourth version of rapid assessment	22/03/2019	05/04/2019
Formatting	05/04/2019	12/04/2019
Final version of rapid assessment	12/04/2019	**19/04/2019**

2. PROJECT OUTLINE

2.1 Project Objectives

The rationale of this assessment is to collaboratively produce structured (rapid) core Health Technology Assessment (HTA) information on three-dimensional (3D) printing in surgery. In addition, the aim is to apply those collaboratively produced assessments in a national or regional setting.

Table 2-1: Project objectives

	List of project objectives	Indicator (and target)
1.	To jointly produce a health technology assessments that are fit for purpose, of high quality, of timely availability.	Production of 1 relative effectiveness assessment.
2.	To apply this collaboratively produced assessment into local (e.g. regional or national) context.	Production of ≥2 local (e.g. national or regional) reports based on the jointly produced assessment.
3.	To produce a rapid REA on the use of 3D printing in surgery.	Production of a rapid REA on the use of 3D printing in surgery which can ready to be used in different national contexts.
4.	To assess an innovative technology in its early use at hospitals.	Present usable evidence or knowledge even though the technology is in its early use.

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. This topic was chosen based on a request from reimbursement authorities who commissioned DEFACTUM to do an HTA on 3D printing in surgery. The relevance of the topic lies in the fact that 3D printing in the medical field and especially the field of orthopaedics has experienced increased growth and interest in recent years. Today the healthcare sector has become the greatest user of this technology after the industry and aerospace. The 3D printing technique has been adapted for a wide range of applications and for a large range of clinical specialties. 3D printing is used to print patient-specific anatomic models for pre-operative planning and education, implants, prosthesis, splints, external fixators, and surgical instrumentation and guides. 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. In some cases, 3D printed implants or cutting guides are used in cases where standard implants or cutting guides is not an alternative. In these cases 3D printed implants and cutting guides will be compared to "usual care" or "no treatment".

Taking these circumstances into consideration, 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, or cranial surgery and to assess the effectiveness and safety of this technology.

2.2 Project Method and Scope

2.2.1 Project approach and method

Table 2-2: Project approach and method

Project approach and method
• **Core model application:** The selection of assessment elements will be based on the HTA Core Model Application for Rapid Relative Effectiveness (REA) Assessments (4.2). In order to determine whether there are specific ethical, organizational, social and legal issues which need to be addressed, the checklist for potential ethical, organizational, patient and social and legal aspects for the HTA Core Model® for rapid REA will be completed. The short version of the Medical Devices Evidence Submission template will be sent to all relevant manufacturers of the technology under assessment. Manufacturers will be asked to submit non-confidential evidence with focus on the technical characteristics and current use of the technology. The evidence provided will be used in addition to the literature identified by a literature search. • **Literature search, information sources, and selection:** o A systematic search for published literature will be conducted in the following databases: Pubmed/Medline, Embase and Cochrane Library. We will additionally double check the existence of HTA or Horizon Scanning reports conducted by international HTA agencies (through the CRD-INAHTA database). Additional studies will be identified through experts and a review of the included studies reference lists. Furthermore, a search for on-going trials will be conducted in http://www.clincialtrials.govhttp://apps.who.int/trialsearch/and https://www.clinicaltrialsregister.eu/ctr-search/search. The timing of the assessment will be adapted according to availability of any upcoming published new evidence from these trials. o For the "Description and Technical Characteristics" (TEC) and "Health problem and Current use of the Technology" (CUR) domains, the completed EUnetHTA submission files from the manufacturers will be used as a starting point. Furthermore, information for these domains will be obtained from external experts with first hand knowledge of the technology, and from literature (i.e. descriptive publications) and grey literature as well as anecdotal information from general web-searches. o Potential social, ethical, legal, and organizational aspects will be identified through external experts, legal documents and scientific reports. o Literature selection will be performed independently by two researchers (from DEFACTUM) in accordance with the defined PICO. This process will be checked by the co-author (Osteba). • **Quality of evidence assessment:** Study and outcomes validity and level of evidence will be assessed according to the EUnetHTA guidelines. In the clinical effectiveness (EFF) and Safety (SAF) domains the review will be prepared in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" (PRISMA) statement. The quality of the included reviews will be assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool. This tool involves assessment of four domains to cover key review processes: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis and findings. The Cochrane Risk of bias tool will be used to assess the quality in the included RCT's according to the EUnetHTA Guidelines on medical devices for study and outcome level. Risk of bias in cohort and case-control studies will be assessed with the methodology checklists from the Scottish Intercollegiate Guidelines Network (SIGN). The quality of the body of evidence will be assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE). Relevant subgroup analyses will be assessed especially for the most important outcomes. The quality assessment will be

performed independently by two researchers from DEFACTUM. The process will be double-checked by the co-author (Osteba). Any disagreement will be resolved by consensus. For the TEC and CUR domains no quality assessments will be applied, but multiple sources will be used in order to validate potential biased sources. Descriptive analyses of different information sources will be applied.

- **Data extraction:** Data from the included studies will be extracted using a standardized data extraction form (see Table 2-4: Plan for data extraction). Data extraction will be performed independently by two researchers from DEFACTUM. The process will be double-checked by the co-author (Osteba).

- **Presentation of evidence:** For each outcome, an evidence profile will be prepared based on the GRADE profile software. Results from studies of high quality will be given most emphasis in the synthesis. Results will be presented as narrative synthesis. For the EFF and the 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 modelling allowing for differences in the association from study to study. Heterogeneity across studies will be statistically assessed using the Q-test and quantified by the inconsistency (I^2) index. I^2 represents the percentage of total variation across studies attributable to heterogeneity rather than (statistical) chance. In cases with substantial heterogeneity across studies ($I^2 >$ 50%), the robustness of the results will be checked using the “fixed effects” model. Meta-analyses will be performed using Review Manager (RevMan) provided by the Cochrane Collaboration. A two-sided P-value of ≤ 0.05 (and 95% confidence interval excluding the null) will be considered to be statistically significant in all analyses.

- **Involvement of external experts:** Two external experts will be involved in the assessment. Both a clinical expert (physician) and a technical expert are included in the assessment team. The tasks for the external experts in this assessment will be to qualify the scope of the assessment, to answer specific questions from the assessment team and to review the Project plan and 2nd draft of the assessment to ensure its clinical correctness.

Table 2-3: Planned literature search strategy

Literature search strategy
The systematic literature search to cover TEC, CUR, EFF and SAF, will be performed in the following databases: PubMed, EMBASE and Cochrane. We will consider CRD-INAHTA database and EuroScan for Horizon Scanning to double checked studies of interest that could have been missed in the broad literature search. Structured keywords to be used (MeSH and EMTREE): Three-Dimensional printing, Stereolithography, Computer-Aided design. Text words to be used: rapid prototyping, patient-specific implants, patient-specific instruments, surgical guides, additive manufacturing, medical additive manufacturing, subtractive manufacturing, computer numerical machine. Inclusion: Human population, controlled clinical trial, observational study (cohort or case-control but prospective), randomized controlled trial, systematic review, meta-analysis.

For systematic reviews and meta-analysis, time limitation will be five years. This short timeline is justified by the fact that it is a new and evolving technology, and the reviews will include studies produced before this timeline.

For primary studies, time limitation will be ten years.

For the TEC domain, information will be drawn from manufacturers' submission files and the literature in general. Horizon scanning reports could aid to identify manufacturers. FDA, PBAC (Australia) and CE mark for manufacturers that have received market authorization will be double checked.

Table 2-4: Plan for data extraction

Planned data extraction
The following data will be extracted from the primary studies:

Study characteristics
Authors
Year of publication
Setting
Study design
Clinical trial identification number/ registry identifier and funding source
Search date (if systematic review)
Searched databases (if systematic review)
Number of included studies (if systematic review)

Patient characteristics
Number of participants in the trial
Age
Diagnosis/Disease

Intervention and control characteristics
Application type (implant, cutting guide)
Anatomic location of implant or use of cutting guide for surgery
Description of the surgical procedure
Material of 3D printed device
Type of printer used
Software used
Imaging modality

Outcomes
Endpoints examined
Decease
Measurement tools applied
Methods used to analyse outcome data
Length of follow-up and loss to follow up
Results (effect estimates including confidence intervals)

2.2.2 Project Scope

Table 2-5: Project Scope: PICO (please see HTA Core Model® for rapid REA)

<table>
<tr><th>Description</th><th>Project Scope</th></tr>
<tr><td>Population</td><td>3D printed medical devices are applied for a broad variety of indications. To narrow the scope in this assessment, the focus will be on the three clinical areas where 3D printed medical devices are most frequently applied and where most of the published evidence lies. Data from a systematic review published in 2016 (Tack et al. 2016) shows that studies on the use of implants for cranial and maxillofacial surgery account for almost 90 % of the current published evidence. In studies on cutting guides; knee, maxillofacial and cranial surgery accounts for more than 70 % of the total evidence. Unpublished data from manufacturers collected recently in another project (Vinck et al. 2018) indicate that surgery in these three clinical areas (knee, maxillofacial and cranial) are the most common indications for the use of 3D printed devices. Thus, based on both indications and the expectations of available evidence, the scope for this assessment is adult patients (>18 years) undergoing knee, maxillofacial, or cranial surgery.</td></tr>
<tr><td>Intervention</td><td>The intervention under assessment is 3D printed custom-made or customisable implants and cutting guides used in patients undergoing knee, maxillofacial, or cranial surgery (For product names, see Table 2.6 below).

The following MeSH terms will be applied: Three-Dimensional printing, Stereolithography, Computer-Aided design.</td></tr>
<tr><td>Comparison</td><td>Comparators of interest are conventional/standard non-3D printed implants, or 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 are no standard solutions available, comparison will be "no treatment" or "usual care."</td></tr>
<tr><td>Outcomes</td><td>Outcomes for patients undergoing knee arthroplasty

Primary outcomes of interest:

• Patient Reported Outcome Measures (PROMs):
  ○ Pain measured by Visual Analogue Scale (VAS) or Numerical Pain Ranking Scale (NPRS)
  ○ Health-related quality of life (generic or disease-specific)
  ○ Patient satisfaction
• Post-operative function/performance measured by validated test i.e. Timed-Up-and-Go, Stair Climb test, or 6 Minute Walk Test.
• Function measured by validated clinical outcome scores i.e. Knee injury and Osteoarthritis Outcome Score or Lower Extremity Functional Scale.

Secondary outcomes of interest:

• Operation time (in relation to minimize risk of infection, ischaemia and blood loss)
• Overall limb alignment (of functional relevance).
• Durability of the device
• Longevity of the device
• Adverse events</td></tr>
</table>

	Outcomes for patients undergoing maxillofacial surgery Primary outcomes of interest: • PROMs: o Oral health measured by validated specific outcome scales: i.e. Oral Health Impact Profile (OHIP-14), or The United Kingdom Oral Health related Quality of Life measure (OHQoL-UK) o Health-related quality of life (generic or disease-specific) o Pain measured by Visual Analogue Scale (VAS) or Numerical Pain Ranking Scale (NPRS) o Patient satisfaction Secondary outcomes of interest: • Operating time (in relation to minimize risk of infection, ischaemia and blood loss) • Amount of bone harvest used in surgery • Durability of the device • Longevity of the device • Adverse events **Outcomes for patients undergoing cranial surgery** Primary outcomes of interest: • PROMs: o Health-related quality of life (generic or disease-specific) o Pain measured by Visual Analogue Scale (VAS) or Numerical Pain Ranking Scale (NPRS) • Precision/accuracy (of cosmetic/aesthetic and functional relevance) • Patient satisfaction Secondary outcomes of interest: • Operating time (in relation to minimize risk of infection, ischaemia and blood loss) • Durability of the device • Longevity of the device • Adverse events
Study design	• For the domains EFF and SAF the following study types will be eligible for inclusion: o High quality systematic reviews or meta-analyses of randomised controlled trials (RCT´s) or controlled trials published within the last 5 years and RCT´s or controlled trials published within the last 10 years. o If the subject under assessment does not allow the possibility to conduct an RCT or other controlled trails (e.g. the comparator is "no treatment"), evidence of lower quality will be included in the assessment. o Studies that compare different types of 3D printed implants or cutting guides will be excluded. Studies addressing 3D-printing of products incorporating biomaterials like drugs, xenogenic cell therapy preparations, 3D printed drugs or 3D bioprinting (3D fabrication technology involving biological tissues, organs and cells for medical and biotechnology applications) will also be excluded.

	• For the TEC and CUR domains, the completed EUnetHTA submission files from the manufacturers will be used as a starting point. Furthermore, information for these domains will be obtained from external experts with knowledge of the technology and literature (i.e. descriptive publications) and grey literature as well as anecdotal information from general web-searches. Potential social, ethical, legal, and organizational aspects will be identified through clinical experts and legal documents.

Table 2-6: Overview over manufacturers and relevant products

Manufacturer	Relevant products
Anatomics	**AnatomicsC3D**: Customs implant (cranial)
Bespokemedical (Australia)	**Bespoke solutions**: 3D custom-made prostheses
Biomet (Denmark)	**The Signature™ System**
CADskills BVBA (Belgium)	**CADCAMise:** Anatomical models, cutting/drilling guides and 3D print implants
Cerhum	Medical Ceramic 3D printing
Cusmed	No information found
Evonos	**Evo_Shape:** Skull implants
Finceramica	**CustomBone**: Custom-made implant for cranioplasty
Fit-production	**FIT production**: Custom-made implants
Gsell	**Gsell Medical**: Implants
Implantcast	**C-Fit 3D®:** Patient specific instruments and implants
Johnson & Johnson Medical (DePuySynthes)	**TruMatch 3.0** SYSTEM: Cutting guides/Patient specific instruments. **SIGMA Total Knee Implants, ATTUNE Total Knee System**
Kelyniam	**Kelyniam Implants**: Cranial implants
KLS Martin	**IPS Implants®**: Implants and implant systems for craniomaxillofacial surgery
Materialise	**TRUEMATCH®:** CMF Titanium 3D printed implant and patient-specific cranio-maxillofacial implants
Mathys Orthopaedics	**BalanSys and Affinis Architec**
Medacta (Belgium)	**MYKNEE**
Medcad (Germany)	**ACCUMODEL®**
Mimedis	**MIMEDIS**: Cutting guides and drill guides upon individual planning steps.
OssDSIGN	**OssDsign® Cranial:** CAD (Computer Assisted Design) technology and 3D printing
Osteosymbionics	**ClearShield**: Craniofacial implant
Raomed	**Raomed implants**
ResMed	**Narval**

Smith & Nephew	**Visionaire**: PMI (Patient Modeled Instrument). Total knee system
Stryker	**Triathlon Knee System**
3Dceram (Netherlands)	3Dceram custom-made or small series of bone substitutes skull implants
3D-Side	**3D Model**: Patient specific anatomical model
3D Systems	**3D Systems Healthcare**
Synimed	**Synicem ISM**: Cranioplast custom made implants.
Tecres	**Cranos**
Tissue Regeneration Systems	TRS (Tissue Regeneration systems) technology
Xilloc	Patient Specific Implants and surgical Guides
4webmedical	**Osteotomy Truss System™**

Usually EUnetHTA project plan would feature a list with identified specific product names produced by specific manufacturers. To generate such a list, was not straightforward in this particular project, and there are two reasons for this. As is evident from Table 1.2 and Table 2.6, there are many manufacturers in the area of 3D printing. The majority of these manufacturers have chosen not to submit a submission file or react to our enquiry about their products, and thereby not highlighting products relevant for this assessment. The second reason is connected to the fact that the project is supposed to assess custom-made devices and thereby are assessing devices which are not produced as standard. The devices are therefore different every time, and they do not hold a specific product name. The different manufacturers can use specific materials for their device, a specific production method or a specific image processing system to produce the custom-made device. These systems or methods may hold a specific name, but not the device itself. Table 2.6 is based primarily on information from the internet and represents a mixture of available information and as far as we can identify, it is primarily the names of specific systems used in 3D printing. In the assessment report, the 3D printed devices will be grouped in meaningful categories in order to be able to assess the effects.

3. COMMUNICATION AND COLLABORATION

Table 3-1: Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	To internally discuss and reach consensus on the scoping	23/03/2018	E-meeting	Author, co-author, dedicated reviewers, project manager.
Draft Project Plan with timelines	Review of methods and assessment elements chosen, discussion of time-lines	26/03/2018	E-mail	Author, co-author, dedicated reviewers, project manager.
Final Project Plan	Review of the final project plan	16/11/2018	E-mail	Author, co-author, dedicated reviewers, project manager.
Feedback on draft submission file	To point out the requirements for the final submission file by manufacturers	04/06/2018	E-mail	Author, project manager, manufacturers
First draft of the rapid assessment	To be reviewed by dedicated reviewers	20/12/2018	E-meetings may be planned	Dedicated reviewers
	To discuss comments of dedicated reviewers (optional)	TBD	E-meeting	Author, co-author, dedicated reviewers, project manager.
Second draft of the rapid assessment	To be consulted with ≥2 clinical experts (other potential stakeholders)	04/02/2019	E-meeting or E-mail	Author, co-author, dedicated reviewers; external experts, manufacturers

3.1 Dissemination plan

The final rapid assessment will be published on the EUnetHTA website: http://www.eunethta.eu/joint-assessments.

All stakeholders and contributors are informed about the publication of the final assessment by the project manager.

At the moment, there are no specific plans to disseminate the results in scientific journals or conferences. However, there will be an on-going attention on relevant forums for dissemination.

3.2 Collaboration with stakeholders

Collaboration with manufacturer(s)

There will be a review of the preliminary PICO and a fact check of the 2nd draft project plan and the 2nd draft assessment by the manufacturer(s). All identified manufacturers will be offered the change to participate in the assessment process.

3.3 Collaboration with EUnetHTA WPs

For the individual rapid assessment, some collaboration with other WPs is planned: WP7 [Implementation] will be informed of the project, in order to prepare activities to improve national uptake of the final assessment. Feedback on the WP4 REA process will be asked from the involved

parties by WP6 [Quality Management], and this information will be processed by WP6 to improve the quality of the process and output.

3.4 Conflict of interest and confidentiality management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised “Declaration of Interest and Confidentiality Undertaking” (DOICU) statement.

Authors, co-author and dedicated reviewers who declare a conflict of interest will be excluded from parts of or the whole work under this specific topic. However, they still may be included in other assessments.

For external experts, patients or other stakeholders involved, conflict of interest declarations are collected regarding the topic. External experts or patients who declare conflict of interest will be excluded from parts of or the whole work under this specific topic. However, they still may be included in other assessments.

Manufacturer(s) will sign a Confidentiality Undertaking (CU) form, regarding this specific project.

4 References

- Tack et al. 2016: Tack, P., Victor, J., Gemmel, P., & Annemans, L. (2016). 3D-printing techniques in a medical setting: a systematic literature review. BioMedical Engineering OnLine, 15, 115. http://doi.org/10.1186/s12938-016-0236-4

- Vinck et al. 2018: Vinck I, Vijverman A, Vollebregt E, Broeckx N, Wouters K, Piët M, Bacic N, Vlayen J, Thiry N, Neyt M. Responsible use of high-risk medical devices: the example of 3D printed medical devices. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2018. KCE Reports. D/2018/10.273/03.

5. Appendix

5.1 Selected Assessment Elements

Table 5-1 shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessment elements contained in the 'Model for Rapid Relative Effectiveness Assessment'. Additionally, assessment elements from other HTA Core Model® Applications (for medical and surgical interventions, for diagnostic technologies or screening) have been screened and included/ merged with the existing questions if deemed relevant.

Table 5-1: Selected Assessment Elements

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology					
B0001	Features of the technology and comparators	What is the technology and the comparator(s)?	Yes	M	What are 3D printed implants and cutting guides versus conventional implants and cutting guides?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes	M	For which indications has 3D printed implants and cutting guides received marketing authorisation (FDA or CE marking)?
B0002	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparator(s)?	Yes	M	What is the claimed benefit of 3D printed implants and cutting guides in relation to conventional implants and cutting guides?
B0004	Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?	Yes	M	Who administers 3D printed implants and cutting guides and conventional implants and cutting guides and in what context and level of care are they provided?
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	Yes	NM	What kind of special premises are needed to use 3D printed implants and cutting guides and conventional implants and cutting guides?
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	Yes	NM	What equipment and supplies are needed to use 3D printed implants and cutting guides and conventional implants and cutting guides?
A0021	Regulatory Status	What is the reimbursement status of the technology? [This assessment element can be placed either in the TEC OR in the CUR domain]	No	NM	
Health problem and current use of technology					
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	M	What are the most frequent diseases or health conditions which lead to knee, maxillofacial, or cranial surgery?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	No	NM	
A0004	Target Condition	What is the natural course of the disease or health condition?	Yes	M	What is the natural course of the disease or health condition?
A0005	Target Condition	What are the symptoms and the burden of disease or	Yes	M	What are the symptoms and the burden of disease or health condition for the patient?

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
		health condition for the patient?			
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	Yes	NM	What are the consequences of the disease or health condition for the society?
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	Yes	M	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes	M	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	Target Population	What is the target population in this assessment?	Yes	M	What is the target population in this assessment?
A0023	Target Population	How many people belong to the target population?	Yes	M	How many people belong to the target population?
A0011	Utilisation	How much are the technologies utilised?	Yes	M (NM for diagnostics)	How much are the 3D printed implants and cutting guides utilised?
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	Yes	M	What is the expected beneficial effect of 3D printed implants and cutting guides on mortality?
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	Yes	M	How does use of 3D printed implants and cutting guides affect symptoms and findings (severity, frequency) of the patients undergoing surgery?
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes	M	How does 3D printed implants and cutting guides affect progression (or recurrence) of the disease or health condition?
D0011	Function	What is the effect of the technology on patients' body functions?	Yes	M	What is the effect of 3D printed implants and cutting guides on patients' body functions?
D0016	Function	How does the use of technology affect activities of daily living?	Yes	NM	How does the use of 3D printed implants and cutting guides affect activities of daily living?
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes	M	What is the effect of 3D printed implants and cutting guides on generic health-related quality of life?
D0013	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes	M	What is the effect of 3D printed implants and cutting guides on disease-specific quality of life?
D0017	Patient satisfaction	Were patients satisfied with the technology?	Yes	NM	Were patients satisfied with the use of 3D printed implants and cutting guides?
Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	Yes	M	How safe is the use of 3D printed implants and cutting guides in relation to conventional implants and cutting guides?

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	No	NM	
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	Yes	M	How does the frequency or severity of harms change over time or in different settings?
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Yes	M	What are the susceptible patient groups that are more likely to be harmed through the use of 3D printed implants and cutting guides?
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	No	NM	
B0010	Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	Yes	M for medical devices NM for screening and diagnostics	What kind of data/records and/or registry is needed to monitor the use of 3D printed implants and cutting guides and conventional implants and cutting guides?

5.2 Checklist for potential ethical, organisational, patient and social and legal aspects

The following checklist has been completed in order to determine whether there are specific ethical, organisational, social and legal aspects which also need to be addressed. Since the assessment is comparative in nature, only new issues are dealt with which arise from a difference between the technology to be assessed and its major comparator(s). Already known problems/issues with regard to ethical, organisational, social and legal aspects which are common to the technology to be assessed and its comparator(s) will, as a rule, not be addressed, as it is not to be expected that the addition of a new technology will lead to changes.

If a question is answered with 'yes', further analysis of these issues may be warranted. If they are answered with no, the domains need not be dealt with further.

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes/<u>No</u>
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	Yes/<u>No</u>
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	<u>Yes</u>/No
The utilization of 3D printed medical devices could lead to organisational changes. These changes will mainly consist of changes in work flow at the hospital department and changes in competences for the personal. The impact of these changes depends on the scenario implemented. E.g. is the medical device printed on a 3D printer located at the hospital (surgical department or a central 3D printer department) or is the medical device printed by an external 3D print manufacturer and send to the surgical department.	

2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes/No
See above (section 2.1)	
3. Social	
3.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	Yes/No
3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	Yes/No
4. Legal	
4.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	Yes/No

The following legal issues have been identified by KCE in their report on *"Responsible use of high-risk medical devices: The example of 3D printed medical devices"* and may be relevant to address in this assessment as well:

- **Requirements for market access:** In the current EU-regulations the requirements for putting 3D-printed medical devices on the market depends on their classification as a "standard", "customisable" or "custom-made" device. "Custom-made" devices are unique devices fitted to an individual patient whereas "customisable" medical devices are devices that can be (mass) produced via a standard process and individualized according to individual parameters. Currently customisable devices are regarded as prescription devices that are made once for a certain patient. As a consequence they are usually classified with the custom-made devices. In contrast to "standard" medical devices, manufacturers of custom-made medical devices, regardless of the risk profile, do not need to apply any CE marking to their product, there are no specific quality system requirements and for the higher risk classes there is no prior external evaluation of the device by a notified body. Manufacturers do have to draw up a statement (Annex VIII MDD) with identification data and characteristics of the device, the identity of the patient (coded or not), the prescribing physician, and as applicable the hospital concerned. They must in addition declare that the essential requirements of Annex I MDD (among others, justification of material choice, biocompatibility requirements, and sterility requirements are fulfilled. However, they need not demonstrate that the 3D-printed device is safer or more effective than (possibly) existing alternatives. According to the new EU-regulations stricter requirements for 3D-printed medical devices made in larger quantities will be imposed. This means that customisable medical devices will have to comply with the same conditions as standard medical devices for marked access. An exception to the stricter legislation for standard medical devices was made for medical devices that are made in hospitals. Aside from the essential requirements of Annex I, the requirements of the MDR (among others, CE marking, assessment by a notified body for certain risk classes) are not applicable under a number of conditions. The new regulations took effect on May the 25th 2017 and will be directly applicable in spring 2020 for the Medical Devices Regulation (MDR) and spring 2022 for the In Vitro Diagnostics Regulation (IVDR). Thus, based on the above there are currently (and in the future) different legal requirements between the different types of 3D printed medical devised and between 3D printed medical devices and the comparators (standard medical devices).

- **Liability:** According to the principles of product liability the producer is liable for any defect in its product. In 3D printing, however, there is a deviation from the traditional chain of production, distribution and use. Who is the producer here? Many parties are involved in the production of 3D devices: the surgeon who makes the initial design, the software engineer who develops the 3D design, the producer of the 3D printer, of the material, of the software and of the implant, the implanting surgeon, the hospital, etc. The Product Liability Directive

(PLD)[2] states that member states 'must impose strict liability on' producers when their products are defective and cause bodily injury, without the need for the victim to demonstrate that the producer has committed an error. The PLD also encompasses all medical devices that are made in the EU or imported. This strict liability is however only applicable to 'industrially made products'. It has not yet been determined by the EU whether 3D-printed medical devices fall under this PLD, and no EU case law yet exists on the concept 'industrially produced'.

- **Protection of person data:** The 3D printing process unavoidably also involves the processing of health data of the individual patient. In addition these data can be used for other than therapeutic purposes, e.g. for scientific research or reimbursement purposes (see below). The Privacy Legislation protects the processing of personal data and has developed rules for this.[3] It is very important to know who is regarded as "responsible for processing" by the law. This person is in fact charged with almost all the legal obligations to guarantee protection of the processed data. Hospitals will generally be regarded as responsible for processing the personal data of the patient that are required for the 3D printing process. If hospitals outsource 3D printing to an external producer, they will have to conclude a processing agreement with it. If the conditions of the privacy legislation are met, no specific problems arise in 3D printing.

- **Patients' rights:** Patients' have the right to be properly informed about alternatives. This could be an issue if only one alternative is reimbursed in the health care system.

4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	Yes/No

See above (section 4.1)

[2] Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products, PB L 210 of 7/8/1985, pp. 29–33.

[3] EU: Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, PB L 281 of 23/11/1995 pp. 0031 - 0050 and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC, PB L 119 of 4/5/2016, pp. 1–88; Belgium: Law of 8 December 1992 on the protection of privacy in relation to the processing of personal data, *Belgian Official Gazette*, 18 March 1992 and its implementation decrees.