Protocol for implantable medical devices

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Executive Summary

This document aims to provide a protocol for the steps involved in developing and additively manufacturing implantable medical devices, from image acquisition to use in clinics. This document is developed using a partial mandibular reconstruction implant as an example. The information in this document is only intended to describe a general process for designing and additively manufacturing a partial mandibular reconstruction implant and should not be used as a final guideline at this time. Furthermore, this document is subject to future updates, as this document is based on the initial design of the mandibular implant and the design is still under development. As a result, the 3DMed project accepts no liability or responsibility for the clinical use of the first version of this document. This document is directly linked with Deliverable 3.4.2 "Materials database for 3D printed patient-specific implants", and Deliverable 3.4.4 "Materials database for 3D printed spinal cages".

1. Introduction

In this document, a partial mandibular reconstruction implant (hereafter referred to as “Mandibular Implant) is used as an example to set up a protocol to design and manufacture such an implantable medical device. According to MDR 2017/745 [1], all implantable or long-term surgically invasive devices are classified as class IIb medical devices, unless they are either a total or partial joint replacement (e.g., mandibular implant), a spinal disc implant or the implants in contact with the spinal column, which would make them class III medical devices. Expectations are made for screws, wedges, plates, or instrument components, making them not class III devices. For class IIb and III medical devices, a summary regarding their primary safety and performance, including clinical evaluation, is required to be publicly available.

The outcomes regarding long-term complications, loosening of implants, bone ingrowth and possible late infections, are also meaningful to collect. These outcomes are a decisive factor in many cases. The ability to compare several cases also relies on the availability of 3D printing data. The material, process and post-processing conditions and parameters are recommended to be recorded so that in further studies these data can be compared with each other.

From image acquisition to clinical use in surgery, the workflow for producing a patient-specific mandibular implant is depicted in Figure 1. The procedure and details of each step should be recorded using the forms in Annex I.

2. Design specifications

The design of a mandibular implant begins with medical imaging of the region of interest and continues with the image post-processing. These steps are necessary to prepare an input file to produce the device using additive manufacturing (AM) technique [1].

The design of the patient-specific implants can be modified either directly by clinical staff, the implant manufacturer or by a third party in response to clinical inputs. These inputs can be generated by person measurements, clinical evaluations, patient imaging, or a combination of these sources. Changes to the final implant, as well as the methods used to make the changes, may have an immediate effect on the patient. As a result, it is critical to define the clinically relevant design parameters, their pre-determined range (min/max) for these parameters, and which of these parameters can be adjusted for patient-matching [1]. Steps related to the design of a mandibular implant are detailed in the following sections. All these steps should be documented in accordance with Annex I, Section 1-4.

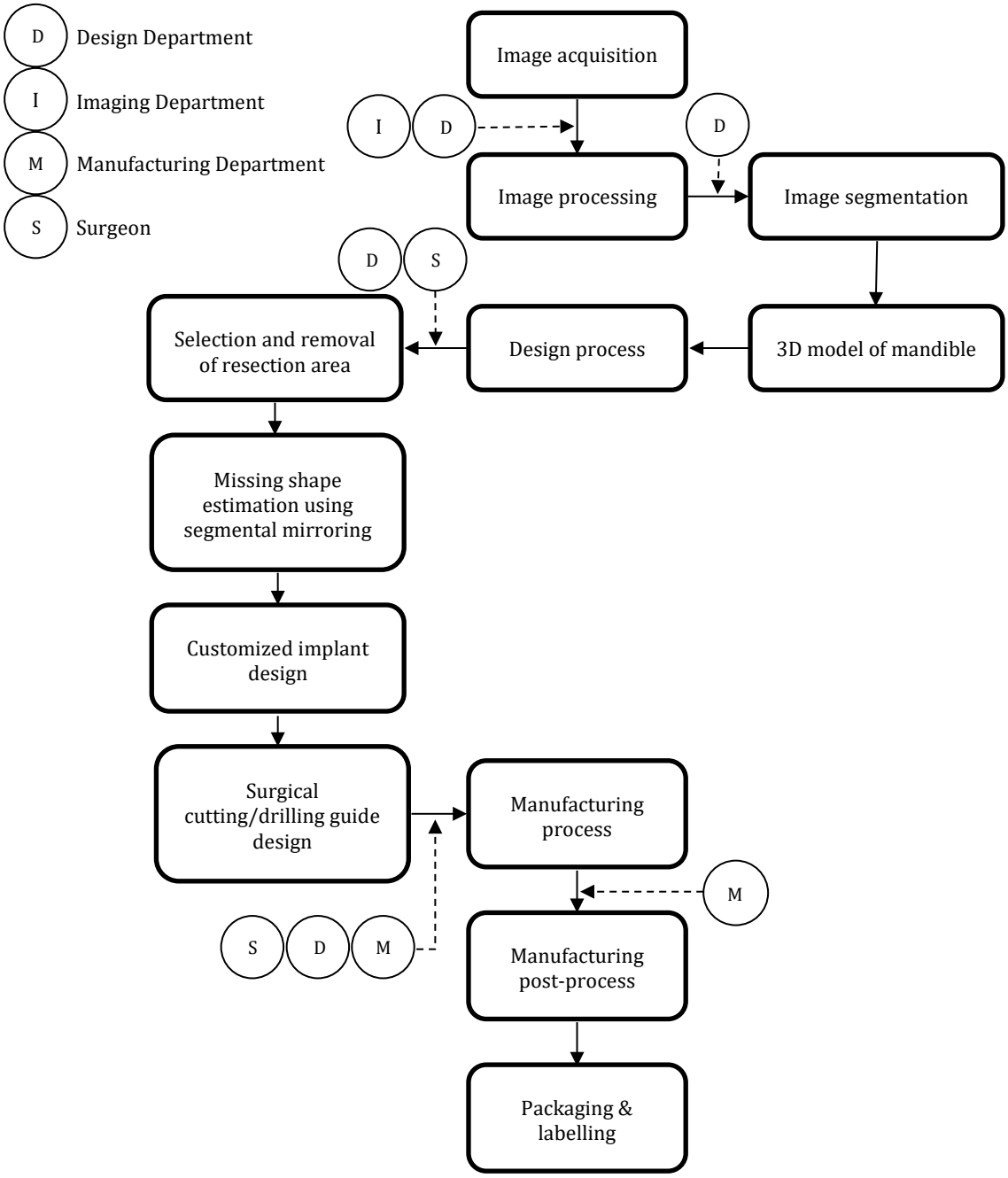


Figure 1 Workflow for producing a patient-specific mandibular implant; the steps are specified with required actions and the corresponding departments to monitor each step.

2.1 Image acquisition and analysis

Non-destructive medical images, such as computed tomography (CT) and/or magnetic resonance imaging (MRI) scans, can be used as input data for designing a patient-specific mandibular implant. Based on these medical images, surgical guides and implants can be designed by using computer-aided design (CAD) tools.

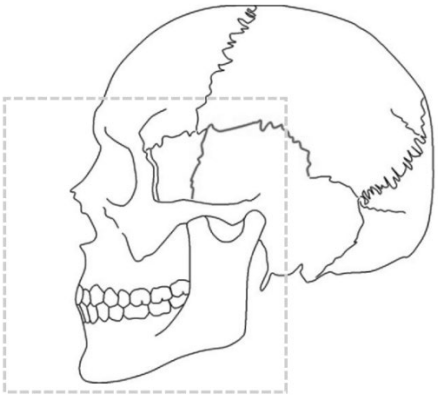
The following factors, among others, can have an effect on the precise control of the size and shape of a patient-specific medical device (whether AM manufactured or not) [2]:

- The minimum image feature quality and resolution (e.g., low-resolution may hamper the depiction of the structure of interest)
- Image post-processing algorithms (e.g., too much smoothing of a bone contour may have an adverse effect on bone shape/size determination)
- The rigidity of the anatomic structure of interest (e.g., the deformation of a soft tissue during respiration may cause difficulties)

Since image quality and medical data post-processing impact the final quality of a designed product, a protocol to obtain a validated medical image should be followed. This document considers CT and CBCT (cone beam computed tomography) scans as an imaging tool for patient-specific mandibular implants, and clarifies the procedure to obtain a validated image.

2.1.1 Image acquisition

A typical CT protocol comes with 120 kV, 100 mA, 1 mm collimation, 1 mm/rotation (pitch). The typical field of view (FOV) used for the surgical planning of the mandibular implants should encompass the full mandible, the orbitals and the auditory meatus (Figure 2).



Considering all these factors, a procedure followed to acquire medical images plays an important role in the design of a patient-specific medical device. In this document, CT and CBCT imaging procedures are presented for an accurate design and manufacturing of patient-specific mandibular implants.

Before image acquisition starts, the clinician should consider the following points:

- (If contrast-enhancement is needed) perform image acquisition on an empty stomach,
- (scanning with possible iodine contrast medium administration) let the patients with thyroid pathology to have their TSH (thyroid stimulating hormone) blood level tested before scanning,
- (scanning with possible iodine contrast medium administration) let the patients with kidney failure to have their creatinine blood level tested before scanning
- The scan must not be taken sooner than four (4) months prior to the surgery, as the changes in patient anatomy occurring after the CT/CBCT may result in a suboptimal fit of the implant.
- remove any non-fixed metal prosthesis or jewellery within the FOV.

- Minimize the artifacts caused by metallic dental restorations or orthodontic brackets by aligning the patient's occlusal plane as much as possible with the axial slices.
- Patient should be scanned in good occlusion when possible. The patient is preferably scanned with the jaw slightly open with a very thin bite jig that does not influence the facial soft tissues. This reduces the chance of artifacts from the opposing jaw interfering with the images of the jaw. Please contact the ordering surgeon if you have any questions about what is appropriate.
- Inform the patient when the actual scanning process starts. Instruct them to not move or swallow until the scan is complete. Every movement, such as tilting and/or rotating the head, can add motion artifacts and compromise the reconstructed images, however natural breathing is permitted. In the case of movement, rescanning of the patient is necessary

During the scanning:

- Take a scout view (also called a Localizer, Topogram, Scanogram, Pilot or Surview depending on the CT manufacturer) and locate the first slice position. Make sure the head is positioned symmetrically so that the first slice is positioned correctly for both the left and right mandibular.
- Start the scan so that it includes both the sella and nasion. Be sure that both inferior orbital borders and external auditory canals (EAC's) are included. Scan through the tip of the chin.
- Use the following parameters (or the closest approximation possible):

Field of view	Nose and chin, full mandible, the orbitals and the auditory meatus
Matrix	512×512 pixels
Gantry tilt	0°
kVp	90-120
Pitch	Use 1 or smaller
Slice thickness	Maximum 1.0 mm
Feed per rotation	Maximum 1.0 mm
Reconstructed slice increment	Maximum 1.0 mm
Preferred algorithms	FC30 or FC09
Export format	DICOM (uncompressed standard)

After scanning, the image should be inspected and approved by the imaging department and design department; and then documented according to the Section 2 of Annex I "Patient anatomy data".

2.1.2 Image segmentation

Following the acquisition of medical images, the image processing will take place. If the medical images received are deemed acceptable, CE-marked software including Synopsys Simpleware ScanIP™ and Mimics® Materialise must be used to create a precise digital model of the anatomy. Mimics® version 21 was used to process images in this document.

To understand the impact of the in-plane resolution and the slice thickness in the geometrical error associated with the imaging process, please see Annex II of this document.

An accurate segmentation of the mandible can be obtained using an optimum foreground-background segmentation of the DICOM data, such as using the so-called Otsu threshold [3]. The custom design process

utilizes a mirror reconstruction technique based on healthy bone in the unaffected side. Mirror reconstruction relies on the accurate computation of the craniofacial symmetry and therefore maximize functionality and aesthetics.

The segmentation steps for Mimics® Materialise software could be as follows (For Synopsys ScanIP™, please refer to Annex II):

- Load the DICOM image dataset into Mimics®
- Foreground-background segmentation with an *optimum threshold*; Normally, the predefined threshold set will be set at *Bone (CT).*
- *Split mask* to separate the mandible from the base;
- *Region growing* to obtain a new and clean mask from the mandible and remove extraneous (noise) structures around the mandible;
- Surface mesh computation was performed using *Calculate Part* with a quality set to *optimal*;
- Export the part to 3-Matic®
- Complete the form in section 3 of Annex I- "segmentation".

2.2 Patient-specific design

After image segmentation, a patient-specific mandibular implant will be designed. The patient specific design shall be determined on the basis of the patient anatomy and the validated segmentation that the surgeon or practitioner who prescribes the implant has examined and approved.

Usually, the reconstruction procedure includes a planning phase in which the surgeon and design department consider the resection options and define the overall shape and characteristics of the customized reconstruction implant. Many physiological and technical parameters are involved in these considerations, and sufficient feedback from the surgeon is essential in the design process.

Several factors must be considered during the design process, including implant material, implant appearance, implant thickness, implant porosity, implant edge diameter, screw shape, and screw holes. These factors, as well as the considerations taken into account during the 3DMed project, are presented in the following sections.

Implant material

The reconstruction implant will be made of Ti-6Al-4V (grade 23). According to D 3.4.4, this material is the current standard for load-bearing orthopedic implants due to its high strength, low weight, good corrosion resistance and excellent biocompatibility properties. Besides, titanium alloy is very suitable for metal 3D printing through selective laser melting (SLM) or electron beam melting (EBM).

Implant appearance

For the shape of the implant, a cage design should be considered, and the appearance and dimensions of the final implant design should be considered in close collaboration with maxillofacial surgeons.

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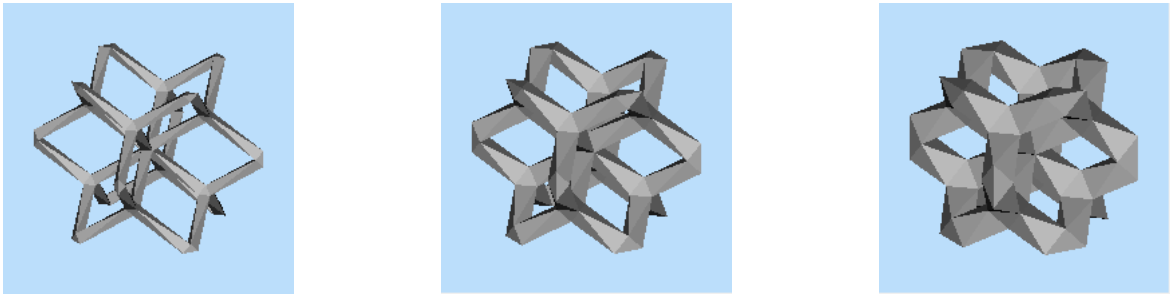
Implant thickness

Considering implant weight restrictions and implant comfort, the implant thickness should set at 1.5 mm.

Implant porosity

The implant should be designed with a lattice structure that extends across the entire implant volume, with the exception of the solid edges around the screw holes and implant extremities, which are added for structural and mechanical support. The most important unit cell parameters to be considered are pore size, strut thickness, and porosity.

The unit cell used for this graft carrier is a dode unit cell structure, created with the Materialise Magics® software (version 24.01). In Magics, three different versions of the dode unit cell type are available by default, namely the dode thin, dode medium, and dode thick unit cell (see Figure 3). The pore and strut parameters for each of the dode structures are listed in Table 1. The dode medium unit cell was selected for the final implant design and the unit cell size was kept constant at 1.5 mm.



(a) (b) (c)

Figure 3 (a) Dode thin, (b) dode medium and (c) dode thick unit cell structures available in the Materialise Magics® software.

Table 1 Theoretical values for pore and strut parameters of three different dode unit cell structures.

Unit cell structure	Dode thin	Dode medium	Dode thick
Pore size in-plane (µm)	420	325	230
Pore size smallest (µm)	590	460	320
Strut thickness (µm)	110	210	300
Porosity (%)	96.2	87.5	75.4

Implant edge diameter

Initially, the reconstruction implant would be designed to be fully solid. The implant would then have lattice structuring applied to it. Due to mechanical constraints, only a portion of inner volume of the implant can be made available for lattice structuring, leaving certain edges solid. These edges are located at the upper boundaries of the implant and around the screw holes. These solid edges provide mechanical

support to the implant and shield the patient from the sharp ends of the struts. The solid edge width of the current design was set at 1.5mm.

Screw shape and position

A minimum of three bicortical screws (four if possible) are required for optimal resistance to deformation in case of a conventional reconstruction plate [4]. Depuy Synthes 2.4 mm Titanium MatrixMANDIBLE Cortex Screws are being considered for use in the 3DMed project for fixing implants to the mandibles.

Each implant should be fixed to the mandible by a total of eight screws of varying lengths. Screw lengths should be determined by visual inspection in the mandible using Materialise 3-Matic®. Four screws should be placed at the remaining anterior mandibular segment with a 14 mm length. The two screws on the remaining posterior mandibular segment nearest to the resection should be 8 mm long, while the two screws on the most distal posterior mandibular segment should be 5 mm long.

The distance between the centers of screw holes should not be less than $2\,{}^{2}/_{3}$ times the nominal screw diameter, and that a distance of 3 times the screw diameter is preferred. Therefore, a minimum screw spacing of 7.2 mm between the screw holes should be applied to the mandible model. For simplicity, the screw hole distance should be set at 8 mm. Furthermore, it is important to mention that for mechanical reasons the screw closest to the resection border should be positioned at least 5-7 mm away from the osteotomy line, as the bone density and vascularity surrounding the defect can be reduced.

The positions of the screws in the posterior mandible closely follow the inferior border of the mandible, so that possible damage to the mandibular nerve and interference with tooth roots and possible future implants can be avoided.

The options for different screw positions in the chin region is limited, given the specified requisites and available amount of space. As a result, these four screws may simply be positioned next to each other in the horizontal plane, similar to fixation plates used for mandibular resection or fracture repairs.

2.2.1 Design workflow

Initially, the reconstruction implant would be designed to be completely solid. Afterwards, lattice structuring would be added to the implant. For mechanical reasons, only a certain inner volume of the implant can be made available for lattice structuring, leaving some edges to remain solid. These edges are located at the upper boundaries of the implant and around the screw holes. These solid edges provide the implant extra mechanical support and protect the patient from the sharp ends of the struts.

The design can be performed by biomedical engineers with 3-Matic® (Materialise, Leuven, Belgium). The design workflow in 3-Matic consists of six steps: (1) segmental resection, (2) segmental mirroring, (3) missing shape estimation, (4) implant surface definition, (5) screw positioning, and (6) creating a lattice structure.

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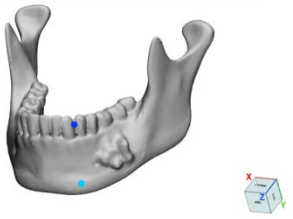
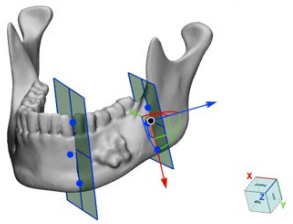
Step 1 – Segmental resection

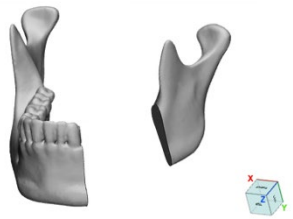
- Define two cutting planes by creating two datum planes: mark three points on the mandible surface where the datum planes will be generated.



- Tune the orientation of the plane by translating or rotating it.

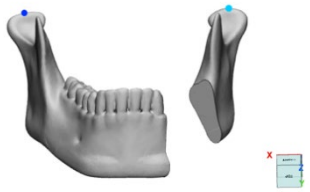


- Use cutting operation to perform the segmental resection along the created datum planes.

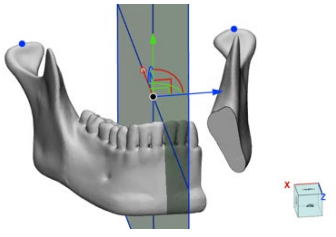


Step 2 – Segmental mirroring

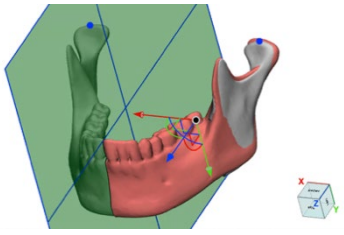
- Select two points, one on each condylar or coronoid process, in between which the mid-sagittal (datum) cutting plane will be created.



- The position and orientation of the plane can be fine-tuned after creating it.



- Copy and mirror the healthy side of the mandible over the affected side across the mid-sagittal datum plane. Fine-tune the position of the mirrored segment (salmon colored) such that it aligns best with the affected side of the mandible.



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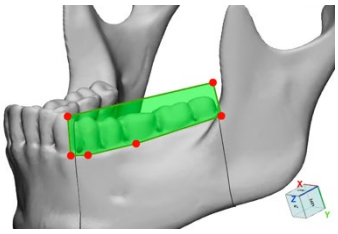
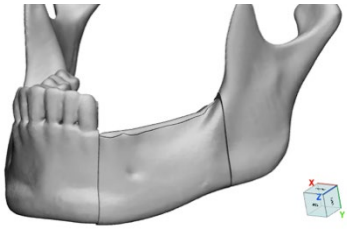
- Cut the mirrored segment using the cutting planes created in Design step 1 and keep only the middle segment that fits the gap in the affected side of the mandible.

Step 3 – Missing shape estimation

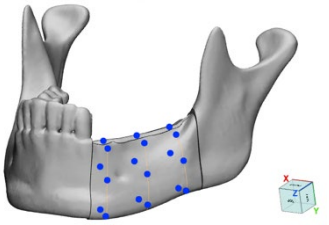
- If teeth are present, remove them first by using the 'trim' function.



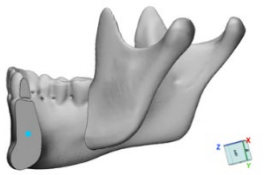
- 'Fillet' the remaining contour to get smooth borders

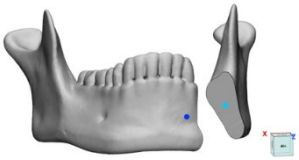


- Select 6 points lying in one plane around the bridging part. This operation will be performed on the bridging part 3 times; first about 1 cm away from one end, one in the middle and finally about 1 cm away from the other end.

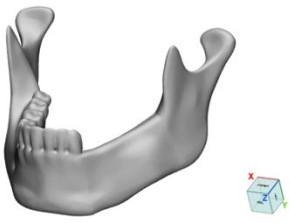


- Select two points, one in approximately the middle of the flat surface on each bony end. A curve will be created between these two points that will serve as a path for the sweeping operation.



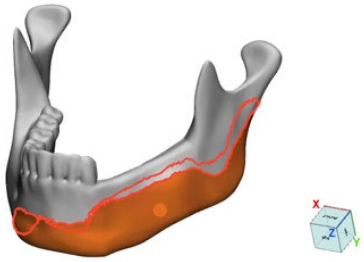


- Perform a sweep-loft operation using the previously created curves as sweep path and intermediate profiles. Perform a Boolean union on the three separate parts and complete the shape estimation with the filter small surfaces, wrapping and smoothing operations to end up with a smooth reconstruction.

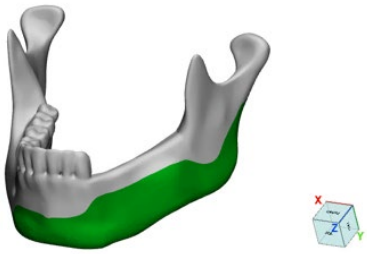


Step 4 – Implant surface definition

- Mark the surface of the mandible to define the desired implant region.



- Smooth the marking borders to get a cleaner surface area and copy the implant surface to a new part.

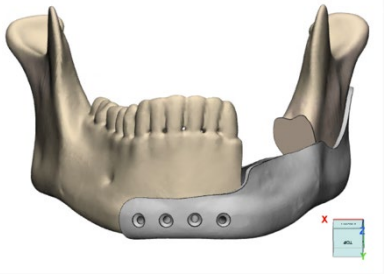


- Define the desired implant thickness and create the solid implant.

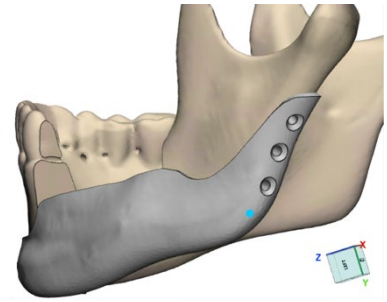
- Check the implant and trim off any protrusions or unwanted areas.

Step 5 – Screw positioning

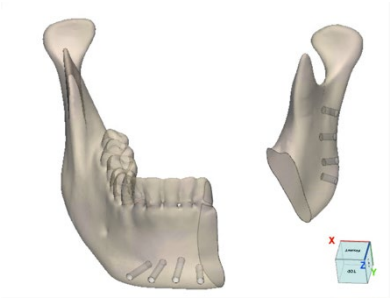
- Position the specified number of screws in the interior region.



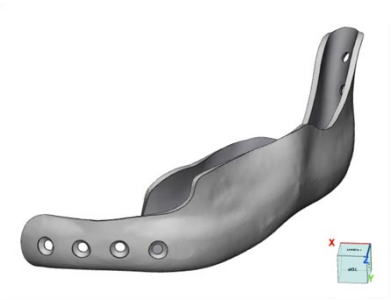
- Position the specified number of screws in the posterior region.



- Create holes in the mandible with lengths corresponding to the screw lengths

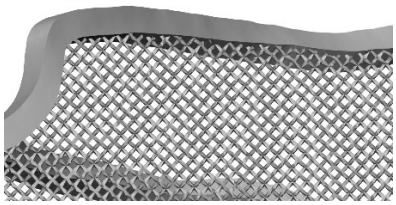


- Final solid design



step 6 – Creating a lattice structure

- Lattice structuring of the mandibular implant should be performed in the Materialise Magics® software.



2.3 Surgical cutting/drilling guide

A surgical guide should be developed in 3-Matic® based on the final implant design (Figure 4). The guide design can be clicked onto the mandible and secured tightly with two screws on the lateral side of the mandible. Two slits should be created with an opening narrow enough for a surgical oscillating saw to accurately cut the mandible at the predefined cutting planes. Eight holes should be positioned at locations that correspond to the screw holes inside the reconstruction implant. Insertion of self-tapping 2.4 mm screws in dense cortical bone requires predrilling with a 1.8 mm drill bit. Therefore, the cylindrical apertures present in the surgical guide should have a diameter of 2 mm to enable smooth insertion of the drill bit.

The surgical guide can be 3D printed through fused deposition modeling (FDM) using tough PLA material. The guide can be reattached and reused for the other fixation procedures, such that printing of only one guide is required.

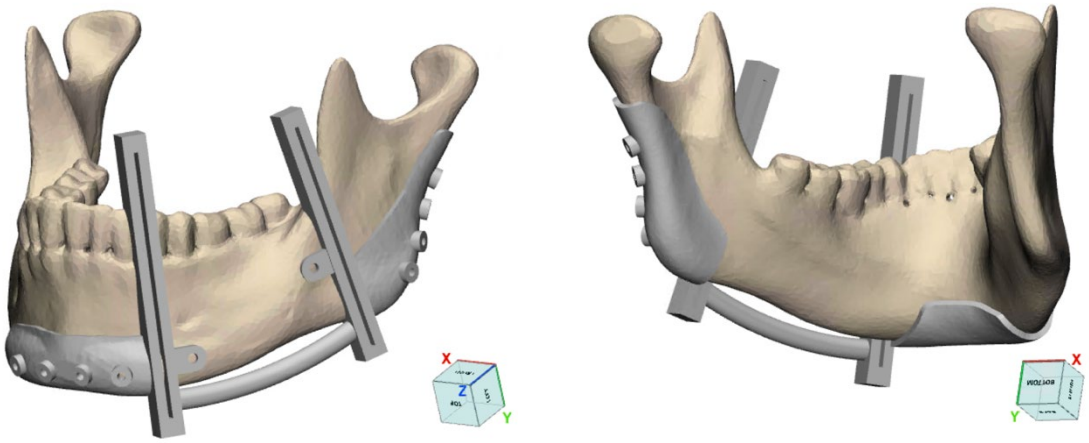


Figure 4 A surgical cutting/drilling guide for a surgical oscillating saw and drilling developed in 3-Matic®.

3. Material specifications

Different materials can be selected to create a mandibular implant. Properties such as biocompatibility, machinability, corrosion resistance, osseointegration, elastic modulus, strength and costs should be considered in the selection.

In the 3DMed project, Titanium-6 Aluminum-4 Vanadium (Ti6Al4V) was chosen as the material for the patient-specific mandibular implants. The titanium alloy provides stability and allows bony ingrowth in the mandibular implants. The titanium alloy is used as well for fixation screws and corresponds to the ASTM F136 standard [5]. Table 2 contains details on the mechanical properties and material characterization of Ti6Al4V grade 23 provided by AP&C.

Table 2 Mechanical properties and material characterization of Ti6Al4V (Grade 23)

General information	
Material Name	Titanium-6 Aluminum-4 Vanadium (Ti6Al4V)
Supplier	AP&C (www.advancedpowders.com)
Young's Modulus (GPa)	122.3±2.5
Yield Strength [MPa]	>900
Ultimate strength [MPa]	>980
Elongation [%]	>14%

Hardness	>340 HV
Melting temperature (°C)	1626

All used materials and their specifications, such as material properties, material supplier, and material storage condition, should be documented by manufacturing department in Section 5 of Annex I, titled "Material and Manufacturing".

For more information on polymeric biomaterials and bio-metals that can be used for maxillofacial implants, please see Deliverable 3.4.2 "Materials database for 3D printed patient-specific implants" and Deliverable 3.4.4 "Materials database for 3D printed spinal cages."

4. Manufacturing specifications

4.1 3D printing

The manufacturing methods of the mandibular implants from Ti6Al4V powder are either direct metal laser sintering (DMLS) or selective laser melting (SLM). The SLM technique is used to create the mandibular implants in the 3DMed project.

The principle of SLM is based on the process where a high-powered laser melts and fuses metallic powder particles together. After melting the first layer of the build, a fresh layer of powder material is distributed over the built platform. Subsequent fusion occurs between adjacent layers until the build has completed.

Before the implant can be additively manufactured, additional preparatory processes are needed. This is commonly achieved with build preparation software such as Materialise Magics® which is divided in four steps: (i) build volume placement, (ii) addition of support material, (iii) slicing, and (iv) creating build paths. Each AM technology and machine model has its own set of parameters and configurations, and the optimal settings and parameters for a single machine model will differ significantly when printing different devices or components. Furthermore, even when printing the same devices or components, optimal settings and parameters will differ between machines of the same type. Therefore, manufacturing department should document parameters for each particular design according to the Section 5 of Annex I. Table 3 lists the printing parameters for the material used in the 3DMed project.

Table 3 Printing parameters for producing a mandibular implant made of Ti6Al4V.

General information	
L-PBF scanning strategy	Continuous laser-based (CLB)
L-PBF machine type	SLS Solutions, 280^{HL}

Fiber laser	Twin (2×400W) IPG Photonics
Laser power (W)	320
Wavelength range (nm)	1070 ± 10
Maximum emitting power (W)	400
Layer thickness (µm)	30-60
Scan speed (m/s)	10
Exposure tie (µs)	-
Powder particle size (µm)	20-63 (grade 23)

The design department and manufacturing department should inspect the quality of the implant after it has been printed, and if the quality of the product is acceptable, the implant should go through the required post-processing.

4.2 Post-treatment

The following are some of the most common procedures for post-processing an additively manufactured implant. All post-processing actions that are considered, should be documented under the Section 6 of Annex I "Post-processing", and a discussion of the effects of post-processing on the materials and the final device should be included.

4.2.1 Laser marking

Laser marking is often used to mark the UDI (Unique Device Identification), brand or even the QR code on the implant as well as marks that can be used for measurements during the surgery (tools).

4.2.2 Support removal

Support material can be removed physically or by chemical means. For producing mandibular implant, the 3DMed project recommends the physical removal of the support materials. Removal of support material may cause surface marks or leave residues on or in the device. Manufacturing material removal processes should ensure that residues are removed to the level where they do not impact the safety or effectiveness of the product. The complete description of the support material geometry and the removal process method should be documented.

4.2.3 Heat treatments

One common heat treatment method for metal devices is Hot Isostatic Pressing (HIP). This process can reduce residual stresses by reducing the internal pore sizes in the material and increase fatigue life but has also been shown to reduce the modulus and yield strength of the material. However, this effect is more

pronounced at low cycle fatigue life due to the higher loads. Therefore, care should be taken to ensure both the AM and HIP processes maintain device performance. Devices that are intended for applications where fatigue is a factor may require minimum surface finish or roughness specification to reduce the chance of failure. The desired surface roughness, which is described in this document as being between 5 and 15 microns, can often be achieved through various post-processing steps (e.g., mechanical polishing, sandblasting or chemical etching); however, hard-to-reach spaces may remain in the as-built state. These spaces should be assessed for their effects on mechanical performance (including fatigue) of the device or component.

4.2.4 Coating

Depending on the intended use of the implant, certain coatings can be applied to the implant to increase the bone ingrowth or certain drug release. For mandibular implants, the mandibular component is mostly sprayed with roughened titanium plasma coating to increase bone adherence. The titanium plasma-coating is tested and validated on bone healing capacity before clinical introduction [6]. Another technique is sandblasting the medial surface of the mandibular component. Additionally, hydroxyappetite coating is reported to increase fast and strong osteointegration of the implants [7]. The chosen method should be recorded in the Section 6 of Annex I.

4.2.5 Cleaning

Cleaning can be done using citric acid passivation under validated process conditions per ASTM A 967, subjected to a final cleaning step using an alcaline solution, and rinsed under validated process with deionized water.

Passivation involves exposing the surface of the device to standard solutions in order to remove free metal and exogenous matter from the metallic parts in order to enhance the uniform exposure of the material to oxygen. The technique allows the formation of a thin, passive enriched oxide layer that increases the corrosion resistance at the surface level and makes the metallic surface of the device inert and non-reactive. ASTM A967 specifies that after the last cleaning step, just before passivation, the resulting pre-treated metallic surface shall be substantially free of oil, grease, rust, scale, and other foreign matter. This is due to the fact that passivation cannot form or enhance the protective film when grease, oil, fingerprints or other organic contamination are present on product-contact surfaces.

4.2.6 Sterilization

For metal implants Gamma radiation is often used to sterilize implant and toolset. Therefore, first a bioburden test needs to be performed according to ISO 11137 “Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose”, to determine the min/max dose, which in the case of this document is 25 kGy- 50 kGy. The minimal dose is needed to validate if the product is sterile after

sterilization. The maximal dose is needed for the accelerated shelf-life tests, which is considered the worst case. Furthermore, endotoxin according to PhEur/USP as well as batch validation and dose mapping need to be carried out.

5. Packaging and labeling

5.1 Packaging

The final packaging may consist of a blister system with Tyvek® lid placed in a paper carton box as secondary packaging which is ready for sterilization. This process needs to be performed in a clean room and validated according to ISO 11607.

5.2 Labeling

Considering the requirements for labelling that are specified in "General Safety and Performance Requirements, Chapter III, paragraph 23 of the Medical Device Regulation 2017/745" and internationally recognized symbols in the "ISO 15223-1:2016 Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied", labels provided in Table 4 shall be used where appropriate and documented in the form given in the Section 8 of Annex I.

Table 4: General Safety and Performance Requirements and statement from (MDR) 2017/745 and their related symbols from ISO 15223-1:2016

Text from the MDR 2017/745	Symbols and their title
-The details strictly necessary for a user to identify the device, the contents of the packaging and, where it is not obvious for the user, the intended purpose of the device; -If the device is custom-made, the words 'custom-made device'.	*Trade name of the device* Custom-made device
-The name, registered trade name or registered trade mark of the manufacturer and the address of its registered place of business;	 Manufacture
-Patient's ID	 Patient number

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-Where there is no indication of the date until when it may be used safely, the date of manufacture. This date of manufacture may be included as part of the lot number or serial number, provided that the date is clearly identifiable;	 Date of manufacture
-An unambiguous indication of the time limit for using or implanting the device safely, expressed at least in terms of year and month, where this is relevant;	 Use-by date
-If the device is supplied sterile, an indication of its sterile state and the sterilization method;	 Non-sterile
-If the device is intended for single use, an indication of that fact. A manufacturer's indication of single use shall be consistent across the European Union;	 Do not re-use
-Warnings or precautions to be taken that need to be brought to the immediate attention of the user of the device, and to any other person. This information may be kept to a minimum in which case more detailed information shall appear in the instructions for use, taking into account the intended users.	 Do not use if package is damaged  Fragile, handle with care
The following information is recommended to be stated	
the name of the ordering physician	

An example of some labels used for patient-specific devices are provided in Figure 5, where the parts in italic should be replaced by the specific information for each device.

Figure 5: Examples of labels used in patient-specific devices according to ISO 15223-1:2016

6. Validation test

6.1 Biocompatibility

D 3.4.2 “Materials database for 3D printed patient-specific implants” and D 3.4.4“ Materials database for 3D printed spinal cages” provide information about the biocompatibility of the raw materials and test certificates are available. It is the responsibility of the end-manufacturer to prove the biocompatibility of the final medical device. Therefore, it is recommended to evaluate the biocompatibility of the final finished device as described in the guidance “Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing within a Risk Management Process”[8]. If chemical additives with known toxicities are used (*e.g.*, certain additives, catalysts, binding and curing agents, uncured monomers, or plasticizers), additional information, as outlined in the guidance, may be necessary.

The purpose of the Biological Risk Assessment (BRA) or Biological Evaluation Plan is to serve as an initial risk assessment to identify the biocompatibility approach to be taken to demonstrate the patient safety for the implant. The risks of the devices included in the kit will be evaluated in this plan, and mitigation steps

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in the form of testing or further written risk assessment will be determined. This evaluation plan includes the reasoning behind determining a representative sample to be used in the testing outlined herein.

In the BRA, all the biological endpoints according to the "Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing within a Risk Management Process" need to be addressed (see Table 5).

Table 5: Biocompatibility Evaluation Endpoints [8].

Medical device categorization by			Biological effect												
Nature of Body Contact		Contact Duration	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity#	Degradation@
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)													
Surface device	Intact skin	A	X	X	X										
		B	X	X	X										
		C	X	X	X										
	Mucosal membrane	A	X	X	X										
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O			
	Breached or compromised surface	A	X	X	X	O	O								
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O	O		
External communicating	Blood path, indirect	A	X	X	X	X	O				X				
		B	X	X	X	X	O	O			X				

Table 5: (continued)[8]

Medical device categorization by			Biological effect												
Nature of Body Contact		Contact Duration	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity#	Degradation@
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)													
device		C	X	X	O	X	O	X	X	O	X	O	O		
	Tissue+/bone/ dentin	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Circulating blood	A	X	X	X	X	O		O^		X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		
Implant device	Tissue+/bone	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Blood	A	X	X	X	X	O		O	X	X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		

X = ISO 10993-1:2009 recommended endpoints for consideration*
O = Additional FDA recommended endpoints for consideration*
Note * All X's and O's should be addressed in the biological safety evaluation, either through the use of existing data, additional endpoint-specific testing, or a rationale for why the endpoint does not require additional assessment.
Note + Tissue includes tissue fluids and subcutaneous spaces
Note ^ For all devices used in extracorporeal circuits
Note # Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, devices with relevant target populations (e.g., pregnant women), and/or devices where there is the probability for local presence of device materials in the reproductive organs.
Note @ Degradation information should be provided for any devices, device components, or materials remaining in contact with tissue that are intended to degrade.

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This matrix is divided into 3 types of body contact; surface devices, external communication devices (*e.g.*, toolset) and implantable devices. Each group is subdivided in certain categories according to its intended use. Furthermore, each contact duration determines the number of biological endpoints that need to be addressed.

A permanent implant, like a mandibular implant, is categorized in Implant devices, Tissue/Blood and contact duration C (Permanent > 30 days). The associated toolset is categorized as an external communication device with a short contact duration A (<24 hr). Not all biological endpoints need to be tested though. This depends on the reasoning according to the BRA. It is possible that some of the endpoints can be addressed based on literature rather than tests. The tests consist of a combination of chemical tests, *in-vitro* tests and animal tests if *in-vitro* tests are not possible.

After the BRA and recommended biological tests and chemical characterization, a final biological evaluation needs to be performed to show that the implant is biocompatible.

Following tests need to be performed for a permanent Ti6AL4V mandibular implant;

- Chemical characterization
- Cytotoxicity
- Sensitization
- Irritation
- Pyrogenicity
- Acute systematic toxicity
- Implantation tests
    - Short (1-4 weeks)
    - Long (>12 weeks)

The proposed endpoints and their intention and corresponding standards for the implant made of Ti6AL4V, are given in Table 6.

Table 6 The biocompatibility endpoints and their intention for implantable medical devices

Endpoints	Standard	Intention
Cytotoxicity	ISO 10993-5	This *in vitro* test is intended to screen biologically harmful extractables in the absence of protective mechanisms that normally assist cells within the body.
Sensitization	ISO 10993-10	This *in vivo* test is intended to determine whether significant quantities of leachables/extractables could induce delayed-type hypersensitivity (Type IV) reactions from repeated or prolonged contact with the body's immune system. The guinea pig maximization test (GPMT) should be considered.
Irritation	ISO 10993-10	This *in vivo* test is intended to evaluate irritation potential. As the Vertebral Augmentation Implant is an implantable device, the intracutaneous reactivity method should be considered for

		assessing the irritation potential of leachables/extractables after a short-term exposure by the intradermal route.
Acute systemic toxicity	ISO 10993-11	This *in vivo* test is intended to estimate, during a period of occurring at any time within 72 hours after exposure of a test sample for 24 hours, the adverse effects on general health status resulting from absorption, distribution and metabolism of potential toxic leachables/extractables in extracts.
Material mediated pyrogenicity		
Pyrogenicity from chemicals	ISO 10993-11	This *in vivo* test is intended to detect substances inducing a material-mediated pyrogenic reaction, inducing rise in temperature that could lead to a febrile reaction in the patient. The total rise of temperature during the 3-hour observation period is determined to be within acceptable European and U.S. Pharmacopoeia limits or not.

Section 7 of Annex I (Biological evaluation) should be completed by referring to comparable existing implants (those with good biocompatibility and known and documented endpoints), and it does not need to evaluate the biocompatibility of the implant if the new device has the same:

- Material formulation
- Manufacturing process
- Geometry and physicochemical properties
- Contact area
- Sterilization process/method/dose

6.2 Transportation tests

"ISTA 3 Series: General Simulation Performance Tests" designed to provide a laboratory simulation of the damage-producing motions, forces, conditions, and sequences of transport environments. In the test, the capability of the product and packaging to withstand transport hazards is described. The tests are applicable across broad sets of circumstances, such as a variety of vehicle types and routes, or a varying number of handling exposures. Characteristics will include simple shaped random vibration, different drop heights applied to the sample package, and/or atmospheric conditioning such as tropical wet or winter/frozen.

6.3 Transit Testing

Test Procedure 3A- "Packaged-Products for Parcel Delivery System Shipments 70kg (150 lb) or Less (standard, small, flat or elongated)" is a general simulation test for individual packaged-products shipped through a parcel delivery system. The test is appropriate for four different package types commonly distributed as individual packages, either by air or ground. The types include standard, small, flat and elongated packages. After transport testing, an integrity test will be performed to prove that the sterile barrier is still intact.

6.4 Shelf life or accelerated aging testing

To determine an expiration date that is supported by shelf-life data is described. Accelerated-aging tests should be used to generate data needed for the regulatory submission of the product. These tests need to be supported by real-time studies for the same shelf-life period.

Accelerated tests are also needed for biocompatibility testing to show that aging of the material does not affect the biocompatibility of the implant. Often a cytotoxicity tests is performed in the initial stage as well as after accelerated aging to determine this.

6.5 MR compatibility

The MR compatibility of the implant is required to demonstrate the safety and compatibility of the product with Magnetic Resonance Imaging (MRI). The plan for demonstrating MRI compatibility includes many MRI tests chosen from ASTM standards that are applicable to the product, such as Magnetic Force, Torque, and Heating.

The purpose is to demonstrate compatibility with the current standards for passive implantable medical devices by performing a risk assessment in a 1.5 and 3 Tesla MRI environment.

A test protocol according to the associated ASTM standards will be made for the following risks assessments:

- ASTM F2052 Magnetic force
- ASTM F2213 Magnetic torque
- ASTM F2182 Magnetic heating
- ASTM F2219 MR image artifacts

7. References

[1] E.p.a. Council, Regulation (EU) 2017/745, Official Journal of the European Union, 2017.

[2] FDA FaDA. Technical Considerations for Additive Manufactured Medical Devices. Guidance for Industry and Food and Drug Administration Staff2017.

[3] Otsu, N., "A Threshold Selection Method from Gray-Level Histograms." *IEEE Transactions on Systems, Man, and Cybernetics*. Vol. 9, No. 1, 1979, pp. 62–66.

[4] Mandibular Plating, Jesse E Smith, 2018

[5] Fakih-Gomez, N., Gonzalez-Perez, L. M., & Perez-Somarriba, B. G. (2014). Total joint replacement: Biomaterials for application in the temporomandibular joint. In Ifmbe proceedings (Vol. 41, pp. 77–80). doi.org/10.1007/978-3-319-00846-2_19

[6] Vercaigne, S., Wolke, J. G., Naert, I., & Jansen, J. A. (1998). Bone healing capacity of titanium plasma-sprayed and hydroxylapatite-coated oral implants. Clinical Oral Implants Research, 9(4), 261–271. doi:10.1034/j.1600-0501.1998.090407.x

[7] Heimann, R.B. Plasma-Sprayed Hydroxylapatite-Based Coatings: Chemical, Mechanical, Microstructural, and Biomedical Properties. J Therm Spray Tech 25, 827–850 (2016). https://doi.org/10.1007/s11666-016-0421-9

[8] Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process", FDA Guidance "

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Annex I: Requirements regarding design, manufacturing, and post-processing of the patient-specific mandibular reconstruction implants

During design, manufacturing, and post-processing of the patient-specific scaphoid drill guide, the following information shall be documented by each related department. In this annex, the required information is provided in the order of the production process.

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1. General Information	
Patient name	Click or tap here to enter text.
Patient number	Click or tap here to enter text.
Date of receiving order (DD/MM/YYYY)	Click or tap to enter a date.
Date of planned surgery (DD/MM/YYYY)	Click or tap to enter a date.
Date of delivery (DD/MM/YYYY)	Click or tap to enter a date.
Mandibular implants	☐ Right side ☐ Left side
Does the patient have anatomical obstacles related to the surgery? (Specify below) Click or tap here to enter text.	
Surgical approach	Click or tap here to enter text.
Surgeon name	Click or tap here to enter text.
Hospital	Click or tap here to enter text.
Phone	Click or tap here to enter text.
E-mail	Click or tap here to enter text.
Secondary contact information: (name, e-mail, phone)	Click or tap here to enter text.
Shipping address (country, city, postal code)	Click or tap here to enter text.
Click or tap here to enter text.	Click or tap to enter a date.
Initial & Signature of the Person Submitting this Form	Date (DD/MM/YYYY)

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2. Patient Anatomy Data

Notes: Use scanning protocol in the section 2.1.1 of the Deliverable 1.1.1 as a guideline

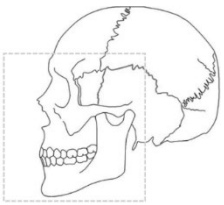
Image Acquisition

Date of image acquisition	Click or tap here to enter text.
Image acquisition technique	☐CT ☐CBCT

☐The scan is taken less than four (4) months before the surgery.

File format	☐DICOM

☐The scan covers the region of interest (ROI) (According to the picture)



☐Image does not contain major artifacts such as metal and motion artifacts.

Scan Parameter

Scanner Model	Click or tap here to enter text.
Image reconstruction algorithm	☐FC30 ☐FC09
kVp	Click or tap here to enter text.
mAs	Click or tap here to enter text.
Matrix (pixels)	Click or tap here to enter text.
Reconstructed slice increment (mm)	Click or tap here to enter text.
Slice thickness (mm)	Click or tap here to enter text.
Gantry Tilt (˚)	Click or tap here to enter text.
Pitch (mm/rotation)	Click or tap here to enter text.

Click or tap here to enter text.	Click or tap to enter a date.
Imaging department approval	Date (DD/MM/YYYY)
Click or tap here to enter text.	Click or tap to enter a date.
Design department approval	Date (DD/MM/YYYY)

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3. Segmentation

Software	☐ Mimics® Version: Click or tap here to enter text.
HU range	☐Bone (CT)
	☐Custom; range (Min-Max): Click or tap here to enter text.

☐*Foreground-background* segmentation with an *optimum threshold was used.*

☐*Split mask* was used to separate the mandible from the base.

☐*Region growing* was used to obtain a new and clean mask from the mandible.

☐ *Calculate Part* was used to perform surface mesh computation with a quality set to *optimal.*

☐File was exported to 3-Matic®.

Brief description of segmentation procedure (in case manual work has been employed):

Click or tap here to enter text.

Click or tap here to enter text.	Click or tap to enter a date.
Surgeon approval	Date (DD/MM/YYYY)
Click or tap here to enter text.	Click or tap to enter a date.
Design department approval	Date (DD/MM/YYYY)

4. Patient-Specific Design

Date of receiving validated segmentation	Click or tap to enter a date.
Design software	☐3-Matic® version: Click or tap here to enter text.

Describe or illustrate mandible resection(margin) and holes (location) requirements:

Click or tap here to enter text.

Implant material	☐Ti-6Al-4V
Implant appearance	☐Cage design
Implant thickness (mm)	☐1.5

Lattice structure specification

Software	☐Magics® version: Click or tap here to enter text.
Type of unit cell	☐Dode- Medium
Size of unit cell (mm)	☐1.5
Pore size in-plane (μm)	☐325
Pore size smallest (μm)	☐460
Strut thickness (μm)	☐210
Porosity (%)	☐87.5
Solid edge width (mm)	☐1.5

Screw

Number of screws in anterior segment	☐4	
Number of screws in posterior segment	☐4	
Screw manufacturer, model & code	Click or tap here to enter text.	
Screw type	☐Locking	☐Non-locking

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Drill bit diameter (mm)	☐1.8
Screw diameter (mm)	☐2.4
Screw hole distance (mm)	☐8
Screws length in anterior segment (mm)	☐14
Screw length in posterior segment (screws close to the resection)	☐8
Screw length in posterior segment (the most distal screws)	☐5

Design workflow

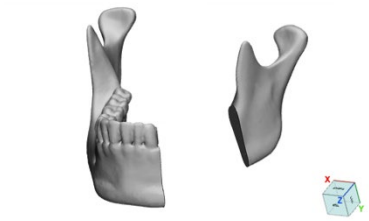
Step 1 – Segmental resection

☐Create two datum planes.

☐Tune the orientation of the plane by translating or rotating.

☐ Use cutting operation to perform the segmental resection along the created datum planes.

Insert the segmental resection mandibular here (See below for an example)



Step 2 – Segmental mirroring

☐Create mid-sagittal (datum) cutting plane.

☐Check the position and orientation of the mid-sagittal datum plane.

☐Copy and mirror the healthy side of the mandible over the affected side across the mid-sagittal datum plane.

☐Cut the mirrored segment using the cutting planes created in Design step 1 and keep the middle segment.

Step 3 – Missing shape estimation

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☐Remove teeth using the 'trim' function (if any).

☐'Fillet' the remaining contour to get smooth borders.

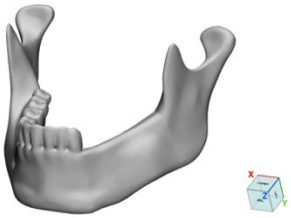
☐Create a curve to serve as a path for the sweeping operation.

☐Perform a sweep-loft operation.

☐Perform a Boolean union.

☐Filter small surfaces, and use wrapping and smoothing operations to complete the shape estimation.

Insert the missing shape estimation here (See below for an example)



Step 4 – Implant surface definition

☐Mark the surface of the mandible to define the desired implant region.

☐Smooth the marking borders and copy the implant surface to a new part

☐Define the desired implant thickness and create the solid implant.

☐Check the implant and trim off any protrusions or unwanted areas.

Step 5 – Screw positioning

☐Position the specified number of screws in the interior region.

☐Position the specified number of screws in the posterior region.

☐Create holes in the mandible with lengths corresponding to the screw lengths

Insert the remaining mandible with holes here (See below for an example)

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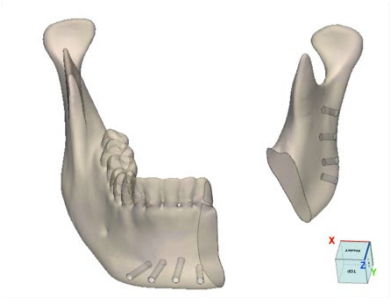
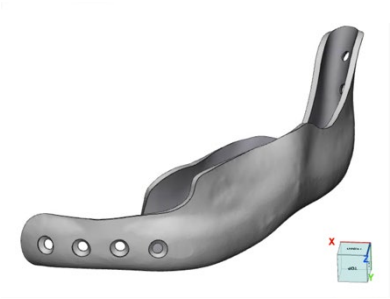


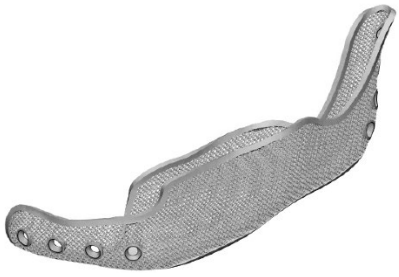
Insert the final solid design here (See below for an example)



step 6 – Creating a lattice structure

☐Create lattice structure of the solid mandibular implant

Insert the final design with lattice structure here (See below for an example)



Surgical guide

Design Software	☐3-Matic® version: Click or tap here to enter text.
Minimum thickness (mm)	Click or tap here to enter text.
Number of drilling channel	☐8
Drilling channel diameter (mm)	☐2
Printing technique	☐FDM

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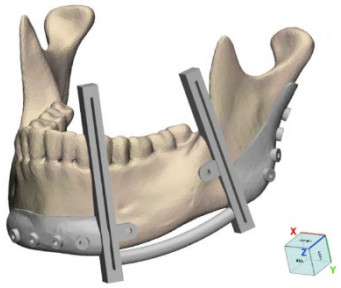
Material	☐PLA

Insert the surgical guide design here (See below for an example)



Acceptable manufacturing tolerance	Click or tap here to enter text.

Click or tap here to enter text.	Click or tap to enter a date.
Design department approval	Date (DD/MM/YYYY)
Click or tap here to enter text.	Click or tap to enter a date.
Surgeon approval	Date (DD/MM/YYYY)
Click or tap here to enter text.	Click or tap to enter a date.
Manufacturing department approval	Date (DD/MM/YYYY)

5. Material and Manufacturing	
Received validated design on (DD/MM/YYYY)	Click or tap to enter a date.
Material specification	
Material Name	☐Titanium-6 Aluminum-4 Vanadium (Ti6Al4V) ☐Fresh ☐Re-used
Material supplier	Click or tap here to enter text.
Identification/ Catalogue No.	Click or tap here to enter text.
Particle size (μm)	☐20-63 (grade 23)
Particle shape	☐Spherical
Young's modulus [GPa]	Click or tap here to enter text.
Yield strength [MPa]	Click or tap here to enter text.
Ultimate strength [MPa]	Click or tap here to enter text.
Elongation [%]	Click or tap here to enter text.
Hardness	Click or tap here to enter text.
Storage conditions	Click or tap here to enter text.
Expiration date (MM/YYYY)	Click or tap to enter a date.
Manufacturing Specifications	
Printing technique	☐Selective Laser Melting (SLM)
Scanning strategy	☐Continuous laser-based (CLB)
Machine Model	Click or tap here to enter text.
Manufacturing time estimation (min)	Click or tap here to enter text.
Printing parameters	

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Print orientation	Click or tap here to enter text.
Laser power (W)	Click or tap here to enter text.
Wavelength range (nm)	Click or tap here to enter text.
Maximum emitting power (W)	Click or tap here to enter text.
Layer thickness (µm)	Click or tap here to enter text.
Scan speed (m/s)	Click or tap here to enter text.

Click or tap here to enter text.	Click or tap to enter a date.
Design department approval	Date (DD/MM/YYYY)
Click or tap here to enter text.	Click or tap to enter a date.
Manufacturing department approval	Date (DD/MM/YYYY)

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6. Post-processing

Received printed part on (DD/MM/YYYY) Click or tap to enter a date.

☐ Support removal ☐Physically removed

Explain:Click or tap here to enter text.

☐ Laser marking

Explain:Click or tap here to enter text.

☐ Heat treatment ☐Hot Isostatic Pressing (HIP)

Explain:Click or tap here to enter text.

☐ Coating ☐Titanium plasma

☐Hydroxyappetite

☐Sandblasting

Explain: Click or tap here to enter text.

☐Cleaning

Explain:Click or tap here to enter text.

☐The surface roughness of the final product is between 5 and 15 microns.

Note: Sterilization instruction should be provided in the package to the hospital.

☐Sterilization ☐Gamma radiation

Minimum & Maximum dose ☐25 kGy- 50 kGy

Click or tap here to enter text.	Click or tap to enter a date.
Manufacturing department approval	Date (DD/MM/YYYY)

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7. Biological evaluation

☐Sufficient justification/clinical data for risk assessment is documented.

☐Sufficient data for all chemicals in the material is documented.

☐Product was tested according to EN-ISO 10993-5 and was NOT found cytotoxic.

☐Product was tested according to EN-ISO 10993-10 and was NOT found sensitizing.

☐Product was tested according to EN-ISO 10993-10 and was NOT found irritating.

☐Product was tested according to EN-ISO 10993-11 and was NOT found acute systemic toxicity.

☐Product was tested according to EN-ISO 10993-11 and was NOT found material-mediated pyrogenicity.

☐Biocompatibility sufficiently demonstrated according to EN-ISO 10993-1.

☐The biological risk is acceptable.

Click or tap here to enter text.	Click or tap to enter a date.
Technician	Date (DD/MM/YYYY)

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8. Packaging & Labelling

Date of packaging (MM/DD/YYYY)	Click or tap to enter a date.
Expiration date (MM/DD/YYYY)	Click or tap to enter a date.
Catalog number of the product	Click or tap here to enter text.
Batch number or serial number (if applicable)	Click or tap here to enter text.

Labelling checklist

☐ Manufacturer & address details

☐ Name of ordering surgeon

☐ Number of products in the package

☐ Barcode

☐ Warnings and precautions

☐ Logo

☐ Sterilization status

☐ Package includes instruction for Sterilization

☐ Can be used once

☐ Storage and handling instructions

☐ Indication of how to open the packaging

☐ Specific information: Click or tap here to enter text.

☐ Special instructions for use:Click or tap here to enter text.

Click or tap to enter a date.	Click or tap here to enter text.
Date of shipping (MM/DD/YYYY)	Operated by

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Annex II: The effect of in-plane resolution and slice thickness on geometrical error in the imaging process

The common FOV used for surgical planning of mandibular reconstruction should include the entire mandible, orbitals, and auditory meatus (Figure 6a). To understand the impact of the in-plane resolution and the slice thickness in the geometrical error associated with the imaging process, a study was conducted with a phantom model printed in poly-methyl methacrylate (PMMA), with different linear and circular shapes (Figure 6b). The CT images were acquired using the Canon Aquilion One system with 120 kV and 100 mA but with different FOV. Furthermore, image reconstruction was performed using two reconstruction filters, namely the FC09 typically used for abdominal CT imaging and FC30 often used for bone imaging.

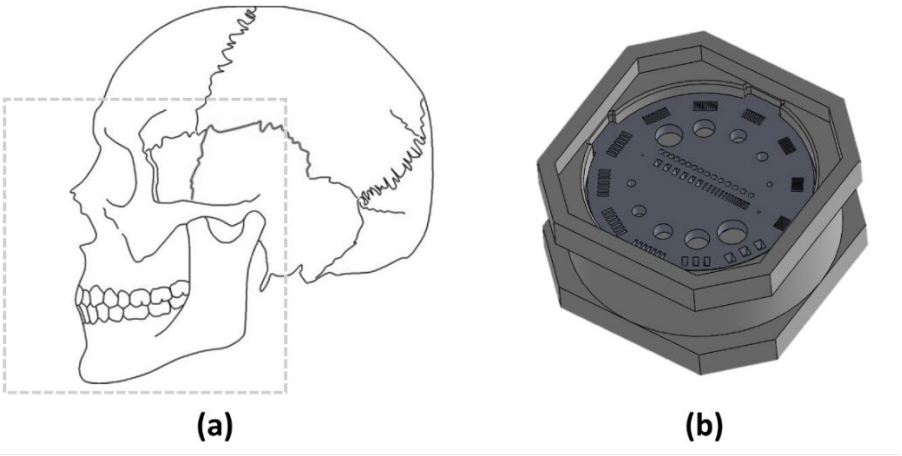

Figure 6 Typical FOV specified during CT image acquisition for the surgical planning and design of a mandibular implant (a); phantom used for the sensitivity analysis on the resolution of the CT images (b).

Image segmentation was performed by two different users, using both *Synopsys ScanIP™* and *Materialise Mimic®*, respectively. For user 1, the segmentation steps in *Synopsys ScanIP™* were the following:

- Creation of the first mask using a high threshold;
- Use of mask *Flood fill* tool to separate the disk from the base;
- Manual addition of missing details using *Paint with threshold* tool. This tool allows the addition of parts to the mask, which are within a specific threshold range. The threshold selected here was lower than the threshold used to create the first mask.
- Visual inspection of the mask in all slices and in 3d, and addition or deletion of features if necessary.
- Export the part in *.stl format.

For user 2, the amount of manual segmentation was minimized to avoid subjectivity in the results. The segmentation in *Materialise Mimics®* was performed as follows:

- Foreground-background segmentation with an *optimum threshold*;
- *Split mask* to separate the disk from the base;
- *Region growing* to obtain a new and clean mask from the disk;

- Surface mesh computation was performed using *Calculate Part* with a quality set to *optimal*;
- Export the part in *.stl format

The results show that good geometrical accuracy can be obtained using both filters, however the bone filter (FC30) consistently produces smaller average errors (Figure 7a-d). In the segmentation from user 1, the ratio between the in-plane/through-plane resolution is 1/2 and 2/5 seems to produce the best results (Figure 7a-b), whereas in user 2, the average errors a very similar across different scanning resolutions (Figure 7c-d).

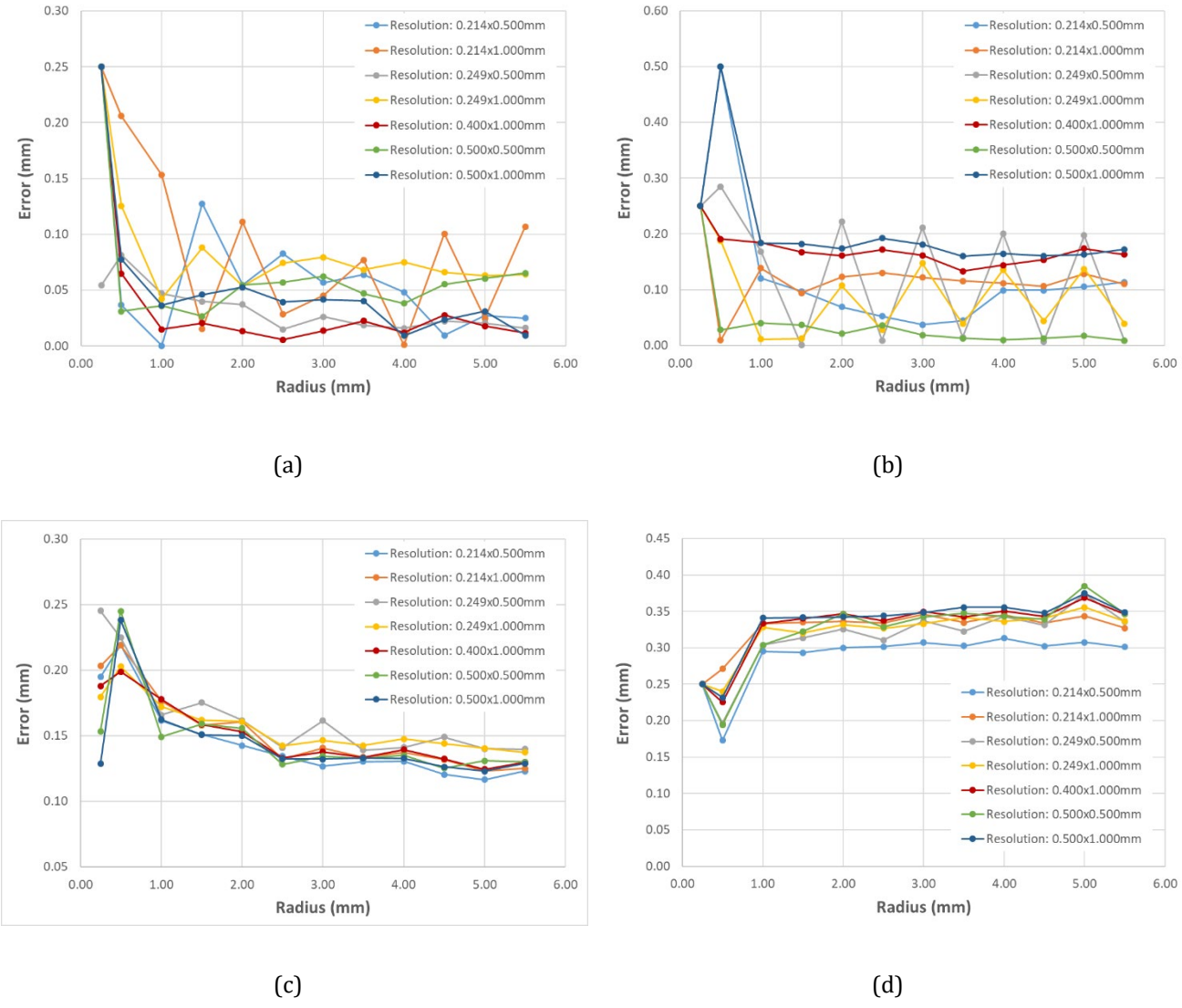

Figure 7 Average geometrical error (mm) of the segmentation performed in Synopsys ScanIP *across different scanning resolutions for circular shapes (a) FC30 and (b) FC09; average geometrical error (mm) of the segmentation performed in* Materialise Mimics *across different scanning resolutions for circular shapes (c) FC30 and (d) FC09.*

In both cases for a radius smaller than the in-plane resolution, the geometry was not visible or unrecoverable. For FC30, the average geometrical error decreases rapidly and stabilizes below the 0.10 mm limit as the radius increases for user 1 and around 0.15mm for user 2. For FC09, the error stabilizes

below the 0.20 mm limit as the radius increases. For user 2, the segmentations obtained from the data reconstructed with filter FC09 the error stabilizes around 0.35 mm. According to the results of user 2, the geometrical features with a radius greater or equal to 1.0 mm can be recovered with similar accuracy. Furthermore, the variability observed in the segmentations of user 1 may be due to the manual editing of the mark during volume segmentation, which was purposely avoided by user 2.

The linear patterns with thickness and spacing smaller than 0.70 mm were not recognizable in the reconstructed images due to partial volume averaging. Only the linear patterns with thicknesses of 0.7, 0.8, 0.9, 1.0, 2.0 and 3.0 mm were reconstructed accurately (Figure 8a-c).

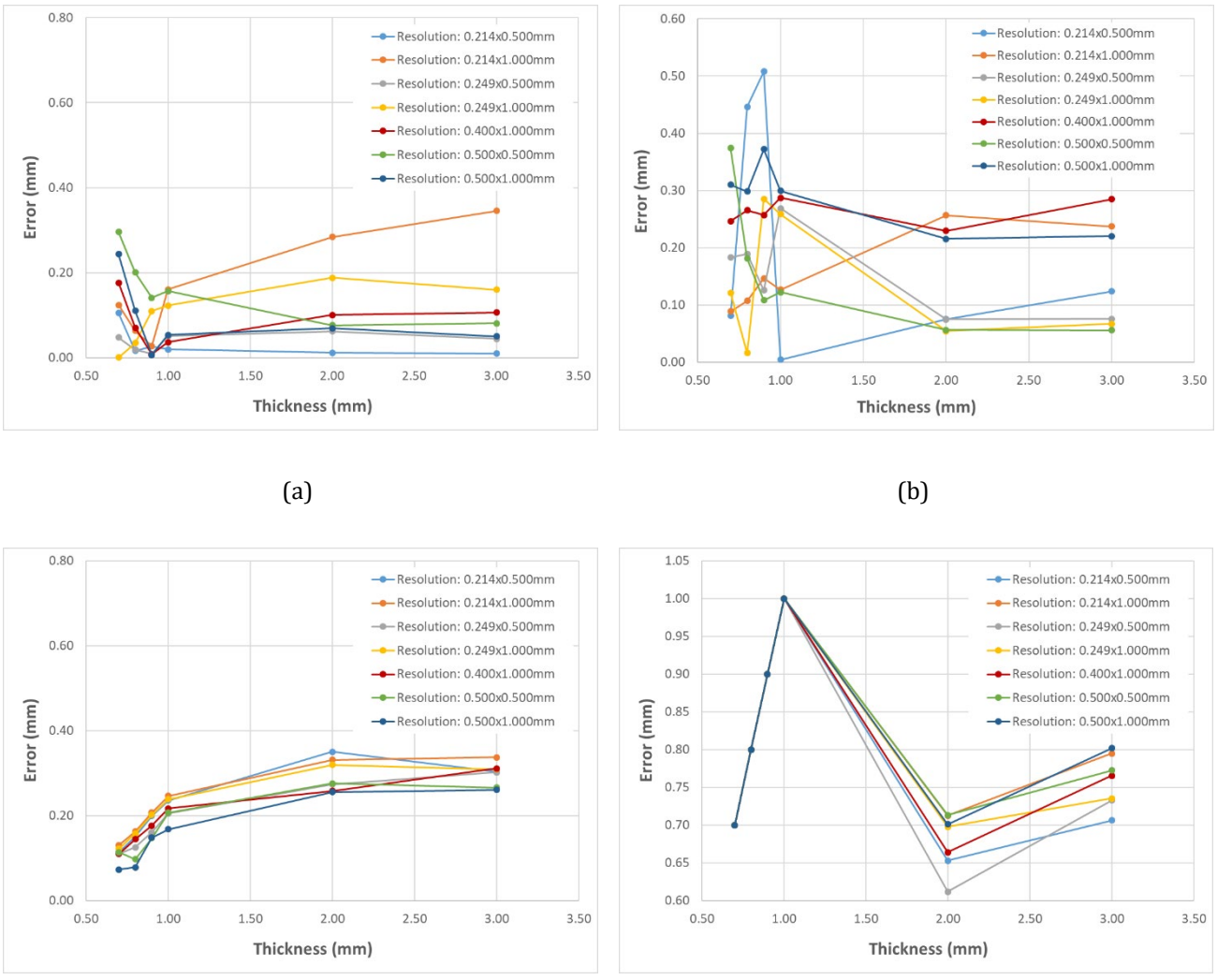

Figure 8 Average geometrical error (mm) of the segmentation performed in Synopsys ScanIP *across different scanning resolutions for linear shapes (a) FC30 and (b) FC09; average geometrical error (mm) of the segmentation performed in* Materialise Mimics *across different scanning resolutions for linear shapes (c) FC30 and (d) FC09.*

The absence of the linear details from 0.7 mm to 0.9 mm in the segmentations of user 2 for the images reconstructed with filter FC09 (Figure 8d) may be explained by the use of automatic thresholding without

any manual adjustment to the amount of partial volume averaging in the dataset. The global optimum threshold was not able to capture these structures and therefore they were completely missed in all subsequent steps of the segmentation.

Finally, a good agreement between the phantom model and the segmented data was obtained for all datasets and reconstruction filters. In this small experiment, the segmentation performed by a trained professional showed a lower average error but more variability when compared with a purely semi-automatic, rigid segmentation protocol. It is also important to note that the maximum slice thickness tested was 1.0 mm, therefore, caution must be taken when using these guidelines with lower through-plane resolutions.