Developing a Certification Framework to Manufacture Patient-Specific Implants using Selective Laser Melting

by

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Declaration

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Abstract

Additive Manufacturing (AM) has proven to be an attractive alternative manufacturing process compared to Subtractive Manufacturing (SM) with many advantages, such as mass customisation, less material wastage and others, as listed in this dissertation. However, AM of certified implants does not have the same degree of documentation and standardisation as the SM process. As part of this research project, the problem statement stated that "in offering AM as an implant manufacturing solution, the complete process (design, manufacturing and post processing) had to be investigated in order to develop a certified manufacturing solution".

Objective 1 addressed the risk identification and ways to mitigate these risks through developing procedures, standard operating procedures (SOPs) and supporting documents. This can be seen as the technical certification of this certified manufacturing solution. In this project, a total of 68 risks were identified in the following areas: design, machine setup, powder handling, SLM process, part removal, density checks, heat treatment, non-destructive testing, destructive testing, surface finishing and coating, cleaning, sterilisation and packaging. The action plan was to mitigate these risks by developing procedures, SOPs, supporting documents and where needed, full machine and process validation.

Objective 2 focussed on developing an integrated documentation framework, keeping traceability and repeatability in mind. Nineteen procedures, thirty-four SOPs, five supportive protocols, three machine validations and five process validations were identified and developed. Process and machine validations were developed that form part of the quality certification process and evaluated the consistency of the technical certification to prove repeatability and traceability of the products manufactured.

Objective 3 focussed on identifying shortcomings in the framework and an in-depth analysis on ways to rectify these problems though continual improvement. Throughout this dissertation it was important not only to address some areas of concern but to explain the methodology behind risk mitigation, procedure and SOP development and validation and how these individual areas link to each other. The ISO 13485:2016 system is based on continual improvement principles which would mean that where new risks arise, the process of addressing these risks will be fast-tracked through this framework development.

An initial process risk assessment was done before the framework development and after the framework development and it showed a significant reduction in the risk index.

Four software, three hardware, two insourced process developments and one quality management system recommendations were compiled and four further research projects were identified as continual improvement.

Opsomming

Laagvervaardiging (LV) is as sinvolle alternatiewe vervaardigingsproses in vergelyking met konvensionele-vervaardiging (KV) bewys, asook dat dit baie voordele, soos bv. massa-aanpassing, minder materiaal vermorsing en ander, soos in hierdie proefskrif gelys word, bied. LV van gesertifiseerde inplantate beskik egter nie oor dieselfde mate van dokumentasie en standaardisering as die KV-proses nie. As deel van hierdie navorsingsprojek het die probleemstelling verklaar dat "in die aanbied van LV as 'n inplantaat-vervaardigingsoplossing, die volledige proses (ontwerp, vervaardiging en na-vervaardigingsverwerking) ondersoek moes word om 'n gesertifiseerde vervaardigingsoplossing te ontwikkel."

Doelstelling 1 het die risiko-identifikasie aangespreek en wyses waarop sodanige risiko's deur die ontwikkeling van prosedures, standaard bedryfsprosedures (SBP's) en ondersteunende dokumente versag kan word. Dit kan as die tegniese sertifisering van hierdie gesertifiseerde vervaardigingsoplossingbeskou word. In dié projek is 'n totaal van 68 risiko's op die volgende gebiede geïdentifiseer: ontwerp, masjienopstelling, poeierhantering, Selektiewe Laser Smelt-proses (SLS), onderdeelverwydering, digtheidstoetse, hittebehandeling, nie-vernietigende toetsing, vernietigende toetsing, oppervlakafwerking en deklaagtoediening, skoonmaak, sterilisasie en verpakking. Die aksieplan was om hierdie risiko's deur prosedures soos b.v. SOPs aan te spreek, ondersteunende dokumente te ontwikkel en waar nodig, volle masjien- en proses validasie te doen.

Doelstelling 2 het op die ontwikkeling van 'n geïntegreerde dokumentasie-raamwerk wat naspeurbaarheid en herhaalbaarheid in berekening bring, gefokus. Negentien prosedures, vier-en-dertig SOP's, vyf ondersteunende protokolle, drie masjien-validasies en vyf proses-validasies is geïdentifiseer en ontwikkel. Proses- en masjienvalidasies wat deel van die gehalte-sertifiseringsproses en die konsekwentheid van die tegniese sertifisering vorm, is ontwikkel en geëvalueer ten einde herhaalbaarheid en naspeurbaarheid van die vervaardigde produkte te bewys,

Doelstelling 3 het op die identifisering van tekortkominge in die raamwerk gefokus en 'n diepgaande analise oor werkswyses waarmee probleme deur voortdurende stelselverbetering gekorrigeer kan word, is gedoen. Gedurende die proefskrif was dit belangrik om nie net sekere kommerwekkende areas aan te spreek nie, maar om die metodologie agter risiko-mitigasie, prosedure en SOP ontwikkeling en validering te verduidelik, asook hoe sodanige individuele areas integreer.

Die ISO 13485:2016-sertifiseeringstelsel is op voortdurende verbeteringsbeginsels gebaseer, wat sou beteken dat waar nuwe risiko's ontstaan, die proses om hierdie risiko's aan te spreek, gebaseer deur dié raamwerkontwikkeling opgelos kan word. Aanvanklike prosesrisiko-assessering is voor die raamwerkontwikkeling gedoen en na die raamwerkontwikkeling het dit 'n beduidende vermindering in die risiko-indeks getoon.

Vier sagteware-, drie hardeware-, twee inhuis-prosesontwikkelings en een verdure aanbeveling vir ‘n gehaltebestuurstelsel is voorgestel. Vier verdere navorsingsprojekte is as voortdurende stelsel-verbetering geïdentifiseer.

Acknowledgements

I dedicate this work to my late father, mother and beautiful son, Gerrie Jean, who is the joy of my life.

I also thank our Lord for providing me with the strength and perseverance to complete this work.

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Glossary

Acronyms and Abbreviations

AM	Additive Manufacturing
ASTM	American Society for Testing and Materials
BD	Building Direction
BMS	Business Management System
CAD	Computer-Aided Design
CNC	Computerised Numerical Control
CPAM	Collaborative Program for Additive Manufacturing
CRPM	Centre for Rapid Prototyping and Manufacturing
CSIR	Council for Scientific and Industrial Research
CSSD	Central Sterile Services Department
CT	Computerised Tomography
CUT	Central University of Technology, Free State
DMLS	Direct Metal Laser Sintering
EADS	European Aeronautic Defence and Space Company
FDA	Food and Drug Administration
FDM	Fused Deposition Modelling
FEA	Finite Element Analysis
IFU	Instruction For Use
ISO	International Organization for Standardization
IQ	Installation Qualification
LM	Layer Manufacturing
MAM	Metal Additive Manufacturing
NASA	National Aeronautics and Space Administration
OQ	Operational Qualification
PQ	Performance Qualification
QMS	Quality Management System
SAHPRA	South African Health Products Regulatory Authority
SI	International System of Units
SOP	Standard Operation Procedure
SM	Subtractive Manufacturing
Ti64	Ti-6Al-4V
3DP	3D Printing

Chapter 1 - Introduction

Additive manufacturing (AM), or better known as 3D printing (3DP), describes a number of processes where a product is fabricated through a layer-wise construction method. The direct metal laser sintering (DMLS) AM process at the Centre for Rapid Prototyping and Manufacturing (CRPM) can offer a unique solution for the manufacturing of custom-designed maxillofacial implants, using Ti64 (Ti6Al4V). As AM matures from a prototyping technology to a real manufacturing solution, it is imperative to prove to prospective users that AM can manufacture parts with repeatable and consistent mechanical properties over time. The only way of addressing this is to develop a quality management system as part of a certification framework. This chapter will cover aspects of current AM applications in different sectors such as consumer products, aerospace, automotive and even medical. The literature will continue with advancements in the AM biomedical field and why AM is suitable for patient-specific medical applications. AM medical devices such as implants, cutting jigs, drill guides, pre-operative planning models and even bio-engineered organs can be manufactured. The conventional manufacturing routes will be compared to AM methods to try to highlight possible advantages. The last aspect that will be covered in this chapter is the need to certify the process linked to the exponential growth of the Selective laser melting (SLM) process.

Background

1.1 History of Additive Manufacturing

1.1.1 Started as Rapid Prototyping

The genesis of AM developed from the concept of rapid prototyping. The first 3D printing technology, stereolithography, was invented by Charles Hull in the early 1980s. It was mostly applied for the fabrication of visual prototypes to support design and marketing. As the 3D technology evolved, these prototypes were used as functional prototypes which could be used in fully functional mechanical systems. The elimination of the need for tooling and fixturing, results in printed prototypes being more cost effective and take far less time than

conventionally manufactured prototypes, which shortens the production development steps. (Brett, Manogharan, Martof, Rodomsky, Rodomsky, Jordan, Limperos, 2014:3)

1.1.2 Advancement from RP to AM in the biomedical field

Vandenbroucke & Kruth (2007) also state that as a result of technical improvements of layer manufacturing (LM) processes and the possibility to process different metals (and compounds), rapid prototyping (RP) has moved beyond its initial applications into rapid manufacturing (RM). They also point out that the progress made could benefit medical and dental applications beyond polymer applications for visual (anatomical) models or single-use surgical guides, to also support the manufacturing of functional implants or prostheses.

1.2 Different AM Applications

Size of AM sectors

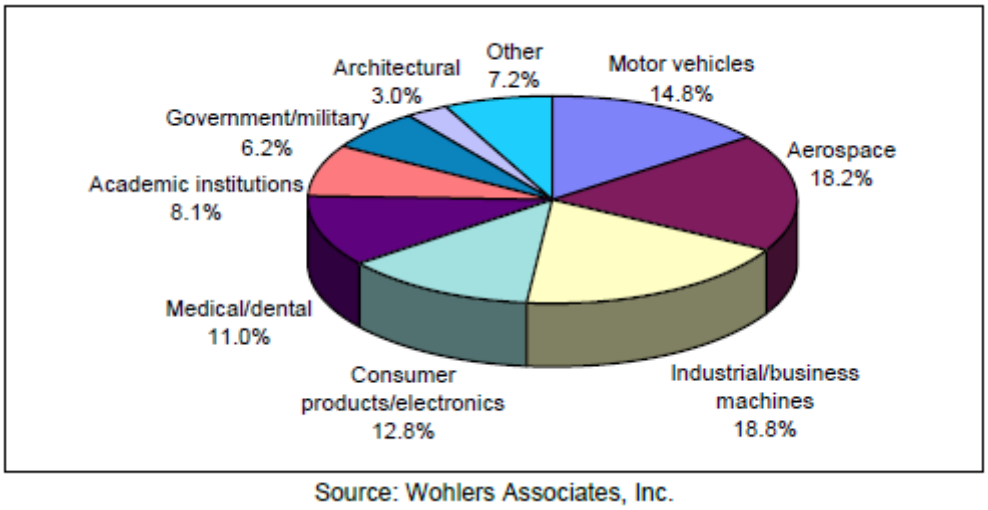


Figure 1.1: Wohlers survey conducted with 180 companies indicating which industries they serve and approximate revenues (as percentage) (Wohlers Report 2017)

The 2017 Wohlers Report concluded that the leading industrial sector was industrial/business machines for the fourth consecutive year, as shown in Figure 1.1. This broad category includes office equipment, such as computers, document printers, and routers as well as industrial automation equipment, such as CNC machines and robots. The aerospace sector grew 1.6% in 2016, while motor vehicles grew by 1,0%. The “Other” category includes a wide range of industries, such as oil and gas, non-consumer sporting goods, commercial

marine products, and various other industries that do not fit into the named categories. The medical/dental sector formed 11.0% of the global 3D industry. Academic institutions (8.1%) form a vital link the in AM chain of research and development and expose students to the latest developments in AM technology.

1.2.1 Consumer products

The consumer products and electronics category covers a broad range of products including mobile phones, home electronics, kitchen appliances, hand tools, and toys. These industries typically produce parts in large volumes and product life cycles are relatively short. AM accelerates product development by enabling rapid design iteration and optimisation for companies in these industries (Wohlers, 2017:22).

1.2.2 Aerospace, automotive, etc.

According to the Wohlers Report, the aerospace industry was an early adopter of AM (Wohlers, 2017:23). As the technology developed, companies such as Boeing installed tens of thousands of flying production parts in their aircraft. Boeing has been utilising SLS for flight hardware in regular production since 2002, for both military and commercial programmes (Lyons, 2011). NASA and other space agencies trialled the use of AM for igniters, injectors, and combustion chambers on rocket engines (Wohlers, 2017:23).

The development of AM is an activity that spans the entire EADS group, with early applications in the production of fixtures and tooling for Airbus, and flying applications being implemented by Eurocopter and Astrium. The group has developed the technology to the extent that it can manipulate metals, nylon, and carbon-reinforced plastics at a molecular level, which allows it to be applied to high-stress, safety critical aviation uses. When compared to a traditionally machined part, those produced by AM are up to 65% lighter but still as strong as a traditionally machined part would be (Peter, Izsak, Bruno, Caste & Roman, 2013).

BMW produces prototypes of metallic parts using AM. Engine parts for motor sports racing cars also have been fabricated using DMLS. Furthermore, luxury car manufacturers Bentley and Rolls-Royce can produce some parts more economically using AM instead of

conventional manufacturing. Tesla, the producer of electric cars, also manufactures automobile components using 3D printers (Öko-Institut e.V.,2013).

1.2.3 Medical

AM technology has disrupted many sectors in the medical industry as more opportunities are seen for change and improvement and innovations are introduced.

The process used to manufacture hearing aids demonstrates the disruption that has resulted from the introduction of AM into the industry. Ventola (2014) states that today, 99% of hearing aids that fit into the ear are custom-made using 3D printing. As each patient's ear has a unique shape, 3D printing allows custom-shaped devices to be produced efficiently and cost-effectively.

The dentistry sector has transformed their manufacturing processes by embracing 3D printing and rapidly producing crowns, bridges, plaster/stone models and a range of orthodontic appliances such as surgical guides and aligners. Commercial 3D printing of orthodontic braces provides a good example of how 3D printing can be used efficiently and profitably to print 50 000 custom-made braces daily (Dodziuk, 2016).

Apart from surgical models, implants and prostheses, 3D models have been utilised to aid the understanding of biological and biochemical structures. The use of 3D models of molecular structures, such as a polypeptide chain, have shown that students are better able to conceptualise molecular structures when such 3D models are used (Gross, Meisel, Lockwood & Chen cited in Ventola, 2014). Living human tissue has been fabricated while personalised drug dosing and drug delivery devices with novel drug-release profiles can be created using 3D printing (Ventola, 2014).

Applicability of Direct AM for Biomedical Applications

1.3 Applicability of laser sintering technologies for metal powders

In an article by Tolochko, Arshinov, Gusarov, Victor, Titov, Laoui & Froyen (2003), the authors confirm that laser sintering technology can be used to create functional metal parts through direct laser sintering methods. They point out that the further study and improvement of this technology is of special interest. Furthermore, the authors identify the significant potential of using both single- and double-component metal powders without experiencing complex process difficulties when double-component metal powders are used.

1.3.1 AM vs conventional processes

Uklejewski, Winiecki, Rogal & Mielniczuk (2011) report that mass-produced orthopaedic end-osseous implants have mainly been produced from wrought or cast bar stock by five- or six-axis computerised numerical control (CNC), computer-aided design-driven (CAD) machining, or powder metallurgy production methodologies, including hot isostatic pressing and powder injection moulding of near-net-shape components. The authors maintain that the traditional process chains followed in using conventional operations (mainly material removal processes), are failing due to their long lead times and material wastage – especially where complex geometries need to be created. In an article by Murr, Quinones, Lopez, Rodela, Martinez, Hernandez, Medina & Wickers (2009), the authors confirm that through material removal processes, often 20% or less of the feedstock is utilised. However, these traditional technologies often fail if the manufacture of an implant component involves complex shape, including thin-walled sections where cutting operations can take a long time owing to significant material removal. The authors furthermore maintain that in many individual cases, where patient-fitted components are required or if new constructional solutions are under development, low effectiveness and relatively high cost of conventional (removal) machining is disadvantageous.

1.3.2 Proven advanced manufacturing and biomedical applications

In a number of articles reviewed, the authors all agree (Gibson, Cheung, Chow, Cheung, Beh, Savalani & Lee, 2006, Vandenbroucke & Kruth, 2007, Murr et al., 2009) that extensive development of the direct digital manufacturing has recently provided new (promising) perspectives for advanced manufacturing technology including biomedical applications. The authors are in agreement that recent material/compounds and process advances create both new challenges and significant opportunities for orthopaedic implant designs, (Hollander, Wirtz, Von Walter, Linker, Schultheis & Paar, 2003), cranioplasty implants (Hieu, Bohez, Vander Sloten, Phien, Vatcharaporn, Binh, An, & Oris, 2003, 2005), oral and maxillofacial implants, finger joint implants (Gibson, Cheung, Chow, Cheung, Beh, Savalani & Lee, 2006; Singare et al. 2006), bone substitute implants (Hoeges, Lindner, Fischer, Meiners & Wissenbach, 2009), customised hip and knee implants (Sercombe, Jones, Day & Kop, 2008; Murr et al. 2009) and dental implants (Santos, Shiomi, Osakada & Laoui, 2006; Vandenbroucke & Kruth, 2007). In the report, Additive Manufacturing: Opportunities and Constraints, published by the Royal Academy of Engineering for a roundtable forum discussion held on 23 May 2013, biomedical implants were shown as one of the key developments for the timeline 2013 to 2018, as shown in Figure 1.2. (Additive Manufacturing: Opportunities and constraints, 2013).

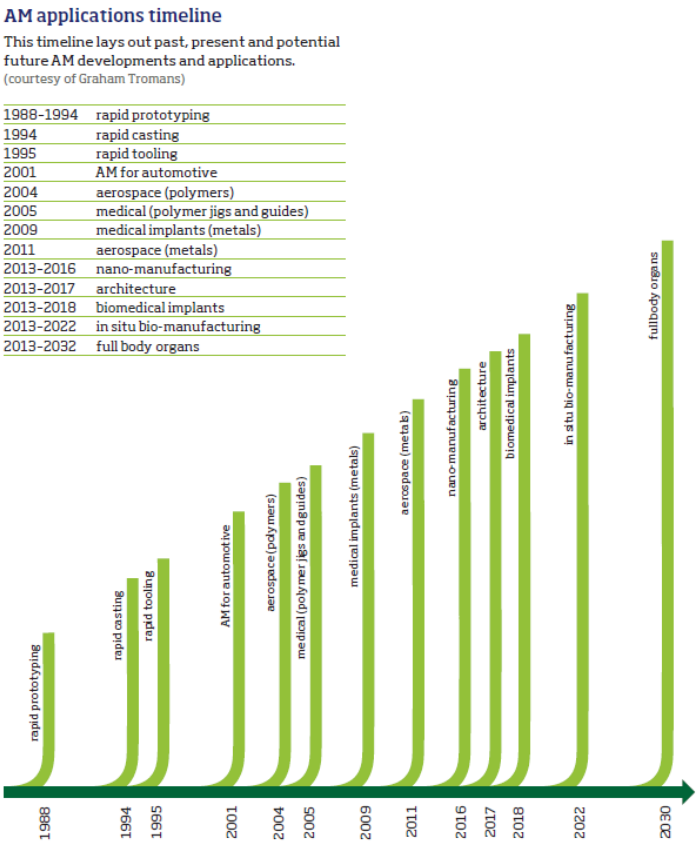


Figure 1.2: AM applications timelines (Royal Academy of Engineering)

1.3.3 Process followed to design and manufacture implants using AM

In the case of medical implants, the process starts with scanning the area of the patient where the implant will be required with a Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scanner. The Digital Imaging and Communications in Medicine (DICOM) files from the scanner are converted to Standard Triangulation Language (STL) format using dedicated software, namely Mimics™ from Materialise. The software allows one to alter the grey-scale values from the DICOM images to differentiate between soft tissue and bone. In this case, the bone data are exported in STL format to show the skeletal features of the patient. The STL file is opened in Magics™ or 3 Matic™ software — also from Materialise — where the implant can be designed. Support structures need to be added to the part to anchor it to the base onto which it will be manufactured. This is done through Magics™ software. The design file is exported to RP Tools™ from Electro Optical Systems (EOS), where the design is sliced into virtual slices. The slice file is then exported to the DMLS machine where it will be manufactured. Figure 1.3 shows the basic principle of manufacturing metal parts through DMLS.

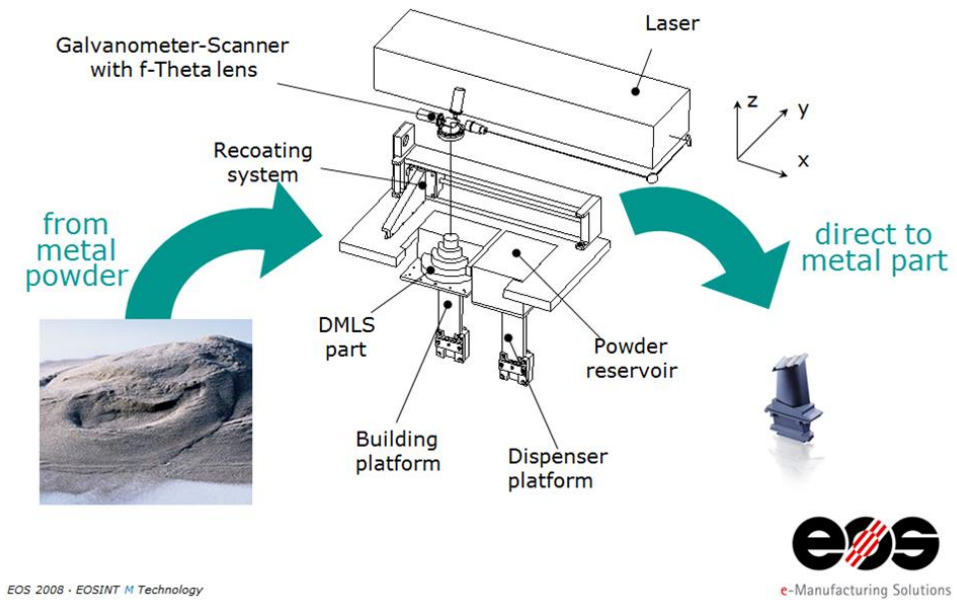


Figure 1.3: The DMLS process: from metal powder to part (EOS)

A layer of titanium alloy (Ti64) powder is laid down on the build platform inside the EOS M280 DMLS machine. The powder layer is the same thickness as that of the slices used in the virtual slicing of the part. The first cross-section of the part is scanned with a laser onto the powder. The laser fuses the powder particles (also referred to as selective laser melting (SLM)) in an argon atmosphere to prevent oxidation. A second layer of powder is laid down on top of the previous one and the next cross-section is scanned. This process is repeated until the part is completed. The build platform with the parts attached is removed from the machine and the parts are separated from the base using a wire cutter. The support structures are removed from the parts and the attachment points are ground smooth.

1.3.4 Need to certify and standardise the SLM process

In the report, 3D Printing – Risks and Opportunities (Öko-Institut e.V., 2013), it was emphasised that common standards need to be developed to ensure that a printed product is identical, independent from the 3D printer used (for the same type of technology). The idea behind this is to ensure the same part integrity anywhere in the world where these standards are used. ASTM and ISO have established technical committees for the development of standards for AM.

Naguy (2014) showed in a presentation entitled "Additive Manufacturing Air Force Perspective" the challenges faced in implementing AM. Concerns were raised, amongst others, about the lack of constrained process controls and undefined post-processing requirements, as shown in Figure 1.4.

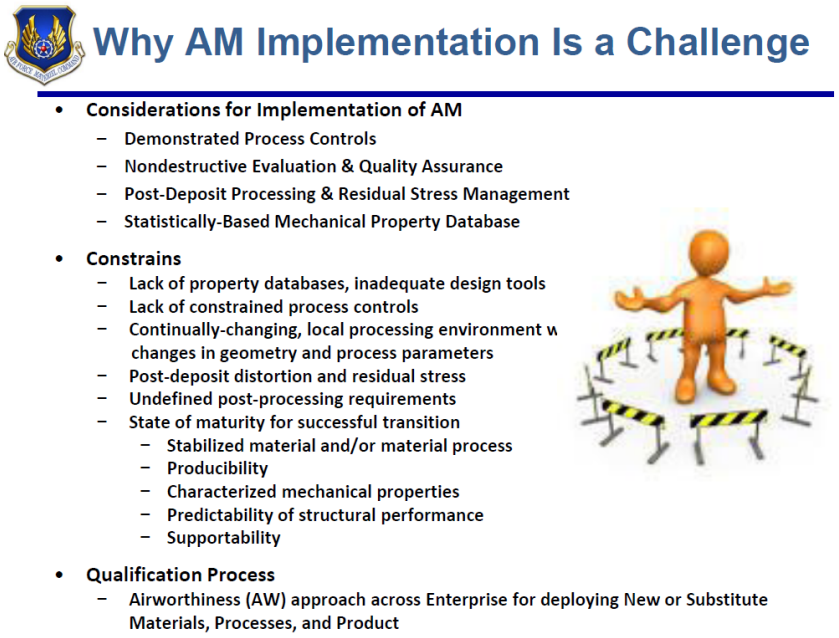


Figure 1.4: A perspective of the U.S. Air Force on challenges faced in implementing AM (Naguy 2014)

Furthermore, Naguy (2014) showed five key entrance criteria necessary for AM to be qualified as a manufacturing technology. These five factors are: stability, producibility, characterised mechanical and physical properties, predictability of performance and supportability, as shown in Figure 1.5.

Figure 1.5: Proposed AM qualification process for aerospace (Naguy 2014)

1.3.5 Growth of metal AM

The revenue generated from metal AM grew by 43.9% in 2016 to an estimated $126.8 million; up from $88.1 million in 2015 and $48.7 million in 2014 (Figure 1.6), and the 2017 Wohler's Report showed an 80.9% market growth in metal AM in 2015 and 49.4% in 2014. The more systems sold will necessitate more standardisation of process conditions to ensure part quality repeatability.

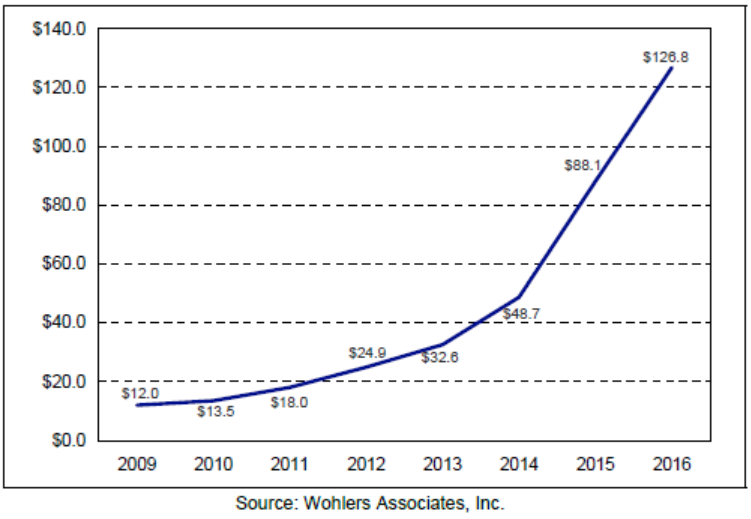


Figure 1.6: Growth in metal AM in millions of dollars (Wohler's Report 2017)

The same type of certification process described by Naguy (2014) is necessary for medical applications. Figure 1.7 shows a medical case study conducted by CRPM. This was the first ever South African 3D-printed mandible, which was designed and manufactured by the CRPM, in 2014. The case study highlighted the diversity of patient-specific implant manufacturing and the need for AM certification. The question is why? Because the parts manufactured in these cases are load-bearing components and not for cosmetic use only.

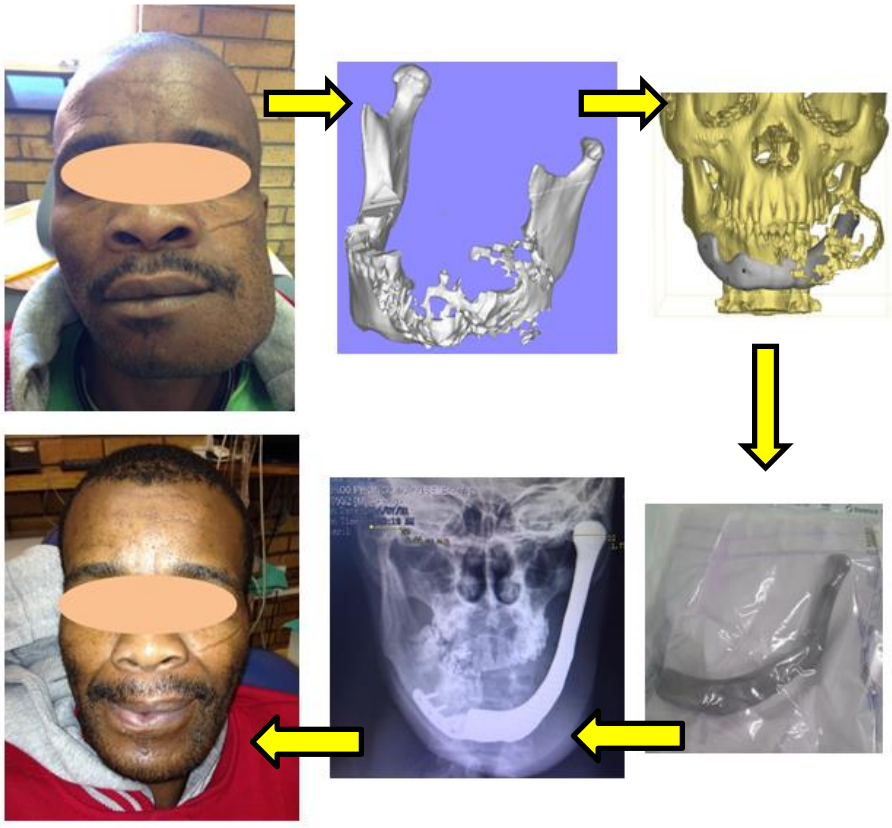


Figure 1.7: First South Africa 3D-printed mandible implanted (designed and manufactured at CRPM)

Chapter 2 - Roadmap of research

2.1 Problem Statement

Conventional manufacturing (also known as subtractive manufacturing (SM)) of custom-designed titanium implants proved to be a reliable but lengthy process. Another disadvantage of SM is that typically between 70–80% of the billet material has to be cut away to achieve the finished product, which in the case of titanium can result in high costs. An advantage of SM is that it starts with a standard certified material billet, which minimises the risk in product deviation.

AM has shown itself to be an attractive alternate manufacturing process since it only uses the powder needed for the end use product with no wastage, and theoretically any shape design can be manufactured. However, AM of certified implants does not have the same degree of documentation and standardisation as the SM process. In offering AM as an implant manufacturing solution, the complete process (design, manufacturing and post processing) must be investigated in order to develop a certified manufacturing solution.

2.2 Research Aim

The aim of this research project is to develop a certification framework focusing on Ti64 titanium powder (as the material) and SLM (as the process) for patient-specific implant manufacturing.

2.3 Definitions

Technical standard conformance means that a process and a component conform to a relevant and applicable standard with respect to measurable SI units. The measurement process is a SOP of the quality system. Quality standard conformance means that a system is in place to ensure the consistent conformance to technical standards. The quality system includes pro-active and reactive processes of correction. The system includes a risk assessment plan to mitigate and the system is accredited.

2.4 Research Objectives

1. Identify key risks in the SLM process and develop work instructions and protocols as part of the technical certification process. These instructions will, in turn, assist in proving repeatability and stability of the manufacturing process. An initial process risk assessment will be conducted before the framework development and thereafter a reassessment will be undertaken to determine whether the risk was reduced.

2. Develop an integrated documentation framework, keeping traceability in mind. This framework forms part of the quality certification process and evaluates the consistency of the technical part as well as the traceability of the products manufactured.

3. Identify shortcomings in the framework and do in-depth analysis on ways to rectify these problems. Developing this framework will entail constant evaluation to improve and optimise this complex manufacturing process.

2.5 Limitations

Due to the complexity of the process and the expensive nature of titanium research, not all the factors influencing this process will be tested. The critical factors stipulated in this proposal will be tested and some of the parameters will be fixed, as prescribed by the machine manufacturer.

2.6 Significance/Importance/Value of Study

The importance of this study is to deliver a framework to adhere to implant certification criteria that will offer a valuable contribution to those in industry that want to follow the path of certified AM implant production. The complete certification process of AM has not been published as only a handful of international service bureaus are working on this topic and the in-house knowledge created is seen as a trade secret and therefore not disclosed. As no research on this topic has been conducted in South Africa, this study will lay the foundation for future studies on certification of medical devices manufactured using AM technology.

Furthermore, the intended study can potentially have a significant impact on the use of technology platforms at CUT, Stellenbosch University and the CSIR National Laser Centre. The study fits into the Metal Additive Manufacturing (MAM) programme funded by the Department of Science and Technology (DST). The MAM programme forms part of a national Collaborative Program for Additive Manufacturing (CPAM) and one of the deliverables after two years is a fully qualified medical implant. The proposed certification framework will play a significant role in this MAM deliverable.

2.6.1 Statement of unique contribution

The unique contribution to the science of engineering is the framework can be used to manage the conformance to technical and quality standards.

2.7 Methodology

In order to address all the research objectives in this proposal, it is necessary to divide the research methodology into an overarching proposed framework and a detailed descriptive process (showing design, AM and post processing). Figure 2.1 shows a summary of a proposed workflow which must be adhered to for certification of the DMLS process. This is essential to minimise the variables in the manufacturing process and to be able to interpret the results/variables.

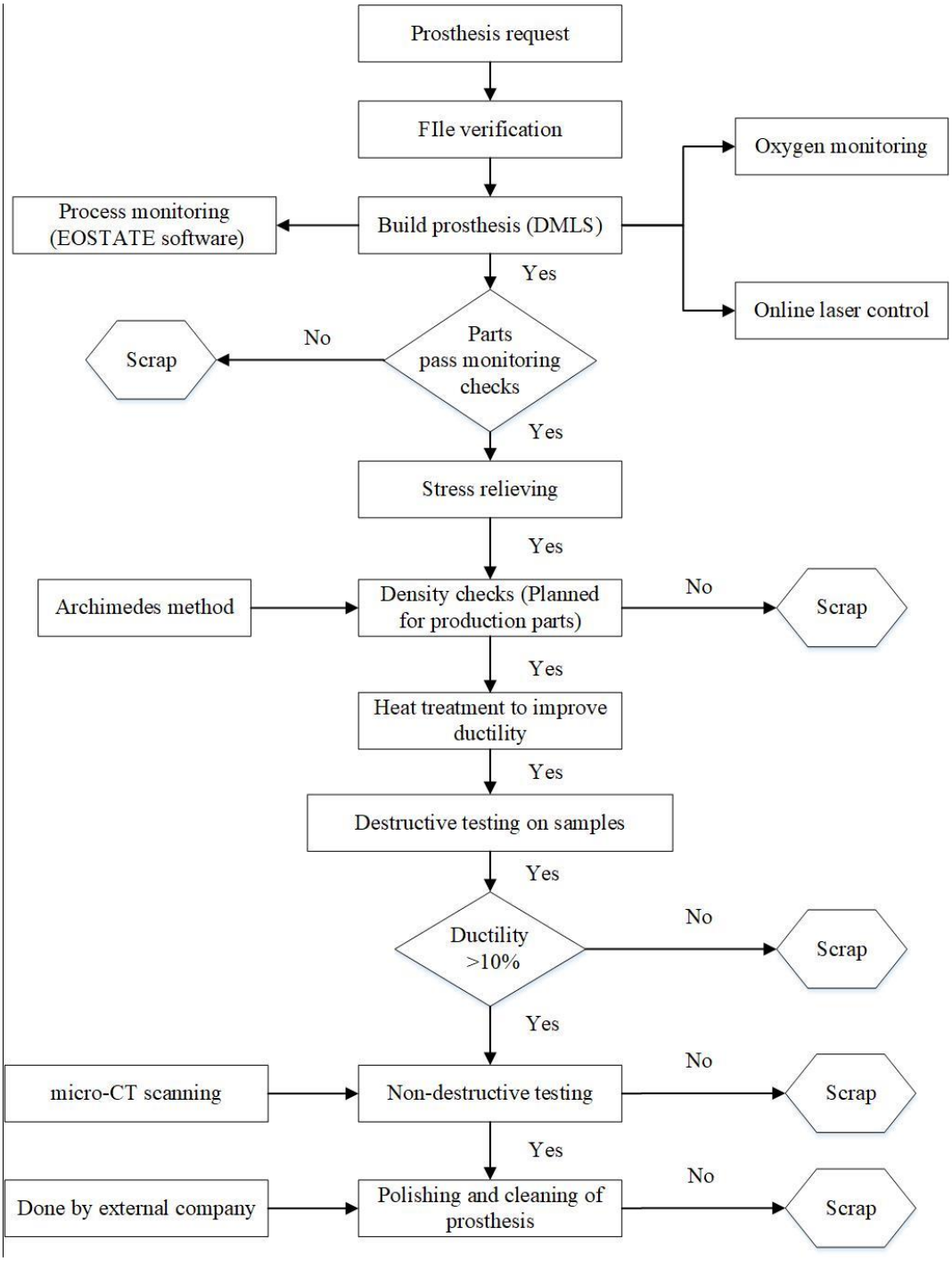


Figure 2.1: The proposed AM of titanium implants workflow (author's own creation in 2015)

The proposed dissertation layout is shown in Figure 2.2. The argument for the need for certification of the SLM process is set out in chapter 1, with some background literature on AM. AM is compared to conventional manufacturing, with particular focus on medical implant manufacturing.

The problem statement, research aim, delimitations, value of study, and research objectives are addressed in chapter 2. The research methodology is also described, whereafter all process risks are identified. It is important to quantify these risks and link them in chapter 3, where mitigation actions are discussed.

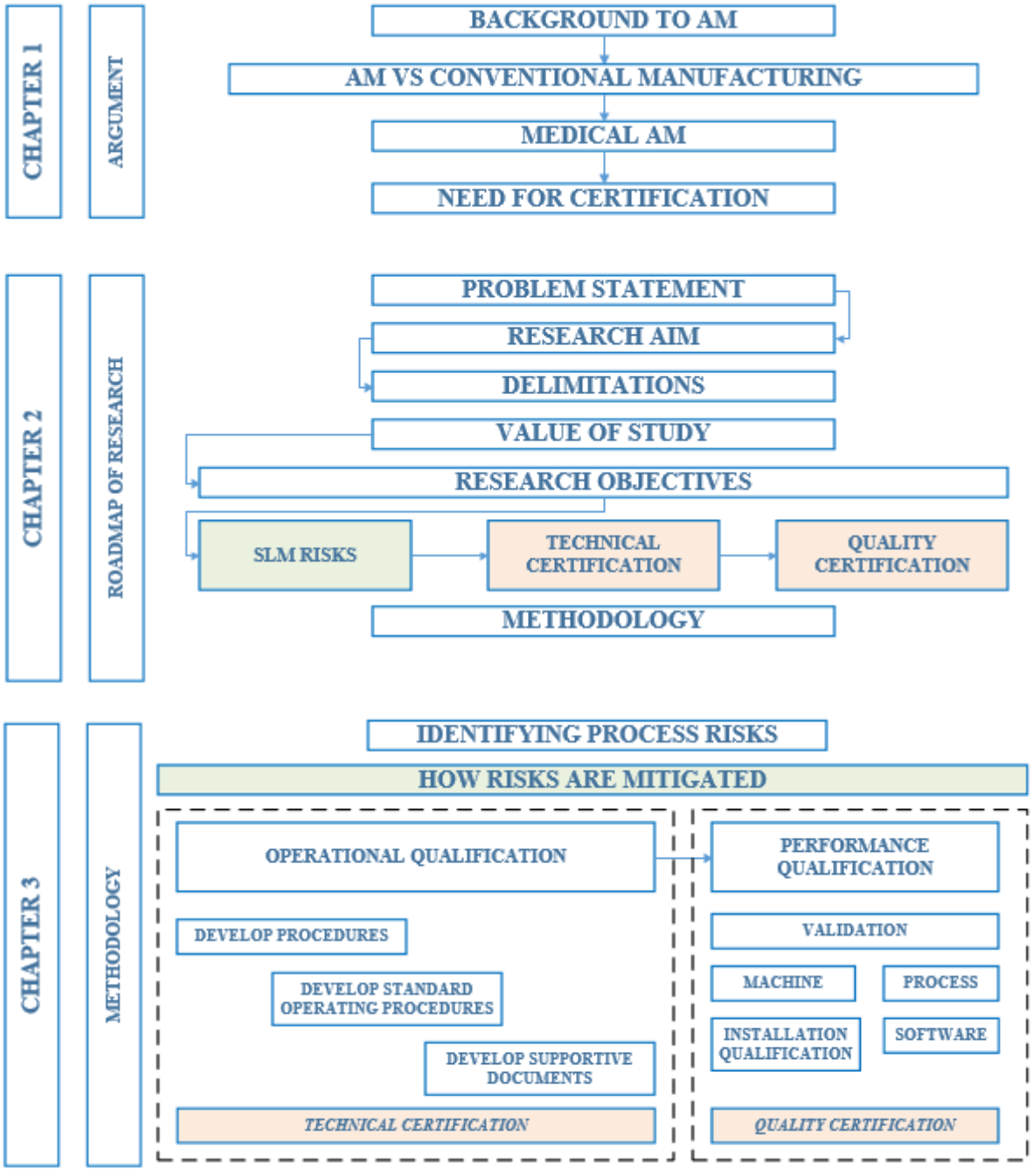


Figure 2.2: Proposed dissertation layout (Author's creation)

The second research objective focusses on quality certification which addresses validation as part of the performance qualification. The machine validation is done through an installation

qualification that professes the system's fitness and calibration. All other in-house process validations, such as heat treatment and destructive testing, need to be performed. The quality certification proves that the technical certification is constant over a period of time. This may include, among others, the accuracy and mechanical properties of parts over a period of time. The validation of software is crucial in the 2016 version of ISO 13485 as all design and process control software must be validated. The standard stipulates that the specific approach and activities associated with software validation and revalidation shall be proportionate to the risk associated with the use of the software, including the effect on the ability of the product to conform to specifications. Chapter 4 covers the risk mitigation as part of the critical evaluation of the framework, as shown in Figure 2.2. Product risk assessments were done before and after the framework was developed in order to assess its impact.

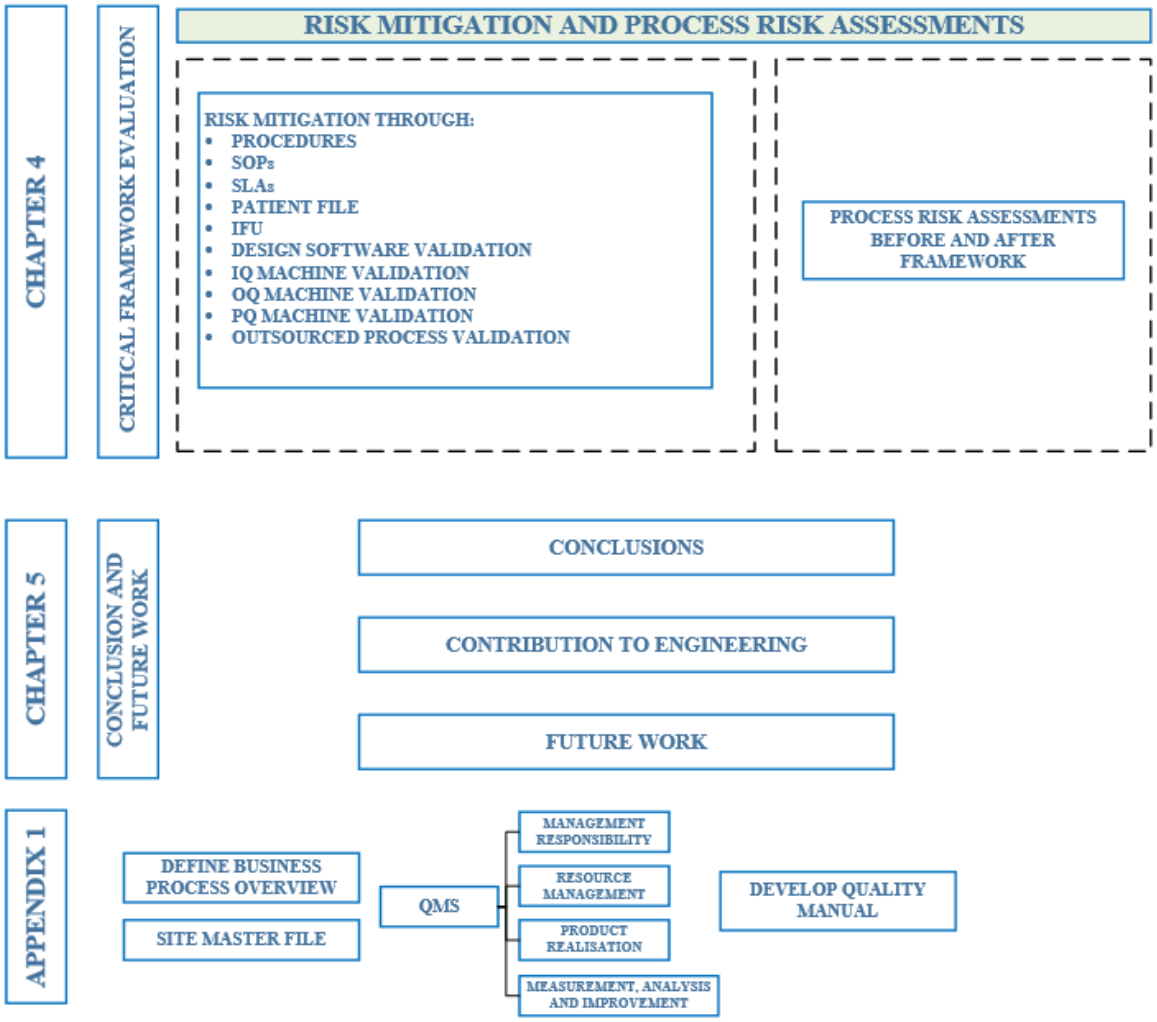


Figure 2.2 Proposed dissertation layout (continued)

Chapter 5 will discuss the conclusions relating to the three research objectives that were set and contributions this research has made to engineering. Lastly, some future work will be proposed.

Appendix 1 continues with defining the Business Process Overview in order to map all processes. The mapping will include all main business-, management-, support- and outsourced processes. This will be used to develop a quality manual for the AM company with relevant overarching procedures, standard operating procedures and protocols. All these inputs and documents are used as part of the technical certification (operational qualification) defined as one of the research objectives. The technical certification ensures that the process is stable and repeatable.

The process chain to design and manufacture patient-specific SLM implants can be divided into three main areas, as shown in Table 2.1:

- Design
- Manufacturing process
- Implant post processing

Table 2.1: Detailed AM certification aspects to consider (author's own creation)

<table>
<tr><th>Design</th><th colspan="3">AM</th><th>Post Processing</th></tr>
<tr><td></td><td>Pre-Process</td><td>Process</td><td>Part Removal</td><td rowspan="2">➢ Density verification

➢ Heat treatment
○ What is needed for medical implants?
○ Develop heat treatment protocol

➢ Non-destructive testing
○ Process must be able to detect micro voids and cracks
○ Process must be repeatable

➢ Destructive testing
○ Tests samples must represent SLM parameters

➢ Surface finishing and coating

➢ Cleaning, sterilisation and packaging</td></tr>
<tr><td>➢ Data management

➢ Design input requirements
○ Surgeon's requirement

➢ Design rules
○ Self-supporting structures
○ Minimum wall (lattice structures)
○ Optimal height/width ratio

➢ Optimal design
○ Finite Element Analysis</td><td>➢ Machine setup
○ Machine calibration
○ Machine maintenance
○ Platform alignment
○ Recoating

➢ Powder handling
○ Certificate of Analysis
○ Aging
○ Storage</td><td>➢ Slice data
➢ First exposure adhesion to substrate
➢ Quality management
○ QM of energy + online laser control
○ QM of process parameters + errors
○ QM documentation – compile a report</td><td>➢ Powder removal
➢ Part surfaces preserved
➢ Stress relieving
○ Correct cycle to relieve residual stress

➢ Test different support methods to ease part removal</td></tr>
<tr><td colspan="5">ISO 13485 CERTIFICATION</td></tr>
<tr><td colspan="5">COMPARISON WITH CONVENTIONAL MANUFACTURING</td></tr>
<tr><td>➢ Known design parameters</td><td>➢ Known machine setup</td><td>➢ Known quality management</td><td>➢ Known heat treatment</td><td>➢ Known mechanical testing, heat treatment, surface finishing and cleaning</td></tr>
</table>

As mentioned earlier in the problem statement, AM of certified implants does not have the same degree of documentation and standardisation as the conventional manufacturing process. However, when identifying the different AM process steps, it is important to cross-reference them to known steps in the conventional process.

The first step will be to analyse the design process and identify the risks inherent in each step. The design methodology can then be broken down further to determine the design input as part of the surgeon's requirements. This is linked with data management to capture the correct Computed Tomography (CT) scan data and translate the data effectively. The AM design rules are used as input by the designer, whereafter the design will be verified using Finite Element Analysis (FEA). The FEA is an outsourced process and only performed on load-bearing implants to verify the design principles followed by the in-house designer.

The next step will be to identify the possible risks associated with the AM process. This process consists of three stages: pre-process, process and part removal. In order to identify the risks, each stage in the process must be described and fully understood. The pre-process incorporates all the actions before the machine is started. This entails actions such as machine setup that talks to the machine calibration and maintenance, correct platform alignment and correct recoating to ensure even powder layers are distributed. It is important to develop the correct powder handling protocol and to investigate the effects of powder aging over a period of time. The process refers to the stage where the slice data is imported into the machine, followed by the first exposure on the substrate, to where the build is completed. The quality assurance of the laser output, oxygen levels in the build chamber, process parameters and errors are captured using EOSTATE™ software. A complete report is exported from the software with all relevant information. After the build is completed, the unused powder must be removed from around the parts and this powder will go back into the recycling process. The parts, still fixed on the substrate, will undergo heat treatment to relieve the residual stress induced by the SLM process and then be cut from the substrate using a wire cutter or band saw.

The post processing addresses process steps like density verification, heat treatment to improve ductility, non-destructive testing to check for internal flaws, destructive testing to verify mechanical properties (such as ultimate stress and ductility), surface finishing and coating and lastly, cleaning, sterilisation and packaging. As can be imagined, there are risks in all of the above process steps that can affect the final part mechanical properties, accuracy and performance.

2.8 Chapter Summary

The problem statement was identified in this chapter and the importance of a structured certification framework was highlighted as part of the research aim. Three key objectives were introduced, with the first being to identify risks pertaining to the process as part of the technical certification section. It is important to develop procedures and work instructions to mitigate these risks. The second objective focuses on developing an integrated documentation framework that proves that the technical certification is consistent over time. This part refers to the quality certification process and includes the process validation section. The third objective is to critically evaluate the framework in order to identify shortcomings and ways to rectify them. Developing this framework will entail constant evaluation to improve and optimise this complex manufacturing process.

The research methodology was introduced to address all the research objectives. It is necessary to divide the research methodology into an overarching proposed framework and a detailed descriptive process (showing design, AM and post processing). A proposed workflow which must be adhered to for certification of the DMLS process was introduced and will be tested throughout this dissertation.

Limitations were introduced, as not all the factors influencing this process will be tested due to the complexity of the process and the expensive nature of titanium research. The critical factors stipulated in this proposal will be tested and some parameters will be fixed, as prescribed by the machine manufacturer.

The significance of this study is to develop a framework of implant certification criteria to adhere to that will offer a valuable contribution to sectors of industry wishing to follow the path of certified AM implant production. The methodology of risk identification and mitigation linked to relevant procedures, SOPs and process and/or machine validation will be discussed in detail in this research project and can be adapted to other AM technologies. To date, only sections of the proposed research have been conducted internationally, and there is no SLM certification available in South Africa.

Chapter 3 - Research Methodology

Risk identification as part of Objective 1

In the medical device industry, risk management is critical throughout the entire life cycle of a device and it is vital to successfully implement a risk management system to ensure that a safe, effective product is manufactured on time and within budget. ISO 14971 (International Standards Organization: 2012) is the harmonised standard for risk management which defines the international requirements of risk management systems for medical devices. Using ISO 14971 (International Standards Organization:2012) and ISO 13485 (International Standards Organization:2016) as guidelines, it is important to develop a Risk Management Procedure (see Appendix 2); including relevant flow diagrams to define how the AM company will do risk assessment and management. Figure 3.1 shows an example of such a flow diagram on risk management.

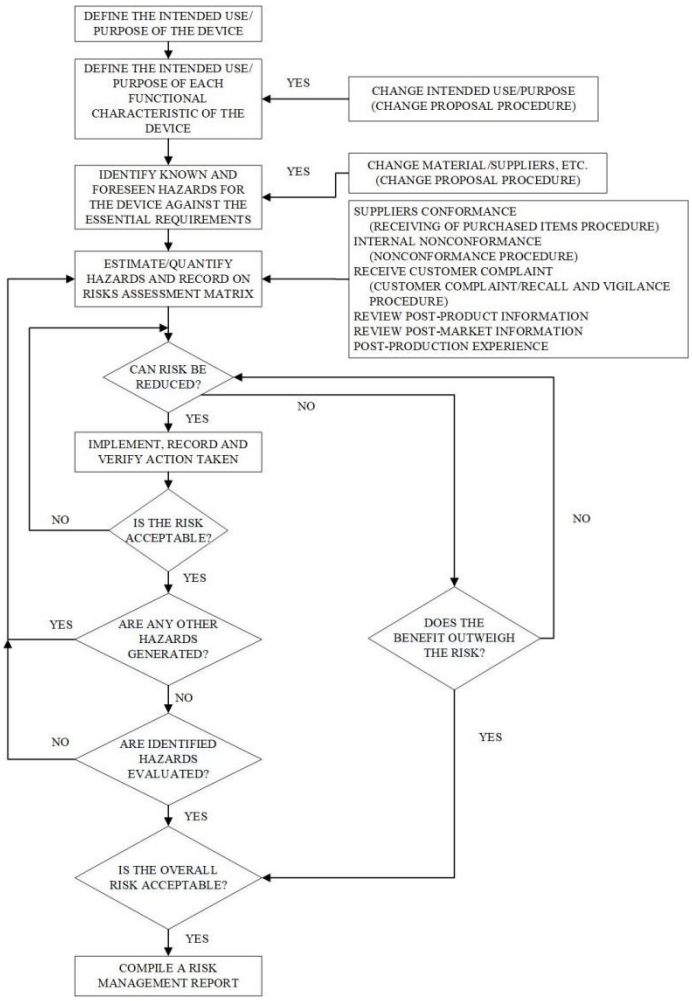


Figure 3.1 Risk Management Flow Diagram (CRPM ISO 13485: 2016 Quality Management System)

An overarching process risk assessment will be done to determine the current risk index. The risk index is the level of risk multiplied by the probability of occurrence. As these patient-specific implants are manufactured in relatively low volumes, the probability of occurrence figures will be significantly lower than in a production environment, as seen in Table 3.1.

Table 3.1 Risk calculation

		LEVEL OF RISK				
		Negligible	Limited	Moderate	Severe	Critical
PROBABILITY OF OCCURRENCE		1	2	3	4	5
Frequent (10 per day)	40	40	80	120	160	200
Probable (1 per day)	15	15	30	45	60	75
Remote (1 per month)	13	13	26	39	52	65
Unlikely (1 per annum)	9	9	18	27	36	45
Improbable (1 in 5 years)	6	6	12	18	24	30
Incredible (1 in 10 years)	3	3	6	9	12	15
Not possible	1	1	2	3	4	5

Any figure above 27 will receive attention to determine methods to minimise or eliminate the risk. Where the residual risk cannot be reduced or eliminated and the benefits outweigh the risk, a warning will be issued. The CRPM Risk Review team comprises Executive Management (15 years' medical AM experience), Management (10 years' medical AM experience), Design and Quality Engineer (4 years' AM experience) and a Clinical Advisor (35 years' clinical experience). Collectively, the team successfully designed and manufactured 45 AM implants, more than 40 cutting and positioning guides and in excess of 60 pre-operative planning models.

The scope of the overarching process risk assessment is on design, AM, cleaning, delivery and patient interface, as shown in Table 3.2. Furthermore, the classification is on custom-designed medical implants manufactured by SLM technology in titanium. The potential hazard, failure or impact on patient and possible cause are identified by the CRPM Risk Review team.

Table 3.2: Overarching Process Risk Assessment

PROCESS RISK ASSESSMENT						
	REFERENCE: Medical implant		MANUFACTURED BY: SLM	REV		
Classification		Custom made	Scope of risk assessment: Design, AM, cleaning, delivery and patient interface			
NO.	POTENTIAL HAZARD	FAILURE/IMPACT ON PATIENT	POSSIBLE CAUSE	LEVEL OF RISK	OCCURRENCE	RISK INDEX
DESIGN						
1	Structural failure of implant	Discomfort, pain, potential revision surgery	Fluctuating process conditions	5	13	65
			Poor design	5	9	45
			Excessive stress on implant	5	9	45
			Inadequate heat treatment	5	9	45
2	Design not within tolerance	Implant does not fit, potential revision surgery	Incorrect patient data	5	9	45
			Bad scan quality	4	13	52
			Incorrect scan orientation	5	13	65
			Design error	3	13	39
			Machine not calibrated	4	13	52
			Software not validated	4	9	36
			Inadequate stress relieving	5	9	45
3	Ineffective operational planning model	Model does not meet expectations of surgeons	Incorrect patient data	6	9	54
			Bad scan quality	3	13	39
			Incorrect scan orientation	5	13	65
			Machine not calibrated	3	9	27
ADDITIVE MANUFACTURING AND CLEANING						
4	Infection	Pain, discomfort, potential revision surgery	Powder contamination	5	13	65
			High bioburden	5	13	65
			Contamination during post processing and cleaning	5	9	45
			Inadequate sterilisation procedure	5	9	45
			Powder out of specification	4	9	36
	Sensation and irritation after implantation	Discomfort	Material not biocompatible	3	9	27
	Implant deformed during manufacturing	Implant does not fit	Implant warped during manufacturing	5	13	65
			Incorrect manufacturing orientation	3	9	27

PROCESS RISK ASSESSMENT						
	REFERENCE: Medical implant		MANUFACTURED BY: SLM	REV		
Classification		Custom made	**Scope of risk assessment:** Design, AM, cleaning, delivery and patient interface			
NO.	**POTENTIAL HAZARD**	**FAILURE/IMPACT ON PATIENT**	**POSSIBLE CAUSE**	**LEVEL OF RISK**	**OCCURRENCE**	**RISK INDEX**
TRANSPORT AND DELIVERY						
5	Design of packaging	Implant can be damaged during transport	Inadequate packaging design/selection	**3**	**13**	**39**
	Implant lost/damaged during shipping	Delay of operation, prolonging of pain/discomfort	Inadequate packaging	**3**	**13**	**39**
			Incorrect address	**2**	**13**	**26**
			Waybill poorly attached	**3**	**9**	**27**
			Box not marked properly	**3**	**13**	**39**
SURGERY AND PATIENT INTERFACE						
6	Infection	Pain, discomfort, potential revision surgery	The Central Sterile Services Department (CSSD) does not follow cleaning procedure	**5**	**13**	65
			CSSD does not follow the sterilisation procedure	**5**	**13**	65
			Gamma irradiation is not effective	**5**	**13**	65
			Clinical error (from theatre to surgeon)	**5**	**13**	65
POST PROCESSING						
7	Implant deformed during post processing	Implant does not fit	Implant warped after heat treatment	**5**	**13**	65
			Implant warped after support removal	**5**	**13**	65

From the risk assessment it can be seen that the largest risk index relates to the design-, manufacturing- and post processing steps. The risk of infection, as part of the surgery and patient interface, is also high, but as part of this research project the implants will be delivered **non sterile to the hospital** even though some cleaning and packaging is done. This is to shift the responsibility to the hospital as they need to sterilise all instruments required for the surgery. In order to unpack the high risks that relate to the design-, manufacturing- and post processing processes, it is important to describe and understand the process steps in each of these activities.

The risks in each process step will be classified under internal (in-house) and/or external risks. This must be seen as an indication of possible risks identified (as a baseline) by the author's research preceding this dissertation and used in implant design and SLM processes for more than 15 years at the CRPM. It must be noted that the Process Risk Assessment is not an exhaustive list and users of other technologies could identify additional risks. The complexity of the process can be seen in Figure 3.2.

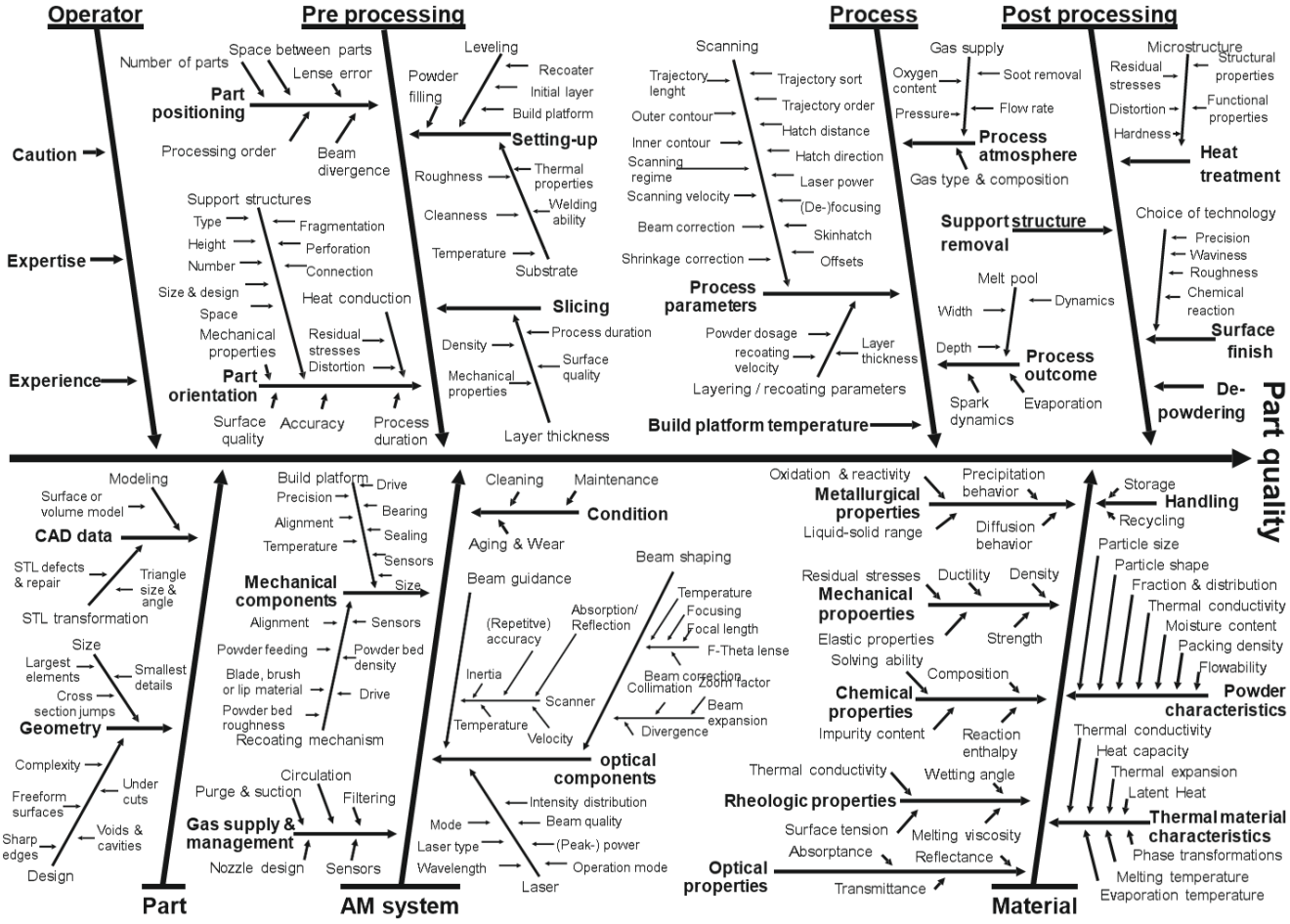


Figure 3.2: Some factors which influence the DMLS process courtesy of Dr. Christop Haberland, Siemens

3.1 Design

3.1.1 Overview of design process

In the case of medical implants, the process starts with scanning the area of the patient where the implant will be required with a CT or MRI scanner. The DICOM files from the scanner are converted to STL format using dedicated software, namely Mimics™ from Materialise. The software allows one to alter the grey-scale values from the DICOM images to differentiate between soft tissue and bone. In this case, the bone data are exported in STL format to show the skeletal features of the patient. The STL file is opened in Magics™ or 3 Matic™ software – also from Materialise – where the implant can be designed. Support structures must be added to the part to anchor it to the base onto which it will be manufactured. This is done through Magics™ software. The design file is exported to RP Tools™, from EOS, where the design is sliced into virtual slices. The slice file is then exported to the DMLS machine where it will be manufactured.

Design process followed for developing a patient-specific AM implant:

- Doctor requests a patient-specific device
- CT/MRI of patient's affected area is received
- Where necessary, the patient's impression is requested
- Check quality of scan data
- Doctor submits requirements/inputs
- Convert CT/MRI conversion with Mimics™ software
- Manufacture pre-operative model in nylon
- Where necessary, surgeon cuts model and prosthodontist makes a wax mock-up of proposed implant
- Wax mock-up is reverse engineered to be used as input geometry for design software
- Do initial design with 3 Matic™ software
- Send concept through to surgeon
- Do final design
- Finite Element Analysis (FEA) analysis on design
- Design cutting and drill guides
- Manufacture implant in nylon – fit on pre-operative model and use as sizer in theatre
- Do design review – Design Team sign-off
- Surgeon completes sign-off
- Manufacture implant in titanium

Figure 3.3 shows a generic flow diagram pertaining to all new product developments.

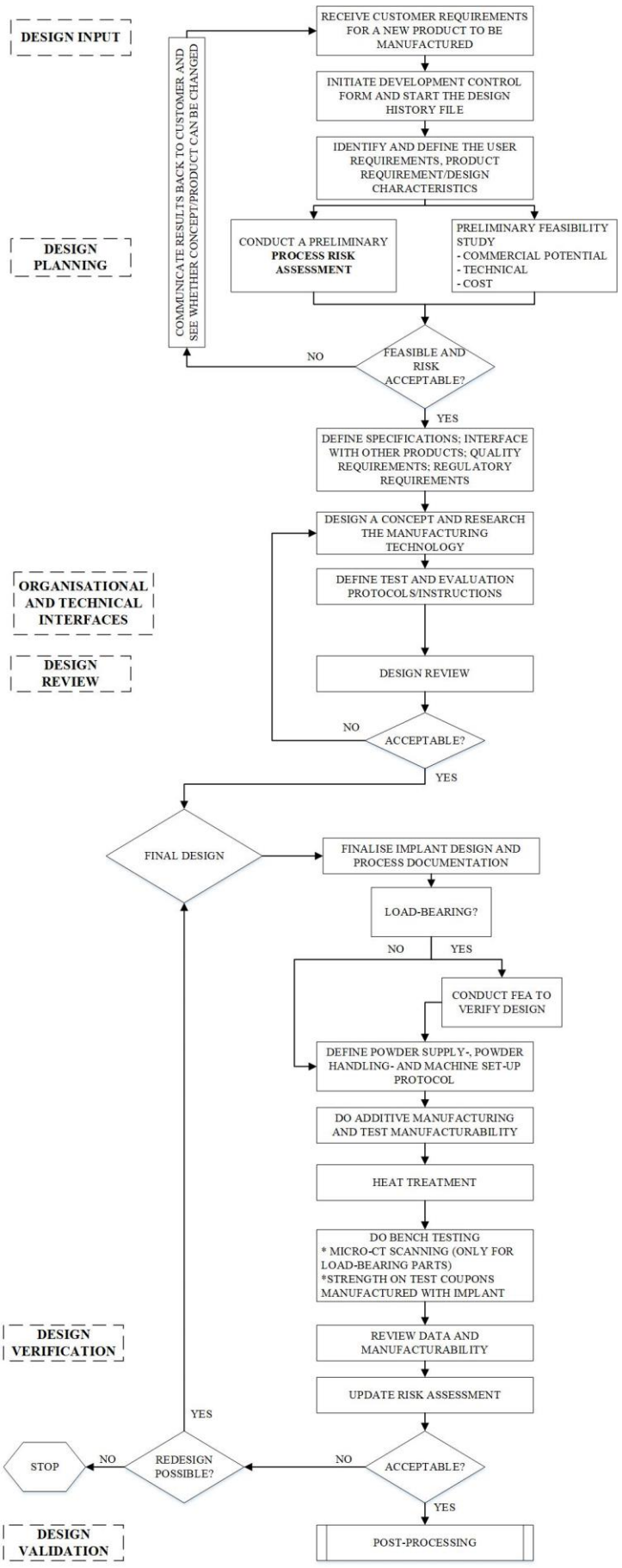


Figure 3.3: Generic new product development flow diagram

Current risks associated with design process

It is important to identify current risks associated in the design process and develop ways to mitigate these risks. These risks will be quantified in this section. The risks are split between internal and external factors which can influence the outcome.

a) Internal Risks

It is critical to ensure when importing the slice data into Mimics™ that the anterior of the scan data is the patient's anterior data and that the scan data is not flipped when shown in the software. Inaccurate slice data to STL conversion can result in inaccurate implant designs. Another risk is that the implant is under- or overdesigned: where the first can result in implant failure, the second could mean discomfort to the patient. Lastly, it is important not to design something that cannot be additively manufactured, and here factors like minimum wall thickness and height-to-width ratio of design features must be kept in mind. Table 3.3 shows the different internal risks inherent in the design process and quantifies a factor of risk to the sub-risks. The percentages shown in the tables represent the average value obtained from a questionnaire that was completed by experts in the field of AM. The composition of the experts was a spread between design-, application-, quality- and risk engineers, and AM centre managers. The risk level was categorised, where one = 0 to 24%, two = 25 to 49%, three = 50 to 74% and four = 75 to 100%.

Table 3.3: Internal risks pertaining to the design process

Risks	***%***	***Level***	***Possible ways to mitigate***
Flipped import CT slice data	10	1	Develop Standard Operating Procedure (SOP)
Slice data to STL conversion	30	2	Software validation
Over- or underdesign	30	2	A team of engineers will conduct the formal design review that is captured in Patient File. FEA analysis on implant will assist with this design review
Design not suited for AM	30	2	Develop design rules

b) External Risks

Firstly, the wrong patient information could be received from radiologists resulting in the design being created on incorrect patient anatomy. The scan quality must be checked as slices that are too thick can result in inaccurate data extraction, for example, using this data can result in the condyle

of the mandible not fitting into the glenoid fossa. Another risk is when the doctor's requirements to guide the designer in the appropriate direction are not captured accurately. A summary of external risks are shown in Table 3.4.

Table 3.4: External risks pertaining to the design process

Risks	***%***	***Level***	***Possible ways to mitigate***
Wrong patient information	10	1	Develop comprehensive Patient File with ID number, etc.
Bad quality scan data	40	2	Develop CT scan protocol
Incorrect doctor's input requirements	50	3	Develop doctor input sheet linked to patient file

Furthermore, it is important to check the design process against the doctor's requirements and structure a design review process. The design can be prototyped and checked against the pre-operative planning model and a metrology comparison can be conducted. To minimise the risk of under- or overdesigning, it is proposed to do a FEA to check the maximum stress in the implant induced for a specific loading.

It is important to develop a Checklist of Compliance to Essential Requirements for the implant, a pre-operative planning model and drill/cutting guides. A risk assessment is proposed for the implant, pre-operative planning model and drill/cutting guides, as part of the essential requirements.

3.2 Pre-process

The second research area will focus on AM, including pre-process, process and part removal sub-areas. Factors like machine setup, powder handling and platform alignment will be examined to determine how they affect the successful outcome of parts. Furthermore, the laser power will be tested before and after the process to establish a baseline value.

3.2.1 Overview of machine setup process

The machine setup is a critical forgoing process as this setup could influence the outcome of the manufacturing process. Factors like in-house and outsourced maintenance and calibration, substrate flatness tolerance, platform alignment and even recoating all play important roles in successful manufacturing outcomes.

Current risks associated with machine setup process

a) Internal Risks

The in-house machine calibration and maintenance is divided into pre-job checks, weekly-, monthly- and six-monthly first line maintenance. This includes the checks that the F-Theta lens is clean between the optics and chamber. If this lens is not cleaned regularly, it could affect the amount of laser power available at the powder bed that, in turn, can cause variable mechanical properties. The substrate machining is subcontracted for levelling and this must be done at tolerances of 45 µm ± 5 µm. The substrate must be levelled inside the machine to ensure an even layer of powder can be coated as a first layer. Table 3.5 shows the internal risks relating to the machine setup process and quantifies a factor of risk to the sub-risks.

Table 3.5: Internal risks pertaining to the machine setup process

Risks		***%***	***Level***	***Possible ways to mitigate***
Improper in-house machine calibration and maintenance		10	1	Develop in-house maintenance plans and schedules as part of Operational Qualification (OQ)
Incorrect substrate tolerances		25	2	Develop SOP
Incorrect platform alignment		25	2	Develop SOP Wrong platform tolerance larger than 45µm will result in too thick first powder layer.
Uneven recoating	Powder flow ability?	15	1	Develop SOP for Drying of Powder
	Operator powder contamination?	25	2	Develop SOP for Powder Handling

b) External Risks

The in-house calibration and maintenance is checked by the machine manufacturer once a year when a thorough service and calibration is done. Any drift in the machine performance is logged by the service technician to ensure that the machine will manufacture constant and repeatable parts for the next twelve months. The service technician checks the laser focus over the entire platform and all axes control will be checked.

Table 3.6 shows the external risks relating to the machine setup process and quantifies a factor of risk to the sub-risks. Possible ways to mitigate the risks are proposed, which include SOPs, monitoring and installation qualification.

Table 3.6: External risks pertaining to the machine setup process

Risks	***%***	***Level***	***Possible ways to mitigate***
Insufficient machine performance at installation	5	1	Develop Installation Qualification (IQ)
Insufficient machine calibration and maintenance	40	2	Linked to machine manufacturer's yearly maintenance
Inadequate operator training	10	2	Training forms part of OQ
Inconsistent machine performance	40	2	Develop Machine and Calibration SOP Performance Qualification (PQ) for the machine
Inconsistent *z*-axes control	5	1	Linked to machine manufacturer's yearly maintenance Platform not consistently lowering by the required layer thickness Powder dispenser not consistently moving up with required dosage

3.2.2 Overview of powder handling process

The powder handling process is an important process as variable powder properties can result in variable part qualities. Factors that need to be considered are:

- Each batch of powder delivered must be checked to ensure that it has the correct chemical composition and a certificate of conformance.
- The correct powder mixing, sifting and storage procedures are followed.
- The powder aging through multiple builds must be tracked to ensure the chemical analysis does not change over time.

Current risks associated with powder handling process

a) Internal Risks

One of the largest risks, as shown in Table 3.7, is that powder is not correctly mixed and sifted, as impurities could be reintroduced into the manufacturing process. Titanium powder will oxidise if exposed to oxygen at elevated temperatures and the powder storage and handling is crucial to minimise the risk.

Table 3.7: Internal risks pertaining to powder handling

Risks	***%***	***Level***	***Possible ways to mitigate***
Powder mixing and sifting	40	2	Develop SOP Contamination of powder through debris from building chamber, platforms and recoater blade Powder contaminated inside process (debris not sifted out)
Powder storage	35	2	Develop SOP Log conditions using software solutions
Powder exposed to O_2 at elevated temperatures	25	2	Develop SOP

b) External Risks

Powder quality plays such a vital role in the manufacturing process chain where consistency is essential. Therefore, the choice of powder supplier must be carefully considered. According to the American Society for Testing and Materials (ASTM) F136 standard, (ASTM International, 2013), the supplier of the powder must provide certification with each shipment that the batches of powder were tested in accordance with this specification.

Table 3.8 shows the external risks pertaining to powder handling. SOPs can be developed for the powder mixing and sifting. It is essential to log the powder storage conditions and some hardware and software solutions are available for this purpose. As mentioned above, the powder supplier needs to supply a Certificate of Analysis with the powder delivery and this includes a chemical analysis of the powder. Powder ageing analysis tracks the chemical analysis, including the levels of oxygen in the powder. Furthermore, it is essential to analyse the powder elements to see whether impurities are introduced through the process.

Table 3.8: External risks pertaining to powder handling

Risks	***%***	***Level***	***Possible ways to mitigate***
Certificate of analysis with powder delivery	10	1	Powder not in specification (size, morphology, O_2, N, C elements) Develop Procedure for Purchasing
Conduct local chemical analysis with powder delivery	40	2	Powder not in specification (size, morphology, O_2, N, C elements)
Powder aging	50	3	Develop SOP. Create history on the number of builds executed before O_2 levels in the powder reach unacceptably high levels

3.3 SLM Process

AM is a complex process with many variables influencing the manufacturing of parts, as shown in Figure 3.2. These include, among others: laser power, scanning speed, laser spot diameter, scanning strategy and layer thickness. An ideal relationship between laser power, scanning speed, laser spot diameter and scanning strategy is needed for the material to be laser melted successfully and ensure repeatability.

3.3.1 Overview of SLM process

The EOSINT M280 machine employs DMLS technology, which is a trademark of EOS. The broader term currently used to describe metal laser technology is selective laser melting (SLM) and it was decided to use the generic term, SLM, to refer to this technology in this research project.

Current risks associated with SLM process

a) Internal Risks

The operator must load the slice files on the machine and ensure that the part exposure parameter is assigned to all parts. The build and the support exposures are assigned to all slice files that have been loaded. The slice files must be rearranged so that the exposure will start from the back of the machine, as the filtration works from the back to the front of the machine. Each one of these steps is operator-dependant and this risk can be mitigated by ensuring that all operators receive training and a SOP is developed. It is important that the first exposure penetrates into the substrate to ensure all support structures are fixed onto the substrate. As residual stress is inherent in the process, the fixation of the part to the support and then to the substrate is essential to manufacture successful parts that are not warped. The operator must ensure that enough argon is available to complete the build and that the recirculating filters are clean enough to finish the build. Table 3.9 shows the internal risks linked to the SLM process.

Table 3.9: Internal risks pertaining to the SLM process

Risks	***%***	***Level***	***Possible ways to mitigate***
Incorrect slice file	10	1	Develop SOP Part exposure type loaded Support exposure type loaded Rearrange slice files starting exposure from back
First exposure not penetrating into substrate	15	1	Visual inspection
Incorrect recoating	25	2	Visual inspection
Part coming loose from substrate	25	2	Visual inspection
Insufficient argon supply	5	1	Develop SOP and a Pre-Job Checklist Process will stop automatically and if continued, the next layer can separate from the cool-down layer
Air circulation filters clog during build	10	1	Develop a Pre-Job Checklist to log these values
Incorrect laser power with pre-check	10	1	Develop SOP

b) External Risks

As part of the quality monitoring process, the laser power is checked with a handheld power meter and this value is logged before the process is started. After the build is completed, the machine's output process monitoring system logs the oxygen levels and laser output through the process. The laser power is checked after the process and together with the input and output values, is combined with the monitoring log curve. An assessment can be made if enough laser power was available through the process. The process monitoring logs must be exported after the build as part of the Quality Management System (QMS). Table 3.10 shows the internal risks linked to the SLM process.

Table 3.10: External risks pertaining to the SLM process

Risks	***%***	***Level***	***Possible ways to mitigate***
Inconsistent mechanical properties of parts	50	3	Develop PQ
Process not repeatable over time (accuracy)	40	2	Develop PQ
Incomplete process monitoring logs	10	1	This will be captured in a Procedure for Maintenance and Calibration

3.4 SLM Post Processing

Another concern is the residual stresses that are generated in the parts during the manufacturing process. This is due to the great temperature difference between the building platform and the intense temperature caused by the laser melting the Ti64 alloy during manufacturing. To prevent the parts from warping when removed from the build platform, the platform with parts are stress-relieved in a furnace in an inert atmosphere to prevent oxidation. Furthermore, the ductility of the SLM parts, as grown, is too low for medical applications and needs to be improved through an annealing cycle in an inert atmosphere.

All parts manufactured through the DMLS process are scanned at the Central Analytical Facilities at Stellenbosch University (micro-CT) to ensure that there are no flaws, such as micro cracks or voids, inside the parts that may negatively influence their mechanical properties.

3.4.1 Overview of part removal process

The platform must go through a stress-relieving cycle before the parts are removed from the substrate. This must be done to relieve the internal stress induced by the SLM process in order to minimise distortion in the parts after removal. It is essential to remove all loose powder in support and lattice structures as the loose powder can agglomerate during the stress-relieving cycle, whereafter it will be difficult to remove.

Current risks associated with part removal process

a) Internal Risks

One of the biggest risks relating to part removal is that part surfaces or features could be damaged during removal. This is why it is important to determine the right number of support structures needed. Too little support will cause the part to come loose from the support structures due to the internal stress induced, whereas too much support will be problematic to remove afterwards. All loose powder must be removed from support and lattice structures before the stress-relieving cycle commences. Powder that is trapped inside lattice structures could cause clinical problems for the patient who receives such an implant. It is important to use the correct stress-relieving cycle and to log ramp-up, hold and cool-down temperatures and times. Oxygen present during stress-relieving cycle could cause parts to oxidise which can influence mechanical and fatigue properties. The powder that is removed around the part geometry must be recycled and sifted and the correct SOP has to be followed. Table 3.11 summarises the internal risks linked to part removal as part of post processing.

Table 3.11: Internal risks pertaining to part removal process

Risks	***%***	***Level***	***Possible ways to mitigate***
Part surfaces/features are damaged during removal	40	2	Develop SOP
Not all powder around/inside part is removed	30	2	Develop SOP
Inaccurate stress-relieving cycle	15	1	Develop SOP Log oxygen level through cycle Log temperatures: • Ramp up • Hold • Cool down Validate temperature measurements through IQ and PQ
Incorrect powder handling	15	1	Develop SOP

b) External Risks

The furnace cycle must be precisely controlled as a deviation could cause deformation in the parts as not all internal stress induced in the parts is relieved. A deviation could alter the mechanical properties of the SLM-produced parts and the manufacturing process unrepeatable. Residual stress induced in the parts by the SLM process is still a largely unexplored research field. The EOSINT M280 machine uses no pre-heating in the platform which results in a large temperature gradient between the melt pool and the substrate or previous layer that was exposed. Many researchers are working on solving this phenomenon and simulation software is being developed to simulate this process. Experienced users can predict areas of concern and add extra support structures in these areas or change the orientation. The parts are cut from the substrate with a wire cutter or a band saw. The correct height must be communicated to the machine operator otherwise he could inadvertently cut into the part. Table 3.12 shows the external risks pertaining to the part removal process

Table 3.12: External risks pertaining to part removal as part process

Risks	***%***	***Level***	***Possible ways to mitigate***
Incorrect furnace cycle outputs	15	1	Develop heat-treatment validation Do stress-relieving furnace cycle on all parts on platform Test residual stress in some parts after stress relieving
Residual stress deform final part	45	2	Develop heat-treatment validation See whether part orientation plays a role in residual stress induced in parts If possible, try to simulate to residual stress with software Test different support methods to ease part removal and reduce residual stress induced Different support structures like tree, support, solid, different intersect, block and sacrificial methods
Part is cut from platform incorrectly	40	2	Develop SOP for part removal

3.4.2 Overview of density verification

Ramping-up the production of implants will result in not all the parts being sent for non-destructive testing and an in-house density protocol must be developed to verify the density of the batch production. The most important factor is to identify and validate a process that will be accurate enough in detecting flaws in the SLM samples after which the outliers can be checked with NDT methods.

Current risks associated with density verification

a) Internal Risks

One of the significant risks related to density verification is that the process accuracy is not fine enough to detect micro cracks and flaws that could be caused by unsintered powder inside the part. The implant geometry can be relatively complicated and some methods could prove to be not accurate enough. The process chosen must be repeatable and it will be crucial to identify go and no-go values for the in-house density verification as shown in Table 3.13.

Table 3.13: Internal risks pertaining to density verification

Risks	***%***	***Level***	***Possible ways to mitigate***
Density checks not accurate enough	40	2	Develop density validation documents (proposed as future work in chapter 5) Check accuracy of different methods: • Archimedes method • Ultrasonic • Dye penetrate • Other
Process not repeatable	60	3	Develop density validation documents such as a PQ • What are acceptable levels? • What is best achievable level? • What is average achievable level? • What is lowest achievable level? ***Link to tensile results***

b) External Risks

Any in-house process must be validated externally to be included in a QMS, as shown in Table 3.14. A correlation needs to be found between the in-house testing values and that of an external certified company.

Table 3.14: External risks pertaining to density verification

Risks	***%***	***Level***	***Possible ways to mitigate***
Internal density results cannot be verified externally	100	4	Develop validation protocol

3.4.3 Overview of heat treatment process

The ductility of the as-grown SLM parts have proved to be too low for medical implants and this is the reason why the SLM parts need to be heat treated to improve the ductility to above 8% (ASTM International, 2014:4-5). This heat treatment cycle needs to be tailored for each application, such as medical, aerospace and automotive.

Current risks associated with heat treatment process

a) Internal Risks

The first step is to determine what mechanical properties are needed for the specific application: even within this application, variations might be necessary. In medical, there could be different mechanical properties required for maxillofacial compared to orthopaedic. The risk is to determine this optimal heat treatment process for the required mechanical properties and lock this cycle for all the parts thereafter. Furthermore, it is essential that this heat treatment process is repeatable and that all temperatures, times and oxygen levels are logged. Table 3.15 shows the internal risks linked to the heat treatment process.

Table 3.15: Internal risks pertaining to heat treatment process

Risks	***%***	***Level***	***Possible ways to mitigate***
Heat treatment cycle not correct for medical implants	10	1	Develop SOP Different applications like: • Maxillofacial • Orthopaedic • Non-load-bearing Develop heat treatment protocol, keeping in mind required stress and strain
Process not repeatable	45	2	Develop PQ
Parts oxidise through cycle	35	1	Develop SOP
Inadequate operator training	10	1	Training forms part of OQ

b) External Risks

The furnace output must be consistent otherwise there could be a variation in mechanical properties in all the parts manufactured using the SLM process. The user could investigate possible problems in the process where the deviations are caused during the post-processing stage. The furnace must be calibrated and maintained to ensure a consistent output. It is essential to have logs of the entire furnace cycle as part of the QMS. Table 3.16 shows the internal risks linked to the heat treatment process.

Table 3.16: External risks pertaining to heat treatment

Risks	***%***	***Level***	***Possible ways to mitigate***
Furnace output inconsistent	80	4	Develop IQ and OQ
Incomplete furnace cycle logs	20	1	This will be captured in a Procedure for Maintenance and Calibration

3.4.4 Overview of non-destructive testing

Non-destructive testing of SLM parts is the only way to detect flaws such as micro cracks, voids and unsintered powder inside the parts. As this will be the last stage in verifying part integrity, it is imperative that the NDT technology being used is accurate enough to detect flaws in the ranges of 5 µm (Du Plessis, Yadroitsev, Yadroitsava & Le Roux, 2018:3). The NDT report must be formulated in such a way that the position and size of the flaws are shown.

Current risks associated with non-destructive testing

a) Internal Risks

As mentioned above, the biggest risk is that the NDT method is not accurate enough to detect micro flaws inside the part at critical areas. The implant designs are complex and freeform in nature and the NDT method selected must be repeatable. Table 3.17 shows the internal risks linked to the non-destructive testing process.

Table 3.17: Internal risks pertaining to non-destructive testing

Risks	***%***	***Level***	***Possible ways to mitigate***	
NDT methods not accurate enough	40	2	Evaluate different NDT methods and develop CT validation documents	
			If CT scanning is the option	Evaluate micro- or nano scanning
				Develop part CT scan protocol
				What slice thickness is suited for detecting what size defect?
Process not repeatable	60	3	Develop CT validation documents Position of pore/crack: • On surface • In core of part What effect the position will have on long-term durability? On different wall thicknesses – what is the safe value linking it to slice thickness selected?	

b) External Risks

The NDT report generated by a subcontractor must capture the correct information, such as density of the part as well as minimum and maximum pore sizes and their perspective position. The NDT reports will be reviewed by the legal manufacturer and the format and information must be correctly captured. Most of the SLM implants will be patient-specific and some will be done for trauma cases that require short lead times. The availability of the NDT facility at short notice must be ensured, as shown in Table 3.18.

Table 3.18: External risks pertaining to non-destructive testing

Risks	***%***	***Level***	***Possible ways to mitigate***
NDT reports not capturing correct information	25	2	Develop suitable CT Scan Report Template as part of Service Level Agreement (SLA)
			Aspects to be covered such as density, min/max pore size, position Go and no-go values Part to CAD comparison CT Scan Report Review Committee When should CT scanning be done – with every implant, etc.?
NDT facility not available for urgent cases	75	4	Develop SLA highlighting aspects such as scan protocol and lead times

3.4.5 Overview of destructive testing (DT)

Some destructive testing samples will be manufactured on the same platform as the implant to represent the mechanical properties of the implant. It is important that these samples are processed in the same way as the implant, both on the SLM process and the post-processing steps. These samples will be machined and tested at a certified laboratory. The AM company saw the need to insource this process, as it will assist in better and more frequent quality assurance of the SLM process (will be discussed in chapter 4 as part of risk mitigation). The number of samples must be decided on as well as the surface finish, as shown in Table 3.19.

Table 3.19: Deciding on number and surface finish requirements of destructive testing samples

Destructive testing	Decide on the number of samples to manufacture	3 samples before stress relieving
		3 samples after stress relieving
		3 samples after heat treatment
		1 for storage
	Decide on as-grown or machined samples	Complex medical implants cannot always be machined in all areas (lattice structure, complex geometries) What will represent the real life case? Develop machining protocol
	Broken samples must be returned for microscopic analysis	

Current risks associated with destructive testing

a) Internal Risks

The machining of the samples is crucial to achieve the required results. The sample geometry, surface finish and accuracy of the machining will predict the outcome. The machining must be done in a controlled manner that must by repeatable in batches of parts. If the destructive testing is to be insourced, it is important that the equipment can be used repeatedly and this process will have to be validated against an outsourced certified laboratory. It is also important to identify what are acceptable mechanical properties of the samples linking them to available standards. Table 3.20 shows the internal risks linked to the destructive testing process.

Table 3.20: Internal risks pertaining to destructive testing process

Risks	***%***	***Level***	***Possible ways to mitigate***
Machining of samples not consistent	35	2	Develop SLA with machining company that addresses the below-mentioned issues
			Decide on the number of samples to manufacture Decide on as-grown or machined samples
			What are acceptable surface finish, accuracy and tolerance values
			Flat or round? Grown horizontally or vertically?
Internal DT testing not repeatable	40	2	Develop PQ Validation of in-house testing equipment and processes and compare to certified laboratory results on same batch samples
Inadequate operator training	10	1	Forms part of OQ
Outdated calibration	10	1	Forms part of PQ

b) External Risks

It is essential that the outsourced destructive testing must be consistent and repeatable over time. These tests will be the final evaluation to prove that the mechanical properties of the manufactured platform adhere to the requirements and therefore the high importance factor. As mentioned earlier, some of these SLM implants can be manufactured for trauma cases that require short lead times. The availability of the destructive testing facility at short notice must be ensured. Table 3.21 shows the external risks linked to the DT process.

Table 3.21: External risks pertaining to destructive testing process

Risks	***%***	***Level***	***Possible ways to mitigate***
Inconsistent external DT results	35	2	Develop SOP and SLA with external test facility
DT facility not available for urgent cases	65	3	Develop SLA highlighting aspects like sample machining, test protocol and lead times

3.4.6 Overview of surface finishing and coating process

It could be necessary to outsource polishing some of the implants using the different surface finishing techniques available. The effectiveness of the different surface finishing techniques must be evaluated and this should include the risks inherent in each process. Caution must be taken not to contaminate the surfaces during the finishing process.

Current risks associated with surface finishing and coating process

a) Internal Risks

There could always be a risk that the implants' surface finish quality does not meet that required by the surgeons and therefore it is essential to evaluate the effectiveness of the different techniques. Caution must be taken not to contaminate the surface with any foreign materials. The chosen surface finishing technique must be repeatable over time. It is also important to quantify the effects that the heat generated in the finishing techniques has on part morphology. Table 3.22 shows the internal risks pertaining to surface finishing and coating processes.

Table 3.22: Internal risks pertaining to surface finishing and coating processes

Risks	***%***	***Level***	***Possible ways to mitigate***
Surface finishing quality not acceptable	30	2	Develop SOP and outsourced validation protocol with supplier Evaluate effectiveness of different surface finishing techniques: • Hand polishing • Shot blasting • Tumbling • Laser polishing
Surface contamination	20	1	Develop outsourced validation protocol Develop Instruction for Use (IFU) Link to cleaning specifications – bioburden tests What cleaning technique can clean which surface contamination?
Surface finish process not repeatable	40	2	Develop outsourced validation protocol

Effects that heat generated with finishing process have on part morphology	10	1	Develop SOP and outsourced validation protocol with supplier

b) External Risks

It is sometimes necessary to coat the implant with a biocompatible material to enhance clinical performance (Haermawan, H., Ramdan, D., and Djuansjak, R.P., 2011:418). This coating process will be an outsourced process and must be repeatable. The coating material must be biocompatible and the process must not contaminate the implant with impurities. Table 3.23 shows the internal risks pertaining to surface finishing and coating processes.

Table 3.23: External risks pertaining to surface finishing and coating processes

Risks	***%***	***Level***	***Possible ways to mitigate***
Coating process not repeatable	70	3	Develop outsourced validation protocol with supplier
Coating process not biocompatible	30	2	Develop outsourced validation protocol with supplier

3.4.7 Overview of cleaning, sterilisation and packaging processes

The implant has to be cleaned in-house after which it is sent for sterilisation and packaging. Different cleaning techniques are available and their effectiveness must be tested. A bioburden test must be performed after the in-house cleaning process to determine a baseline. Another bioburden test needs to be conducted after the sterilisation process to determine whether all the micro-organisms have been killed. The correctly certified packaging material must be used and an IFU should be included in the parcel.

Current risks associated with cleaning, sterilisation and packaging processes

a) Internal Risks

The effectiveness of in-house cleaning of the implant must be quantified, as shown in Table 3.24. The Instructions for Use (IFU) document must be clear and easily understood. The theatre staff must acknowledge receipt of the IFU. The packaging must be effective and the pouches used must adhere to certified standards.

Table 3.24: Internal risks pertaining to cleaning, sterilisation and packaging processes

Risks	***%***	***Level***	***Possible ways to mitigate***
In-house cleaning process not satisfactory	40	2	Develop SOP Develop implant handling protocol When is it considered to be clean enough – links to IFU and bioburden tests?
IFU not clear enough and not received by theatre staff	40	2	Develop Procedure of Identification Develop IFU showing: • Implant is sterile or non sterile • Show sterilisation procedure for hospital Who signs the "Acknowledge receipt and sterility" form at the hospital to receive IFU and implants
Ineffective packaging	20	1	Develop packaging validation through IQ and PQ Pouch rolls must be ISO certified Place steri-strip inside pouch to confirm the parcel was sterilised Design label accordingly to ISO standard Design boxes

b) External Risks

The effectiveness of the sterilisation process is important to ensure the cleanliness of the implant. Furthermore, the outsourced sterilisation process should be repeatable over a period of time. The sterilisation process should be validated as far as possible and protocols must be developed to ensure this. Table 3.25 shows the external risks pertaining cleaning, sterilisation and packaging processes.

Table 3.25: External risks pertaining to cleaning, sterilisation and packaging processes

Risks	***%***	***Level***	***Possible ways to mitigate***
Sterilisation process not effective enough	50	3	Develop outsourced validation protocol with supplier
Sterilisation process not repeatable	50	3	Develop outsourced validation protocol with supplier

The most important risks were identified in this section. This must be seen as identifying a baseline of risks pertaining to the SLM process. Possible ways to mitigate these risks were also identified in the above-mentioned tables and will be further discussed in chapter 4. In order to group these risks, it was decided to develop Table 3.26 and plot the risks against possible procedure, SOP, document and validation developments. It can be said that some of these risks require a procedure, SOP and validation to fully mitigate them.

Table 3.26: Risk plot

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES										DEVELOP DOCUMENTS						VALIDATION								
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	PROCEDURES SUB TOTAL	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	SOP SUB TOTAL	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	DOCUMENTS SUB TOTAL	MACHINES			PROCESSES					VALIDATION SUB TOTAL
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
DESIGN	INT	Flipped import slice data						1	1										0						0									0
		Slice data to STL conversion						2	2										0						0				2					2
		Over- or underdesign	2						2										0		2				2									0
		Design not suited for AM							0										0				2		2									0
	EXT	Wrong patient information							0										0		1				1									0
		Bad quality scan data							0										0	2					2									0
		Incorrect doctor's input requirements							0										0		3				3									0
DESIGN SUB TOTAL			2	0	0	0	0	3		0	0	0	0	0	0	0	0	0		2	6	0	2	0		0	0	0	2	0	0	0	0	

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES									DEVELOP DOCUMENTS						VALIDATION							
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	**PROCEDURES SUB TOTAL**	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	**SOP SUB TOTAL**	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	**DOCUMENTS SUB TOTAL**	MACHINES			PROCESSES					**VALIDATION SUB TOTAL**
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
MACHINE SETUP	INT	Improper in-house machine calibration and maintenance		1					1	1	1								2						0		2							2
		Incorrect substrate tolerances							0	2									2						0									0
		Incorrect platform alignment							0	2									2						0									0
		Uneven recoating: Powder flow ability?							0			1							1						0									0
		Uneven recoating: Operator powder contamination							0			2							2						0									0

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES									DEVELOP DOCUMENTS						VALIDATION								
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	**PROCEDURES SUB TOTAL**	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	**SOP SUB TOTAL**	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	**DOCUMENTS SUB TOTAL**	MACHINES			PROCESSES					**VALIDATION SUB TOTAL**
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
	EXT	Insufficient machine performance at installation							0										0						0	1								1
	EXT	Insufficient machine calibration and maintenance		2					2		2								2						0		2							2
	EXT	Inadequate operator training							0	1	1	1	1	1					5						0		1							1
	EXT	Inconsistent machine performance							0	2									2						0			2						2
	EXT	Inconsistent z-axes control		1					1										0						0									0
MACHINE SETUP SUB TOTAL			0	4	0	0	0	0		8	4	4	1	1	0	0	0	0		0	0	0	0	0		1	5	2	0	0	0	0	0	

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES									DEVELOP DOCUMENTS						VALIDATION								
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	PROCEDURES SUB TOTAL	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	SOP SUB TOTAL	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	DOCUMENTS SUB TOTAL	MACHINES			PROCESSES					VALIDATION SUB TOTAL
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
POWDER HANDLING	INT	Powder mixing and sifting							0			2							2						0									0
		Powder storage							0			2							2						0									0
		Powder exposed to O_2 at elevated temperatures							0			2							2						0									0
	EXT	Certificate of analysis with powder delivery			1				1										0						0									0
		Conduct local chemical analysis with powder delivery			2				2										0						0									0
		Powder aging							0			3							3						0									0
POWDER HANDLING SUB TOTAL			0	0	3	0	0	0		0	0	9	0	0	0	0	0	0		0	0	0	0	0		0	0	0	0	0	0	0	0	

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES									DEVELOP DOCUMENTS						VALIDATION							
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	PROCEDURES SUB TOTAL	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	SOP SUB TOTAL	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	DOCUMENTS SUB TOTAL	MACHINES			PROCESSES				VALIDATION SUB TOTAL
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
SLM PROCESS	INT	Incorrect slice file							0				1						1						0									0
		First exposure not penetrating into substrate							0	1									1						0									0
		Incorrect recoating							0	2									2						0									0
		Part coming loose from substrate							0	2									2						0									0
		Insufficient argon supply							0	1									1						0									0
		Air circulation filters clog during build							0	1									1						0									0

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES									DEVELOP DOCUMENTS						VALIDATION								
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	**PROCEDURES SUB TOTAL**	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	**SOP SUB TOTAL**	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	**DOCUMENTS SUB TOTAL**	MACHINES		PROCESSES					**VALIDATION SUB TOTAL**
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
		Incorrect laser power with pre-check							0	1									1						0									0
	EXT	Inconsistent mechanical properties of parts							0										0						0	3		3						6
	EXT	Process not repeatable over time (accuracy)							0										0						0			2						2
	EXT	Incomplete process monitoring logs		1					1										0						0									0
SLM PROCESS SUB TOTAL			0	1	0	0	0	0		8	0	0	1	0	0	0	0	0		0	0	0	0	0		3	0	5	0	0	0	0	0	

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES									DEVELOP DOCUMENTS						VALIDATION								
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	PROCEDURES SUB TOTAL	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	SOP SUB TOTAL	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	DOCUMENTS SUB TOTAL	MACHINES			PROCESSES					VALIDATION SUB TOTAL
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
PART REMOVAL	INT	Part surfaces/ features are damaged during removal							0					2					2						0									0
		Not all powder around/inside part is removed							0					2					2						0									0
		Inaccurate stress-relieving cycle							0						1				1						0					1				1
		Incorrect powder handling							0	1		1							2						0									0
	EXT	Incorrect furnace cycle outputs							0										0						0					1				1

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES									DEVELOP DOCUMENTS						VALIDATION							
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	PROCEDURES SUB TOTAL	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	SOP SUB TOTAL	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	DOCUMENTS SUB TOTAL	MACHINES			PROCESSES				VALIDATION SUB TOTAL
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
		Residual stress deforms final part							0										0						0					2				2
		Part is cut from platform incorrectly							0					2					2						0									0
PART REMOVAL SUB TOTAL			0	0	0	0	0	0		1	0	1	0	6	1	0	0	0		0	0	0	0	0		0	0	0	0	4	0	0	0	
DENSITY CHECK	INT	Density checks not accurate enough							0										0						0						2			2
	INT	Process not repeatable							0										0						0						3			3
	EXT	Internal density results cannot be verified externally							0										0						0							4		4
DENSITY CHECK SUB TOTAL			0	0	0	0	0	0		0	0	0	0	0	0	0	0	0		0	0	0	0	0		0	0	0	0	0	5	4	0	

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES									DEVELOP DOCUMENTS						VALIDATION								
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	PROCEDURES SUB TOTAL	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	SOP SUB TOTAL	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	DOCUMENTS SUB TOTAL	MACHINES	PROCESSES						VALIDATION SUB TOTAL
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
HEAT TREATMENT	INT	Heat treatment cycle not correct for medical implants							0						1				1						0					1				1
	INT	Process not repeatable							0										0						0					2				2
	INT	Parts oxidise through cycle							0						1				1						0					2				2
	INT	Inadequate operator training							0										0						0		1							1
	EXT	Furnace output inconsistent							0										0						0	4		4						8
	EXT	Incomplete furnace cycle logs		1					1										0						0									0
HEAT TREATMENT SUB TOTAL			0	1	0	0	0	0		0	0	0	0	0	2	0	0	0		0	0	0	0	0		4	1	4	0	5	0	0	0	

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES									DEVELOP DOCUMENTS						VALIDATION								
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	PROCEDURES SUB TOTAL	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	SOP SUB TOTAL	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	DOCUMENTS SUB TOTAL	MACHINES			PROCESSES					VALIDATION SUB TOTAL
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
NON-DESTRUCTIVE TESTING	INT	NDT methods not accurate enough							0										0						0							2		2
	INT	Process not repeatable							0										0						0							3		3
	EXT	NDT reports not capturing correct information							0										0					2	2									0
	EXT	NDT facility not available for urgent cases			4				4										0					4	4									0
NON-DESTRUCTIVE TESTING SUB TOTAL			0	0	4	0	0	0		0	0	0	0	0	0	0	0	0		0	0	0	0	6		0	0	0	0	0	0	5	0	

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES									DEVELOP DOCUMENTS						VALIDATION							
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	PROCEDURES SUB TOTAL	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	SOP SUB TOTAL	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	DOCUMENTS SUB TOTAL	MACHINES	PROCESSES					VALIDATION SUB TOTAL
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
DESTRUCTIVE TESTING	INT	Machining of samples for DT not consistent							0							2			2					3	3									0
	INT	Internal DT testing not repeatable							0										0						0			2						2
	INT	Inadequate operator training							0							1			1						0		1							1
	INT	Outdated calibration		1					1										0						0			1						1
	EXT	Inconsistent external DT results							0							2			2					2	2									0
	EXT	DT facility not available for urgent cases			3				3										0					3	3									0
DESTRUCTIVE TESTING SUB TOTAL			0	1	3	0	0	0		0	0	0	0	0	0	5	0	0		0	0	0	0	8		0	1	3	0	0	0	0	0	

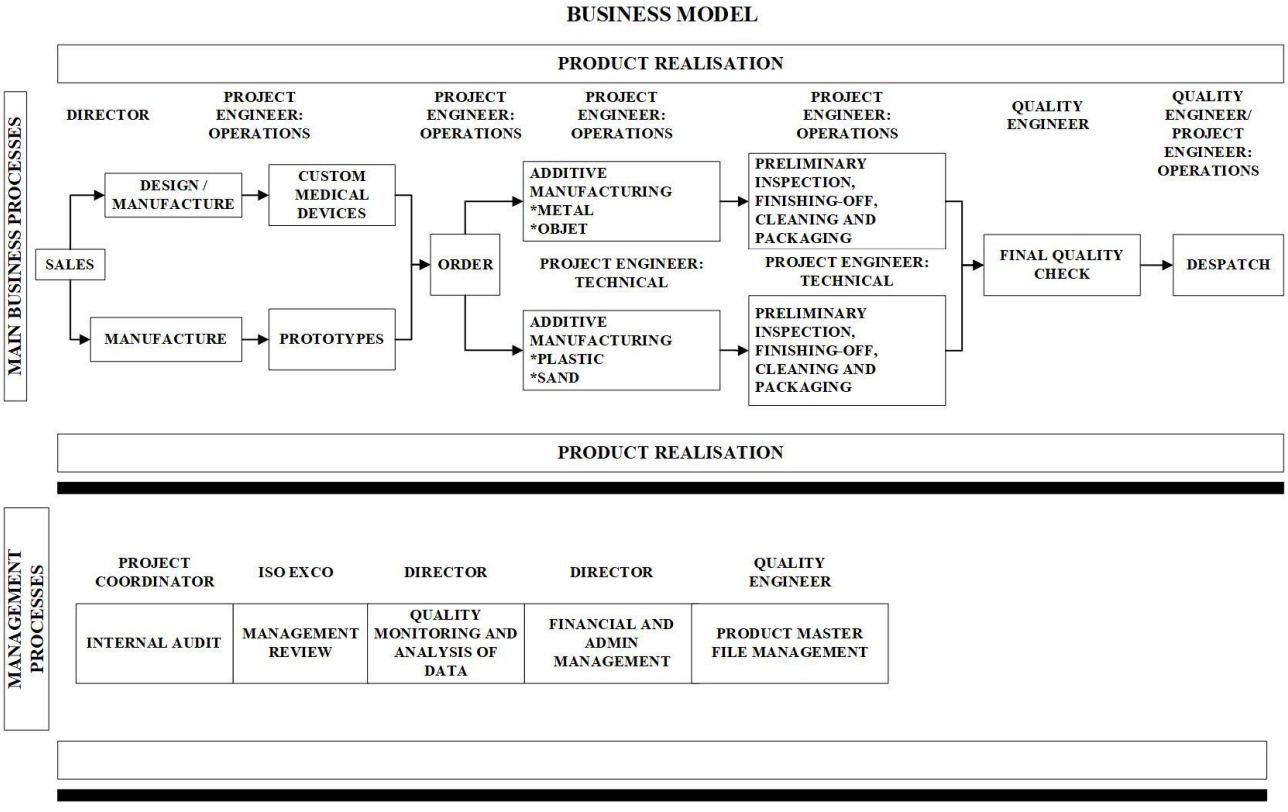
PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES										DEVELOP DOCUMENTS						VALIDATION									
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	PROCEDURES SUB TOTAL	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	SOP SUB TOTAL	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	DOCUMENTS SUB TOTAL	MACHINES			PROCESSES					VALIDATION SUB TOTAL
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
SURFACE FINISHING AND COATING	INT	Surface finishing quality not acceptable							0								2		2						0							2		2
		Surface contamination							0										0			1			1							1		1
		Surface finish process not repeatable							0										0						0							2		2
		Effects that heat generated with finishing process have on part morphology							0								1		1						0							1		1
	EXT	Coating process not repeatable							0								2		2						0							3		3
		Coating process not biocompatible					2		2										0					2	2							2		2
SURFACE FINISHING AND COATING SUB			0	0	0	0	2	0		0	0	0	0	0	0	0	5	0		0	0	1	0	2		0	0	0	0	0	0	11	0	

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES										DEVELOP DOCUMENTS						VALIDATION								
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	PROCEDURES SUB TOTAL	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	SOP SUB TOTAL	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	DOCUMENTS SUB TOTAL	MACHINES			PROCESSES					VALIDATION SUB TOTAL
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			2	7	10	2	8	3	32	17	4	14	2	7	3	5	5	2	59	2	6	11	2	16	37	8	7	17	2	9	5	26	1	75
TOTAL																																		
STERILISATION AND PACKAGING	INT	In-house cleaning process not satisfactory							0									2	2			2			2			2						2
		Instructions for Use not clear enough and not received by theatre staff				2			2										0			2			2									0
		Ineffective packaging							0										0						0			1					1	2
	EXT	Sterilisation process not effective enough					3		3										0			3			3							3		3
		Sterilisation process not repeatable					3		3										0			3			3							3		3

PROCESS	RISK	DESCRIPTION	PROCEDURES							STANDARD OPERATING PROCEDURES									DEVELOP DOCUMENTS						VALIDATION							
	EXTERNAL = EXT; INTERNAL = INT		DESIGN REVIEW	MAINTENANCE AND CALIBRATION	PURCHASING	IDENTIFICATION	CLINICAL EVALUATIONS	DESIGN	PROCEDURES SUB TOTAL	MACHINE SETUP	MAINTENANCE AND CALIBRATION	POWDER HANDLING	SLM PROCESS	PART REMOVAL	HEAT TREATMENT	DESTRUCTIVE TESTING	SURFACE FINISHING & COATING	IMPLANT CLEANING AND HANDLING	SOP SUB TOTAL	CT SCAN PROTOCOL	MEDICAL DEVICE FILE_PATIENT FILE	INSTRUCTION FOR USE	DESIGN RULES	SERVICE LEVEL AGREEMENTS	DOCUMENTS SUB TOTAL	MACHINES			PROCESSES				VALIDATION SUB TOTAL
																										IQ	OQ	PQ	SOFTWARE	HEAT TREATMENT	DENSITY	OUTSOURCED	PACKAGING	
SUM OF ROWS			**2**	**7**	**10**	**2**	**8**	**3**	**32**	**17**	**4**	**14**	**2**	**7**	**3**	**5**	**5**	**2**	**59**	**2**	**6**	**11**	**2**	**16**	**37**	**8**	**7**	**17**	**2**	**9**	**5**	**26**	**1**	**75**
CLEANING, STERILISATION AND PACKAGING SUB TOTAL			0	0	0	2	6	0		0	0	0	0	0	0	0	0	2		0	0	10	0	0		0	0	3	0	0	0	6	1	

A total of 68 risks were identified with 41 being classified as internal risks and 27 as external risks. The action plan to mitigate these risks will be to develop procedures, SOPs, supportive documents and where needed, full machine and process validation. The yellow-highlighted procedures, SOPs, supportive documents and validation protocols will be discussed in point 3.5.

Human resource has a significant weight and effect on the realisation of the medical devices and meeting customer and regulatory requirements. Adequate resources necessary for the risk management activities must be allocated and ISO 13485 presents a method to analyse, plan and determine the human resources. The AM company must ensure that personnel performing work that affects the quality and conformity of the product are competent and have acquired the adequate skills. Furthermore, it is essential to map out the Business Management System (BMS) linking the personnel to specific business processes. The model is divided into the main business-, management- and support business processes, as shown in Figure 3.4.



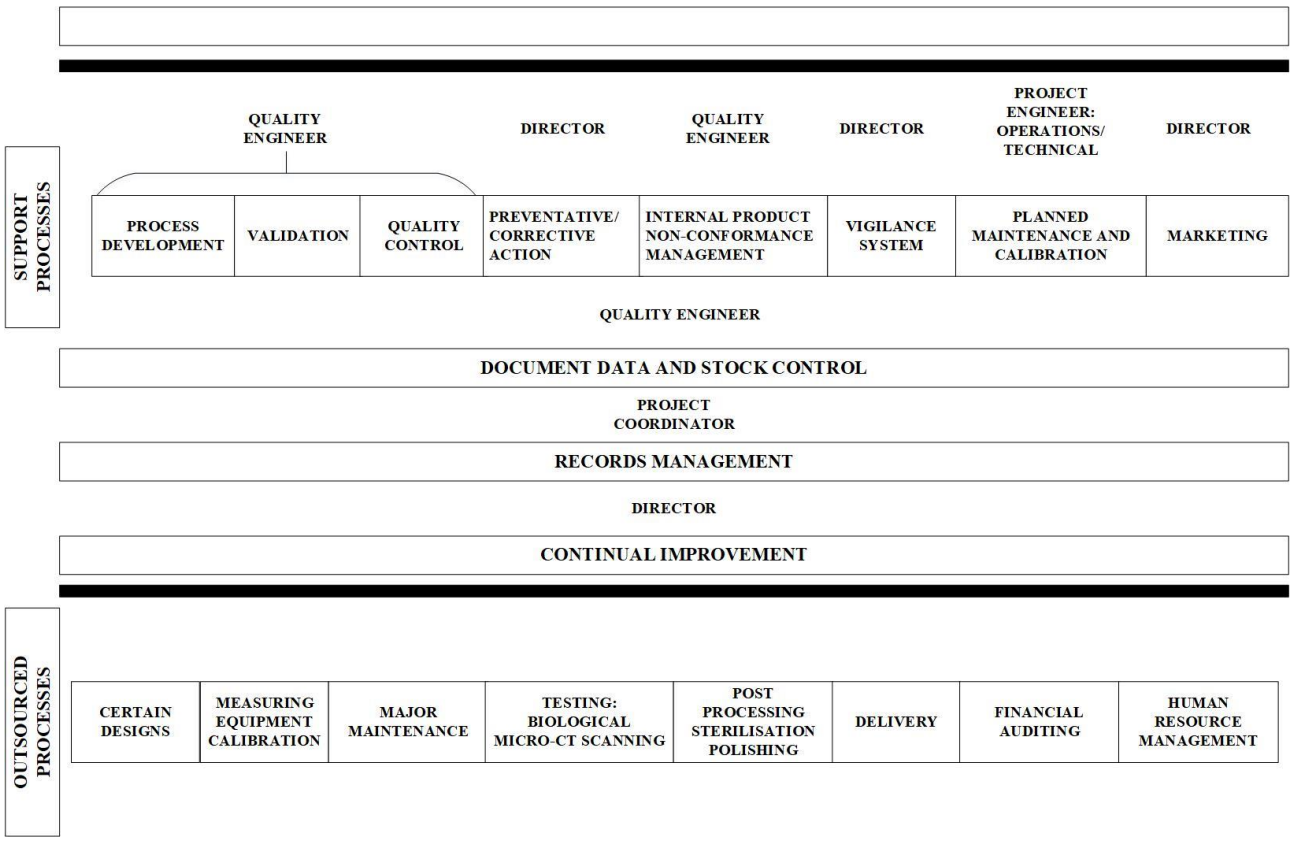


Figure 3.4: The key business model processes flow diagram (CRPM ISO 13485: 2016 Quality Management System)

The flow diagram details the person responsible for each process in the manufacturing of a product. However, not all the processes are carried out by the AM company – some are outsourced to other companies, as shown in Figure 3.3. Outsourced processes that affect product conformity with the requirements must be monitored to ensure control over these processes. It is important to note that the AM company retains responsibility of conformity to ISO 13485, the South African Medical Device Regulations, to customers and applicable regulatory requirements for outsourced processes. The controls are proportionate to the risk involved and the ability of the external party to meet the purchasing and supply requirements. Supplier Agreements and/or Service Level Agreements are established with all critical outsourced suppliers and subcontractors.

The AM company currently outsources certain designs (overflow work), calibration, major maintenance, biological testing, micro-CT scanning, post processing, sterilisation, polishing, delivery, financial auditing and human resource management.

Policies, Procedure, SOPs, Protocols as part of Objective 2

A Business Management System is structured in three tiers, as show in Figure 3.5. Each tier conforms to a particular aspect of the ISO 13485 standard. The first tier encompasses the AM company Business Plan and all statutory and regulatory documentation to which the company must comply.

Tier Two sets out the various processes and procedures put in place to effectively manage all aspects of the AM company's business. From the processes and procedures in place in Tier Two, all the SOPs, protocols, instructions and work sheets used in the AM company are generated in Tier Three. Forms are created to enable effective management of the processes and procedures. From the forms, records are created which provide the means to validate and verify the effective management of ISO 13485.

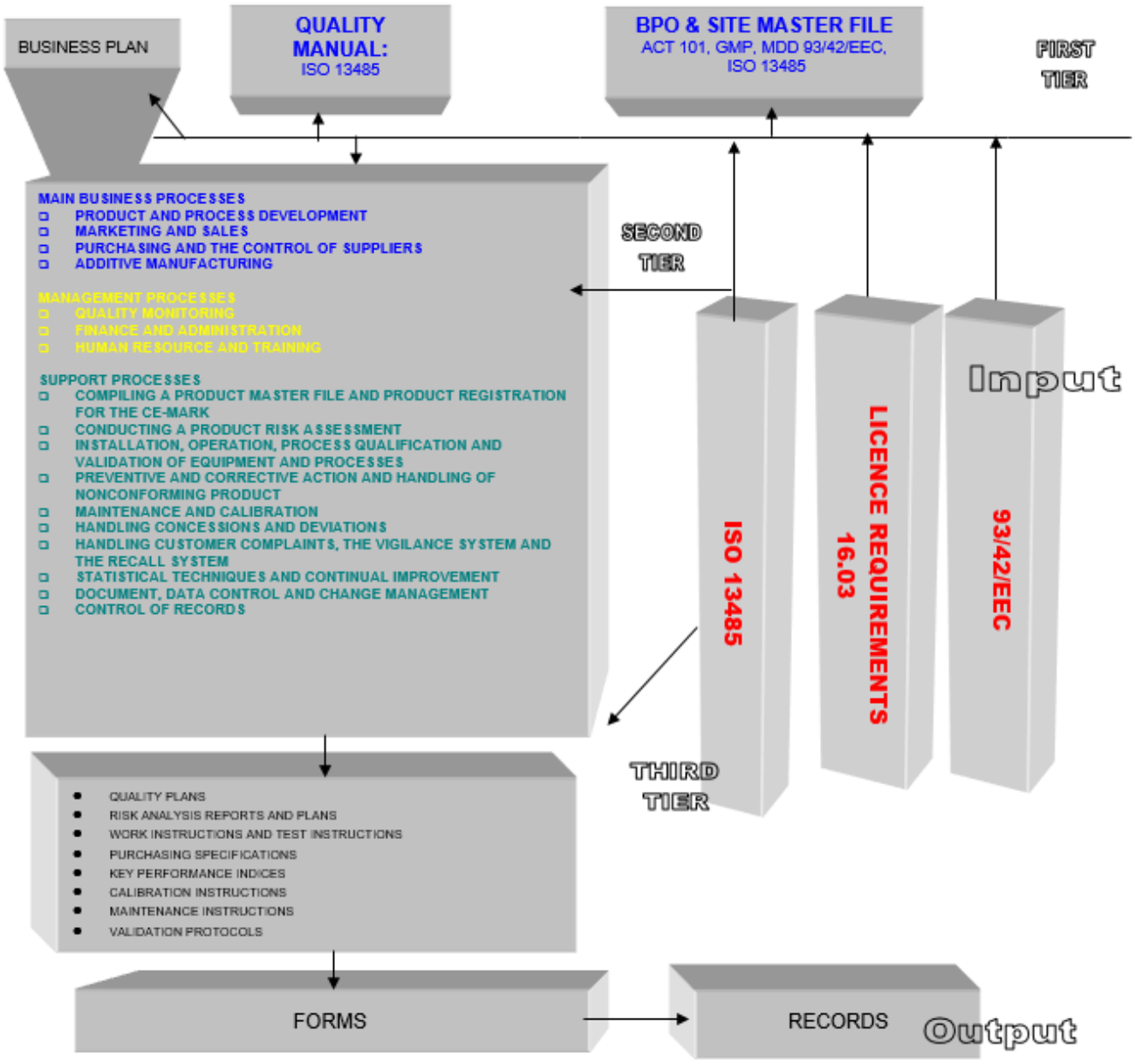


Figure 3.5: The outline structure of the Quality Manual (CRPM ISO 13485: 2016 Quality Management System)

As stated above, policies and procedures are put in place to effectively manage the AM company's business.

3.5 Policies and Procedures

A full list of policies and procedures linked to AM can be seen in Table 3.27.

Table 3.27: Index of Policies and Procedures needed for AM process (CRPM ISO 13485: 2016 Quality Management System)

Policies and Procedures								
No.	Description	Doc. No.	Flow Diagram	No.	Effective date	Review date	Next review date	Rev
1.	Business Process Overview, Site Master File and Quality Manual	**X-01**	Business Model See Appendix 1 for more information	**F1**	X	X	X	X
Main business processes								
2.	Procedure for Product and Process Development	**X-03**	Product development new design Process development Implant design pre-operative models and cutting guides	**F1** **F2** **F3** **F4**	X	X	X	X
3.	Procedure for Marketing and Sales	**X-04**	Customer Sign-up Marketing and Sales	**F1** **F2**	X	X	X	X
4.	Procedure for Purchasing and the Control of Suppliers Purchasing specifications	**X-05**	Purchasing Supplier and Subcontractor Selection	**F1** **F2**	X	X	X	X

5.	Procedure for AM AM manual	**X-06**	AM Prosthesis AM Prototypes	**F1** **F2**	X	X	X	X
Management processes								
6.	Procedure for Analysis of Data and Quality Monitoring	**X-07**	Internal Audits	**F1**	X	X	X	X
7.	Procedure for Human Resource Management and Training Human resource File	**X-08**	Functional Organisation Structure	**F1**	X	X	X	X
8.	Procedure for Financial and Administration Management	**X-09**	Debtors Creditors Cashbook	**F1** **F2** **F3**	X	X	X	X
Support processes								
9.	Procedure for compiling a Technical File and Product Registration	**X-10**	Compiling a Product Master File and CE Mark	**F1**	X	X	X	X
10.	Procedure for Conducting a Product Risk Assessment	**X-11**	Risk Assessment	**F1**	X	X	X	X
11.	Procedure for Clinical Evaluations	**X-12**	Clinical Evaluation	**F1**	X	X	X	X

12.	Procedure for Installation, Operation, Process Qualification and Validation of Equipment and Processes Validation protocols	**X-13**	Validation Protocol	**F1**	X	X	X	X
13.	Procedure for Preventive and Corrective Action and Handling of Non-conforming Product	**X-14**	PCA Product Non-conformance	**F1** **F2**	X	X	X	X
14.	Procedure for Plant Maintenance and Calibration Maintenance Manual Calibration Manual	**X-15**	Monthly Calibration and Scaling Pre-job Maintenance	**F1** **F2**	X	X	X	X
15.	Procedure for Handling Concessions and Deviations	**X-16**	Concessions and Deviations	**F1**	X	X	X	X
16.	Procedure for Handling Customer Complaints, the Vigilance System and the Recall System	**X-17**	Customer Complaints Recall and Warning	**F1** **F2**	X	X	X	X

17.	Procedure for Statistical Techniques and Continual Improvement	**X-18**	Continual improvement	**F1**	X	X	X	X
18.	Procedure for Document, Data Control and Change Management	**X-19**	Change proposal	**F1**	X	X	X	X
19.	Procedure for the Control of Records Forms manual Records	**X-20**	Records		X	X	X	X

It is important to incorporate the following elements in a procedure:

- Approval: The approval process should identify the person who created the procedure, the person responsible for reviewing the document and finally the person responsible for approving the procedure/document. (ISO 13485, 2016)

- History: The changes made from the previous version of the procedure should be described. This is important to track when something new was implemented.

- Goals and objectives: The objectives and goals must be described in detail to give the reader a clear understanding of the purpose of the procedure.

- The scope of the procedure is also important to set out precisely where this procedure is applicable, i.e. identify different places, offices, or plants.

- Process Owner: The owner of the procedure must be identified so that the person responsible can be contacted should a query arise.

- KPI: A section on the KPI (Key Performance Indicator) can be incorporated to measure the effectiveness of the procedure.

- Definitions and Abbreviations: The terminology used in the procedure should be clarified in a section listing all definitions and abbreviations to remove any incorrect interpretations by readers unfamiliar with the procedure.

- Standards: Define the standards and version used in the procedure, such as ISO 13485:2016, ISO 14971, or any other technical standards that are referred to in the compilation of the procedure.

- Related documents: In the document structure, the procedure follows after the Quality Manual. However, there can be other documents referred to in the procedure. A procedure can relate to another procedure. Forms might be required to implement the procedure. It is, therefore, good practice to dedicate a section to listing all documents. Ensure that there is a link between the Quality Manual and all documents referred to in the procedure.

- Process description: The process to be followed can now be described, incorporating images, figures and flowcharts to assist the reader visually with the interpretation of the process.

3.5.1 Procedure for Additive Manufacturing

3.5.1.1 Purpose and scope

This document is used to direct and control all manufacturing activities, inspection and testing functions of the AM company.

The procedure is applicable to the Planning-, Manufacturing-, Inspection-, Packaging- and Sterilisation Functions of the AM company and the following documents were used as guidelines in establishing the procedure, as shown in Table 3.28.

Table 3.28: Guidelines in establishing the AM Procedure

1	Medical Device Regulation	EU 2017/745	2017
2	Quality System – Medical Devices – Particular requirements for the application of ISO 9001	ISO 13485	2016
3	Quality Management Systems – Requirements	ISO 9001	2015
4	European Council Directive concerning Medical Devices	93/42/EEC	2007

3.5.1.2 Procedure

The flow diagrams, as shown in figures 3.6 and 3.7, explain the process steps of the prosthesis and prototype manufacturing and is the first step in developing a procedure. The index of the AM Manual is shown in Table 3.29 and gives a broad overview of all SOPs needed for the AM company. These SOPs will form part of the OQ to be discussed in section 3.10.2.2.

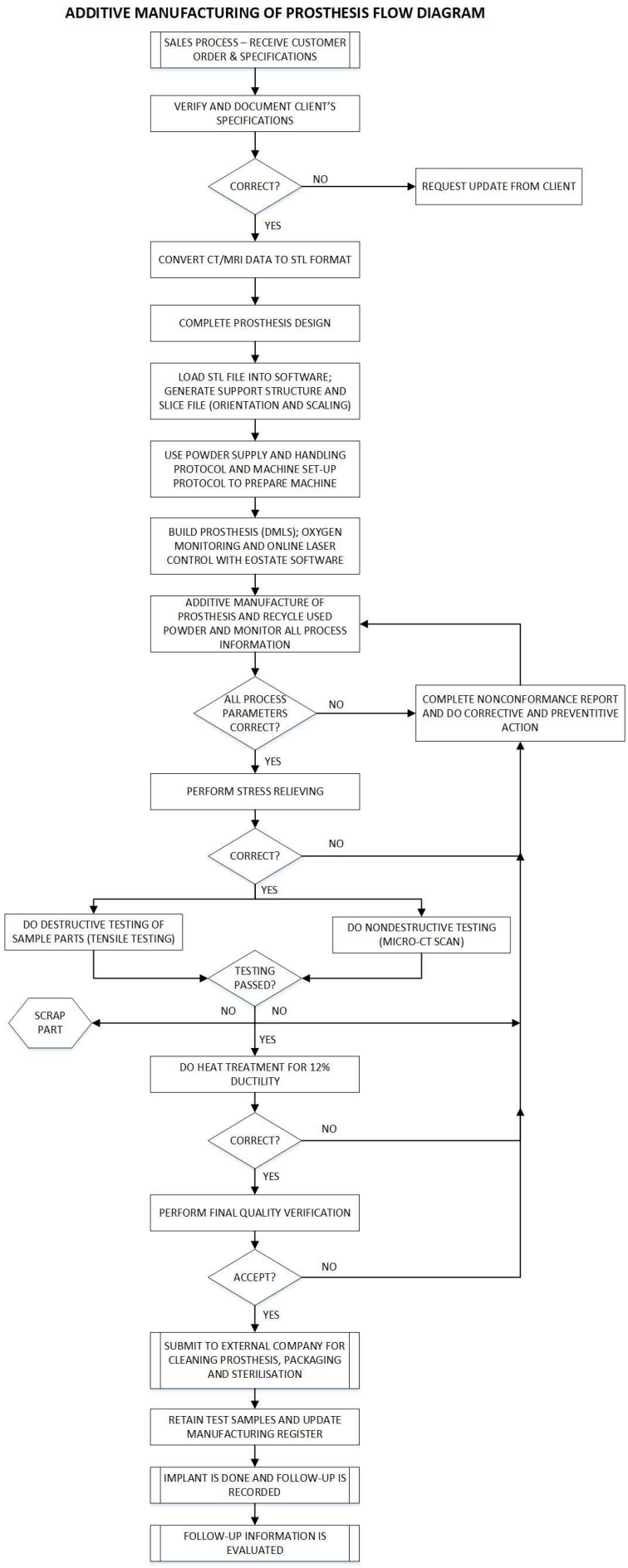


Figure 3.6: AM of Prosthesis Flow Diagram (CRPM ISO 13485: 2016 Quality Management System)

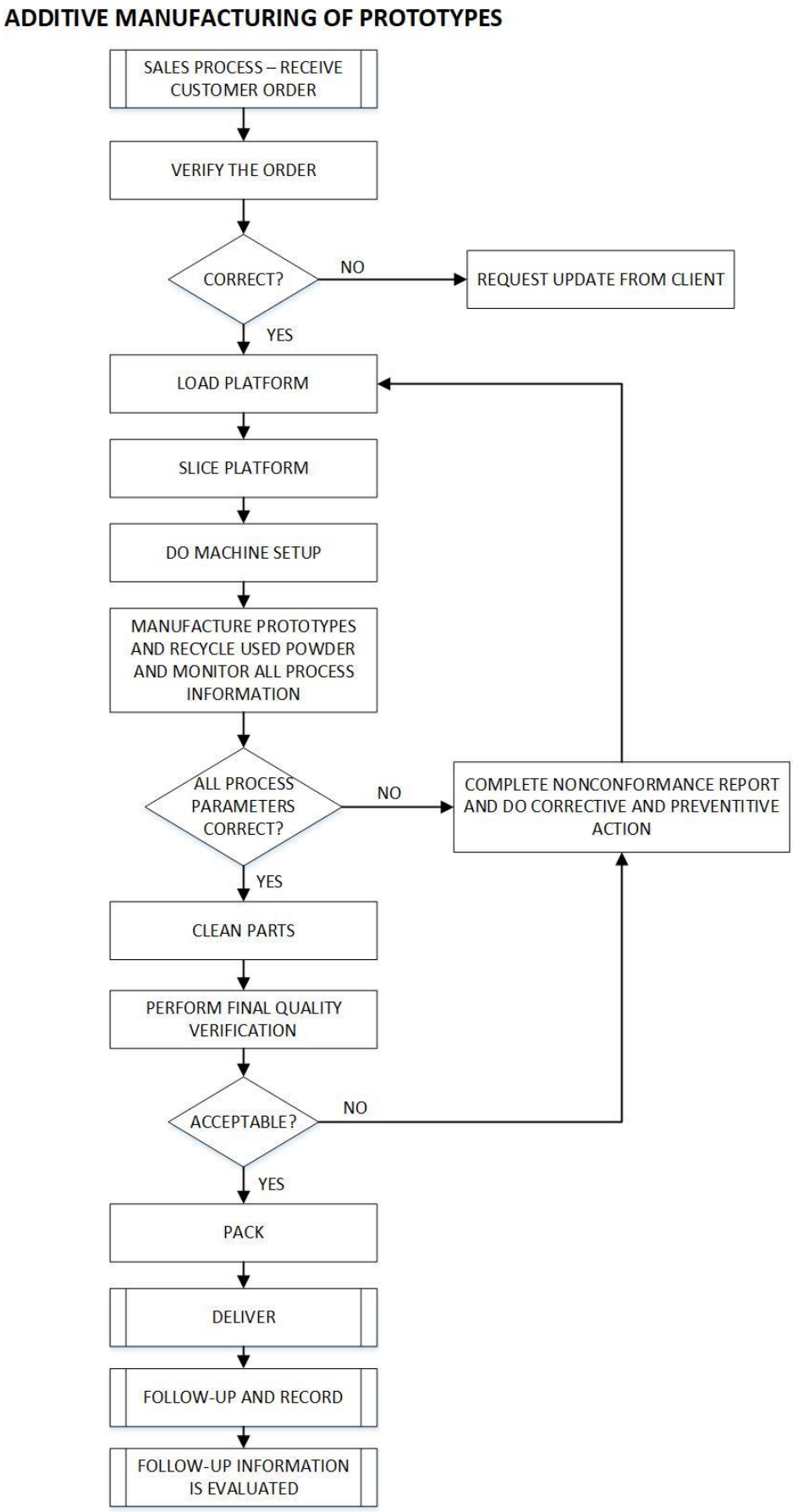


Figure 3.7: AM of Prototypes Flow Diagram (CRPM ISO 13485: 2016 Quality Management System)

Table 3.29: Index of AM Manual (CRPM ISO 13485: 2016 Quality Management System)

AM Manual Index

NO.	Description	DOC. NO.	REV
	General		
1.	General manufacturing area rules and regulations	WI-GEN-01	X
2.	Manufacturing area cleaning instruction	WI-GEN-02	X
3.	CCTV monitoring	WI-GEN-03	X
4.	Quoting & invoicing instruction	WI-AD-01	X
5.	Implant manufacturing process flow	WI-AD-02	X
6.	Guides and models manufacturing process flow	WI-AD-03	X
7.	Surface grinding	WI-MC-01	X
8.	Destructive testing	WI-DT-01	X
9.	Medical device heat sealing	WI-HS-01	X
	EOSINT Metal AM		
10.	Process overview	WI-PT-01	X
11.	Data preparation	WI-PT-02	X
12.	Implant design	WI-PT-03	X
13.	Equipment maintenance	WI-PT-04	X
14.	Material handling	WI-PT-05	X
15.	Machine setup	WI-PT-06	X
16.	Process monitoring	WI-PT-07	X
17.	Machine cleaning after process	WI-PT-08	X
18.	Part removal	WI-PT-09	X
19.	Support removal	WI-PT-10	X

AM Manual Index

NO.	Description	DOC. NO.	REV
20.	Thermal processing	WI-PT-11	X
21.	Part analysis	WI-PT-12	X
22.	Medical device cleaning	WI-PT-13	X
23.	Post manufacture handling	WI-PT-14	X
24.	Packaging & labelling	WI-PT-15	X
EOSINT Polymer AM			
25.	Process overview	WI-CM-01	X
26.	Work order verification	WI-CM-02	X
27.	Platform preparation	WI-CM-03	X
28.	Machine setup	WI-CM-04	X
29.	Manufacture prototypes	WI-CM-05	X
30.	Recycle powder	WI-CM-06	X
31.	Clean prototypes	WI-CM-07	X
32.	Final quality check	WI-CM-08	X
33.	Packing prototypes	WI-CM-09	X
34.	Equipment maintenance	WI-CM-10	X

3.5.1.3 Notes on identification and traceability

The traceability chain covers aspects from receiving raw material through to AM up to despatch. It is important to have full traceability from top to bottom of this value chain as shown in Figure 3.8.

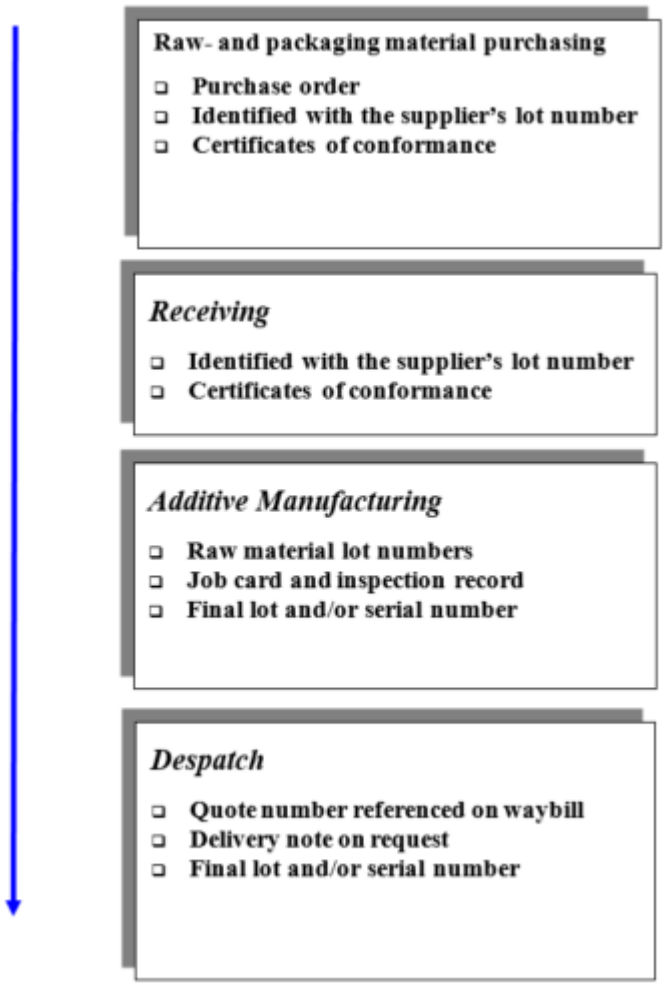


Figure 3.8: Traceability chain (CRPM ISO 13485: 2016 Quality Management System)

3.5.1.4 Notes on handling, storage, packaging, preservation and delivery

Where applicable, special instructions for handling, storage, identification, packaging and delivery are communicated by means of a job card. This job card accompanies the product throughout the manufacturing and inspection process. All handling is done in such a way as to protect the product, semi-finished items and finished items from being damaged or mixed up.

Storage

The principle of good housekeeping is followed at all storage facilities, which include:

- Safe storage heights
- Separation of different materials and products by means of identification
- Clean storage facility
- Rigid racking and bin facilities, and
- Identification of racks and bins
- Data logger to monitor temperature and humidity – data to be kept for 10 years.

Packaging and delivery

Attention must be paid to providing protection against mechanical deformation, ingress of foreign matter into packaging material, etc. Items must be delivered in such a way to not contaminate the outer packaging and to protect the cleanliness of the product.

Clinical feedback

After each operation, the Post-Op Review Document (as discussed in section 3.7 Patient File) with input from the surgeon must be reviewed. Any useful suggestions must be documented and SOPs influenced by new information must be updated. A register with comments and suggestions must be kept.

3.5.1.5 Additional notes on inspection and test status

The job card accompanies the manufactured products to indicate inspection and test status. Operation and inspection points are signed-off on the job cards. The Project Engineer: Operations allocates a unique serial number to patient-specific medical devices.

Example: CRPM-M-PG02-MTAK

CRPM	Manufacturer
M	Metal
P	Plastic
PG02	Job number
M	Patient initial
TAK	First 3 letters of patient's surname

Job number:

P	Years since establishment (1998)
G	Month
02	Number of job in month

3.5.1.6 Non-conforming Product

Any product which is found to be non-conforming or suspected of being so must be segregated and placed into a "**HOLD**" bin.

The details of product placed on "**HOLD**" must be recorded on the manufacturing documents and records and the Director informed. The second Inspector and Final Inspectors record all non-conformances on the Non-Conformance Log as shown in Table 3.30.

Table 3.30: Non-Conformance Log (CRPM ISO 13485: 2016 Quality Management System)

INTERNAL PRODUCT NON-CONFORMANCE LOG						
INITIATION DATE	**SN NO.**	**DESCRIPTION**	**REMEDIAL ACTION**	**PREVENTIVE ACTION**	**DAYS OUTSTANDING**	**COMPLETION DATE**

The Quality Engineer must inspect the non-conforming items and make a decision as to its disposition. The decision must be recorded on the Non-Conformance Log and job card. If the product is to be rejected, it is placed in a **SCRAP** BIN for disposal. If the product is to be returned for any reason, the product must be placed in a **SCRAP** BIN for disposal. Any "Rework" will be done in accordance with a written SOP.

3.5.1.7 Preventive maintenance

A Preventive Maintenance Plan for each major piece of equipment is defined and maintained. The Preventive Maintenance File will contain an index of all equipment that needs maintenance, as shown in Table 3.31.

Table 3.31: Maintenance Manual Index (CRPM ISO 13485: 2016 Quality Management System)

Maintenance Manual Index			
NO.	**Description**	**DOC. NO.**	**REV**
1.	Pre-job maintenance M280 – Ti64	X-15-06	X
2.	Weekly maintenance M280 – Ti64	X-15-07	X
3.	Monthly maintenance M280 – Ti64	X-15-08	X
4.	Pre-job maintenance P385	X-15-15	X
5.	Weekly maintenance P385	X-15-16	X
6.	Monthly maintenance P385	X-15-17	X
7.	Yearly/6-monthly maintenance P380 & P385	X-15-25	X

3.5.1.8 Cleanliness of the workshop

The workshop must be maintained and clean at all times in accordance with SOP for General Workshop Rules and Regulations.

3.5.1.9 Personnel

Personnel in contact with the manufacturing processes or its environment must be suitably attired, clean and in good health and be suitably trained. Access to production areas must be restricted to authorised personnel only.

The ISO Administrator must ensure up-to-date, accurate SOPs and procedures are available. Management must ensure manufacturing and quality control staff is adequately trained for the tasks required.

3.5.1.10 Customer property

The AM company will not divulge any customer information and intellectual property to a third party, unless consent has been given by the customers. A Non-Disclosure Agreement is signed with all employees and the applicable third party to maintain customer confidentiality.

Customer-issued designs are stored electronically under each patient's folder. Any patient data issued on a compact disc (CD) must be recorded on a Customer Property Register, as shown in Table 3.32 and returned to the patient's surgeon once the work has been completed.

Table 3.32: Customer Property Register

CUSTOMER PROPERTY REGISTER					YEAR		
INFO		RECEIVED			RETURNED		
NO.	PATIENT	RECEIVED BY	DATE	SIGNATURE	ACCEPTED BY	DATE	SIGNATURE
1							
2							
3							
4							
5							

3.6 Standard Operating Procedures or Work Instructions

Standard Operating Procedure is described by Wikipedia “as a set of step-by-step instructions compiled by an organisation to help workers carry out complex routine operations. SOPs aim to achieve efficiency, quality output and uniformity of performance, while reducing miscommunication and failure to comply with industry regulations”. (Standard operating procedure, 2018)

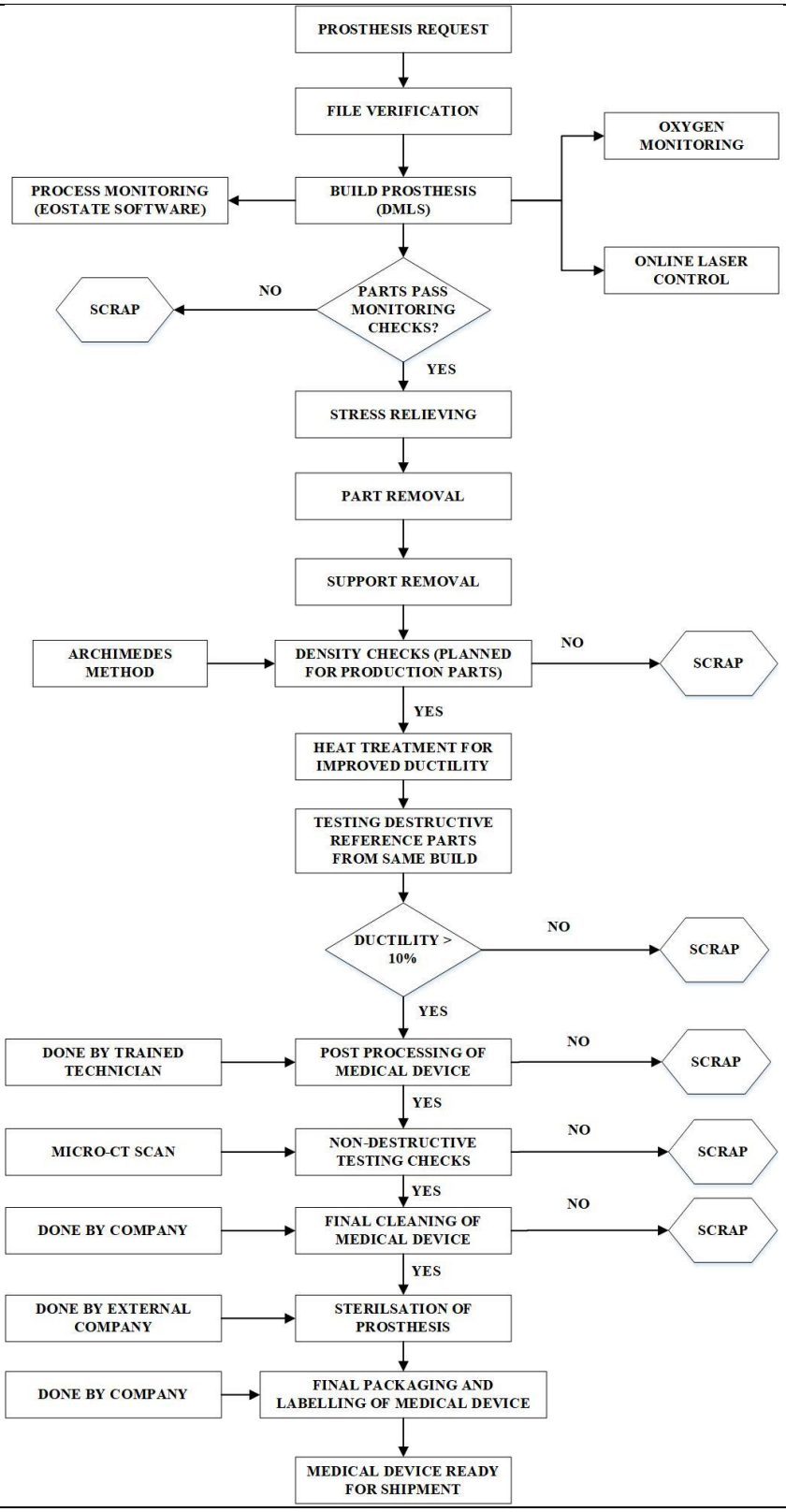
A full list of SOPs was shown in Table 3.29 in the Procedure for AM, where they were split into General, EOSINT Metal AM and EOSINT Plastic AM SOP categories. The Process Overview SOP will be discussed in detail, as it describes the implant manufacturing process in general. An SOP must have a title, flow diagram, line item, photo and description. The SOP can be linked to machine manufacturer’s operating manuals where applicable. Each SOP fits into the AM Manual and SOPs can link to one another.

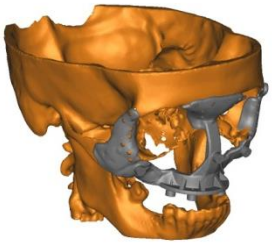
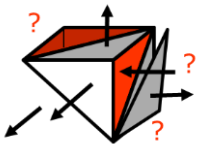
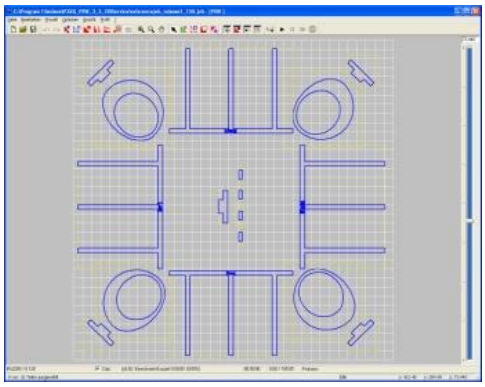
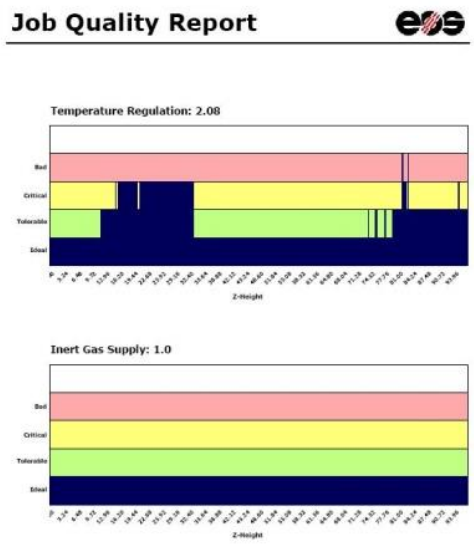
3.6.1 SOP for EOSINT Metal Process Overview

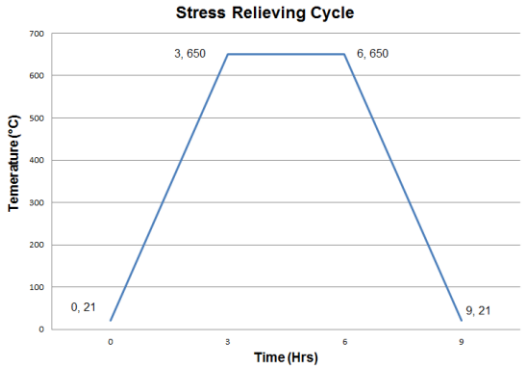
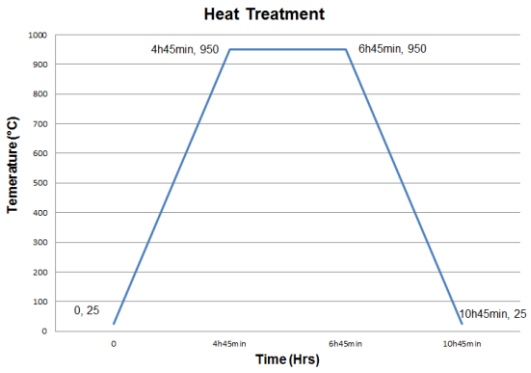
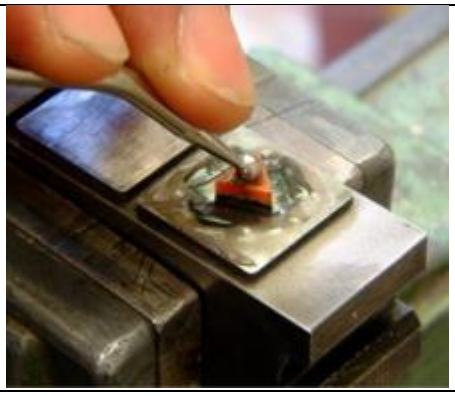
A proposed EOSINT Metal Process Overview was discussed in chapter 2 as part of the methodology. It is noteworthy to see the additions made from the proposed process overview to the final process overview, as seen in Table 3.33 (2018 version).

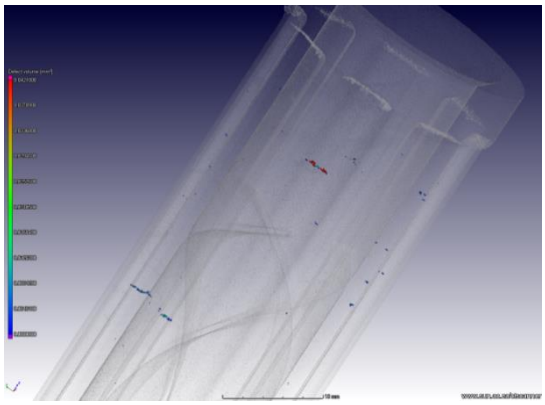
Table 3.33: SOP for EOSINT Metal AM Process Overview

SOP: EOSINT Metal AM Process Overview
WI-PT-01



No.	Photo	Instruction
1.	 	**File verification** The process starts with the implant design sent in STL file format to the AM company. The file quality is verified using Magics® software, including checking for missing or inverted surfaces and bad intersections between the triangulated mesh.
2.		**Build prosthesis** The design file is sliced using EOS RP Tools and sent as a slice file to the DMLS machine for fabrication.
3.		**Monitoring checks** Due to the layer-by-layer mechanics of the AM process, a process monitoring system is essential. Recording that each layer is fully melted to the previous layer will determine whether the part has good part quality/integrity. The process monitoring includes atmosphere and online laser control monitoring. The oxygen level inside the build chamber is controlled by purging argon into the chamber. The set value of the machine is 0.1% oxygen before the laser melting can commence. Furthermore, it is important to verify that enough/constant laser power is supplied to the laser melting surface. The online laser control will monitor this to ensure fully melted parts can be manufactured.
4.		**Stress relieving** After successfully manufacturing the medical device, it undergoes a stress-relieving heat cycle to alleviate the residual stress. The stress-relieving cycle starts off at room temperature. A vacuum or an argon-filled furnace must be used to minimise the chances of oxidation of the implant during

No.	Photo	Instruction
		heat treatment. The furnace is ramped up to 650 °C in 3 hours. Depending on the wall thickness of the part, the dwell time can be around 3 hours at 650 °C. The cooling rate is then set to 200 °C per hour. It is important that the heating up and cooling down rate is constant otherwise residual stresses can be re-introduced into the part.
5.		**Part and support removal** After stress relieving, the part is removed from the building platform by means of a wire Electrical Discharge Machine (EDM) or a band saw, after which the support material is also removed by hand.
6.		**Density checks** Density checks using the Archimedes technique is planned for high volume production parts.
7.		**Heat treatment** To improve the ductility on the DMLS Ti-6Al-4V specimens, beta annealing at 941 °C and cooling using a furnace should be used. Heating to 941 °C and cooling slowly will allow the alpha grains to grow bigger and the material to become softer. Heat treatment should be done at 941 °C; ramp up rate = 200 °C per hour, dwell time = 2 hours and then furnace cooled for 4 hours. This heat treatment cycle improves the percentage elongation to the required value.
8.		**Post processing of medical device** After heat treatment, the post processing of the medical device is done by a trained technician.

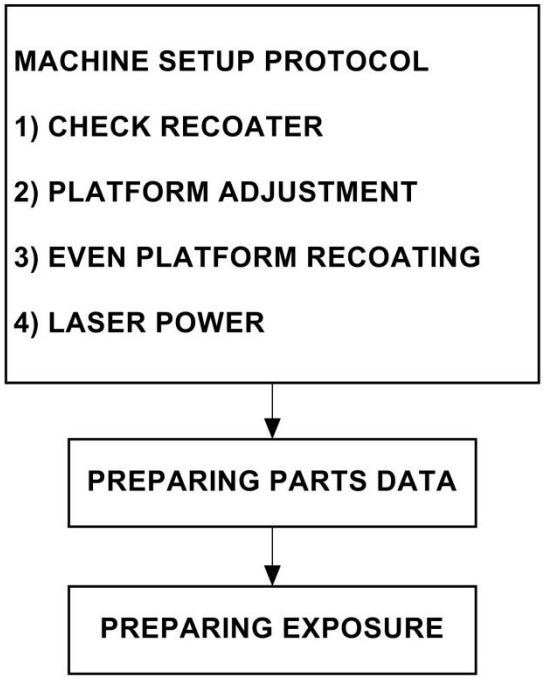
No.	Photo	Instruction
9.		**Non-destructive testing** Non-destructive testing can be performed by means of a micro computed tomography (micro-CT) scanner based at the Central Analytical Facilities, Stellenbosch University. Metal parts can be scanned at a resolution of 25 to 90 micron. The micro-CT scanner used is a General Electric Phoenix V|Tome|X L240 system at 160 kV and 100 uA, 500 ms per image, with 2000 images in one full rotation. Reconstruction is done with the system-supplied software, including beam-hardening correction. Due to the potential for improved image contrast, an improved scan with better resolution and contrast, and less beam-hardening artefacts can be performed at 25 microns. All analyses are done with Volume Graphics VGStudioMax 2.2 including the defect analysis module.
10.	 	**Final cleaning** Final cleaning involves the following: • Soaking in Endozime solution • Hand-scrubbing with brush • Rinsing with clean water • Ultrasonic bathing with Endozime • Rinsing with clean water
11.		**Biological deactivation** After cleaning, the medical device is double-packaged and placed in a box and sent to an external company for biological deactivation. The medical device is treated with gamma radiation before it is sent back to the AM company for final packaging, labelling and shipping. The device is now clean but **NON STERILE**.

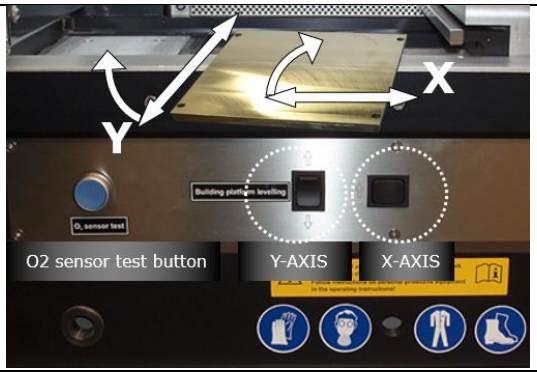
3.6.2 SOP for EOSINT Metal Machine Setup

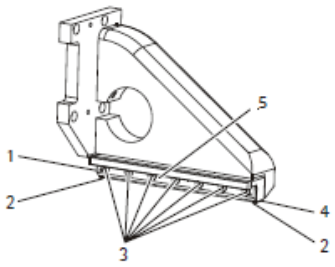
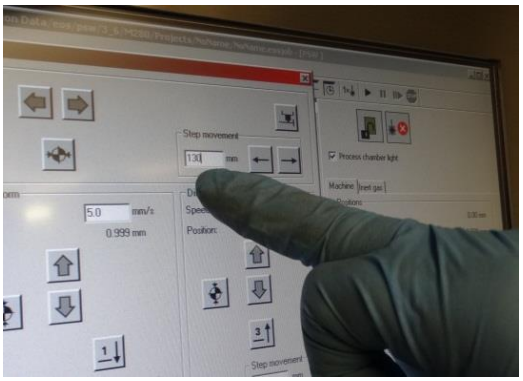
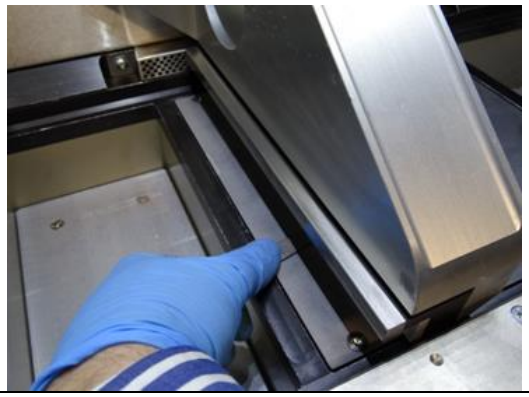
The SOP for EOSINT Metal Machine Setup, as shown in Table 3.34 explains the steps in successfully preparing the machine for the next build.

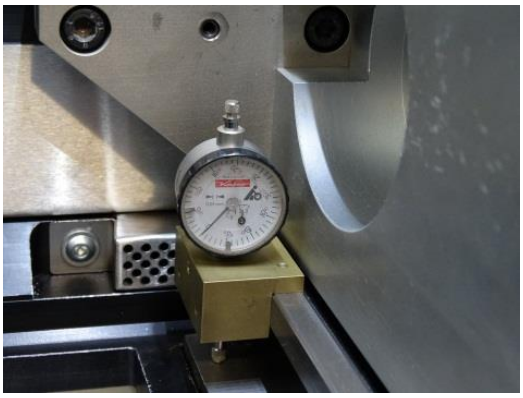
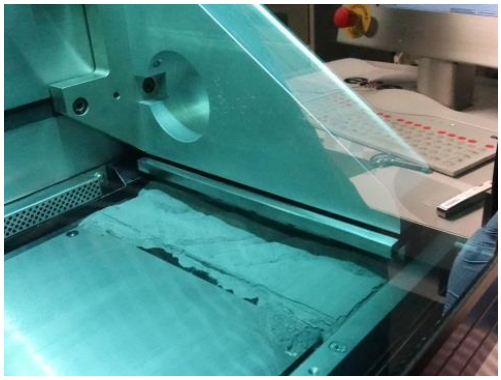
Table 3.34: SOP for EOSINT Metal Machine Setup

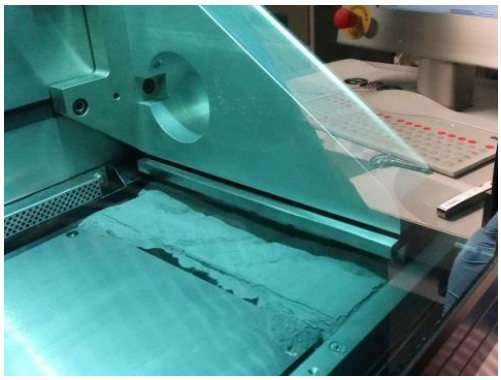
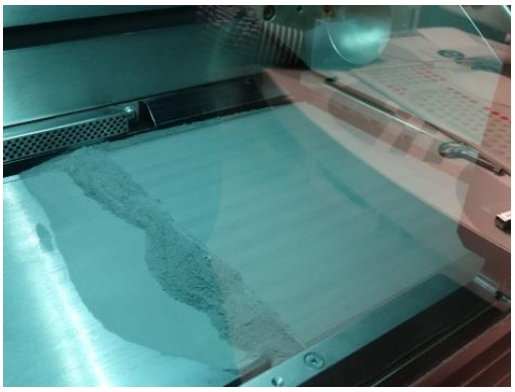
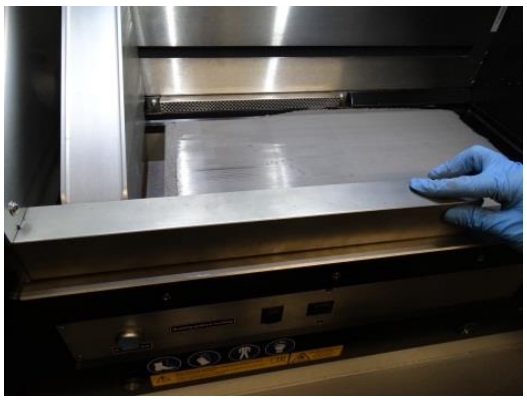
SOP: EOSINT Metal AM Machine Setup
WI-PT-06

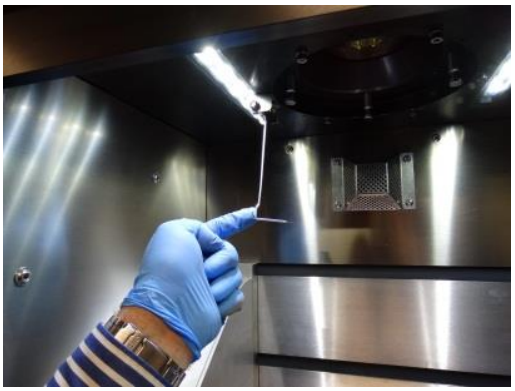
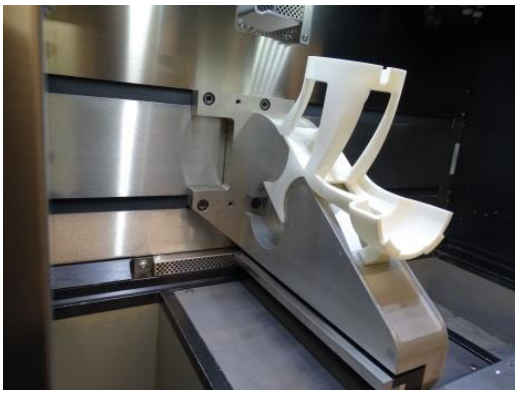


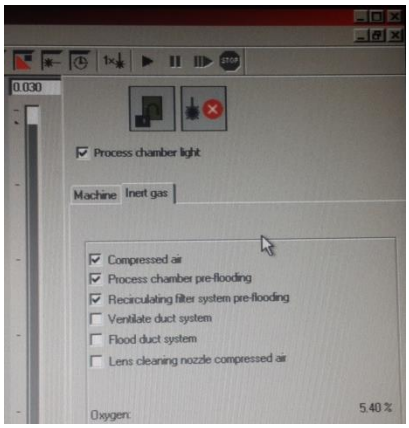
No.	Photo	Instruction
1.		**Machine setup protocol** Operation manual Setting up the machine p. 6.19

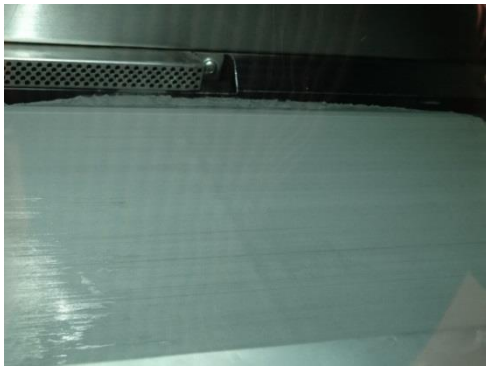
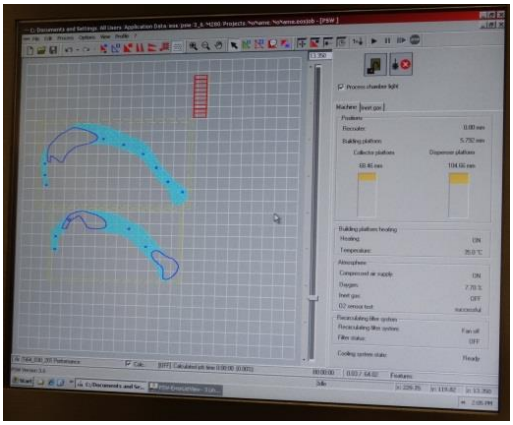
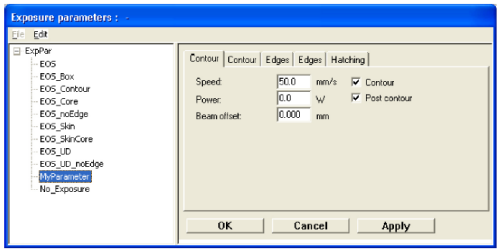
2.	 1 Recoater blade, rear end 2 Recoater blade mount 3 Fastening bolts 4 Recoater blade, front end 5 Clamping strip	**Check recoater blade** Check high-speed steel recoater blade for damage and replace if necessary. Gaps or irregularities in powder applied on base are one of the symptoms which require a blade change. Trouble shooting, maintenance & spare parts manual Section 4: Maintenance p. 4.10
3.1		**Platform adjustment** Operation manual Fitting building platform p. 6.24 Adjusting building platform p. 6.28 Remember to fasten the cap screws in a criss-cross fashion. Torque the cap screws to 15 Nm with the torque wrench.
3.2		**Home all axes**
3.3		Ensure that the heads of the building platform mounting cap screws do not protrude above the top surface of the platform, to prevent collision with recoater.
3.4		With recoater on left side, set the step movement of the recoater to 130 mm.
3.5		Move recoater to the right for the specified 130 mm. Measure the clearance between the recoater blade and platform using a 1 mm feeler gauge.

3.6		Move recoater to left. Increase height of building platform by 1 mm. Repeat above two steps until the tolerance is 1 mm at the back of the recoater. Move recoater to left. Increase height of building platform by 0.7 mm.
3.7		Place dial gauge on recoater arm and zero the measurement. Move gauge to the front of the recoater. Using the UP/DOWN button next to the SENSOR CHECK button, zero the recoater at the front. Move the gauge to check that the left side is within 0.05 mm tolerance.
3.8		Move gauge to middle of recoater arm. Move recoater to right side of building platform.
3.9		Zero the measurement using the LEFT/RIGHT switch next to SENSOR CHECK button.
3.10		Remove gauge and home the recoater. Move the building platform up by 0.3 mm. Move recoater across building platform to check interference. Recoater must be as close to the building platform as possible.

4.1		**Even powder distribution** Operation manual Setting up first layer p. 6.35
4.2		Move recoater to right side of building chamber. Raise the powder in the dispenser slightly higher than the level of the recoater blade. Move the blade from right to left across the powder volume to scrape the surface of the powder evenly. Excess powder is scraped across the building platform and deposited in the overflow bin.
4.3		Repeat until the surface of the powder in the dispenser is level
4.4		Replace duct in front of the building platform.

5.1		**Laser power (Wear eye protection)**
5.2		Check that online laser control arm is lowered.
5.3		Lower all platforms.
5.4		Move recoater to middle of building platform and attach laser powder meter holder.
5.5		Insert pocket laser monitor into holder.

5.6		Remove operating dongle from port X14 and insert service dongle into port X14 on switching cabinet to enable test to be performed.
5.7		Switch on pocket monitor and select “10 second” measurement. Close process chamber door. In PSW, go to Galvocon. Select “scanner test” tab and set laser power to 195 W and duration to 10 000 ms.
5.8		Ensure laser is switched off before opening the door to note the measurement displayed on the screen of the pocket monitor. Write down the value on the relevant job card.
5.9		Remove pocket monitor. Remove service dongle from port X14 and insert operating dongle. Close the process chamber door and switch on the “Flood duct system” in the adjust window.
5.10		When the oxygen concentration is 7%, move all platforms up and switch on “process chamber pre-flooding” and “recirculating filter system pre-flooding”

5.11		Move recoater from left to right and back to make sure powder is evenly distributed on platform one final time.
6.1		**Preparing parts data** Operation manual Preparing parts data p. 6.37 Setting material p. 6.38 Preparing job p. 6.42
6.2		Load slice files into job manager and ensure that there are no intersections between parts.
7.1		**Preparing exposure** Operation manual Preparing exposure p. 6.53 Assign exposure parameters to each slice file in the job manager. M280 Training-manual 04-12.pdf Data preparation Positioning part p7.12
7.2		Check recoater dosage settings to ensure adequate powder dispensing. Default values are : Min 100% Max 120% For small parts the recommended dosage is: • Min 90% • Max 100%

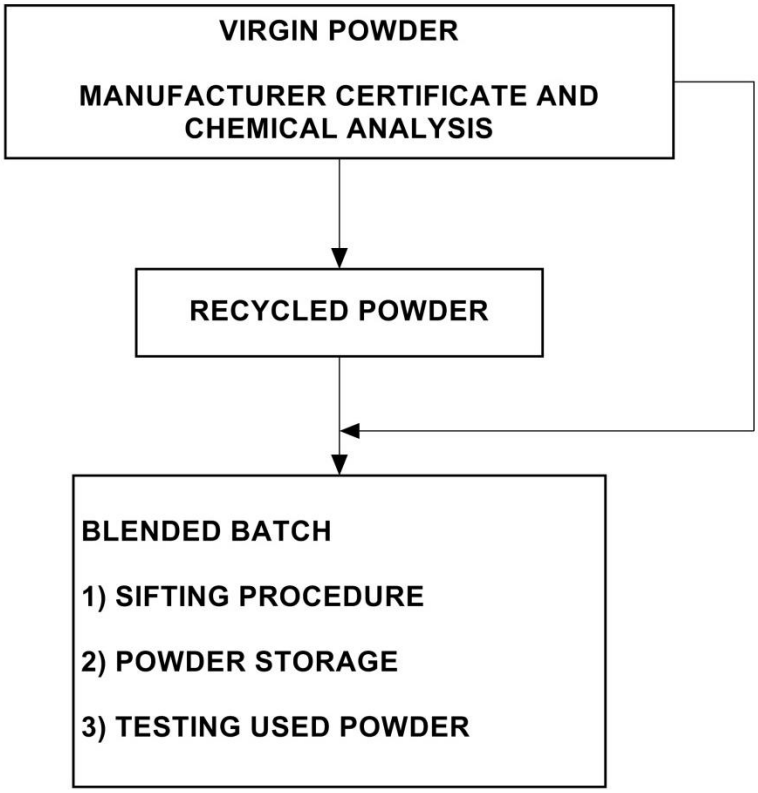
		For larger parts the recommended dosage is: • Min 140% • Max 160% The dosage can be increased or decreased during a job.
8.		**Recoater Jam** In the event of a Recoater Jam, the operator has two options: **Option 1:** Go to "Part parameter" tab and delete the part causing the problem. Do single exposure and continue the manufacturing process. **Option 2:** Write down the original z position. Move the building platform down by 1 mm and try to move the recoater from side to side while moving the building platform up in 0.1 mm steps. If the operator is able to reach the original z position, the operator will be able to do a single exposure and continue the manufacturing process. Any possible manufacturing defects during such an event will be evident during the micro-CT scan analysis. In the event that the whole job needs to be cancelled, the base must be removed from the machine and the scrap parts removed with a band saw. All scrap parts must be stored in the "Titanium – Scrap Parts" bin.

3.6.3 SOP for EOSINT Metal AM Material Handling

The SOP for EOSINT Metal Material Handling, as shown in Table 3.35, explains both virgin and recycled powder handling. The powder handling is important as no powder contamination is allowed and to replace a batch of powder is a costly exercise.

Table 3.35: SOP for EOSINT Metal AM Material Handling

SOP: EOSINT Metal AM Material Handling
WI-PT-05



No.	Photo	Instruction
1.		**Virgin powder** Check reports on chemical analysis certificate of batches of virgin powder from supplier as saved under records. Prior to loading additive manufacturing machine, the virgin powder must be dried in a normal oven at 80 °C for one hour in order to improve the flowability of the powder.
2.		**Recycled powder** Titanium powder that was not consolidated into parts during the laser sintering process can be reused. For the next build, the amount of powder required is determined and virgin powder is added to the dispenser volume, resulting in a blended batch.
3.		**Blended batch**
4.	 	**Sifting Procedure** M280 Training-manual 04-12.pdf Sieving the metal powder section 8.22 Sieving is done inside the DMLS machine: (see point under machine setup). Any powder remaining on the sieve must be removed and stored in the “Titanium – Scrap Powder” bin.

No.	Photo	Instruction
5.		**Powder storage** M280 Training-manual 04-12.pdf Storage of the metal powder section 5.5
6.		**Testing of used powder** A 100 gram sample of powder is sent to the CSIR annually to test the oxygen content of the powder. Powder with an oxygen content higher than 1300 ppm must be refreshed with virgin powder. Maximum oxygen content may not exceed 1500 ppm.

Supportive Document Development as Part of Objective 2

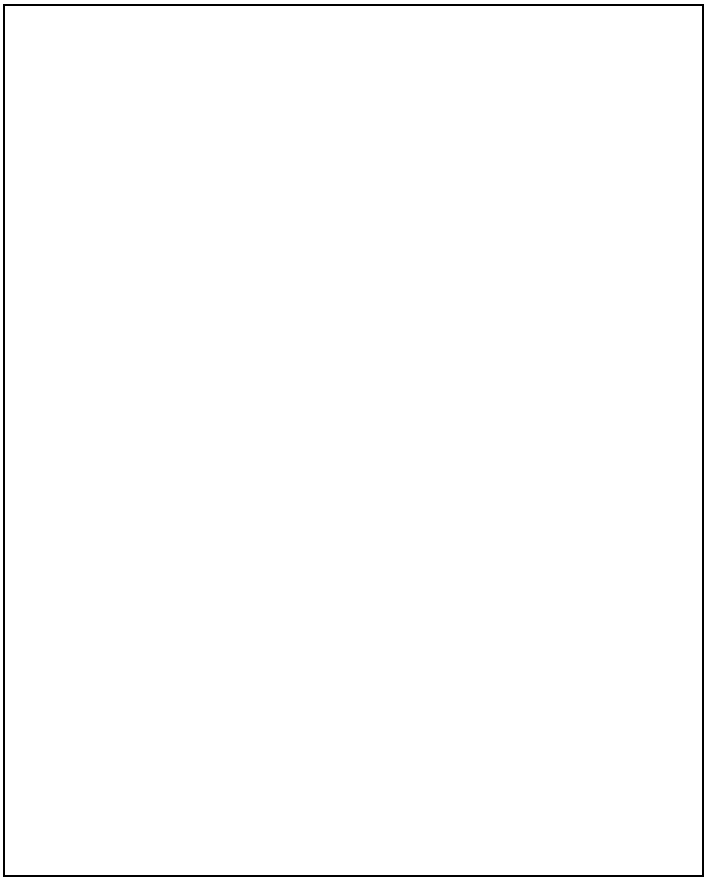
3.7 Patient File

The Patient File is seen as the medical device file mentioned in the ISO 13485 manual. It captures all necessary information such as the patient data, diagnosis and treatment plan but also risk management, design inputs, review questions and finally, the design review process. All relevant process monitoring, job card, heat treatment, tensile test, sterilisation, NDT reports and receipt of IFU are added as appendices. The following section shows the template that was developed over three years that must be treated as **confidential intellectual property (trade secrets)**.

PATIENT DATA

NAME & SURNAME			**ACTING PHYSICIAN**	
GENDER			**SURGEON**	
I.D. NUMBER			**HOSPITAL**	
CONTACT NUMBER			**CONSULTATION DATE**	
ADDRESS				
RSA CITIZEN	**Y/N**			
IF NO, WHICH COUNTRY				

PHOTO



DIAGNOSIS

	YES	**NO**
DOES THE PATIENT HAVE ANY OTHER UNDERLYING CONDITION?		
IF YES, HOW WILL IT INFLUENCE THE PROPOSED TREATMENT PLAN? PLEASE SPECIFY.		

TREATMENT PLAN

PROCEDURAL CHECKLIST

DESCRIPTION	CHECK
CT SCAN CONVERSION	
REVERSE ENGINEERING	
AM PREOPERATIVE MODEL	
AM IMPLANT	
AM SIZER	
CUTTING/DRILL GUIDE	
AURICULAR POSITIONING DEVICE	

RISK MANAGEMENT

DATE:

	YES	NO
DOES THE PRODUCT RISK ASSESSMENT NEED RE-EVALUATION?		
IF YES, WHICH RISK ASSESSMENTS?	**CHECK**	
RISK ASSESSMENT MEDICAL IMPLANT		
RISK ASSESSMENT PREOPERATIVE MODEL		
RISK ASSESSMENT SURGICAL JIGS AND FIXTURES		

DESIGN AND DEVELOPMENT INPUTS

ALL DESIGN AND DEVELOPMENT ACTIVITIES WILL BE IN ACCORDANCE WITH THE FOLLOWING STANDARDS/LITERATURE:

ISO 13485	ISO 14969	ISO 14971
ISO 15223-1	ASTM F 3122	SAE AMS2801B

REVIEW QUESTIONS

IS THE INPUT ADEQUATE TO PERFORM THE DESIGN AND DEVELOPMENT TASKS?
REPORT/COMMENT/ACTION:

ARE PRODUCT DESIGN AND PROCESSING CAPABILITIES COMPATIBLE?
REPORT/COMMENT/ACTION:
HAVE SAFETY CONSIDERATIONS BEEN ADDRESSED?
REPORT/COMMENT/ACTION:
HAVE APPROPRIATE MATERIALS BEEN SELECTED?
REPORT/COMMENT/ACTION:
HAVE APPROPRIATE MANUFACTURING PROCESSES BEEN SELECTED?
REPORT/COMMENT/ACTION:
IF COMPUTER SOFTWARE HAS BEEN USED IN DESIGN COMPUTATIONS, MODELLING OR ANALYSES, HAS THE SOFTWARE BEEN APPROPRIATELY VALIDATED, AUTHORISED, VERIFIED AND PLACED UNDER CONFIGURATION CONTROL?
REPORT/COMMENT/ACTION:
HAVE RISK MANAGEMENT ACTIVITIES BEEN CARRIED OUT AND, IF SO, ARE THEY ADEQUATE?
REPORT/COMMENT/ACTION:
ARE PLANS FOR IMPLEMENTING THE DESIGN TECHNICALLY FEASIBLE (E.G. PURCHASING, PRODUCTION, INSTALLATION, INSPECTION AND TESTING)?
REPORT/COMMENT/ACTION:

SCREEN CAPTURES / DRAWINGS

DATE:

Design input – hand sketches from surgeon on design/concept renderings

DESIGN REVIEW

DATE:

WILL THE DESIGN REASONABLY ACCOMPLISH THE MEDICAL USE INTENDED?
REPORT/COMMENT/ACTION:
DOES THE DESIGN MEET FUNCTIONAL AND OPERATIONAL REQUIREMENTS, FOR EXAMPLE, PERFORMANCE AND DEPENDABILITY OBJECTIVES?
REPORT/COMMENT/ACTION:
IS THERE ADEQUATE COMPATIBILITY OF MATERIALS, COMPONENTS AND/OR SERVICE ELEMENTS?
REPORT/COMMENT/ACTION:
IS THE DESIGN SATISFACTORY FOR ALL ANTICIPATED ENVIRONMENTAL AND LOAD CONDITIONS?
REPORT/COMMENT/ACTION:
HAVE RISK MANAGEMENT ACTIVITIES BEEN CARRIED OUT AND, IF SO, ARE THEY ADEQUATE?
REPORT/COMMENT/ACTION:
IS THE PACKAGING & LABELLING ADEQUATE?
REPORT/COMMENT/ACTION:
IS THE CLEANING PROCESS DEFINED AND ADEQUATE?
REPORT/COMMENT/ACTION:
HOW ARE CHANGES AND THEIR EFFECTS CONTROLLED DURING THE DESIGN AND DEVELOPMENT PROCESS?
REPORT/COMMENT/ACTION:
ARE THERE OPPORTUNITIES FOR DESIGN AND DEVELOPMENT PROCESS IMPROVEMENT?
REPORT/COMMENT/ACTION:

	YES	**NO**
REVIEW ALL SPECIFICATIONS?		
REVIEW DESIGN?		
REVIEW FEA ANALYSIS?		
DISCUSS PART ORIENTATION		

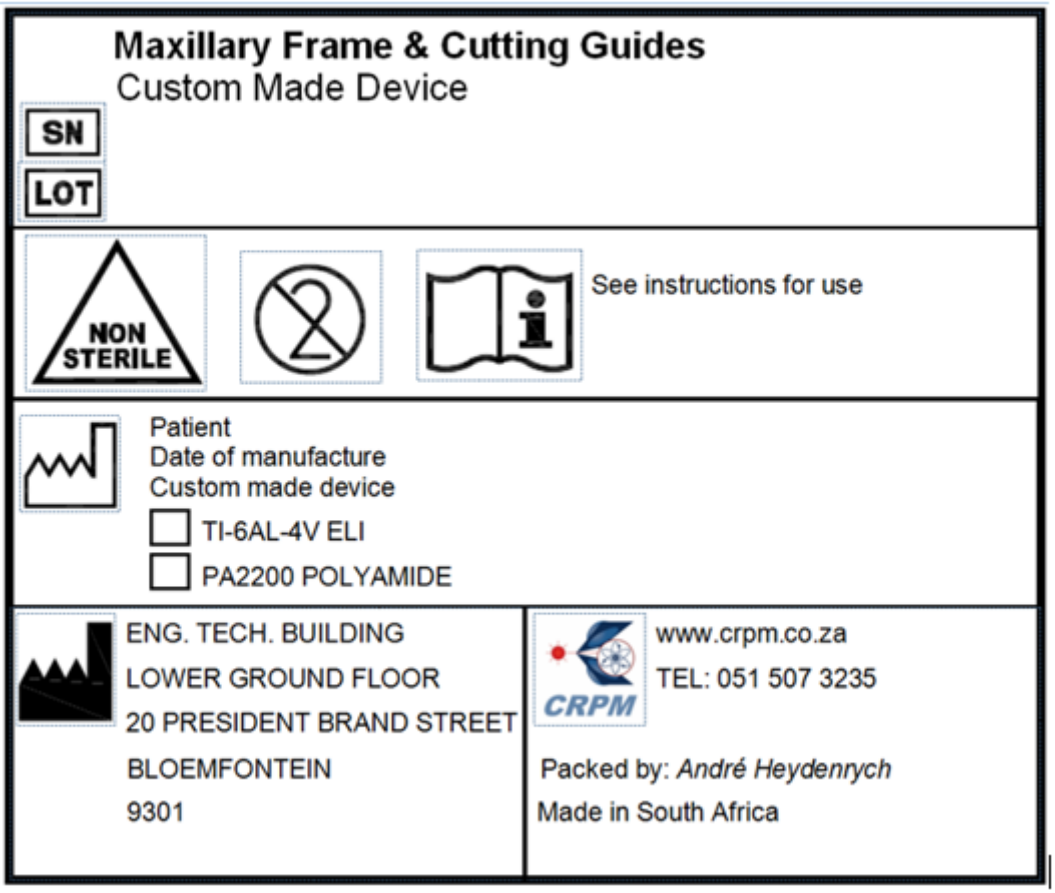
DISCUSS SUPPORT OF PART		
SERIAL NUMBER/S ADDED?		
ASSISTIVE DEVICE REQUIRED?		
SERIAL NUMBER ADDED ON ASSISTIVE DEVICE?		
IMPLANT READY FOR MANUFACTURING?		
GUIDE READY FOR MANUFACTURING?		

PARTS TO GROW	**QUANTITY**

DESIGN APPROVED BY:		**YES**	**NO**
SIGNATURE: SURGEON			
SIGNATURE: DESIGNER			
SIGNATURE: QUALITY			

LABEL

DATE:



LABEL INFORMATION	
DEVICE TYPE	
SERIAL NUMBER	
LOT NUMBER	
STERILITY OPTIONS	
PATIENT NAME	
DATE MANUFACTURED	
MATERIAL OPTIONS	

MANUFACTURING SCHEDULE

Insert Microsoft project schedule

EOSTATE REPORT REVIEW

DATE:	

	YES	**NO**
DID THE LASER POWDER DEVIATE DURING MANUFACTURING?		
DID THE OXYGEN LEVEL DEVIATE DURING MANUFACTURING?		
DID ANY OTHER EVENTS OCCUR DURING MANUFACTURING?		
IF YES, PLEASE ELABORATE		

TENSILE TEST REPORT REVIEW

DATE:	

	YES	**NO**
DOES THE U.T.S MEET THE MINIMUM REQUIREMENT?		
DOES THE % ELONGATION MEET THE MINIMUM REQUIREMENT?		
IS THERE ANY INDICATION THAT THE IMPLANT IS UNSAFE TO PROCEED?		
IF YES, PLEASE ELABORATE		

MINIMUM REQUIREMENTS		**AVERAGE**	
U.T.S	860 MPa	**Fill actual value**	MPa
% ELONGATION	± 10 %	**Fill actual value**	%

CT SCAN REVIEW

DATE:

	YES	**NO**
DOES THE IMPLANT HAVE ANY INTERNAL DEFECTS?		
IF YES, IS IT STILL WITHIN ACCEPTABLE LIMITS?		
DOES SCAN OF THE IMPLANT DEVIATE FROM THE DESIGN FILE?		
IF YES, IS IT STILL WITHIN ACCEPTABLE RANGE?		
IS THERE ANY UNSINTERED POWDER ON/INSIDE THE IMPLANT?		
IS THE IMPLANT FIT FOR IMPLANTING?		
IF NO, PLEASE ELABORATE		

CT SCAN REVIEW APPROVED BY:		**YES**	**NO**
SIGNATURE: DIRECTOR			
SIGNATURE: DESIGNER			
SIGNATURE: QUALITY			

POST-OP REVIEW

DATE:

OVERALL, WERE YOU SATISFIED WITH THE IMPLANT?	**YES**	**NO**
WERE YOU SATISFIED WITH THE FIT OF THE IMPLANT?		
WERE YOU SATISFIED WITH THE SCREW HOLES?		
OVERALL, WERE YOU SATISFIED WITH THE ASSISTIVE DEVICE (CUTTING GUIDE/POSITIONING GUIDE)?		

POSSIBLE IMPROVEMENTS:

NAME OF DOCTOR:	
SIGNATURE:	

6-MONTH REVIEW

DATE:	

	YES	**NO**
Was there a reduction in pain compared to the pain level prior to the operation?		
Pain level prior to operation (mark with "X")		

1	**2**	**3**	**4**	**5**

	YES	**NO**
Was there a reduction in pain compared to the pain level prior to the operation?		
Pain level after the operation (mark with "X")		

1	**2**	**3**	**4**	**5**

	YES	**NO**
Was there an improvement in the patient's state of mind?		
Were X-rays taken with this review?		
Is there any indication on the X-rays that the implant is not in its original fixation position?		

ISSUES REQUIRING FURTHER INVESTIGATION

NAME OF DOCTOR:	
SIGNATURE:	

12-MONTH REVIEW

DATE:

	YES	**NO**
Was there a reduction in pain compared to the pain level prior to the operation?		

Pain level prior to operation (mark with "X")				
1	**2**	**3**	**4**	**5**

	YES	**NO**
Was there a reduction in pain compared to the pain level prior to the operation?		

Pain level after the operation (mark with "X")				
1	**2**	**3**	**4**	**5**

	YES	**NO**
Was there an improvement in the patient's state of mind?		
Were X-rays taken with this review?		
Is there any indication on the X-rays that the implant is not in its original fixation position?		

ISSUES REQUIRING FURTHER INVESTIGATION

NAME OF DOCTOR:	
SIGNATURE:	

18-MONTH REVIEW

DATE:	

					YES	**NO**
Was there a reduction in pain compared to the pain level prior to the operation?						
Pain level prior to operation (mark with "X")						
1	**2**	**3**	**4**	**5**		

					YES	**NO**
Was there a reduction in pain compared to the pain level prior to the operation?						
Pain level after the operation (mark with "X")						
1	**2**	**3**	**4**	**5**		

	YES	**NO**
Was there an improvement in the patient's state of mind?		
Were X-rays taken with this review?		
Is there any indication on the X-rays that the implant is not in its original fixation position?		

ISSUES REQUIRING FURTHER INVESTIGATION

NAME OF DOCTOR:	
SIGNATURE:	

PHOTOS

APPENDICES

01) Job Card

02) EOSTATE Report

03) CT Scan Report

04) Heat Treatment Report

05) Tensile Test Results

06) Sterilisation Certificate

07) Receipt of IFU

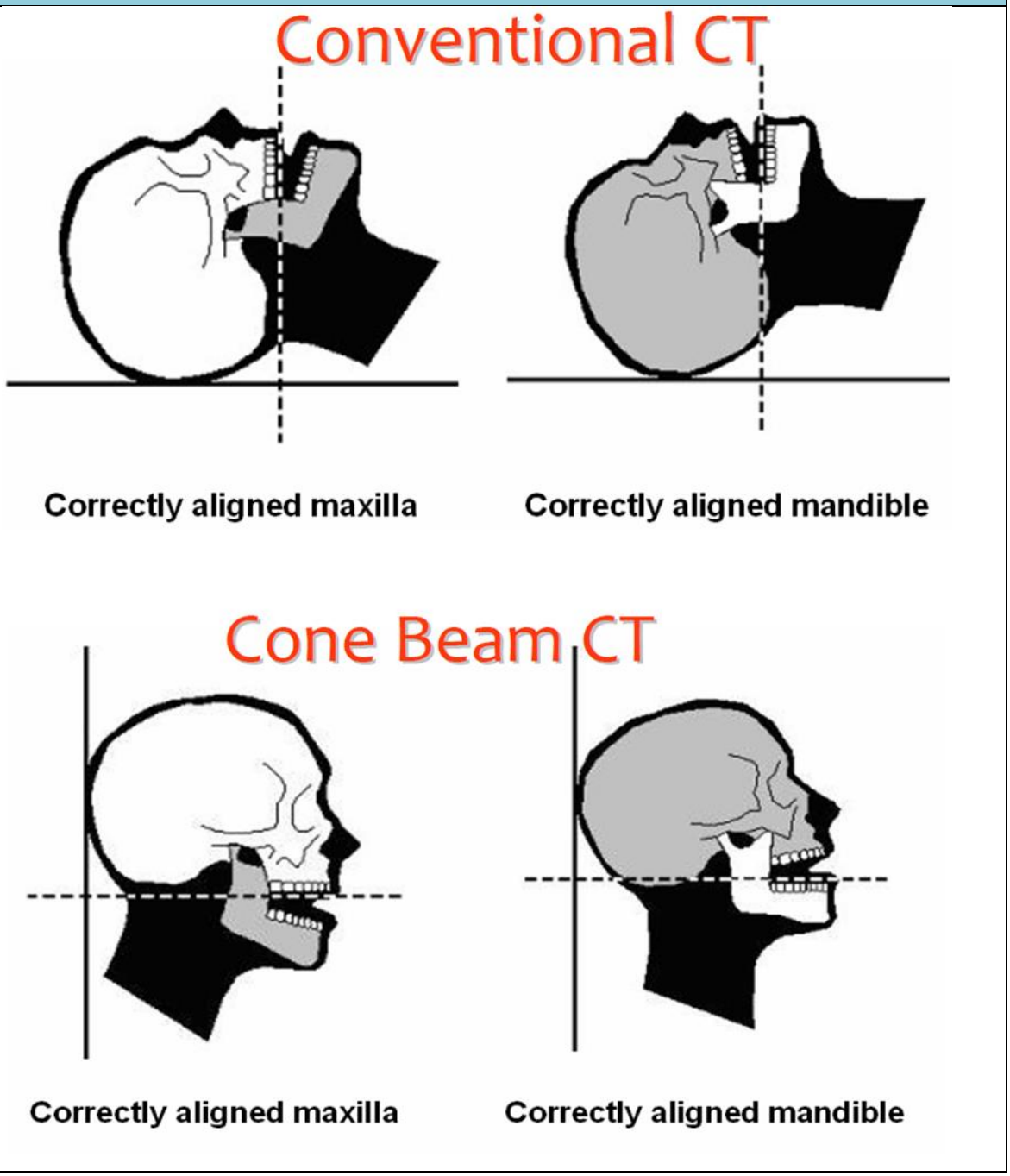
3.8 Patient CT Scan Protocol

The quality of the CT scan is a critical component in the production of high-quality AM models and accurate digital surgical planning. The following CT Scan Protocol (also see Figure 3.36) was derived from what is available in the public domain relating to AM pre-operative planning model manufacturing:

- 100–120kV, 550–700mAs
- Slice thickness: 0.5 mm–0.7 mm (Maximum – 1.0 mm)
- Reconstructed slice increment: (at least) equal to slice thickness
- Algorithm: Bone or high resolution
- Matrix: 512 x 512
- Field of view: 140–200 mm
- Feed per rotation: 1.0 mm
- The gantry tilt: Zero. (The axial slices will be parallel to the occlusal plane and subsequently make the same angle relative to the vertical plane.)
- Remove any non-fixed metal dentures or prosthesis, in addition to any jewellery. Non-metal dentures may be worn during the scan.
- Set the table height with the area to be scanned centred in the scan field.
- The patient must remain completely still during the scan. The scan will have to be repeated if the patient moves during the scan.
- The patient is preferably scanned with the jaws slightly open (a bite block can be used if available). This will reduce the risk of artefacts from the opposing jaw disturbing the images of the jaw of interest.
- The patient must be relaxed, expressionless and the head brace should not create tissue distortion.
- The head must be positioned as anatomically straight as possible.
- The field of view must include all structures of interest including the opposite sides for simulation and mirroring purposes.
- Scan the entire defect as well as 2 cm above and below.
- All slices must have the same field of view, the same reconstruction centre, and the same table height.
- Scan all slices of the study in the same direction.

- Reduction of scatter – radiographer needs to be made aware of metal objects and optimise patient position.
- Patient position in the CT scanner must be in line with the scanner protocols.
- If scanning with prosthetics: obturator density (10% barium sulphate) for accurate threshold manipulation.
- The slice data must be saved on CD in uncompressed standard DICOM format.

Table 3.36: Patient's position in CT/MRI scanner (CRPM ISO 13485: 2016 Quality Management System)

Position in scanner


3.9 Custom AM Implant Product Information and Instructions for Use (IFU)

3.9.1 Description

The **implant** comprises a custom frame that is manufactured by means of DMLS and used for fixation of skeletal fractures, and reconstructions**.**

3.9.2 Material

The implant is made from Titanium-6-Aluminium-4-Vanadium Alloy (ASTM F-136). (ASTM International: 2013).

3.9.3 Clinical Indications

The **implant** is indicated for fixation secondary to trauma or reconstruction of the skeleton. The implant is intended for single use only. Single-use devices cannot be reused and/or reprocessed. The product has been labelled as “single use only” for patient safety. The design of the device and the intricacies of the surfaces may not facilitate cleaning and sterilisation after contact with body tissues or fluids, so there is an increased risk of contamination if reused. This may lead to potential risks of cross-infection/contamination associated with using inadequately cleaned and sterilised devices.

3.9.4 Contraindications

The **implant** is contraindicated in cases of active or suspected infection or in patients who are immunocompromised, in patients previously sensitised to titanium, or in patients with certain metabolic diseases. It is further contraindicated in patients exhibiting disorders which would cause the patient to ignore the limitations of rigid fixation plate and screw implants.

The excellent biocompatibility of titanium and its alloys, such as Ti-6Al-4V alloy, is well-documented. Persons with a history of allergies, including sensitivities to cobalt, chromium or nickel, generally do not exhibit or develop sensitivity to titanium or other constituents of Ti-6Al-4V alloy (Duchna, Nowack, Merget, Muhr, Schultze-Werninghaus, 1998).

3.9.5 Maintaining Device Effectiveness

1. The surgeon should have specific training, experience, and be thoroughly familiar with the use of rigid fixation products and techniques.
2. The implant is not intended to endure excessive abnormal functional stresses.
3. The implant should be carefully inspected prior to use. Implants that are faulty, damaged or suspect should not be used.
4. The manufacturing company recommends that the product be used in a sterile environment.

3.9.6 Warnings

1. Use of an undersized screw in areas of high functional stresses may lead to implant fracture and failure.
2. Plates and screws, wires, or other appliances of dissimilar metals should not be used together in or near the implant site.
3. Any modification to the implant may weaken the implant and could result in implant fracture and failure.

3.9.7 Magnetic Resonance (MR) Safety Information

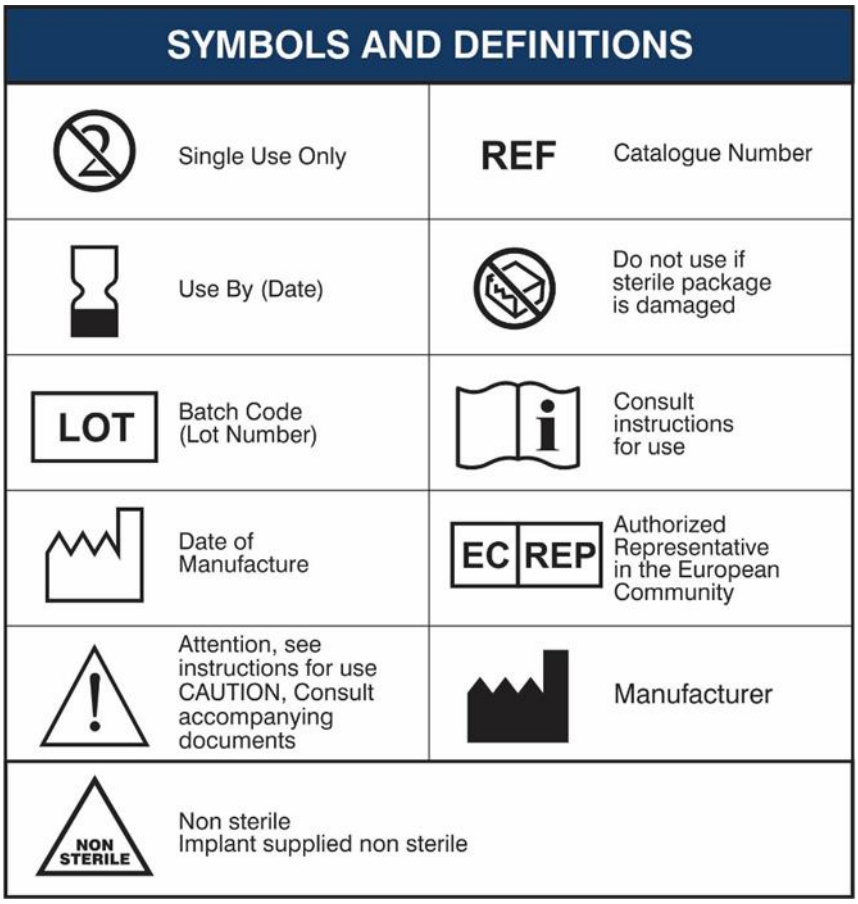
This device has not been evaluated for safety and compatibility in the MR environment. It has not been tested for heating, migration or image artefact in the MR environment. The safety of this device in the MR environment is unknown. Scanning a patient who has this device may result in patient injury.

3.9.8 Sterility

The product is supplied having been gamma-irradiated for biological deactivation. Yet, it must be considered to be "Non sterile", as shown in Table 3.37.

DO NOT USE IF PACKAGING IS DAMAGED.

Table 3.37: Symbols and definitions for IFU (CRPM ISO 13485: 2016 Quality Management System)



3.9.9 Cleaning and Care of Instruments in Accordance with ISO 17664

3.9.9.1 Basic principles

All instruments must be cleaned, disinfected and sterilised before each use as all instruments are supplied non sterile. Remove the shipping protector, clean and disinfect, then wrap before sterilising.

Efficient cleaning and disinfection is absolutely essential for effective sterilisation. As you bear the responsibility for ensuring that instruments are sterile during use, make absolutely certain that only those procedures validated for the equipment and product are used for cleaning/disinfecting and sterilisation.

Ensure that the equipment (ultrasonic unit, steriliser) is serviced and checked regularly. Validated parameters must be adhered to for every cycle. Regard the regulations which apply in your country as well as the hygiene directives applicable to medical practices/hospitals.

This applies especially to the various instructions concerning effective deactivation of prions.

3.9.10 Manual Cleaning and Ultrasonic Cleaning of Implants

3.9.10.1 How?

Use a disinfectant that is aldehyde-free with a proven efficacy that is suitable and compatible for disinfecting implants and instruments. Dilute the Endozime cleansing concentrate with a ratio of 15 ml Endozime to 5 litres of water in a 5 litre container. Submerge the implants for a minimum of 2–10 minutes in the disinfectant then scrub by hand. Rinse thoroughly under running water for a minimum of 60 seconds. Dilute the Endozime cleansing concentrate with a ratio of 15 ml Endozime to 5 litres of warm water at 50 °C in the 5 litre container. Add all implants to the Endozime mix and place the container in the ultrasonic bath. Switch on the ultrasonic bath and set for 30 minutes. (This will automatically activate the ultrasonic bath to start the cleansing process). Remove the container from the bath after 5 minutes and separate the contents from the liquid mix. Rinse thoroughly under running water for a minimum of 60 seconds. Store and handle as clean.

3.9.10.2 Equipment and chemicals

Endozime disinfectant with a CE-mark mixed with warm water (15 ml:5 L)
Distilled water
Disinfected stainless steel container
Ultrasonic bath
Always use powder-free nitride gloves during the cleaning process.

3.9.10.3 Test to be performed

Bioburden tests according to Standard: ISO 11737-1 (Sterilisation of medical devices – Microbiological methods – Part 1: Determination of a population of micro-organisms on products) (International Standards Organisation, 2018) after the first hand-cleaning procedure on at least three implants to validate efficacy of the cleaning process. Repeat tests regularly.

3.9.10.4 Acceptance criteria

< 50 Colony Forming Unit (CFU) before
≤20 CFUs after

3.9.11 Automatic Cleaning (machine wash)

3.9.11.1 How?

Place the implants in a disinfectant that is aldehyde-free with a proven efficacy that is suitable and compatible for disinfecting implants and instruments, for at least 5 minutes. Ensure they are immersed properly. Do not allow the implants to touch each other.

Run the cleaning cycle in accordance with ISO 15883.

3.9.11.2 Equipment and chemicals

Endozime disinfectant with a CE-mark mixed with warm water (15 ml: 5 L)
Distilled water
Automatic cleaner in accordance with ISO 15883
Always use powder-free nitride gloves during the cleaning process.

3.9.11.3 Test to be performed

Bioburden tests according to Standard: ISO 11737-1 (Sterilisation of medical devices – Microbiological methods – Part 1: Determination of a population of micro-organisms on products) after the first machine-cleaning procedure on three implants to validate efficacy of cleaning process. Repeat tests regularly.

3.9.11.4 Acceptance criteria

< 50 Colony Forming Unit (CFU) before
≤20 CFUs after

Always use powder-free nitride gloves during the cleaning process.

THE IMPLANT IS NOW CLEAN, BUT NON STERILE.

3.9.12 Steam Sterilisation According to ISO 17665-1

3.9.12.1 How?

Pre-condition: Vacuum pump removes air from chamber.

Sterilisation: After air removal, steam is injected in the chamber at 132 °C and 240 kPa for at least 4 minutes. The upper control limit must be equal to sterilisation temperature plus 3 °C, with no deviation exceeding 1 °C, and temperature difference of any 2 points inferior to 2 °C.

Drying: The pack is dried by the vacuum pump by drawing sufficient vacuum to remove moisture from the packs – 8 minutes of vacuum is normally adequate.

Vacuum break: Sterile air to be filtered into chamber to break the vacuum.

Removal and cool down: Remove and place in a special cooling rack. Avoid touching the hot pack by hand as hot packs can absorb moisture and bacteria from hands.

Place pack in a sterile storage area. Observe expiry dates and re-sterilise if necessary.

3.9.12.2 Cycle specifications

Hold Temperature: 132 °C to 135 °C
Hold Pressure (Chamber): 225 kPa to 230 kPa
Hold Pressure (Jacket): 240 kPa to 250 kPa
Cycle Time: 4 minutes

3.9.12.3 Equipment

Steam Sterilisation Unit complying with ISO 17665 (International Standards Organisation,

3.9.12.4 Test to be performed

Bioburden tests according to Standard: ISO 11737-1 (Sterilisation of medical devices – Microbiological methods – Part 1: Determination of a population of micro-organisms on products) after the first sterilisation procedure on three implants to validate efficacy of sterilisation process. Repeat tests regularly.

3.9.12.5 Acceptance criteria

Sterile = 0 CFUs

3.9.12.6 Storage

Sterile packaged implants should be stored at a controlled room temperature out of direct sunlight. The product package should be inspected prior to use for signs of damage or tampering.

3.9.13 Caution

Do not attempt a surgical procedure with faulty, damaged or suspect guide or model. Inspect all components preoperatively to assure utility. Alternative fixation methods should be available intraoperatively.

Process and Machine Validation as Part of Objective 2

3.10 Process Validation

The importance of Process Validation cannot be overemphasized. Device quality, such as feature geometry, overall dimensions, material characteristics, and mechanical properties are impacted by AM process parameters, process steps, and raw material properties, This is highlighted in the Technical Considerations for Additive Manufactured Medical Devices: Guidance for Industry and Food and Drug Administration Staff (U.S. Food and Drug Administration, 2017). The quality of identical devices may vary when built using different AM machines, even when using the same machine model, settings, process steps and raw materials. Where the results of a process cannot be fully verified by subsequent inspection and testing, the process must be validated with a high degree of assurance and approved according to established procedures. Therefore, process validation must be performed to ensure and maintain quality for all products built in a single build cycle, between build cycles, and between machines, where the results of a process cannot be fully verified by subsequent inspection and test.

In order to achieve Objective 2, process and machine validation must be carried out in a series of steps, as shown in Table 3.38. The definitions of these steps are as follows:

Factory Acceptance Test (FAT) can be defined as the process that evaluates the equipment during and after the assembly process by verifying that it is built and operating in accordance with design specifications. FAT ensures that the components and controls are working properly according to the functionality of the equipment itself. This testing is performed at the factory.

Installation Qualification (IQ) is defined by the FDA as, “establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer’s approved specification and that the recommendations of the supplier of the equipment are suitably considered”.

The FDA definition of Operational Qualification (OQ) is: “Establishing confidence that process equipment and sub-systems are capable of consistently operating within stated limits and tolerances. In practice, the operational qualification is the executed test protocol documenting that a system meets the defined functional requirements, or that the system does what it is supposed to do”.

The FDA defines Performance Qualification (PQ) as “Establishing confidence though appropriate testing that the finished product or process produced by a specified process meets all release requirements for functionality and safety and that procedures are effective and reproducible”.

Table 3.38: Product, Process & Test Method Validation Master Plan (CRPM ISO 13485: 2016 Quality Management System)

Product, Process & Test Method Validation Master Plan

No.	Description	Characteristic	Standard/ target	Tolerance	Validation method	Completion date	Validation results	Re-validation criteria
Processes								
1	Sterilisation validation	Cleanliness of medical devices	ISO 11737-1:2018	$< 1 \times 10^{-6}$	Outsourced to external company for testing	X	0 CFU/ml growth detected during incubation of 3 days at 30 °C	Change in: sterilisation process supplier. Will do revalidation with an accredited lab in future
2	Design process validation	Geometrical accuracy during design process	Software used are ISO 9001 & 13485 certified		Design Validation Protocol and Report	X	Design process within tolerance	Change in software supplier or change in manufacturing process
3	Packaging validation	Peel strength of packaging	ISO 11607-2		Packaging Validation Protocol and Report	X	4.8 N/15 mm	Change in packaging material

No.	Description	Characteristic	Standard/ target	Tolerance	Validation method	Completion date	Validation results	Re-validation criteria
Machines								
EOSINT M280								
4	M280 – IQ	System installed correctly	System should be fit for use Standard ISO 9001		Installation done by machine manufacturer	X	AM system is fit for use	Change in manufacturing process Change in critical components (laser, scanner) Change in supplier
5	M280 – OQ	System ready for routine operation	All SOPs should be followed to ensure correct operation		OQ	X	AM system is ready for routing operation	Should SOP change?

No.	Description	Characteristic	Standard/ target	Tolerance	Validation method	Completion date	Validation results	Re-validation criteria
6	M280 – PQ	System manufactures repeatable quality parts during routine operation	Accuracy Refer to standard	UTS = 1200 ± 50 MPa Accuracy = ± 50 µm	PQ	X	AM system produced repeatable quality parts under normal operating conditions	Change in manufacturing process Change in critical components (laser, scanner) Change in supplier
EOSINT P385								
7	P 385 – IQ	System installed correctly	System should be fit for use		IQ	X	AM system is fit for use	Change in manufacturing process Change in critical components (laser, scanner) Change in supplier
8	P385 – OQ	System ready for routine operation	All SOPs should be followed to ensure correct operation		OQ	X	AM system is ready for routine operation	Should SOP change?

No.	Description	Characteristic	Standard/ target	Tolerance	Validation method	Completion date	Validation results	Re-validation criteria
9	P385 – PQ	System manufactures repeatable quality parts during routine operation	System produces repeatable quality components under normal operation conditions	UTS = 45 ± 3 MPa Accuracy = ± 5 %	PQ	X	AM system produced repeatable quality parts under normal operating conditions	Change in manufacturing process Change in critical components (laser, scanner) Change in supplier
MTS CRITERION 43								
10	MTS – IQ	Equipment installed correctly	System should be fit for use		IQ	X	System is fit for use	Change in critical components (load cell)
11	MTS – OQ	Equipment ready for routine operation	All SOPs should be followed to ensure correct operation		OQ	X	Tensile tester is ready for routine operation	
12	MTS – PQ	System produces accurate results during routine operation	System produces repeatable results under normal operation conditions		PQ	X	Tensile tester produces reliable results	

No.	Description	Characteristic	Standard/ target	Tolerance	Validation method	Completion date	Validation results	Re-validation criteria
FAMOS F70-300 heat sealer								
13	FAMOS F70 – IQ	Equipment installed correctly	System should be fit for use		IQ	X	System installed correctly	Change in critical components
14	FAMOS F70 – OQ	Equipment ready for routine operation	All SOPs should be followed to ensure correct operation		OQ	X	Trained operators	Change in operators
15	FAMOS F70 – PQ	System produces reliable seal during routine operation	System produces repeatable results under normal operation conditions		PQ	X	Seal strength > 1.2N/15mm	Change in equipment
Software								
12	Mimics™ MAGICS 3 Matic™	Software accuracy for different software used during manufacturing	MDR 2017-745 EU	±50 µm	Protocol	X	Protocol clear	Change in software used for manufacturing
					Report	X	Deviation < 50 µm	

3.10.1 Design software validation protocol and report

3.10.1.1 Purpose and scope

The purpose of this protocol is to validate the effectiveness of the design process of the patient-specific medical devices designed by the AM company. The validation is done on the medical devices designed by the company.

3.10.1.2 Validation process

The validation process starts with a CT scan where a phantom is scanned with a slice thickness of 1mm or less using a bone reconstruction filter.

The Project Engineer is responsible for checking that the correct scanning protocol (section 3.7) was actually followed. This is done by inspecting the project information tag (shown in Figure 3.9 below) in where all the scanning information is displayed. If the criteria are not met, the scan is sent back for rescanning, see flow diagram depicted in Figure 3.10.

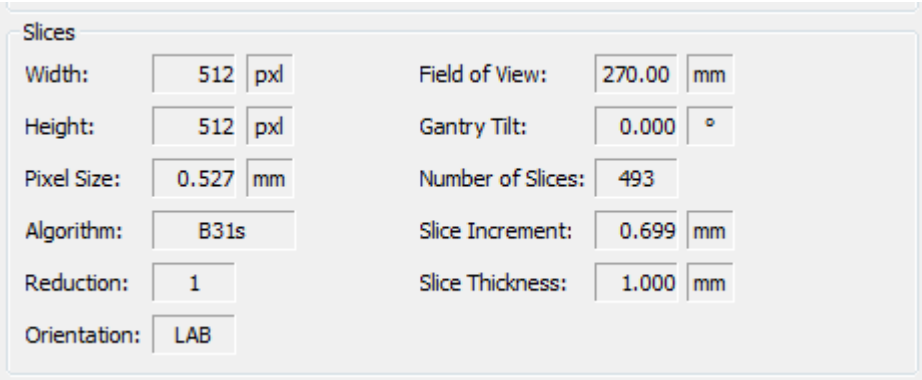


Figure 3.9: Project information showing the acquisition information

The following tests are performed:

- Obtain three scans where different slice thicknesses and reconstruction filters were used and evaluate them with the tag in Mimics™.
- Rescan by following the correct procedure and evaluate with the tag in Mimics™.

Acceptance Criteria

- All three wrongly scanned data sets are rejected by the Project Engineer after inspecting the tag in Mimics™.
- All three rescanned images are accepted by the Project Engineer after inspecting the tag in Mimics™.

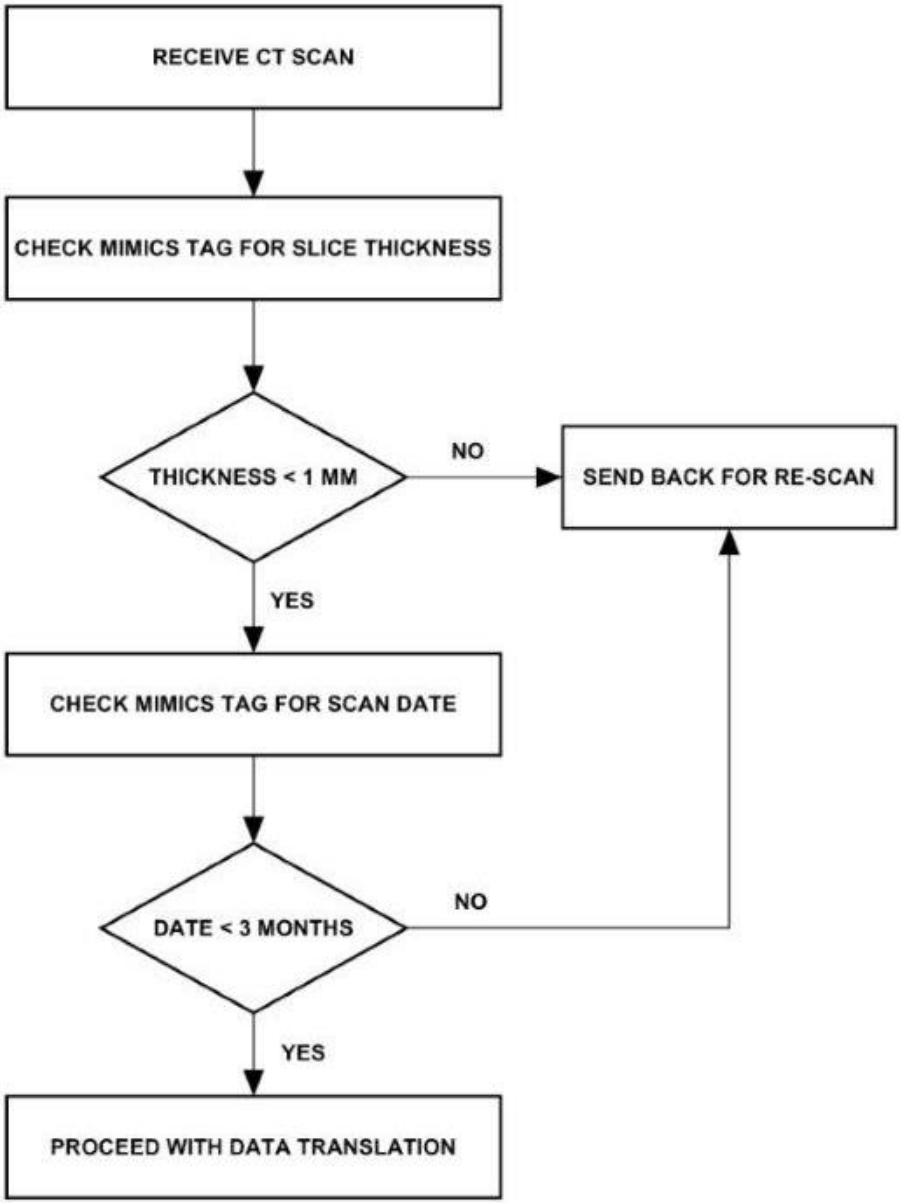


Figure 3.10: Flow diagram for CT Data Translation

Mimics™ conversion

The conversion of the data to Mimics™ is done by identifying the correct side of the patient to be converted. Then a mask is created by accurately selecting the desired anatomy of the patient. Thereafter, 3D objects are created from the mask(s).

The following test is then performed:

- Verify by inspection that the correct side of the anatomy was converted.
- Prepare a PA2200 sample part produced by EOSINT P (has similar density properties to soft tissue) as per Figure 3.11 below, with a cavity that is filled with a bone simulation matrix casting material that simulates cortical bone density.
- Measure the cavity before filling it with the bone simulation matrix.
- After the material has cured, the sample part is CT-scanned using the scan protocol.
- Do three segmentations of the bone matrix cube within the nylon sample part; one by default grey-scale values from the dropdown menu (Figure 3.12); one purposely lower (Figure 3.13) and one with purposely higher (Figure 3.14) grey-scale values.
- Convert all three segmented masks into 3D objects and export them as STLs (Figure 3.15).
- Print the three segmented bone matrix cubes and accurately measure them after printing (Figure 3.16).

Acceptance Criteria

- The accuracy of the printed part must be within 0.5 mm tolerance.

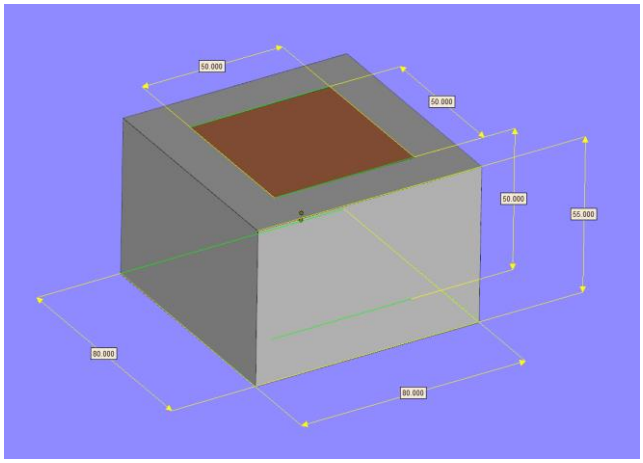


Figure 3.11: Design file of phantom

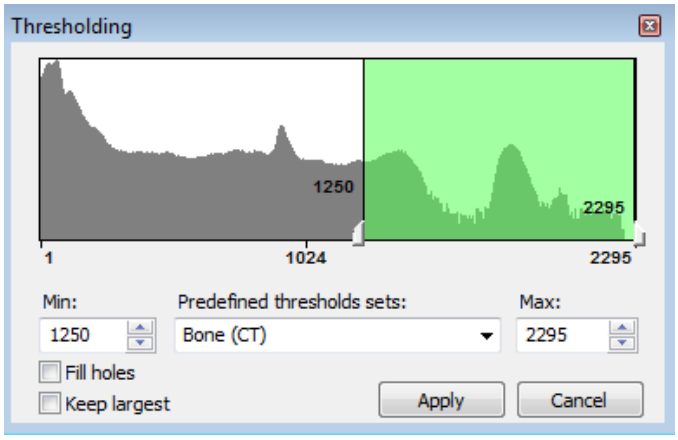


Figure 3.12: Default grey-scale value settings

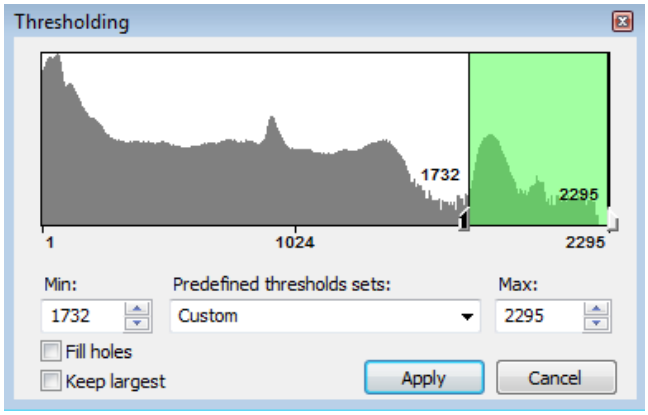


Figure 3.13: Low grey-scale value settings

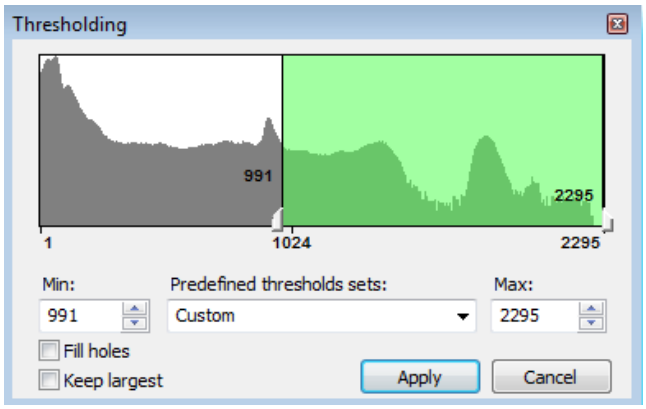


Figure 3.14: High grey-scale value settings

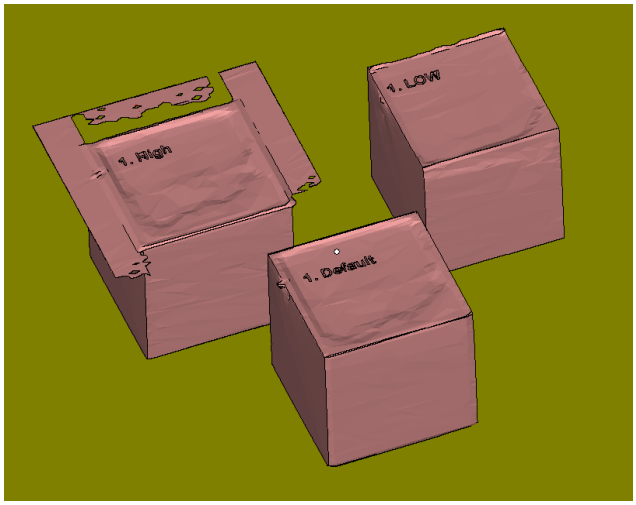


Figure 3.15: STL files of the three different exported masks

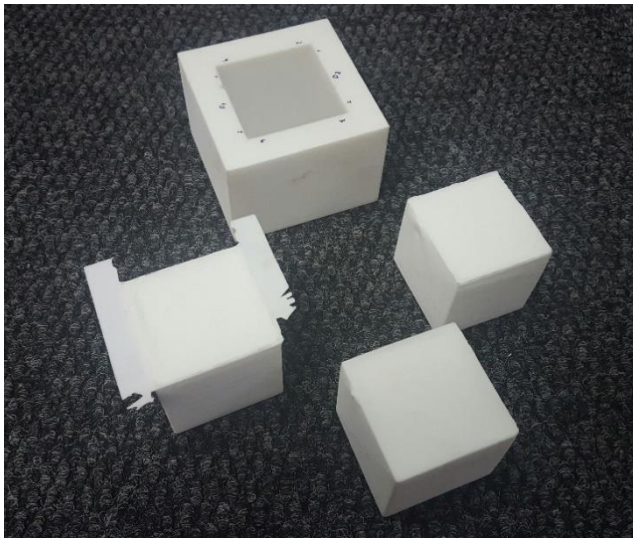
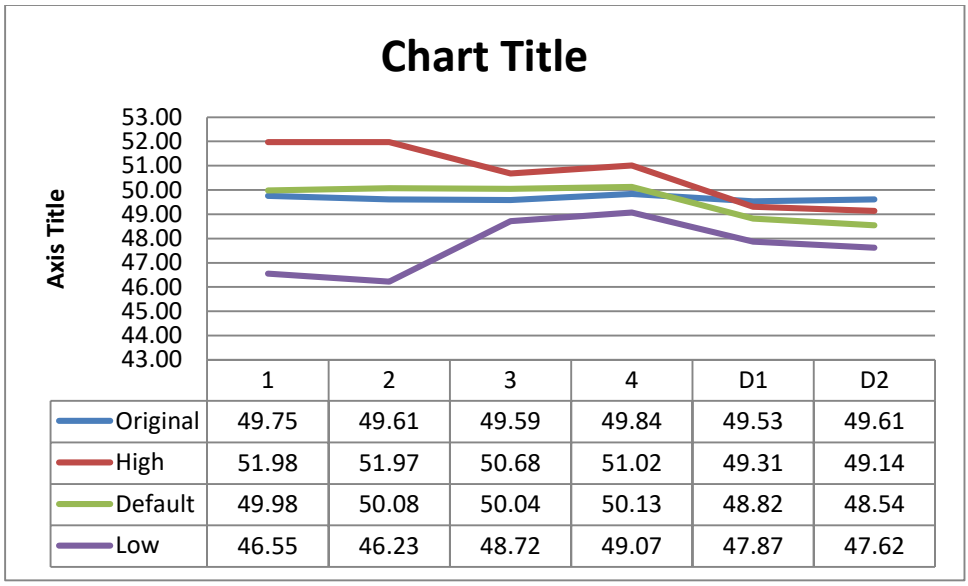


Figure 3.16: SLS PA2200-produced cubes

Results

The dimensional accuracy of all 3D-printed parts are inspected and compared to the original 3D-printed part. Results are shown in Figure 3.17. The default grey-scale values (shown as green line in chart) resulted in the most accurate 3D-printed part from a CT scan conversion. The blue line was the actual part printed geometry that was set as the baseline.



	1	2	3	4	D1	D2
Original	49.75	49.61	49.59	49.84	49.53	49.61
High	51.98	51.97	50.68	51.02	49.31	49.14
Default	49.98	50.08	50.04	50.13	48.82	48.54
Low	46.55	46.23	48.72	49.07	47.87	47.62

Figure 3.17: Thresholding values

From the results it is evident that the default thresholding values produced the most accurate 3D-printed result.

3 Matic™ DESIGN

In order to validate a 3 Matic™ design, a medical sample part is designed using 3 Matic™, as shown in Figure 3.18.

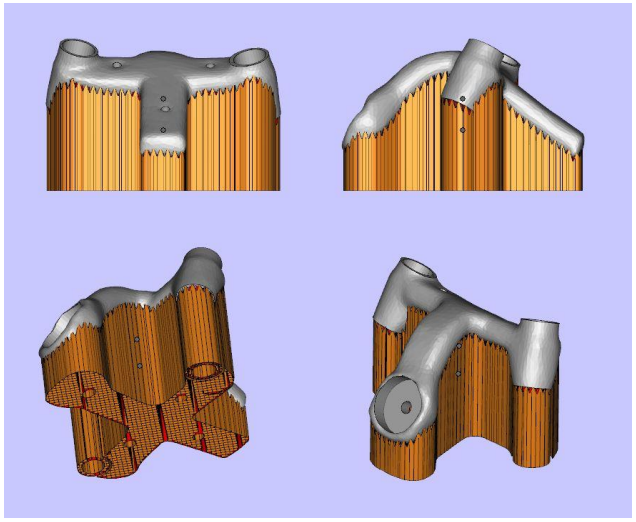


Figure 3.18: CAD design of medical sample part with support structures

Test to be performed

- Do a part-to-CAD comparison between the dimensions of the manufactured sample and the CAD design, by means of micro-CT analysis.

Acceptance Criteria

- An acceptable deviation is 50 micron.

Results

A part-to-CAD comparison was conducted by means of micro-CT analysis. The result showed that the maximum variance was 50 micron, as shown in Figure 3.19.

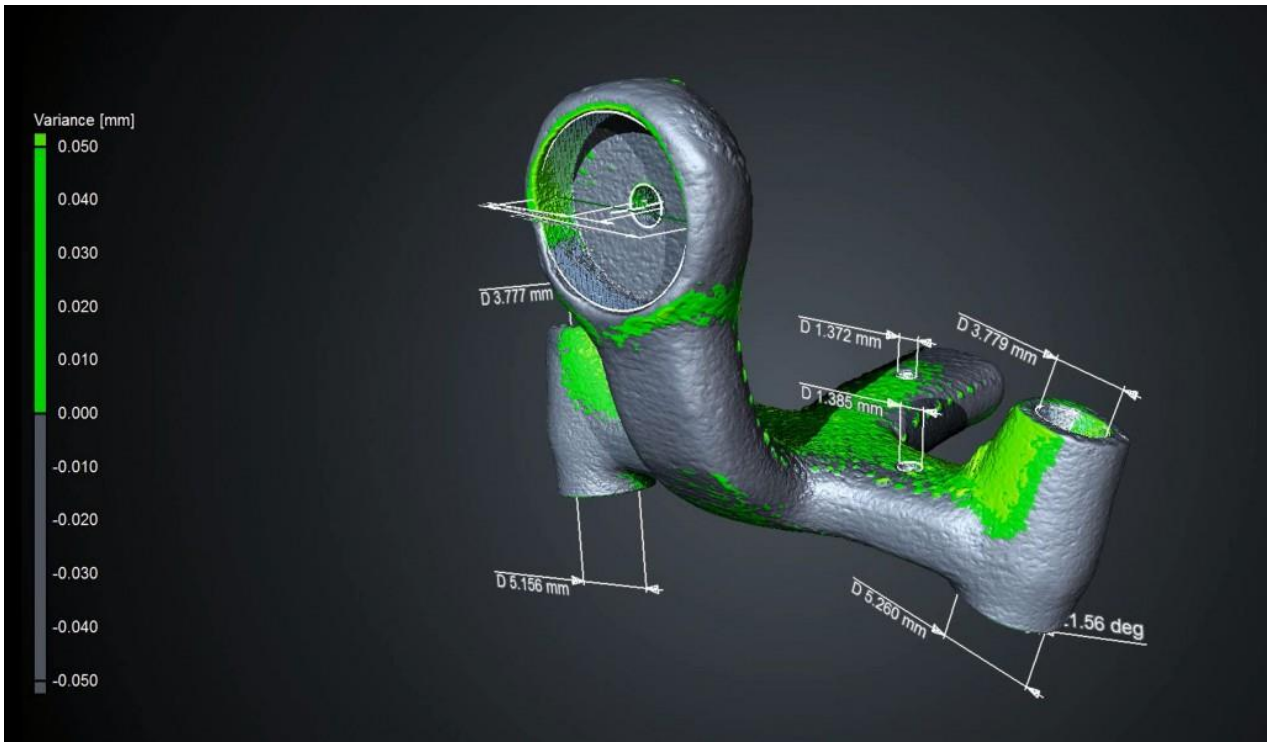


Figure 3.19: Part-to-CAD comparison indicating variances in green

3.10.1.3 Summary

Mimics™ Validation:

The default grey-scale values resulted in the most accurate 3D-printed part from a CT scan conversion.

3 Matic™ Validation:

The part was found to be within the required 50 micron tolerance.

3.10.1.4 Criteria for revalidation

Revalidation will be required in the event of the following:

- Change in manufacturing process
- Change of software supplier

3.10.2 Validation of EOSINT M280 machine

3.10.2.1 Installation Qualification

The purpose of this document is to establish a protocol on the Installation Qualification (IQ) including plan and report of qualification steps. Successful completion of the IQ will ensure that the equipment is ready for routine usage.

This document applies for the following equipment:

This IQ applies to the EOSINT M280 Laser Sinter System with serial identification number 1191 (Table 3.39).

Table 3.39: IQ equipment description

Equipment	Product description	SI Number
M280 – TI64	EOSINT M280 Laser Sinter System	1191

Sub-systems:

Sub-systems include the following:

- Laser
- Compressor
- Mechanical

Reference Documents:

SOPs and technical documents used as reference documents in conducting the IQ, as shown in Table 3.40.

Table 3.40: IQ reference documents

Document no	Description
1	Standard Operation Procedures
2	Technical Documents

Installation Qualification (IQ) Prerequisites

The EOSINT M280 must pass Installation Qualification (IQ) and Operation Qualification (OQ) before the Performance Qualification (PQ) can be performed.

Define Application Field of Laser Sinter System

Identified industries that could benefit from the Laser Sinter System applications are shown in Table 3.41.

Table 3.41: Application Field of Laser Sinter System

Industry	Y/N		Powder type	Y/N
Medical	Y		TI64 ELI	Y
Aerospace	Y			
Automotive	Y			
Tooling				
Lifestyle products				
Prototyping	Y			

IQ – Qualification Plan & Report

Pre-requisites qualification staff

This IQ protocol must be agreed with the responsible customer qualification manager. The inspector must be familiar with the qualification steps and have calibrated test equipment available.

Pre-requisites qualification equipment

Purpose:

To identify the validation test equipment required for IQ.

Acceptance Criteria:

The equipment must have a valid calibration status and evidence. All calibration certificates as well as measurement protocols have to be attached at the end of this document.

Procedure:

Equipment used during IQ is shown in Table 3.42. Review the calibration certificate status and record the next calibration date in the fourth column.

Table 3.42: Equipment used for IQ

Equipment	Description	Calibration Date	Next Calibration Date
PM 4437	PRIMES: Pocket Monitor	Calibrated	
PM 4292	OPHIR: Laser Power Meter	Calibrated	
PM 2813	PRIMES: Focus Monitor	Calibrated	
PM 3342	EOS: Portable Scanner Calibration	Calibrated	
PM 2523	EOS: Tools for Leakage Test	Calibrated	
PM 2523	TESTO: Differential Pressure Gauge	Calibrated	
	EOS Laser Power Measuring Box		
	EOS Service Dongle		
	Standard tool box		

In the Table 3.43, IQ checks are discussed and the actual results compared to the expected results in the execution of the IQ.

Table 3.43: IQ execution document (CRPM ISO 13485: 2016 Quality Management System)

Basic Installation – Customer Facility Checks			
Step	**Expected Result**	**Actual Result**	**PASS/FAIL**
Check the prerequisites for internal transport at the customer's premises	Forklift truck and lifting truck with adequate carrying capacity and fork length available. All transport routes to the site where the machine is to installed are of adequate load-bearing capacity, adequately sized and clear of obstacles.	Machine was already installed	**Pass**
Check the site where the machine is to be installed	Floor characteristics comply with specification: • Hard, flat and level; unevenness of the surface ≤ 5 mm/m^2 • Free of interfering vibration. No heavy machines, such as presses or punches, are to be operated in adjacent rooms as the machine must not be subjected to vibration • The floor covering must have the following characteristics: • The surface must be such that spilt metal powder cannot be trapped • The surface must be easy to clean • The surface must be suitable for wet cleaning	Room temperature/humidity: • Temperature – 20 °C • Humidity – 35%	**Pass**

	• The surface must be anti-slip • The floor covering must be electrically conductive or have anti-static properties The area where the system is to be installed is clean and dry. Minimum space required for the machine and accessories is available. Access to machine and accessories are ensured. Ambient conditions comply with the specification. Permissible room temperatures/humidity for operations status: • 15–20 °C at max – 80% relative atmospheric humidity • 20–25 °C at max – 60% relative atmospheric humidity • 35–30 °C at max – 45% relative atmospheric humidity Check that there is nothing preventing local, single-sided heating or cooling of the machine. Check for compliance with the EMC requirements. No		

	high-frequency device and no interfering electrical installations in room where the machine is to be installed.		
Check connections	Mains connection for machine, accessories and service available. System mains comply with specification: • Connection: CEE socket 400 V/32 A • Voltage: 400 V – 3 Phase • Voltage fluctuations: +6% to -10% • Frequency 50/60 Hz • Rated short circuit current 5 kA Compressed air connection and compressed air quality for machine and accessories are available and comply with specification: Compressed air consumption with nitrogen supplied by the nitrogen generator: approx. 20 m^3/h at 7 bar • Nominal pressure: 7 bar • Minimum pressure: 6 bar • Maximum pressure: 10 bar	Checked and verified	**Pass**

	Compressed air temperature: max 10 °C above temperature of ambient air. Quality of the compressed air in accordance with ISO 8573: • Solids: Class 1 (particle size ≤ 0.1 µm particle density ≤ 0.1 mg/m^3) • Water content: Class 4 (pressure dew point 3 °C) • Oil content: Class 1 (oil concentration ≤ 0.1 mg/m^3) Network connection available for data transfer complies with specification: • Ethernet network • Network protocol TCP/IP • Network connection 10/100 Base-TX		
Check for presence of essential accessories	Recirculating filter system available and complies with specification (Operation Status): • Permissible room temperature: 15–30 °C • Permissible relative atmospheric humidity: non-condensing	Checked and verified	**Pass**

	Cooling system available and complies with specification (Operation Status): • Permissible room temperature: 5–40 °C • Ensure that the cooling air can flow freely. The minimum distance at the side to adjacent equipment/walls must be 0.3 m; the minimum spacing to the rear of the cooling system must be 0.8 m		
Check customer safety precautions	All access doors to the room where the machine is to be installed can be locked. Laser warning beacon on all access doors to the room where the machine is to be installed. Warning signs on all access doors to the room where the machine is to be installed. Laser safety walls available (if there are other workplaces in the room where the machine is to be installed. Suitable fire extinguishers available in sufficient numbers (extinguishing units) and comply with specification. Wash basin with eye washing capability.	√ √ √ **N/A** √ √	**Pass**

Basic Installation – Machine Installation			
Step	**Expected Result**	**Actual Result**	**PASS/FAIL**
Install machine	Install and align machine. Check labels and if necessary, complete and correct. Check seals on the laser in the presence of the customer for presence, completeness and condition. Start measurement of the ambient temperature and relative atmospheric humidity.		**Pass**
Check electrical connection	Mouse and keyboard connected. Check the machine's mains cable for correct seating and damage. Check that the machine does not has any short circuits. Check function of circuit breaker circuits. Check motor cut-out settings. Check wiring harness on the keyboard and monitor. Check earth: • Switching cabinet earth wire inside the housing • Switching cabinet door • Rear maintenance cover		**Pass**

	• Left maintenance cover • Keyboard and monitor shelf • Optics cover • Process chamber body/machine frame (earth wire top right on process chamber roof) • Front maintenance cover • Vertical cable duct • Horizontal cable duct • FI-protection switch cover • Earth socket • Antistatic mat		
Check cooling system	Check the mains cable for correct seating and damage. Check the error signal cable for correct seating and damage. Connect mains cable and error signal cable. Check function of pump, fan and compressor. Check flow direction of the cooling water. Check cooling water system for leaks. Check cooling water level.		**Pass**
Check air pressure	Check hoses for damage.		**Pass**

	Check compressed air system for leaks. Check pressures: • System pressure • Dispenser pressure • Shutter control pressure • Check flow rates: • Flow rate for lens cleaning • Flow rate for pyrometer		
Alignment of building system and recoating system in relation to each other	Check the alignment between building system and recoating system, in relation to each other.		**Pass**

IQ – System version				
Step	**Method**	**Expected Result**	**Actual Result**	**PASS/FAIL**
System SI	Record system SI from type label	-	SI 1191	**Pass**
Manufacturing date	Record manufacturing date from type label	-	Date: 2011	**Pass**

IQ – Software version				
Step	**Method**	**Expected Result**	**Actual Result**	**PASS/FAIL**
PSW software version	Record PSW SW version in menu “info about PSW”	PSW V3.6 (32)	PSW V3.6 (86)	**Pass**

IQ – System Checks – Safety				
Step	**Method**	**Expected Result**	**Actual Result**	**PASS/FAIL**
Door safety – M280	Before job-start: • Open process chamber door • Check Guard master lock for tight fit During job: • Check door status on PSW • Try to open process chamber door during exposure	Before job-start: • No damages During job: • Door status is locked • Process chamber door cannot be opened during exposure		**Pass**
Door Safety RFS	Switch on MAIN switch for the machine. Open front door on the Recirculating filter system by pressing the green ENABLE DOOR button. The indication for the button changes from green to red. After approx. one minute, close front door on the Recirculating filter system. The indication for the ENABLE DOOR button changes from red to green. Try to open front door.	Door cannot be opened after pressing the ENABLE DOOR button. Indication switches from green to red. Door cannot be opened without pressing the ENABLE DOOR button.		**Pass**

Door safety electrical cabinet	Try to open the door of the electrical cabinet when MAIN SWITCH of the machine is switched on.	Door cannot be opened.		**Pass**
Alarms	Check alarm levels and sensor analog.	Levels are set according to reference document. GFG sensor triggers the alarm.		**Pass**
System Off	Switch on the machine: • Start-up the system • Open the "Adjust" window in the process software • Adjust the speed of the recoater to 40 mm/s. Move the recoater to the right end position • "Home" the recoater • When the recoater reaches the middle position, press "EMERGENCY STOP"	"EMERGENCY STOP" button clicks into place and the movement of the recoater stops immediately. A message must appear on the screen. The recoater must not be able to move with the "EMERGENCY STOP" button pressed.		**Pass**
Laser guidance system and covers check	Open left optic cover. Open rear machine cover. Check the laser guiding for damages. Check laser guiding is connected to collimator. Check safety covers at collimator.	No damages and all covers are mounted.		**Pass**

IQ – System Checks – Gas System				
Step	**Method**	**Expected Result**	**Actual Result**	**PASS/FAIL**
Oxygen Standard Test	Open process chamber door. Wait until chamber is flooded with ambient air (approx. 60 s). Press button O_2 -Sensor-Test. Check status of O_2 -Sensor-Test at PSW in register 'machine'.	Status in PSW is passed.		**Pass**
Oxygen accuracy (0–100%)	Check display of O_2-measuring system on the rear side of the machine. Check O_2 -Level at PSW in register 'machine'.	O_2 -Level: 20.9% ±2% Both displayed values match.		**Pass**
Gas leakage	Check gas leakage analog to reference document.	Duration of pressure drop: • 30 hPa–20 hPa ≥ 2 min.	23.7 min	**Pass**

<table>
<tr><th colspan="5">IQ – System Checks – Laser</th></tr>
<tr><th>Step</th><th>Method</th><th>Expected Result</th><th>Actual Result</th><th>PASS/FAIL</th></tr>
<tr>
<td>Laser power at process chamber M280</td>
<td>Switch off 'Main Switch' of the machine.
Place coding plug XS 14.3 to overwrite oxygen safety circuit.
Switch on 'Main Switch' of the machine.
Start-up PSW.

<u>200 W Power-meter measurement:</u>

Set up probe for laser power meter on a block in the middle of the building platform.
Feed data cable and mains cable from the probe through the opening in the process chamber roof to the outside.
Connect cables.
On the Laser tab in the HWI-Status window select the "Red Pilot" Laser check box.
Align the Ophir power meter.
Close process chamber door.
Turn On Ophir power meter and perform zeroing.</td>
<td>200 W: Power measured by power meter

<table><tr><td>Limit [W]</td><td>≥ 185</td></tr></table></td>
<td>200 W: Power measured by power meter

<table><tr><td>Value [W]</td><td>220.2</td></tr><tr><td>Limit [W]</td><td>≥ 185</td></tr></table></td>
<td>Pass</td>
</tr>
</table>

	Select register 'laser power' in Galvocon menu. • Set laser power to 100%. • Set Duration to 40000 ms. • Click on 'Shot' in register 'laser power'. • Leave laser switched on for approximately 30 s. • Switch laser off. Open process chamber door. Read measured value. Clean up system.			
XY Scanner accuracy grid exposure	Switch off 'Main Switch' of the machine. Place coding plug XS 14.3 to overwrite oxygen safety circuit. Switch on 'Main Switch' of the machine. Start-up PSW • Open menu ‘process’ and select register ‘Adjust’ • Adjust building platform carrier to the level of the blades			**Pass**

	• Open process chamber door
	• Place prepared calibration plate in the middle of the building platform carrier
	• Close process chamber door
	• Lower building platform carrier by the following amount: Thickness of the calibration plate + thickness of the film
	• Check correction table:
	  o Select the ‘Correction table settings’ tab in the GALVOCON GUI window
	  o Check the CorrTab type is set to ‘M’ in the CorrTab settings group box
	• Switch on compressed air supply
	• Open register 'HWI Status' and select 'Inert gas'
	• Select ‘compressed air supply’ check box
	• Select register ‘Vario Optic’ in the GALVOCON GUI window and set 'focus' to contour			

<table>
<tr>
<td></td>
<td>

Select register ‘calibration’ in GALVOCON menu
Set laser power to 40 W
Set scan speed to 400mm/s
Click ‘Exposure’ button
Once the exposure is complete, remove calibration plate from the process chamber and wipe off with a damp cloth

</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XY Scanner accuracy grid analysis</td>
<td>Check distances between the exposed comers, and measure distances every 5 mm.

To achieve a high measuring accuracy, it is sensible to measure the distance over several exposed comers and then to divide the nominal.

Scan calibration grid with external EOS Portable Calibration Scanner.

Analyse the grid using EOSCALIB.</td>
<td>Expected results:

<table>
<tr><td></td><td>Limit [mm]</td></tr>
<tr><td>Std - x</td><td>0.020</td></tr>
<tr><td>Std - y</td><td>0.020</td></tr>
<tr><td>Err - x</td><td>0.060</td></tr>
<tr><td>Err - y</td><td>0.060</td></tr>
</table>
</td>
<td>Actual results:

<table>
<tr><td></td><td>Limit [mm]</td><td>Value [mm]</td></tr>
<tr><td>Std - x</td><td>0.020</td><td>0.14</td></tr>
<tr><td>Std - y</td><td>0.020</td><td>0.018</td></tr>
<tr><td>Err - x</td><td>0.060</td><td>0.045</td></tr>
<tr><td>Err - y</td><td>0.060</td><td>0.048</td></tr>
</table>
</td>
<td>Pass</td>
</tr>
<tr><td colspan="5"></td></tr>
</table>

<table>
<tr><th colspan="5">IQ – System Checks – Mechanics</th></tr>
<tr><th>Step</th><th>Method</th><th>Expected Result</th><th>Actual Result</th><th>PASS/FAIL</th></tr>
<tr>
<td>Z-axis building platform:
20 µm steps</td>
<td>Switch on the machine.

Start up the PSW system:
• Open the “Adjust” window in the process software
• Perform homing of the building platform
• Set the speed of the building platform to 3.5 mm/s
• Set the movement parameter to 0.020 mm
• Move the building platform two times down
• Position precise test gauge and set to zero
• Click on the down arrow to move the building platform 0.020 mm down
• Read the measured value of the test gauge and note it down
Repeat the steps for 10 times until the building platform has moved 0.1 mm down</td>
<td>Expected results:

0.020 mm ± 0.002 mm for each step</td>
<td>Z-axis – 20 µm steps
<table><tr><th></th><th>Value</th></tr><tr><td>1</td><td>0.021</td></tr><tr><td>2</td><td>0.020</td></tr><tr><td>3</td><td>0.021</td></tr><tr><td>4</td><td>0.018</td></tr><tr><td>5</td><td>0.020</td></tr></table>
0.020 mm ± 0.002 mm</td>
<td>Pass</td>
</tr>
</table>

<table>
<tr>
<td>Z-axis building platform:
40 µm steps</td>
<td>Switch on the machine.

Start up the PSW system:
• Open the “Adjust” window in the process software
• Perform homing of the building platform
• Set the speed of the building platform to 3.5 mm/s
• Set the movement parameter to 0.040 mm
• Move the building platform two times down
• Position precise test gauge and set to zero
• Click on the down arrow to move the building platform 0.040 mm down
• Read the measured value of the test gauge and note it down
Repeat steps for 10 times until the building platform has move 0.1 mm down</td>
<td>Expected results:

0.040 mm ± 0.002 mm for each step</td>
<td>Z-axis – 40 µm Steps
<table><tr><th></th><th>Value</th></tr><tr><td>1</td><td>0.041</td></tr><tr><td>2</td><td>0.040</td></tr><tr><td>3</td><td>0.038</td></tr><tr><td>4</td><td>0.041</td></tr><tr><td>5</td><td>0.040</td></tr></table>
0.040 mm ± 0.002 mm</td>
<td>Pass</td>
</tr>
<tr>
<td colspan="2">The same procedure was followed with the Z axis dispenser platform as well as the Z axis collection platform</td>
<td></td>
<td>Both tests were acceptable and in tolerance</td>
<td>Pass</td>
</tr>
</table>

<table>
<tr>
<td>Recoater movement</td>
<td>Open the “Adjust” window in the PSW software:
Perform recoater homing
Move the recoater to the right end position
Set the recoater speed to 50 mm/s
Set the step movement to 500 mm
Click on the arrow in the adjust window to start the movement and activate the stop watch at the same time
Stop measuring at the time when the recoater has reached the end position
Recoater speed = 500 mm / measured time</td>
<td>Expected result:

50 mm/s ± 10 mm/s</td>
<td>Actual result:

Recoater speed

<table><tr><td>Value [mm]</td><td>52</td></tr></table>
50 mm/s ± 10 mm/s</td>
<td>Pass</td>
</tr>
</table>

Deviations of IQ

Any deviations reported during the IQ must be listed in Table 3.44. For each deviation, a "Corrective Action" must be specified and the impact of the deviation on the EOSINT M280 must be assessed. A deviation does not necessarily invalidate the qualification, however, the Validation Manager must analyse, document and conclude on any deviation within this document.

Table 3.44: Deviations of IQ

IQ Step	Deviation/Comment	Next Step/Corrective action
None	None	None

Decision criteria

All IQ requirements must be passed and all test equipment must have valid calibration status and report in order to close this qualification. In case of any non-conformity, actions implemented must be closed or followed up with a consistent action plan. Any deviation from requirements of this protocol does not necessarily invalidate the qualification. However, the assigned Validation Manager must analyse, document and conclude on any deviation within this document.

Conclusion

EOSINT M280 SI 1191 passed all IQ requirements

Attachments

- Calibration certificates
- Training records

3.10.2.2 Operational Qualification

The purpose of this document is to establish a protocol on the OQ, including plan and report of qualification steps. Successful completion of the OQ will ensure that the equipment is ready for routine usage. Reference documents used for supporting this OQ development will be the IQ protocol and report, SOPs and technical documents. The OQ applies to the EOSINT M280 laser sinter system, serial number 1191.

Installation Qualification (IQ) prerequisite

Prior to the OQ, an IQ must be completed and approved in the Qualification Summary Report before the OQ can be performed. There are two types of OQ, namely Initial and Follow-up OQs, as shown in Table 3.45. Depending on the type of OQ, certain qualification steps of this protocol apply.

Table 3.45: OQ qualification steps to be performed

OQ type		Qualification steps to be performed
Initial OQ	X	The Initial OQ is performed directly after the IQ. In this case, the OQ steps of this protocol must be performed. The IQ steps of this protocol will be skipped
Follow-up OQ		The Follow-up OQ is performed more than six months after the IQ. In this case, the OQ and IQ steps of this protocol must be performed.

OQ Execution and SOP verification

It must be verified that all SOPs associated with the EOSINT M280 have been fully documented. Each SOP must be clear and relevant and approved as a controlled document. The relevant personnel must be familiar with each SOP and trained in the implementation of them. This is done by completing the SOP verification tables below and verifying that each SOP is a controlled document at the time of OQ. The content of each SOP must be reviewed and ensured that all procedures are clear and can be performed.

Acceptance criteria

- All SOPs are available as approved documents and listed in the verification Table 3.46.
- Training records are available to indicate that relevant personnel have been trained in the content of the listed SOPs.

Table 3.46: OQ Checklist (CRPM ISO 13485: 2016 Quality Management System)

OQ – Laser Sinter Part Design					
Step	**Method**	**Expected Result**	**Actual Result**	**Performed By**	**PASS/FAIL**
1) Implant Design (SOP)	The objective of this test is to check the SOP for Implant Design	1. The SOP is a controlled document and is available for the operator	Document available WI-PT-03	Operations Quality Assurance	**PASS**
	1. Check that a SOP for Implant Design is available	2. Document is approved	Document approved		
	2. Check the recommended SOP content:	3. Procedures are clear	Procedures are clear		
		4. Procedures can be performed	Procedures can be performed		

Table 3.46 continued: OQ Checklist

OQ – Data Preparation					
Step	**Method**	**Expected Result**	**Actual Result**	**Responsible Person**	**PASS/FAIL**
2) Data Preparation (SOP)	The objective of this test is to check the SOP for Data Preparation 1. Check that a SOP for Data Preparation is available 2. Check the recommended SOP content: a. Generating of slice (SLI) files b. Load/Creation of jobs c. Part positioning d. Selection of part/support exposure parameter set	1. The SOP is a controlled document and is available for the operator	Document available WI-PT-02	Operations Quality Assurance	**PASS**
		2. Document is approved	Document approved		
		3. Procedures are clear including understandable instructions	Procedures are clear		
		4. Procedures can be performed	Procedures can be performed		

Table 3.46 continued: OQ Checklist

OQ – Material Handling					
Step	**Method**	**Expected Result**	**Actual Result**	**Responsible Person**	**PASS/FAIL**
3) Material Handling (SOP)	The objective of this test is to check the SOP for Material Handling 1. Check that a SOP for Material Handling is available 2. Check the recommended SOP content: a. Material Storage b. Loading machine with feedstock c. Material refreshment/ Recycling d. Material sieving e. Material drying f. Cleanliness/Risk of contamination	1. The SOP is a controlled document and is available for the operator	Document available WI-PT-05	Operations Quality Assurance	**PASS**
		2. Document is approved	Document approved		
		3. Procedures are clear including understandable instructions	Procedures are clear		
		4. Procedures can be performed	Procedures can be performed		

Table 3.46 continued: OQ Checklist

OQ – Machine Setup					
Step	**Method**	**Expected Result**	**Actual Result**	**Responsible Person**	**PASS/FAIL**
4) Machine Setup (SOP)	The objective of this test is to check SOP for Machine Set-up 1. Check that a SOP for Machine Set-up is available 2. Check the recommended SOP content: a. Check the condition of recoater b. Check laser power using pocket monitor c. Adjusting of building platform d. Homing of all axes	1. The SOP is a controlled document and is available for the operator	Document available WI-PT-06	Operations Quality Assurance	**PASS**
		2. Document is approved	Document approved		
		3. Procedures are clear including understandable instructions	Procedures are clear		
		4. Procedures can be performed	Procedures can be performed		

Table 3.46 continued: OQ Checklist

OQ – Post Processing					
Step	**Method**	**Expected Result**	**Actual Result**	**Responsible Person**	**PASS/FAIL**
6) Post Processing (SOP) / WI10-14	The objective of this test is to check the SOP for Post Processing 1. Check that a SOP for Post Processing is available 2. Check the recommended SOP content: a. Stress-relieving Procedure b. Part-removal Procedure c. Heat-treating Procedure d. Support removal e. CT-scanning Procedure f. Sterilisation Procedure g. Packaging Procedure h. Labelling Procedure	1. The SOP is a controlled document and is available for the operator	Document available WI-PT-10 to WI-PT-14	Operations Quality Assurance	**PASS**
		2. Document is approved	Document approved		
		3. Procedures are clear including understandable instructions	Procedures are clear		
		4. Procedures can be performed	Procedures can be performed		

Table 3.46 continued: OQ Checklist

OQ – Service/Maintenance

Step	Method	Expected Result	Actual Result	Responsible Person	PASS/FAIL
7) Equipment (Service/ Maintenance) (SOP)	The objective of this test is to check SOP for Service/Maintenance 1. Check that a SOP for Service/Maintenance is available 2. Check the recommended SOP content: a. Description of maintenance activities b. Records of maintenance activities	1. The SOP is a controlled document and is available for the operator	Document available WI-PT-04	Operations Quality Assurance	**PASS**
		2. Document is approved	Document approved		
		3. Procedures are clear including understandable instructions	Procedures are clear		
		4. Procedures can be performed	Procedures can be performed		

Table 3.46 continued: OQ Checklist

OQ – Operator Training					
Step	**Method**	**Expected Result**	**Actual Result**	**Responsible Person**	**PASS/FAIL**
8) SOP Training Status	The objective of this test is to check that the operators were initially trained on the content of SOPs 1. Check For Work Instruction Training Records 2. Check actual training status	1. Personnel have been trained on content of all SOPs used and evidence is available	Personnel are trained in SOPs	Operations Quality Assurance	**PASS**

3.10.2.3 Performance Qualification

The purpose of this document is to ensure that the EOSINT M280 produces quality parts after the IQ and OQ have been done. Successful completion of the PQ will ensure that the equipment is ready for routine usage. Reference documents used for supporting this PQ development will be IQ, OQ, SOPs and technical documents.

This document applies to the EOSINT M280 laser sintering system, serial number 1191.

The following sub-systems are included in the PQ:

- Laser
- Gas supply (argon)
- Mechanical

Performance Qualification (PQ) prerequisites

The EOSINT M280 must pass IQ and OQ before the PQ can be performed. The AM company management representative will sign off the IQ and OQ for this specific machine when completed.

Performance Qualification excecution

The focus of the PQ will be dimensional accuracy, mechanical properties and repeatability on the EOSINT M280. Normal production practice will be implemented to manufacture a quality assurance sample on the EOSINT M280. Standard, closed-parameter settings will be used during manufacturing. EOSTATE software module will monitor:

- Platform temperature
- Laser output
- Oxygen concentration

After the build, a detailed report of the manufacturing process will be generated.

Procedural steps – dimensional accuracy

1. Prepare sample for build on software, as shown in Figure 3.20. During the machine's installation, a quality assurance part was manufactured and evaluated. For the purpose of this PQ, the same part will be manufactured and evaluated for comparison.

   Follow SOP: DATA PREPARATION (WI-PT-02)

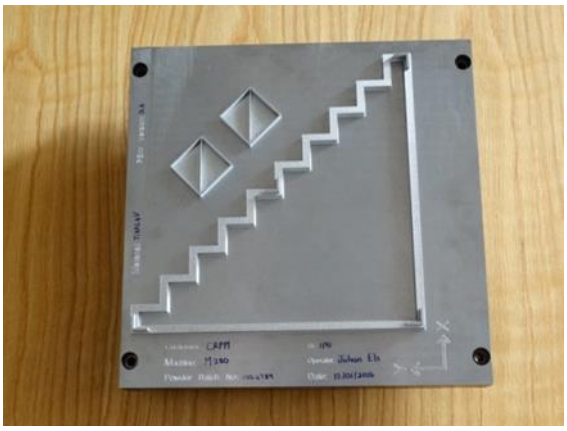


Figure 3.20: Sample geometry for PQ

2. Prepare EOSINT M280 machine and manufacture part.
   Follow SOP: MACHINE SETUP (WI-PT-06)

3. Measure sample.

Table 3.47 shows the dimensional accuracy when the machine was installed in 2012 and then retested in 2016. Some of the dimensions were out of tolerance and the laser scanner of the machine will be calibrated on the next service visit. As implants are manufactured, extra material is added to the design to ensure enough material is available for the polishing procedure afterwards.

Table 3.47: Dimensional accuracy tested in 2012 and 2016

M 280 (1191)									
Date	19 July 2012				25 January 2016				
	Measured	Actual	Difference	% Accuracy	Measured	Actual	Difference	% Accuracy	Change
X1 I	9.995	10	-0.005	99.95%	9.839	10	-0.161	98.39%	1.56%
X2 I	29.964	30	-0.036	99.88%	29.874	30	-0.126	99.58%	0.30%
X3 I	50.024	50	0.024	100.05%	49.923	50	-0.077	99.85%	0.20%
X4 I	70.011	70	0.011	100.02%	69.967	70	-0.033	99.95%	0.06%
X5 I	90.015	90	0.015	100.02%	89.975	90	-0.025	99.97%	0.04%
X6 I	110.02	110	0.02	100.02%	109.992	110	-0.008	99.99%	0.03%
X7 I	130.041	130	0.041	100.03%	129.993	130	-0.007	99.99%	0.04%
X8 I	150.025	150	0.025	100.02%	150.03	150	0.03	100.02%	0.00%
X9 I	170.048	170	0.048	100.03%	169.955	170	-0.045	99.97%	0.05%
X10 I	190.044	190	0.044	100.02%	189.972	190	-0.028	99.99%	0.04%
Y1 I	9.997	10	-0.003	99.97%	9.906	10	-0.094	99.06%	0.91%
Y2 I	29.972	30	-0.028	99.91%	29.962	30	-0.038	99.87%	0.03%
Y3 I	49.999	50	-0.001	100.00%	49.938	50	-0.062	99.88%	0.12%
Y4 I	69.963	70	-0.037	99.95%	69.98	70	-0.02	99.97%	0.02%
Y5 I	89.982	90	-0.018	99.98%	90.034	90	0.034	100.04%	0.06%
Y6 I	109.989	110	-0.011	99.99%	110.063	110	0.063	100.06%	0.07%
Y7 I	129.979	130	-0.021	99.98%	130.035	130	0.035	100.03%	0.04%
Y8 I	149.996	150	-0.004	100.00%	150.004	150	0.004	100.00%	0.01%
Y9 I	169.986	170	-0.014	99.99%	170.01	170	0.01	100.01%	0.01%
Y10 I	189.961	190	-0.039	99.98%	189.863	190	-0.137	99.93%	0.05%
X1 O	20.034	20	0.034	100.17%	20.132	20	0.132	100.66%	0.49%
X2 O	40.02	40	0.02	100.05%	40.147	40	0.147	100.37%	0.32%
X3 O	60.032	60	0.032	100.05%	60.142	60	0.142	100.24%	0.18%
X4 O	79.954	80	-0.046	99.94%	80.154	80	0.154	100.19%	0.25%
X5 O	100.064	100.1	-0.036	99.96%	100.13	100.1	0.03	100.03%	0.07%
X6 O	120.038	120	0.038	100.03%	120.147	120	0.147	100.12%	0.09%
X7 O	140.045	140	0.045	100.03%	140.134	140	0.134	100.10%	0.06%
X8 O	160.057	160.1	-0.043	99.97%	160.178	160.1	0.078	100.05%	0.08%
X9 O	180.049	180	0.049	100.03%	180.187	180	0.187	100.10%	0.08%
X10 O	200.065	200.1	-0.035	99.98%	200.183	200.1	0.083	100.04%	0.06%
Y1 O	20.021	20	0.021	100.11%	20.073	20	0.073	100.37%	0.26%
Y2 O	40.032	40	0.032	100.08%	40.096	40	0.096	100.24%	0.16%
Y3 O	60.029	60	0.029	100.05%	60.145	60	0.145	100.24%	0.19%
Y4 O	80.052	80.1	-0.048	99.94%	80.085	80.1	-0.015	99.98%	0.04%
Y5 O	100.002	100	0.002	100.00%	100.168	100	0.168	100.17%	0.17%
Y6 O	120.014	120	0.014	100.01%	120.185	120	0.185	100.15%	0.14%
Y7 O	140.036	140	0.036	100.03%	140.166	140	0.166	100.12%	0.09%
Y8 O	160.033	160	0.033	100.02%	160.196	160	0.196	100.12%	0.10%
Y9 O	180.001	180	0.001	100.00%	180.205	180	0.205	100.11%	0.11%
Y10 O	199.975	200	-0.025	99.99%	200.211	200	0.211	100.11%	0.12%

4. Evaluate data, as shown in Figure 3.21.

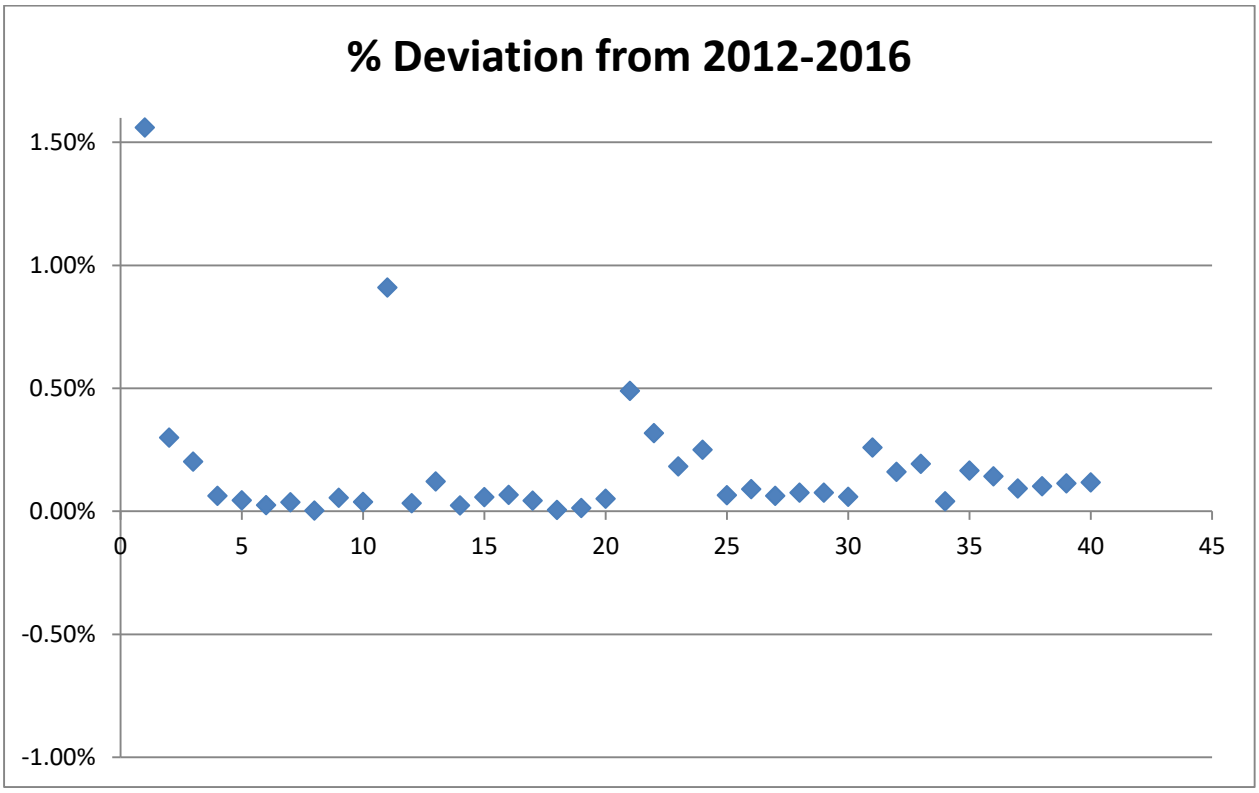


Figure 3.21: Dimensional accuracy deviation plot

5. Acceptance criteria

   The allowable tolerance is ±50 µm deviations.

Remarks

The machine does not perform according to manufacturer's specification, but is still within tolerance for implant manufacturing, as an extra 0.5 mm stock is added to the geometry for polishing afterwards. From the IQ (point 4.11.2) the scanner will be adjusted at the next service, which will improve dimensional accuracy.

Procedural Steps – Mechanical properties & repeatability

The repeatability of the mechanical properties of parts produce on EOSINT metal machine must be tested on various positions on the platform. The following steps will be taken to validate these properties:

1. Prepare samples for build on software, as shown in Figure 3.22.

.

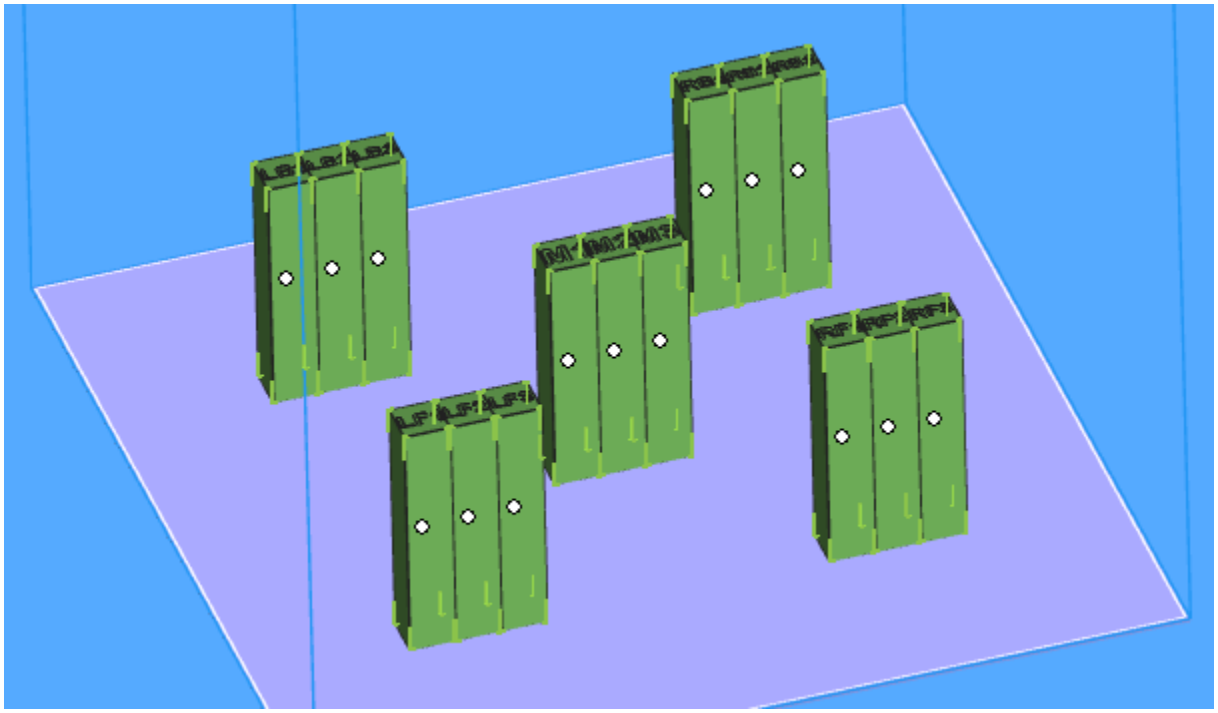


Figure 3.22: Tensile test sample geometry

2. Do destructive testing of three samples at each position to find an average value.
3. Evaluate data, as shown in tables 3.48 and 3.49.
4. Compare results to acceptable results from manufacturer.

Table 3.48: Ultimate Tensile Strength (UTS) results

Position	UTS (MPa)
Left Back 1	1250.940
Left Back 2	1250.280
Left Back 3	1264.450
Average	1255.223

Position	UTS (MPa)
Middle 1	1285.130
Middle 2	1279.260
Middle 3	1282.130
Average	1282.173

Position	UTS (MPa)
Right Back 1	1254.430
Right Back 2	1237.850
Right Back 3	1240.800
Average	1244.360

Position	UTS (MPa)
Left Front 1	1275.180
Left Front 2	1275.400
Left Front 3	1292.320
Average	1280.967

Position	UTS (MPa)
Right Front 1	1288.590
Right Front 2	1265.470
Right Front 3	1268.020
Average	1274.027

Table 3.49: Percentage Elongation results

Position	% Elongation
Left Back 1	11.510
Left Back 2	11.360
Left Back 3	11.610
Average	11.493

Position	% Elongation
Middle 1	9.440
Middle 2	9.490
Middle 3	9.550
Average	9.493

Position	% Elongation
Right Back 1	11.310
Right Back 2	11.360
Right Back 3	11.210
Average	11.293

Position	% Elongation
Left Front 1	9.600
Left Front 2	9.300
Left Front 3	10.250
Average	9.717

Position	% Elongation
Right Front 1	8.530
Right Front 2	9.900
Right Front 3	10.200
Average	9.543

*** Destructive testing was done at CSIR, which is a certified laboratory.**

UTS remarks

From the results, it can be seen in Figure 3.23 that the UTS exceeds the minimum requirement of 1170 MPa (red line). The results are comparable to the machine manufacturer's (EOS) results for as-built samples, as shown in Figure 3.25.

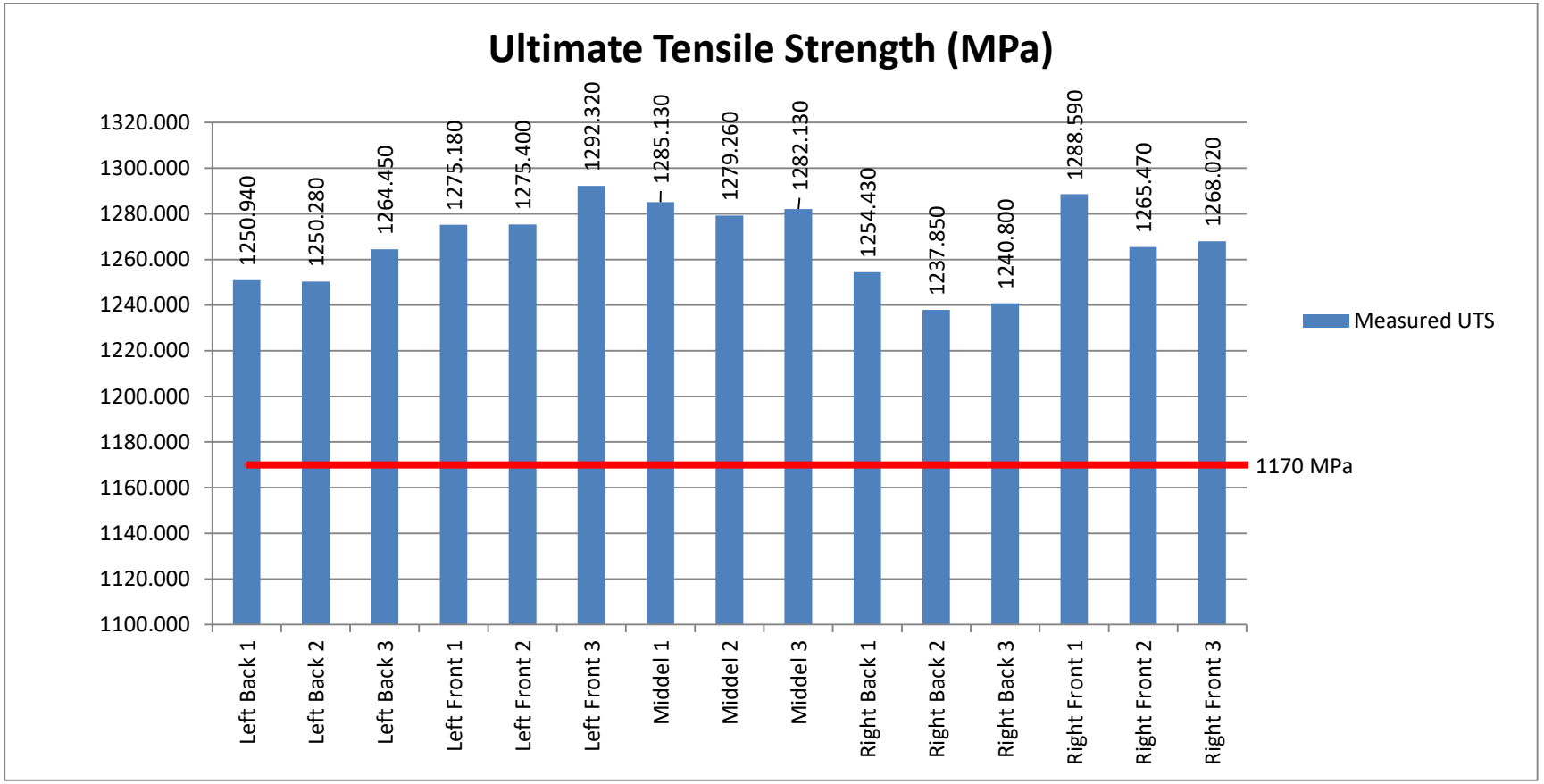


Figure 3.23: Machine UTS results compared to EOS data

Elongation remarks

From the results, it can be seen in Figure 3.24 that the percentage elongation exceeds the minimum requirement of 8%. The results are comparable to the machine manufacturer's (EOS) results for as-built samples, as shown in Figure 3.25.

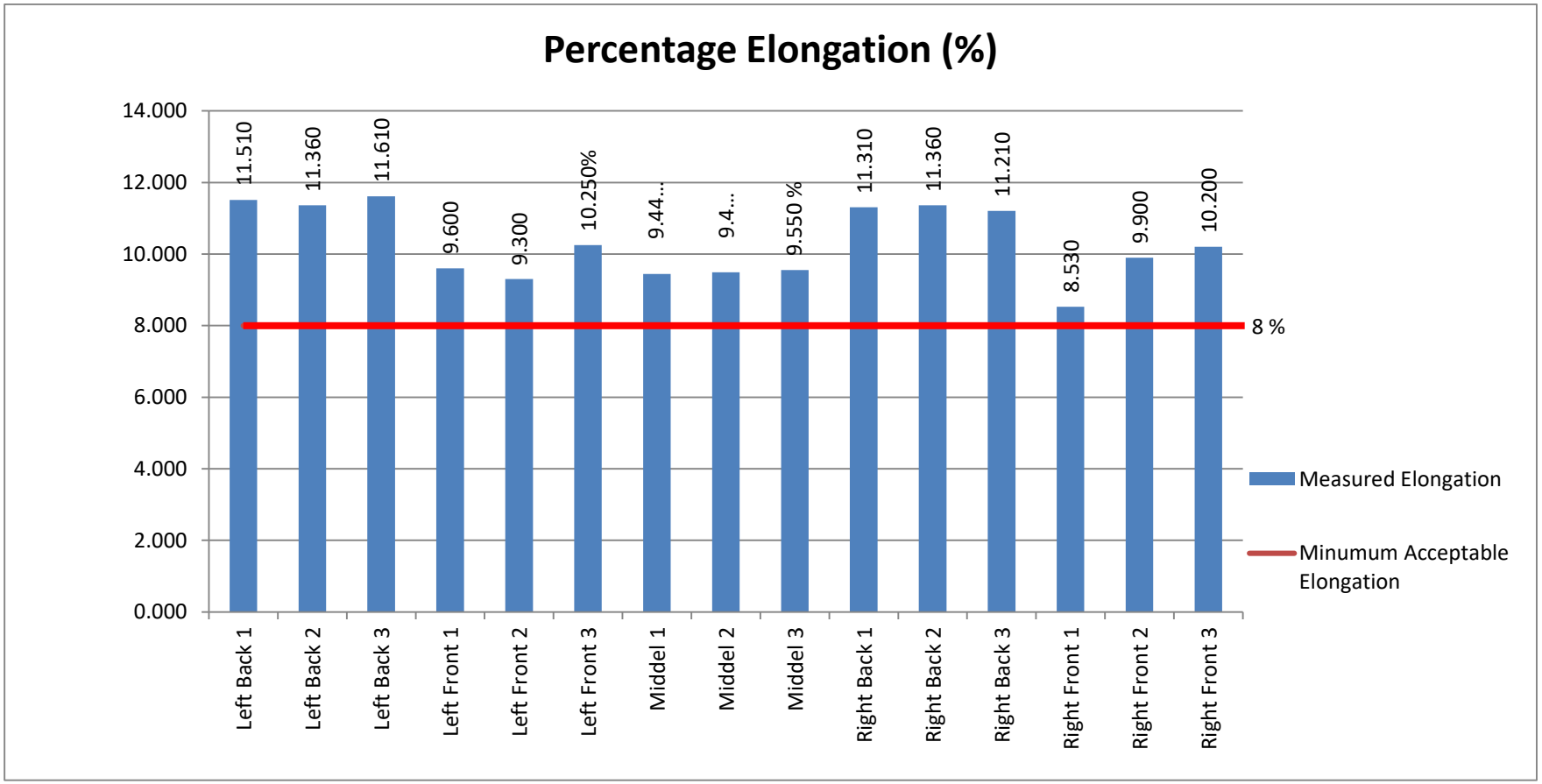


Figure 3.24: Percentage elongation results compared to EOS data

Material data sheet

Mechanical properties of parts

	As built	Heat treated [6]
Tensile strength [5]		
- in horizontal direction (XY)	typ. 1230 ± 50 MPa typ. 178 ± 7 ksi	min. 930 MPa (134.8 ksi) typ. 1050 ± 20 MPa (152 ± 3 ksi)
- in vertical direction (Z)	typ. 1200 ± 50 MPa typ. 174 ± 7 ksi	min. 930 MPa (134.8 ksi) typ. 1060 ± 20 MPa (154 ± 3 ksi)
Yield strength ($R_{p0.2}$) [5]		
- in horizontal direction (XY)	typ. 1060 ± 50 MPa typ. 154 ± 7 ksi	min. 860 MPa (124.7 ksi) typ. 1000 ± 20 MPa (145 ± 3 ksi)
- in vertical direction (Z)	typ. 1070 ± 50 MPa typ. 155 ± 7 ksi	min. 860 MPa (124.7 ksi) typ. 1000 ± 20 MPa (145 ± 3 ksi)
Elongation at break [5]		
- in horizontal direction (XY)	typ. (10 ± 2) %	min. 10 % typ. (14 ± 1 %)
- in vertical direction (Z)	typ. (11 ± 3) %	min. 10 % typ. (15 ± 1 %)
Modulus of elasticity [5]		
- in horizontal direction (XY)	typ. 110 ± 10 GPa typ. 16 ± 1.5 Msi	typ. 116 ± 10 GPa typ. 17 ± 1.5 Msi
- in vertical direction (Z)	typ. 110 ± 10 GPa typ. 16 ± 1.5 Msi	typ. 114 ± 10 GPa typ. 17 ± 1.5 Msi
Hardness [7]	typ. 320 ± 12 HV5	

[5] Tensile testing according to ISO 6892-1:2009 (B) Annex D, proportional test pieces, diameter of the neck area 5 mm (0.2 inch), original gauge length 25 mm (1 inch).

[6] Specimens were treated at 800 °C (1470 °F) for 4 hours in argon inert atmosphere. Mechanical properties are expressed as minimum values to indicate that mechanical properties exceed the minimum requirements of material specification standards. ASTM F1472-08. By fulfilling these minimum values, also the specifications of standards ASTM B348-09 and ISO 5832-3:2000 are meet.

[7] Vickers hardness measurement (HV) according to EN ISO 6507-1 on polished surface. Note that measured hardness can vary significantly depending on how the specimen has been prepared.

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Figure 3.25: As built and after heat treatment mechanical properties as per EOS data sheet

Revalidation criteria

Revalidation will be required in the event of the following:

- Change in manufacturing process
- Change in critical components (laser, scanner)
- Change in supplier

The AM company Management Representative will verify and sign for the PQ approval.

Chapter 4 - Results and Discussion

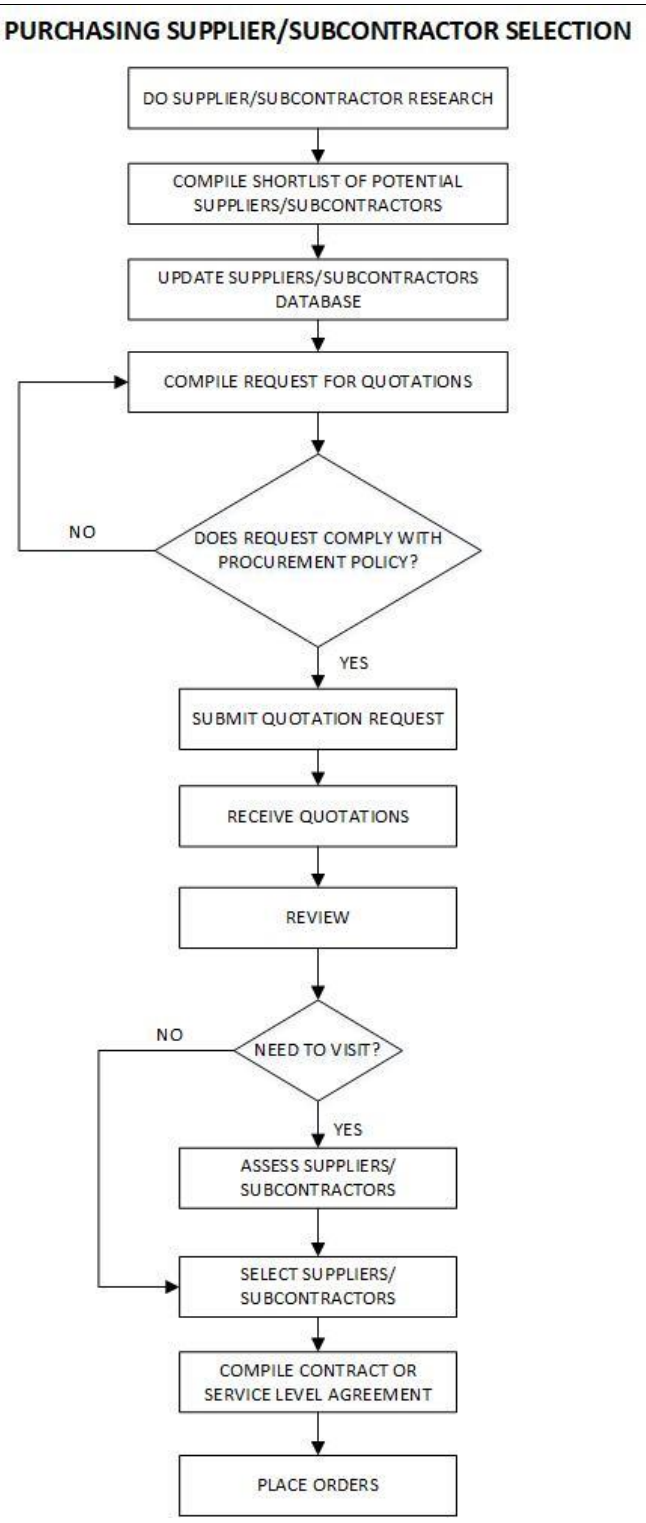
The two procedures, SOPs, supportive documents and validations with the highest cumulative risk number will be discussed in the following sections. Any risk with a level of 3 to 4 will be addressed. Risk identification and mitigation must be seen as a continual improvement process and will need to be evaluated annually.

4.1 Risk Mitigation through the Procedure for Purchasing and the Control of Suppliers

Table 4.1 will address ways to mitigate risks that were identified in Table 3.26 through the Procedure for Purchasing and the Control of Suppliers.

Table 4.1: Risk mitigation through the Procedure for Purchasing and the Control of Suppliers

Name of procedure	Procedure for Purchasing and the Control of Suppliers
Purpose	The purpose of this document is to define the procedure used by the AM company for supplier selection, subcontractual work delegation and purchasing of equipment, components, packaging material and consumables.
Scope	This document is used to direct the purchasing function within the AM company in terms of long-, medium- and short-term planning of the purchasing system
Flow Diagram description	The first step is to research possible suppliers for the particular area of interest, whereafter a shortlist of potential suppliers is compiled. A request for quotations with all relevant specifications is sent to the suppliers. It is important to verify that the request and suppliers comply with the AM company's procurement policy. The quotations are then reviewed. It could be necessary to do a site visit of potential critical suppliers before the suppliers are appointed. A Service Level Agreement will be agreed upon that stipulates specifications, quality assurance, turnaround time and process parameters, where the supplier does not have

	an ISO system in place. However, it is preferable that the supplier operates within an ISO system. The supplier approval and yearly evaluation is handled by the ISO EXCO and ISO Management Review Committee. Once the supplier has been approved and a Service Level Agreement is in place, the AM company may order from the supplier.
Flow Diagram	

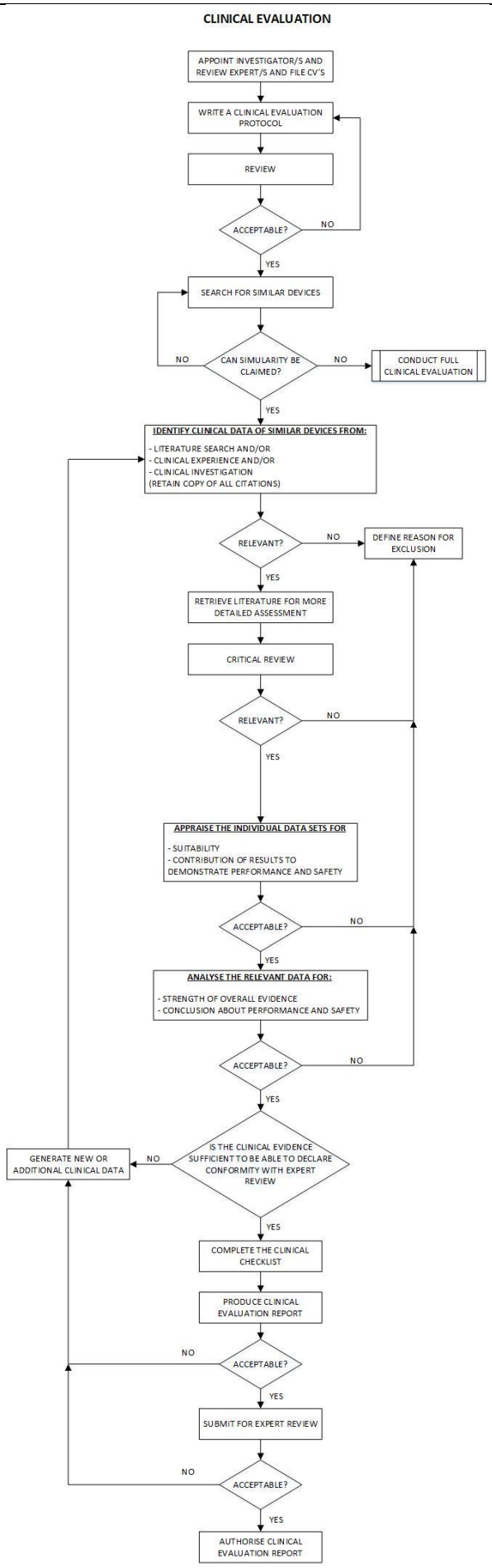
Key risks identified from Table 3.26		How will this procedure reduce these risks?	
	Initial risk index		Mitigated risk index
Certificate of Analysis with powder delivery	1	As shown in the flow diagram above, after the supplier is selected, a Supplier Contract or Service Level Agreement is developed. The agreement should state clearly that a Certificate Of Analysis must be supplied with each powder delivery to ensure traceability of the powder.	1
Conduct local chemical analysis with powder delivery	2	If a decision is taken to check the Certificate Of Analysis locally, as an additional precautionary measure, and non-conformities are found, a formal supplier complaint must be initiated.	1
NDT facility not available for urgent cases	4	As the NDT is outsourced, a Service Level Agreement with the supplier will be signed. The availability of this facility and turnaround time is to be stipulated in the agreement. The supplier will also be required to advise the AM company if major machine maintenance needs to be done on their equipment that could affect the turnaround time.	1
DT facility not available for urgent cases	3	As the DT is currently being outsourced, a Service Level Agreement with this supplier will be signed. The availability of this facility and turnaround time is to be stipulated in the agreement. The supplier will also be required to advise the AM company if major machine maintenance has to be done on their equipment that could affect the turnaround time.	1

4.2 Risk Mitigation through Procedure for Clinical Evaluations

Table 4.2 will address ways to mitigate risks that were identified in Table 3.26 through the Procedure for Clinical Evaluations.

Table 4.2: Risk Mitigation through the Procedure for Clinical Evaluations

Name of procedure	Procedure for Clinical Evaluations
Purpose	The purpose of this document is to define the procedure followed by the AM company in conducting Clinical Evaluations on a medical device using a scientific method.
Scope	This document is applicable to all Clinical Evaluations done on medical devices (custom-made and mass-produced) developed and manufactured.
General	The AM company needs to monitor and measure the characteristics of the AM custom-made medical devices to verify that requirements have been met. This is achieved by follow-up on patients by the Clinical Advisor. Records and photos are kept in the Patient File. Where possible, monitoring is done directly after the operation, six-weekly, annually and after five years.
Flow Diagram description	Firstly, it is important to appoint an investigator, and in this case it will be the Clinical Advisor, who is a specialist doctor. The Clinical Advisor will write and review the protocol and will be responsible to research similar devices and compile a Literature-, Clinical Experience- and Clinical Investigation Report. This will be followed by a critical review of all these reports and appraisal of the data sets for suitability and contribution of results to demonstrate performance and safety. Thereafter, an analysis of the relevant data for strength of overall evidence and conclusion about performance and safety are documented. The clinical evidence must be sufficient for the Expert Review (ER) panel to declare conformity. The Clinical Evaluation Report is then submitted to the ER panel and if accepted, the ER panel will authorise this report.

Flow Diagram	

Key risks identified in Table 3.26		How will this procedure reduce these risks?	
	Initial risk index		Mitigated risk index
Coating process not biocompatible	2	The biocompatibility of the coating or any material will be exposed during the thorough literature study as part of the Clinical Evaluation Report.	1
Sterilisation process not effective enough	3	The sterilisation is an outsourced process and the AM company supplies the implants and guides as non sterile biologically deactivated, as described in the Instructions for Use (IFU), seen in section 3.9.	2
Sterilisation process not repeatable	3	The sterilisation is an outsourced process and the AM company will supply the implants and guides as non sterile biologically deactivated, as described in the Instructions for Use (IFU), seen in section 3.9.	2

4.3 Risk Mitigation through the Machine Setup SOP

Table 4.3 will address ways to mitigate risks that were identified in Table 3.26 through the EOSINT Metal Machine Setup SOP.

Table 4.3: Risk Mitigation through EOSINT Metal Machine Setup SOP

Name of SOP	Machine Setup		
Parent document	Procedure for AM		
Key risks identified from Table 3.26		How will this SOP or other SOPs reduce these risks?	
	Initial risk index		Mitigated risk index
Improper in-house machine calibration and maintenance	1	The in-house machine calibration and maintenance is extensively described, planned and executed in the Machine Maintenance and Calibration SOP. A copy of this SOP is available on request.	1
Incorrect substrate tolerances	2	The Surface Grinding SOP was developed as this is an outsourced process. The tolerance was set to 45 µm ± 5 µm of flatness on the top surface where parts will be manufactured. A quality check will be performed and signed off with each product. A copy of this SOP is available on request.	1
Incorrect platform alignment	2	Points 3.1 to 3.10 of the Machine Setup SOP (**WI-PT-06)** describes the procedure to be followed to minimise the risk of incorrect platform alignment.	1

Inadequate operator training	1	The Procedure for Human Resource Management and Training covers this potential risk and prescribes operator training, including the Training Capability Matrix.	1
Inconsistent machine performance	2	This is covered and mitigated through the machine under 3.10.2 on page 144.	1
First exposure not penetrating into substrate	1	Visual inspection when the SLM process is started. This risk is minimised when the platform alignment and tolerance is done correctly.	1
Incorrect recoating	2	SOP **WI-PT-06,** points 4.1 to 4.4, describe the procedure to follow to minimise the risk of incorrect recoating.	1
Part coming loose from substrate	2	Visual inspection during the SLM process. Application notes on how to optimally support the part and the steps to be followed to minimise the risk of part coming loose from substrate.	1
Insufficient argon supply	1	This is part of the pre-job checks captured on the work order.	1
Air circulation filters clog during build	1	This is part of the pre-job checks captured on the Work Order.	1
Incorrect laser power with pre-check	1	SOP **WI-PT-06,** points 5.1 to 5.11, describe the procedure to follow to minimise the risk of incorrect laser power check before and after build.	1
Incorrect powder handling	1	The SOP for Material Handling explains the correct powder handling procedure.	1`

4.4 Risk Mitigation through the EOSINT Metal Material Handling SOP

Table 4.4 will address ways to mitigate risks that were identified in Table 3.26 through the EOSINT Metal Material Handling SOP.

Table 4.4: Risk Mitigation through the EOSINT Metal Material Handling SOP

Name of SOP	Material Handling		
Parent document	Procedure for AM		
Key risks identified from Table 3.26		How will this SOP reduce these risks?	
	Initial risk index		Mitigated risk index
Uneven recoating • Powder flow ability	1	Prior to loading SLM machine, the virgin powder must be dried in a normal oven at 80 °C for one hour in order to improve the flowability of the powder. This is the first step discussed in 3.6.3.	
Uneven recoating • Operator powder contamination	2	The personal protective equipment is discussed in section 4 of the M280_Training-manual_04-12.pdf. This is to ensure that powder contamination is minimised.	1
Inadequate operator training	1	This is mitigated through the SOPs discussed in 4.10, OQ for EOSINT M280 Machine. The Procedure for Human Resource Management and Training also covers this potential risk and prescribes operator training including the Training Capability Matrix.	1
Powder mixing and sifting	2	This is discussed in the SOP under point 4 and M280_Training-manual_04-12.pdf in section	1

		8.	
Powder storage	2	The powder must be stored in original metal bins filled with argon, as discussed in section 5.5 in M280_Training-manual_04-12.pdf	1
Powder exposed to oxygen at elevated temperatures	2	The EOSINT M280 is a cold bed process and the platform is only pre-heated up to 45 °C to keep the powder dry and the humidity out of the machine. At these low temperatures the titanium will not oxidise and was proved in the CUT master's degree study that focussed on titanium powder aging and chemical analysis of blended batches >15 consecutive builds/job.	1
Powder aging	3	A 100 gram sample of powder is sent to the CSIR (linked to the recycling number) to test the oxygen content and chemical composition of the powder. Powder with an oxygen content higher than 1300 ppm must be refreshed with virgin powder. Maximum oxygen content may not exceed 1500 ppm. A completed CUT master's degree study on the powder aging with blended batches is available on request.	1
Incorrect powder handling	1	This is discussed and mitigated through the procedure shown in M280_Training-manual_04-12.pdf in section 8.26. This EOS training manual is available on request.	1

4.5 Risk Mitigation through SLAs as Part of Supportive Documentation

Table 4.5 will address ways to mitigate risks that were identified in Table 3.26 through SLAs as part of supportive documentation.

Table 4.5: Risk mitigation through SLAs as part of supportive documentation

Name of supportive document or protocol	Service Level Agreement		
Parent document	Procedure for Purchasing and the Control of Suppliers		
Key risks identified from Table 3.26		How will this supportive document reduce these risks?	
	Initial risk index		Mitigated risk index
NDT reports not capturing correct information	2	The annexure attached to the standard SLA will state exactly what information must be captured in feedback reports. For example, aspects such as pore sizes and position, density of part and micro-CT scan slice thickness need to be captured.	1
NDT facility not available for urgent cases	4	The SLA will address issues such as lead times, performance monitoring, payment and minimum processing time for urgent cases	2
Machining of samples for DT not consistent	3	The machining of DT samples is currently an outsourced process and the SLA between the service provider and AM company will stipulate what tolerances and surface finish the completed samples must adhere to.	1
Inconsistent external DT results	2	The service provider is responsible for monitoring its performance in the delivery of the services and must implement appropriate	1

		monitoring, quality control and management procedures in accordance with good industry practice. The AM company may carry out such monitoring and/or audit of the quality of the services as it may from time to time require. The monitoring may include the conducting of audits, spot checks, quality assessments, third party monitoring and independent reviewing and auditing of the service provider's provision of the services.	
DT facility not available for urgent cases	3	The SLA will address issues such as lead times, performance monitoring, payment and minimum processing time for urgent cases.	1
Coating process not biocompatible	2	The annexure attached to the standard SLA will state exactly what coating material must be used as output from the Procedure for Clinical Evaluation.	1

4.6 Risk Mitigation through the Patient File as Part of Supportive Documentation

Table 4.6 will address ways to mitigate risks that were identified in Table 3.26 through the Patient File as part of supportive documentation.

Table 4.6: Risk mitigation through the Patient File as part of supportive documentation

Name of supportive document or protocol	Patient File		
Parent document	Procedure for Product and Process Development		
Key risks identified from Table 3.26		How will this supportive document reduce these risks?	
	Initial risk index		Mitigated risk index
Over- or underdesign	2	In the Procedure for Product and Process Development, the design input, -planning, -interface, -review and verification are discussed. As part of the design review process, a Finite Element Analysis will be done with defined maximum loads on the implant. The maximum stress and displacement will then be discussed during the Design Review and will minimise the over- or underdesign.	1
Wrong patient information	1	Extensive patient information is captured on the Patient File, including patient name, surname, passport or identification number, acting physician and surgeon.	1
Doctor's input requirements incorrectly interpreted	3	The patient's diagnosis, treatment plan, underlying conditions and all design inputs are captured in the Patient File. Hand	1

		sketches on design renderings are saved and compared to design input as part of design review process. See section 3.7 for more detail.	

4.7 Risk Mitigation through the IFU as Part of Supportive Documentation

Table 4.7 will address ways to mitigate risks that were identified in Table 3.26 through the IFU as part of supportive documentation.

Table 4.7: Risk mitigation through the IFU as part of supportive documentation

Name of supportive document or protocol	Instructions for Use (IFU)		
Parent document	Procedure for Product and Process Development		
Key risks identified from Table 3.26		How will this supportive document reduce these risks?	
	Initial risk index		Mitigated risk index
Surface contamination	1	The IFU, as explained in chapter 3.9, describes the steps of cleaning the implants and how the implants must be handled. All equipment, such as powder-free nitride gloves and disinfectant are listed under 3.9.10.	1
In-house cleaning process not satisfactory	2	The IFU lists the acceptance criteria as per colony forming unit, before and after in-house cleaning. This CFU is tested as part of a bioburden test.	1
Instructions for Use not clear enough and	2	The IFU is written in such a way that it is self-explanatory and on delivering the	1

not received by theatre staff		implant, the theatre nurse responsible for sterilising the instruments, must sign for the IFU and implant.	
Sterilisation process not effective enough	3	Although the AM company does gamma radiation on the implant, it is still supplied as non sterile. The responsibility for final sterilisation still lies with the hospital where the implant will be used. The implant is sterilised with all instruments that need to go in theatre and will be exposed to the same procedure.	2
Sterilisation process not repeatable	3	Although the AM company does gamma radiation on the implant, it is still supplied as non sterile. The responsibility for final sterilisation still lies with the hospital where the implant will be used. The implant is sterilised with all instruments that need to go in theatre and will be exposed to the same procedure.	2

4.8 Risk Mitigation through Design Software Validation

Table 4.8 will address ways to mitigate risks that were identified in Table 3.26 through Design Software validation.

Table 4.8: Risk mitigation through Design Software validation

Name of validation	Design Software		
Parent document	Design Software Validation Protocol and Report as discussed in section 3.10.1		
Key risks identified from Table 3.26		How will this validation reduce these risks?	
	Initial risk index		Mitigated risk index
Slice data to STL conversion	2	The accuracy of the CT/MRI conversion to STL file is validated in section 3.10.1. Although the software is ISO-certified, it is up to the final user to validate its in-house use by trained designers of this software. The geometrical accuracy through the process was also validated in section 3.10.1.	1

4.9 Risk Mitigation through IQ machine Validations

Table 4.9 will address ways to mitigate risks that were identified in Table 3.26 through IQ validations.

Table 4.9: Risk mitigation through IQ machine validations

Name of validation	IQ for EOSINT M280 and Vacuum Furnace Equipment			
Parent document	IQ of EOSINT M280 and Vacuum Furnace equipment (full IQ document available on request)			
Process	Key risks identified from Table 3.26		How will this validation reduce these risks?	
		Initial risk index		Mitigated risk index
EOSINT M280	Insufficient machine performance	1	The IQ addressed issues such as the factory acceptance test, installation and machine commissioning. Furthermore, the IQ system checks verified the safety, gas supply, laser, optic system and mechanics of the machine.	1
	Inconsistent mechanical properties of parts	3	The machine performance over time was validated as part of the PQ, as discussed in section 4.11.	1
Vacuum Furnace	Furnace output inconsistent	4	The IQ addressed issues such as the factory acceptance test, installation and machine commissioning. It was important to calibrate the temperature probes as well as the	1

			vacuum system as part of the commissioning. The PQ will prove the consistent output of the furnace.	

4.10 Risk Mitigation through OQ Machine Validations

Table 4.10 will address ways to mitigate risks that were identified in Table 3.26 through OQ validations.

Table 4.10: Risk mitigation through OQ machine validations

Name of validation	OQ for EOSINT M280, Vacuum Furnace and DT (tensile tester)			
Purpose	OQ of EOSINT M280, Vacuum Furnace DT (full OQ document available on request) and DT (full OQ document available on request)			
Process	Key risks identified from Table 3.26		How will this validation reduce these risks?	
		Initial risk index		Mitigated risk index
EOSINT M280	Improper in-house machine calibration and maintenance	2	The OQ illustrates confidence that process equipment and sub-systems are capable of consistently operating within stated limits and tolerances. The OQ is also a checking mechanism that all SOPs, such as Machine Calibration and Maintenance, are successfully executed.	1
	Insufficient machine calibration	2		1
	Inadequate operator training	1	The OQ also verifies that all operators were initially trained, through checking Work	0

			Instruction Training Records and actual training status.	
Vacuum Furnace	Inadequate operator training	1	The OQ also verifies that all operators were initially trained, through checking Work Instruction Training Records and actual training status.	0
DT	Inadequate operator training	1	The OQ verifies that all operators were initially trained, through checking Work Instruction Training Records and actual training status.	0

4.11 Risk Mitigation through PQ Machine Validations

Table 4.11 will address ways to mitigate risks that were identified in Table 3.26 through PQ validations.

Table 4.11: Risk mitigation through PQ machine validations

Name of validation	PQ for EOSINT M280, Vacuum furnace, DT processes,			
Parent document	OQ of EOSINT M280, Vacuum furnace (full PQ document available on request) and DT (full OQ document available on request)			
Process	Key risks identified from Table 3.26		How will this validation reduce these risks?	
		Initial risk index		Mitigated risk index
EOSINT M280	Inconsistent machine performance	2	The PQ, as discussed under section 3.10.2.3, showed the dimensional accuracy over a four-	1

	Inconsistent mechanical properties of parts	3	year period as well as the UTS and elongation of parts with the same geometry on five different positions on the building platform. The results were in line with what the machine manufacturer prescribed.	1
	Process not repeatable over time (accuracy)	3		1
Vacuum furnace	Furnace output inconsistent	4	The furnace output was validated through the PQ, to consistently apply the same vacuum in the process chamber and repeatable ramp-up and cool-down temperature cycles over time. The mitigated risk is scored to be 2, as this furnace had only been installed for a few months and not many statistical results were available.	2
DT	Internal DT testing not repeatable	2	The AM company decided to move the DT to an in-house process as this assisted with the frequent testing of the mechanical properties. The in-house DT was validated by manufacturing, heat treating and machining the same samples and performing DT in-house as well as at an outsourced certified laboratory. The results were satisfactory and repeatable.	1

	Outdated DT calibration	1	During the annual ISO external audit, all calibration certificates must be presented and the auditor will verify the last calibration date.	1
Implant cleaning	In-house cleaning process not satisfactory	2	The in-house implant cleaning process was validated by doing bioburden tests at an outsourced company to determine colony forming unit on implants, before and after in-house cleaning.	1
Implant packaging	Ineffective packaging	1	ISO-certified pouch rolls are used with a FAMOS F70-300 heat sealer to seal both ends. The PQ was done to determine the seal strength of samples before and after sterilisation, and after double sterilisation. The peel strength performed by the tensile tester and the acceptance criteria should be >1.2N per 15 mm. The actual results were between 3.1 to 4.5 N per 15 mm.	1

4.12 Risk Mitigation through Outsourced Process Validations

Table 4.12 will address ways to mitigate risks that were identified in Table 3.26 through Outsourced Process validations.

Table 4.12: Risk mitigation through Outsourced Process validations

Name of validation	Outsourced Process validation for density checks, NDT, surface finishing, coating and sterilisation processes.			
Parent document	Service Level Agreements Procedure for Purchasing and the Control of Suppliers			
Process	Key risks identified from Table 3.26		How will this validation reduce these risks?	
		Initial risk index		Mitigated risk index
Density	Internal density results cannot be verified externally	4	As all these processes are outsourced, the supplier needs to provide evidence of process efficacy and repeatability. This will be stipulated in the Service Level Agreements with each supplier. The service provider is responsible for monitoring its performance in the delivery of the services and must implement appropriate monitoring, quality control and management procedures in accordance with good industry practice. The AM company may carry out such monitoring and/or auditing of the	2
NDT	NDT methods not accurate enough	2		1
	Process not repeatable	3		1
Implant surface finishing	Surface finishing quality not acceptable	2		1
	Surface contamination	1		1

	Surface finish process not repeatable	2	quality of the services as it may from time to time require. The monitoring may include conducting audits, spot checks, quality assessments, third party monitoring and independent reviewing and auditing of the service provider's provision of the services.	1
	Effects on part morphology caused by heat generated in finishing process	1		1
Implant coating	Coating process not repeatable	3		1
	Coating process not biocompatible	2		1
Sterilisation	Sterilisation process not effective enough	3		1
	Sterilisation process not repeatable	3		1

All the risks were discussed and mitigated as far as possible. The highest risks were identified in the outsourced processes. When capital funds are available, steps could be taken to mitigate some of the risks by purchasing equipment required to perform outsourced processes in-house. An example of this would be to supply implants as sterile. However, this would require an in-house clean room to be set up with in-house sterilisation capabilities. This sterilisation process could then be fully validated with an IQ, OQ and PQ.

To mitigate the risks, it is important to allocate people to specific processes and this is the reason for developing a Process Ownership Matrix, where specific processes have been identified and allocated to process owners for effective operation thereof. These process owners are also responsible for continual improvement of these processes. This Process Ownership Matrix summarises responsibilities, authorities and accountability within the management system, which are communicated to each employee by means of Policies, Procedures, Work Instructions and Job Profile/Key Performance Indices. The Process Ownership Matrix is divided into the following process descriptions, as shown in Table 4.13:

- Product/Process Development
- Product Master File
- Risk Assessment
- Installation, Operation, Process Qualification and Validation of Equipment and Processes
- Preventive Actions
- Concessions and Deviations
- Customer Complaints, Vigilance & Recall
- Maintenance and Calibration
- Document Control, Change Management, Back-Up Management
- Control of Records
- Analysis of Data
- Continual Improvement

Table 4.13: The Process Ownership Matrix (CRPM ISO 13485: 2016 Quality Management System)

PROCESS OWNERSHIP MATRIX								
NO.	**PROCESS DESCRIPTION**	**PROCESS DOCUMENTATION**	**PROCESS OWNER**	**KEY PROCESS INDICATORS**	**FREQUENCY OF MEASUREMENT**	**ACTUAL**	**RECORDS**	**PROCESS OWNER**
MAIN BUSINESS PROCESSES								
1	MARKETING	MARKETING	PROJECT ENGINEER: OPERATIONS DIRECTOR	Number of new clients	Every 3 months	Actual number of new clients	Client Evaluation Form	PROJECT ENGINEER: OPERATIONS
	SALES	SALES	PROJECT ENGINEER: OPERATIONS JUNIOR PROJECT ENGINEER: TECHNICAL FINANCIAL OFFICER DIRECTOR	Order book	Every 3 months	Target	Income/Expenditure Sheet	PROJECT ENGINEER: OPERATIONS
	CUSTOMER SATISFACTION MONITORING	CUSTOMER SATISFACTION MONITORING	QUALITY ENGINEER RECEPTIONIST DIRECTOR	Projects completed in time, in accordance with quality and cost requirements	Every 3 months	Zero customer complaints per month	Customer Complaint Register	QUALITY ENGINEER

2	PLANNING	STOCK CONTROL	PROJECT ENGINEER: TECHNICAL QUALITY ENGINEER	Quantity of powder and spares	Monthly	Actual quantities of powder and spares available	Stock Control Sheet	PROJECT ENGINEER: TECHNICAL
		PLANNING	DIRECTOR	Company level objectives	Every 3 months	Are the company objectives met?	Objectives	DIRECTOR
3	PURCHASING	PURCHASING AND THE CONTROL OF SUPPLIERS	PROJECT ENGINEER: OPERATIONS JUNIOR PROJECT ENGINEER: TECHNICAL FINANCIAL OFFICER DIRECTOR	Expenses within parameters of approved budget	Monthly	Monthly expenditure vs. approved budget	Income/Expenditure Sheet	PROJECT ENGINEER: OPERATIONS
4	ADDITIVE MANUFACTURING	STORAGE	JUNIOR PROJECT ENGINEER: TECHNICAL	Safe storage of consumables	Monthly	Stock Control List	Stock Control List	JUNIOR PROJECT ENGINEER: TECHNICAL

		MANUFACTURING	JUNIOR PROJECT ENGINEER: TECHNICAL PROJECT ENGINEER: OPERATIONS	Manage and control operational actions and development of the AM company and initiate new projects	Monthly	Order Book	Order Book	JUNIOR PROJECT ENGINEER: TECHNICAL
		CLEANING	PROJECT ENGINEER: TECHNICAL	Ensure parts are correctly cleaned	Daily	Quality Assurance Document	Monthly Calibration Test	PROJECT ENGINEER: TECHNICAL
		QC TESTING	QUALITY ENGINEER	Machines are manufacturing parts to required mechanical properties	Monthly	Monthly Part Calibration Document	Monthly Calibration Test	QUALITY ENGINEER
		INSPECTION	QUALITY ENGINEER	Evaluate parts for quality, strength and dimensional accuracy	Monthly	Quality Assurance Document	Monthly Calibration Test	QUALITY ENGINEER
		DESPATCH	PROJECT ENGINEER: OPERATIONS RECEPTIONIST	Ensure the correct parts and quantities are shipped to the correct address	Daily	Courier waybill, delivery emails	Waybill	PROJECT ENGINEER: OPERATIONS

4.13 Process Risk Assessment after Framework Development

An initial overarching process risk assessment was completed before the framework development, seen in chapter 3 as Table 3.2. A flow-up overarching process risk assessment was done after taking into account all the procedures, SOPs, supportive document and validation developments, as shown in sections 3.5 to 3.10 in chapter 3. The risk mitigation actions, discussed in sections 4.1 to 4.12, were also taken into account and the results of the process risk assessment (after framework development) are shown in Table 4.14. The risk index score was significantly reduced from the original process risk assessment and can be seen in the green block in Table 4.14.

Table 4.14: Process Risk Assessment after framework development

Process Risk Assessment															
Reference: Medical Implant				**REV**											
Classification	**Custom made**	**Scope of Risk Assessment: Design, AM, cleaning, delivery and patient interface**													
Risk Assessment before framework development							**Risk Assessment after framework development**								
NO.	**Potential hazard**	**Failure/impact on patient**	**Possible cause**	**Level of risk**	**Occurrence**	**Risk index**	**Actions to minimise risk (mitigation)**	**Level of risk**	**Occurrence**	**Risk index**	**Result**	**Other risks affected**	**Reference**		
Design															
1	Structural failure of implant	Discomfort, pain, potential revision surgery	Fluctuating process conditions	**5**	**13**	65	Implement EOSTATE monitoring software	**5**	**6**	**30**	Validated software is used		EOSTATE Validation Certificate		
			Poor design	**5**	**9**	45	Quality/design control via micro-CT scan, destructive tensile testing, FEA	**5**	**3**	**15**	Testing reports		Additive Manufacturing Reports		
			Excessive stress on implant	**5**	**9**	45	Surgeon informs patient of technology limitations and precautions e.g. biting hard food	**5**	**6**	**30**	Instructions For Use		IFU		
			Inadequate annealing	**5**	**9**	45	Use certified service provider	**5**	**3**	**15**	Service Level Agreements		Service Level Agreements		
2	Design not within tolerance	Implant does not fit, potential revision surgery	Incorrect patient data	**5**	**9**	45	Verify patient data	**5**	**6**	**30**	Specification Checklist		Custom Implant Design Specification		
			Bad scan quality	**4**	**13**	52	Establish and enforce proper scan protocol	**4**	**3**	**12**	CT Scan Protocol		CT Scan Protocol		
			Incorrect scan orientation	**5**	**13**	65	Data conversion procedure implemented	**5**	**3**	**15**	Trained personnel		Mimics™ Training Certificate		
			Design error	**3**	**13**	**39**	STL and scan mapping	**3**	**3**	**9**	Part-to-CAD comparison		3D Mapping		

Process Risk Assessment

Reference: Medical Implant		REV		
Classification	**Custom made**	**Scope of Risk Assessment: Design, AM, cleaning, delivery and patient interface**		

Risk Assessment before framework development							Risk Assessment after framework development						
NO.	**Potential hazard**	**Failure/impact on patient**	**Possible cause**	**Level of risk**	**Occurrence**	**Risk index**	**Actions to minimise risk (mitigation)**	**Level of risk**	**Occurrence**	**Risk index**	**Result**	**Other risks affected**	**Reference**
			Machine not calibrated	**4**	**13**	52	Maintain and enforce proper maintenance schedule	**4**	**3**	**12**	Preventative maintenance		Maintenance Records
			Software not validated	**4**	**9**	**36**	Validate design and manufacturing software	**3**	**3**	**9**	Software Validation Protocol		Software Validation Report
			Inadequate stress relieving	**5**	**9**	45	Verify argon levels, stress-relieving procedure	**5**	**3**	**15**	Work Instruction		Thermal Processing
3	Ineffective operational planning model	Model does not meet expectations of surgeons	Incorrect patient data	**6**	**9**	54	Verify patient data	**6**	**3**	**18**	Specification Checklist		Custom-implant Design Specification
			Bad scan quality	**3**	**13**	**39**	Establish and enforce proper scan protocol	**3**	**6**	**18**	CT Scan Protocol		CT Scan Protocol
			Incorrect scan orientation	**5**	**13**	65	Data conversion procedure implemented	**5**	**5**	**25**	Trained personnel		Mimics™ Training Certificate
			Machine not calibrated	**3**	**9**	**27**	Maintain and enforce proper maintenance schedule	**3**	**3**	**9**	Preventative maintenance		Maintenance Records
Additive Manufacturing and cleaning													
4	Infection	Pain, discomfort, potential revision surgery	Powder contamination	**5**	**13**	65	Verify powder composition, handling and storage procedure maintained	**5**	**3**	**15**	Work Instruction		Certificate of Analysis
			High bioburden	**5**	**13**	65	Cleaning procedures, bioburden testing	**5**	**6**	**30**	Microbiological deactivation		Gamma-irradiation Certificate

Process Risk Assessment

Reference: Medical Implant		REV		
Classification	**Custom made**	**Scope of Risk Assessment: Design, AM, cleaning, delivery and patient interface**		

Risk Assessment before framework development							Risk Assessment after framework development						
NO.	**Potential hazard**	**Failure/impact on patient**	**Possible cause**	**Level of risk**	**Occurrence**	**Risk index**	**Actions to minimise risk (mitigation)**	**Level of risk**	**Occurrence**	**Risk index**	**Result**	**Other risks affected**	**Reference**
			Contamination during post processing and cleaning	**5**	**9**	45	Cleaning procedures, bioburden testing	**5**	**6**	**30**	Work Instruction		Medical device cleaning
			Inadequate sterilisation procedure	**5**	**9**	45	Use certified service provider	**5**	**6**	**30**	Approve suppliers		HEPRO
			Powder out of spec	**4**	**9**	**36**	Verification of powder before use	**2**	**2**	**4**	Work Instruction		Report
	Sensation and irritation after implantation	Discomfort	Material not biocompatible	**3**	**9**	**27**	Material with biocompatibility certification to ISO 10993 is procured	**3**	**3**	**9**	No possible sensation or irritation		Certificate of Analysis
	Implant deformed during manufacturing	Implant does not fit	Implant warped during manufacturing	**5**	**13**	65	STL and scan mapping	**5**	**6**	**30**	Part-to-CAD comparison		3D Mapping
			Incorrect manufacturing orientation	**3**	**9**	**27**	Operator training and review design before manufacturing	**3**	**6**	**18**	Training Records and Patient Data		Training Record Patient Data
Transport and delivery													
5	Design of packaging	Implant can be damaged during transport	Inadequate packaging design/selection	**3**	**13**	**39**	Validate primary and secondary packaging	**3**	**5**	**15**			Packaging Validation
	Implant lost/damaged during shipping	Delay of operation, prolonging of pain/discomfort	Inadequate packaging	**3**	**13**	**39**	Packaging Procedure	**3**	**5**	**15**	Work Instruction		Additive Manufacturing
			Incorrect address	**2**	**13**	**26**	Verify details before shipping	**2**	**5**	**10**	Work Instruction		Packing

Process Risk Assessment

Reference: Medical Implant		REV		
Classification	**Custom made**	**Scope of Risk Assessment: Design, AM, cleaning, delivery and patient interface**		

Risk Assessment before framework development							Risk Assessment after framework development						
NO.	**Potential hazard**	**Failure/impact on patient**	**Possible cause**	**Level of risk**	**Occurrence**	**Risk index**	**Actions to minimise risk (mitigation)**	**Level of risk**	**Occurrence**	**Risk index**	**Result**	**Other risks affected**	**Reference**
			Waybill poorly attached	**3**	**9**	**27**	Packaging Procedure	**3**	**5**	**15**	Work Instruction		Additive Manufacturing
			Box not marked properly	**3**	**13**	**39**	Packaging Procedure	**3**	**6**	**18**	Work Instruction		Additive Manufacturing
Surgery and patient interface													
6	Infection	Pain, discomfort, potential revision surgery	CSSD does not follow cleaning procedure	**5**	**13**	65	Issue cleaning and sterilisation instructions	**5**	**6**	**30**	Instructions For Use		IFU
			CSSD does not follow sterilisation procedure	**5**	**13**	65	Issue cleaning and sterilisation instructions	**5**	**6**	**30**	Instructions For Use		IFU
			Gamma irradiation is not effective	**5**	**13**	65	Maintain low bioburden	**5**	**6**	**30**	Sterilisation Validation		Sterilisation Validation Report
			Clinical error (from theatre to surgeon)	**5**	**13**	65	Beyond manufacturer's control. Could assist in corrective post-op support	**5**	**6**	**30**	Instructions For Use		IFU
Post processing													
7	Implant deformed during post processing	Implant does not fit	Implant warped after heat treatment	**5**	**13**	65	STL and scan mapping	**5**	**6**	**30**	Part-to-CAD comparison		3D Mapping
			Implant warped after support removal	**5**	**13**	65	STL and scan mapping	**5**	**7**	**35**	Part-to-CAD comparison		3D Mapping

Chapter 5

Conclusions and Recommendations

5.1 Conclusion

The aim of this research project was to develop a certification framework focusing on Ti64 titanium powder (as the material) and SLM (as the process) for patient-specific implant manufacturing.

5.1.1 Conclusion regarding Objective 1

Objective 1 was to identify key risks in the SLM process and develop work instructions and protocols as part of the technical certification process. These instructions will, in turn, assist in proving repeatability and stability of the manufacturing process.

In this project, a total of 68 risks were identified in the following areas: design, machine setup, powder handling, SLM process, part removal, density checks, heat treatment, non-destructive testing, destructive testing, surface finishing and coating, cleaning, sterilisation and packaging. Of these, 41 were classified as internal risks and 27 as external risks. The risk identification must be seen as an indication of possible risks identified (as a baseline) by the CRPM risk review team that has used this implant design and SLM processes for more than 15 years. The CRPM risk review team comprises executive management, management, a design and quality engineer and a clinical advisor. This is not an exhaustive list and other users of other technologies could identify additional risks. The purpose of this project was to develop a certification framework, and therefore it was more important to explain the methodology behind the risk identification and mitigation. The ISO 13485:2016 system is based on continual improvement principles which would mean that where new risks arise, the process of addressing these risks will be fast-tracked through the framework development. The action plan to mitigate these risks was to develop procedures, SOPs, supportive documents and where needed, full machine and process validation. The two procedures, SOPs, supportive documents and validations with the highest cumulative risk number and any risk with a level of 3 to 4 were discussed. Nineteen procedures were identified on page 86 and the procedure for AM was discussed fully.

The two procedures with the highest cumulative risk number were 1) the Procedure for Purchasing and the Control of Suppliers and 2) the Procedure for Clinical Evaluations.

Purchasing is a very important facet of any organisation, especially one that operates under a QMS system. One key risk that was identified relates to traceability of the raw material (page 96) and the certificate of analysis with powder delivery. This was mitigated by signing a supplier contract, or SLA, with all critical suppliers with specific procedural outcomes. Furthermore, it is important to verify this certificate of analysis locally, which is done as part of an initial chemical analysis. Thereafter it is important to track the powder aging over a period of time (these research results are available). It is essential to sign an SLA with critical outsourced suppliers, such as NDT and DT facilities, that prescribe availability and lead times for urgent medical cases. The SLA can also be used to document procedural steps where the supplier does not have a certified ISO system.

Key risks pertaining to the coating and sterilisation process were also identified as part of the Procedure for Clinical Evaluations. Both processes are currently outsourced, but the research and literature studies conducted (page 198 to 200) as part of the clinical evaluations to be approved by an expert panel, will prove to be valuable to mitigate these risks.

Thirty-four SOPs were identified in the AM manual, (pages 94 to 95), as part of the Procedure for AM. The 34 SOPs were grouped into three categories, namely general, EOSINT metal AM and EOSINT polymer AM. The process overview SOP was discussed to provide an actual overview of the process chain from prosthesis request, through design and manufacturing, until medical device shipment (page 102). A proposed process chain was introduced (page 32) as part of the research methodology and it is interesting to note the similarities.

5.1.2 Conclusion regarding Objective 2

Objective 2 was to develop an integrated documentation framework, keeping traceability in mind. This framework forms part of the quality certification process and evaluates the consistency of the technical part as well as the traceability of the products manufactured.

In objective 1 it was stated that the technical certification must prove to be reliable and repeatable over a period of time. It was important to develop documents like the patient file and CT scan protocol to enable the AM company to capture the correct input data as well as post-operative reviews, which can be seen as part of a critical evaluation and continual improvement. The post-operative remarks are fed back into the QMS for forthcoming procedures as input parameters. This is the reason for the evolution of documents such as the patient file over the past three years.

Furthermore, process and machine validation is invaluable as it proves that:

1) all SOPs are being used as part of the OQ; and
2) the process stability and repeatability, as shown in the PQs.

The ISO 13485:2016 version requires validation of the processes, including the software. This was the reason for the design and software to be validated. The software is supplied as ISO-certified but the user must also validate it in-house. This forms part of the user training capability matrix that is updated annually. The software users must be trained and critically evaluated before they are declared to be able to start designing implants or devices.

The OQ proved that all 34 SOPs are currently being used in the system and where needed new SOPs can be developed where outsourced processes are insourced. All procedures and SOPs are reviewed annually as part of the internal audit (Appendix 1 page 243). An annual management review will study and analyse the audits together with the monthly ISO EXCO meeting minutes, customer feedback, complaint handling, reporting to regulatory authorities, monitoring and measurement of products and processes, corrective and preventative actions and changes that could affect the quality management system (Appendix 1 page 243).

The PQ proved that the process (design, manufacturing and post processing) is consistent over a period of time. It was important to show that from CT scan conversion through to the design and manufacturing, the geometrical accuracy was maintained over time. Furthermore, it was important to show that the mechanical properties of different parts produced in different locations on one build platform is consistent and in tolerance. Re-evaluation criteria were set in the PQ.

5.1.3 Conclusion regarding Objective 3

Objective 3 was to identify shortcomings in the framework and do in-depth analysis on ways to rectify these problems. Developing this framework will entail constant evaluation to improve and optimise this complex manufacturing process.

In chapter 4, results were discussed. Throughout this dissertation it was important not only to address some areas of concern but to explain the methodology behind risk mitigation, procedure and SOP development and validation and how these individual areas link to each other. A fully functional QMS will identify more risks, improvements, customer complaints and preventative and corrective actions before large call-backs of products are launched. An initial process risk assessment was done before the framework development on page 41 to 42 and after the framework development, as part of chapter 4. It can be seen from the initial risk assessment that most identified process risks were classified above the 27 value and marked in red. The process risk assessment discussed in chapter 4 showed a significant reduction in the risk index and ways to mitigate the remaining risks. Transport and delivery are outsourced processes and the only way of mitigation is through a service level agreement. Surgery and patient interface is also beyond the control of the manufacturer and can only be mitigated by means of the IFUs supplied with the implants and devices. As mentioned earlier, the implants are supplied non sterile and the hospital will do the final sterilisation together with all the instruments required in theatre.

5.1.4 Was the Problem Statement Elucidated through the Three Objectives?

AM has proven to be an attractive alternative manufacturing process compared to subtractive manufacturing with many advantages, such as mass customisation, less material wastage and others, as listed in this dissertation. However, AM of certified implants does not have the same degree of documentation and standardisation as the SM process. As part of the problem statement, it stated that “in offering AM as an implant manufacturing solution, the complete process (design, manufacturing and post processing) had to be investigated in order to develop a certified manufacturing solution”.

Objective 1 addressed the risk identification and ways to mitigate these risks through developing procedures, SOPs and supportive documents. This can be seen as the technical certification of this certified manufacturing solution. **Objective 2** focussed on developing an integrated documentation framework, keeping traceability and repeatability in mind. Process and machine validations were developed that form part of the quality certification process and evaluated the consistency of the technical certification to prove repeatability and traceability of the products manufactured. **Objective 3** focussed on identifying shortcomings in the framework and an in-depth analysis on ways to rectify these problems though continual improvement.

It is believed that the three objectives elucidated the problem statement and through this framework development documentation, validation and standardisation steps, similar to the SM process, were developed for the AM process to prove it as a certified manufacturing solution for patient-specific implant manufacturing.

5.2 Contributions to Practice

The importance of this study was to deliver a framework to adhere to implant certification criteria that will offer a valuable contribution to those in industry that want to follow the path of certified AM implant production. The CRPM was the only facility in SA to follow this approach in 2016, but in the past year, two industrial companies invested approximately €500 000 to acquire new AM technologies and is currently addressing ISO certification of AM implants.

The complete certification process of AM has not been published as a limited number of international service bureaus are working on this topic and the in-house knowledge created is seen as a trade secret and therefore not disclosed.

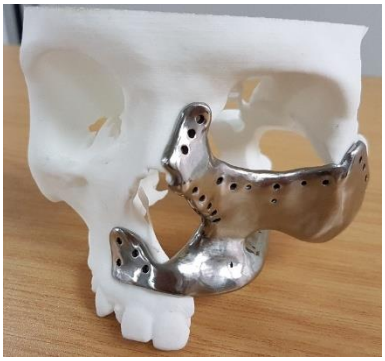
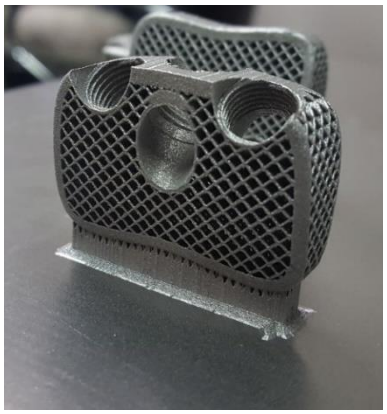
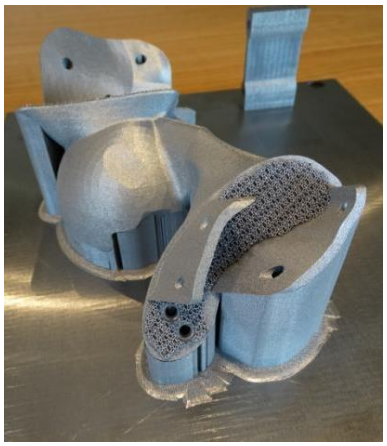
Furthermore, the study can potentially have a significant impact on the use of technology platforms at CUT, Stellenbosch University and the CSIR National Laser Centre, or even some local SMMEs. The study fits into the Metal Additive Manufacturing (MAM) programme funded by the Department of Science and Technology (DST). The MAM programme forms part of a national Collaborative Program for Additive Manufacturing (CPAM) and one of the deliverables is a fully qualified medical implant. The proposed certification framework will be a significant contributor in this MAM deliverable.

The CRPM obtained ISO 13485: 2012 certification (Annexure 5 for certificate) from the international regulating authority TUV SUD in 2016. The scope of this certification is:

- Design, development and production of patient specific custom made titanium implants by means of 3D Printing/Additive Manufacturing
- Design, development and production of patient specific custom made preoperative models, jigs, cutting guides in nylon by means of 3D Printing/Additive Manufacturing
- Contract production of titanium implants by means of 3D Printing/Additive Manufacturing
- Contract production of preoperative models, jigs, cutting guides in nylon by means of 3D Printing/Additive Manufacturing

The CRPM was successful in migrating to the revised ISO 13485 (2016 version) and the external audit was completed by TUV SUD from 22 to 23 March 2018. The International Organisation for Standardisation (ISO) revised the 2012 version, and the ISO 13485:2016 (see Annexure 5 for certificate) was designed to respond to latest quality management system practices, including changes in technology and regulatory requirements and expectations. TUV SUD also audited all the Patient Files as the CRPM assisted more than 25 patients in the past two years. Some of these implants designed and manufactured by CRPM are shown in Table 5.1. *Patient identity is not shown in the images below.*

Table 5.1: Implants manufactured by AM

5.3 Recommendations and Future Work

The aim of this research project was to develop a certification framework for additive manufactured patient-specific implant manufacturing and to develop similar documentation and standardisation as available with the SM process. The following recommendations and future work will assist in fast-tracking this certification process.

Software

Online planning software – Can remotely discuss a patient case with the surgeon as the data or object can be virtually rotated, so as to indicate which area needs to be removed and these parameters can then be locked as design input on the Patient File (shown in 3.7 in chapter 3). This online communicating tool can provide faster feedback from surgeons on design concepts.

Mobile App for surgeons

- Post-operative reviews, where the surgeon can give feedback after operation on possible improvements.
- Meeting minutes translated from voice note to text and logged into QMS system (surgeons are not the best with documentation and approval)

Software is currently being developed to track powder batch numbers as batches are mixed to form recycled powder. The software will need the capability to input essential results from powder aging analysis and linking that to specific powder batches.

Statistical shape modelling techniques can be used to generate swifter patient-specific geometry from a data base, for example mandible shape and sizes.

Hardware

Process monitoring can be further expanded to accommodate recoating monitoring (scan every layer) as well as melt pool monitoring. Software must be developed to translate all this data into a 3D rendering to outline possible areas of concern. Only these areas can then scanned using CT scanning, and not the complete part, which will result in process cost savings.

Hardware is currently being developed to monitor powder storage, especially of reactive materials such as titanium. Oxygen content, temperature and relative humidity can then be monitored in real-time.

An automatic surface finishing system must be acquired as currently hand polishing techniques are used. It is important to note that titanium is not the easiest material to polish and that sharp edges and fine features must be preserved.

Insourced processes

It was mentioned in this dissertation that insourcing of a validated sterilisation process with clean room and plasma sterilisation equipment is needed. This will shorten the lead time on implant delivery and will ease the process of validation.

Ramping-up the production of implants will result in not all the parts being sent for non-destructive testing and an in-house density method must be developed to verify the density of the batch production. The most important factor is to identify and validate a process that will be accurate enough in detecting flaws in the SLM samples after which the outliers can be checked with NDT methods.

QMS

Currently, a manual system is used. However, an automated system, where files are linked to each other and due dates are flagged on procedures and SOPs review dates should be developed. This will assist with the audit planning schedules and responsible persons can be easily assigned. It will be advantageous if such an automated system can link to an Enterprise Resource Planning (ERP) system to assist with resource allocation and product traceability.

Continual improvement

The ISO 13485:2016 system is based on continual improvement and it is important to identify and execute these improvements on a monthly basis.

Further research can be conducted on the following aspects:

- When the SLM process is stopped and if continued after time (extent must be determined), the next layer can separate from the cool-down layer;
- Inadequate part cleaning can cause powder to be trapped inside lattice structures that could cause clinical problems for the patient who received such an implant;
- Verification of a stress-relieving cycle has on an impact on substrate; and
- Effects that heat generated with finishing/polishing process have on part morphology.

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Appendix 1: Quality Documents and Requirements

Why a quality management system?

As previously mentioned, common standards need to be developed to ensure the same part integrity where these standards are used anywhere in the world. These standards are needed, for example, for technical parts of the 3D printers, the specifications of the materials used as a feedstock for AM or the digital file of a 3D object. As a response to the need for standardisation in the field of AM, a number of initiatives on national and international levels were launched. Amongst others, ASTM 8 and ISO 9 established technical committees for the development of AM standards. (Öko-Institut e.V, 2013)

To comply with these standards by demonstrating part integrity, particularly in medical devices where a patient's life can be compromised by a faulty implant, a Quality Management System (QMS) must be developed to address all the risks involved in the AM process used to produce a medical device. The AM company planning to develop an AM QMS must establish, document, implement, maintain and continually be improving a QMS in accordance with the requirements of ISO 13485 and the South African Medical Device Regulation, or applicable regulatory requirement of a country or area.

To implement a QMS, steps must be taken to identify the processes needed to develop the system and its application throughout the AM company. A risk-based approach must be applied to control the processes and determine their sequence and interaction as well as the criteria and methods required to ensure the correct operation and control and effectiveness of the processes. Methods to monitor, measure and analyse the processes must be established to demonstrate compliance with applicable regulatory requirements. These actions are tracked on a Process Ownership Matrix.

It is important that any changes to be made to these processes are evaluated for their impact on the QMS and the medical devices produced under the system. The changes must be controlled in accordance with the requirements of ISO 13485 and the South African Medical Device Regulations and applicable regulatory requirements.

Relationship between ISO 9001:2015 and ISO 13485:2016?

According to Swanson (2018), one of the biggest differences between the two standards is the scope statements. ISO 9001 is defined as a general and generic standard for all QMS, while the scope of ISO 13485 is specific to the medical device sector and related services. ISO 13485:2016 is aimed at including those QMS requirements for organisations that provide medical devices and helping organisations concerned with medical devices ensure they meet not only the customer requirements but also the applicable regulatory requirements for the countries and regions where the medical devices are provided. This difference is further emphasised in the documentation requirements in ISO 13485:2016 for the design history, management review, medical device files, complaint handling, regulatory reporting and other regulatory-focused documentation.

Another big difference is the primary focus of the results. ISO 13485:2016 is primarily driven by the need to ensure that the medical devices placed on the market by organisations are safe and effective, while ISO 9001 focuses on risk-based decisions to minimise the risk of customer dissatisfaction.

The similarities allow the standards to work together without conflict. Both standards outline the need for an organisation to determine their role or purpose in the supply chain of delivering a product to the customer. Customer needs, competency of employees, infrastructure and the analysis of data are key concepts in both standards. A further similarity is the use of risk assessments as the basis of making decisions and the application of risk management to QMS processes.

Structure of ISO 13485:2016

Overview of ISO 13485

As ISO 13485 is aligned with ISO 9001:2008, the standard is divided into eight sections. The first three sections are introductory, while the last five set out the requirements for the QMS (13485 Academy).

Section 4: Quality management system – The general QMS requirements, as well as the documentation is addressed in this section. Important components of the QMS, such as the quality manual, control of documents, and control of records are included.

Section 5: Management responsibility – The standard requires that top management be instrumental in the implementation and maintenance of the QMS. Along with planning for the QMS, there is a need for top management to be involved in the ongoing review of the system to ensure customer satisfaction and improvement.

Section 6: Resource management – This section covers the management of resources and the necessity to control all resources, including human resources, buildings, and infrastructure and the working environment.

Section 7: Product realisation – The process to be followed, as set out in the standard, to deal with all aspects of the planning and creation of the product are covered here. This includes requirements on planning, product requirements review, design, purchasing, creating the product or service, and controlling the equipment used to monitor and measure the product or service.

Section 8: Measurement, analysis and improvement – Here it is required to monitor the functioning of the QMS. This includes assessing customer satisfaction, internal audits, monitoring products and processes, dealing with non-conforming product, and corrective and preventive actions.

The benefits of ISO 13485 cannot be overstated; companies large and small have used this standard to great effect, discovering and securing tremendous cost and efficiency savings. Benefits include improving customer confidence, not only in the product, but also the credibility of the AM company.

One of the key principles of the ISO 13485 QMS is the focus on improving customer satisfaction by identifying and meeting customer requirements and needs, which in turn, leads to repeat business. By implementing ISO 13485, fully-integrated processes are put in place, which show the individual processes and the interactions of those processes. By doing this, areas for improvement and resource savings in the AM company are identified.

Evidence-based decision-making is a key to the success of an ISO 13485 QMS. Problems can be corrected and the AM company's efficiency and effectiveness improved. Continual improvement can be seen as the main output of the QMS as the system focuses all personnel on identifying and improving the processes they are directly responsible for.

Relationship between Business Process Overview (BPO), Site Master File and Quality Manual in the South African Context

Any QMS development must be in accordance with the requirements of ISO 13485 and the South African Medical Device Regulation or applicable regulatory requirement of a country or area. The South African Health Products Regulatory Authority (SAHPRA) was established to govern the manufacture, distribution, sale, and marketing of medicines in SA. SAHPRA requires that the BPO, Site Master File and Quality Manual be integrated into one document. This document must include the scope of the QMS, any ISO 13485 requirements that are excluded, any clauses that are not applicable, references to the documented procedures and a description of the interaction between the processes of the QMS. In this study, none of the ISO 13485 requirements were excluded and as the focus is on design and manufacturing, the following clauses pertaining to installation and servicing are not applicable:

- Clause 7.5.3 – Installation, as no installation activities are performed.
- Clause 7.5.4 – Servicing is excluded, as no servicing is provided.

A Business Management System (BMS) is more effective than a stand-alone QMS, as all personnel participate in a BMS. The BMS is structured in three tiers, as show in Figure A1.1. Each tier conforms to a particular aspect of the ISO 13485 standard. The first tier encompasses the AM company business plan and all statutory and regulatory documentation to which the AM company must comply. Tier Two sets out the various processes and procedures put in place to effectively

manage all aspects of the AM company's business. From the processes and procedures in place in Tier Two, all the SOPs, protocols, instructions and work sheets used in the AM company are generated in Tier Three. Forms are created to enable effective management of the processes and procedures. From the forms, records are created which provide the means to validate and verify the effective management of ISO 13485.

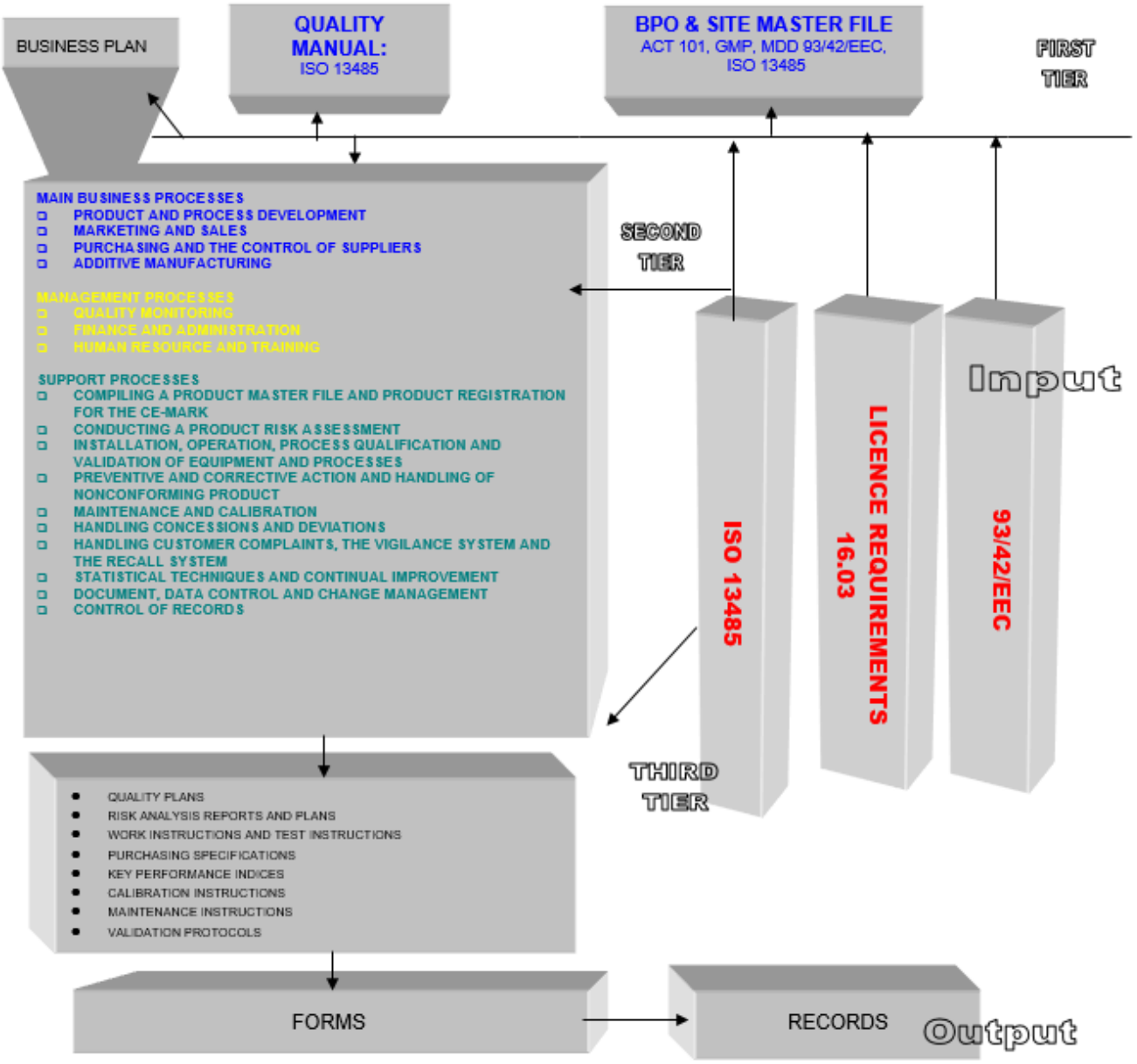

Figure A1.1: The outline structure of the Quality Manual (CRPM ISO 13485: 2016 Quality Management System)

Business Process Overview and Site Master File

The objective of the BPO and Site Master File is to define the business process model, with specific information regarding design, additive manufacturing, quality assurance, quality control and sales of the medical devices. An index of a typical BPO, Site Master File and Quality Manual is shown in Table A1.1. The paragraph numbering, shown below, links to the numbering system used in the ISO 13485 standard.

Table A1.1: A typical Business Process Overview, Site Master File and Quality Manual index (CRPM ISO 13485: 2016 Quality Management System)

Paragraph	Description
1	**Objective of this document**
2	**Scope, AM company history and mission**
2.1	Scope and legal identity
2.2	Authorised Representative: SAHPRA South Africa
2.3	Management Representative: ISO 13485
2.4	AM company history
2.5	Strategic objectives
2.6	List of products
2.7	Site description
2.8	Personnel
2.9	Process ownership
2.10	Responsibilities, authorities and accountabilities
3	**Applicable documents, definitions and abbreviations**
3.1	Applicable documents
3.2	Definitions and abbreviations
4	**Quality Management System**
4.1	General requirements
4.2	Documentation requirements
5	**Management responsibility**
5.1	Management commitment
5.2	Customer focus
5.3	Quality policy

5.4	Planning
5.5	Responsibility, authority and communication
5.6	Management review
6	**Resource management**
6.1	Provision of resources
6.2	Human resources
6.3	Infrastructure
6.4	Work environment and contamination control
7	**Product realisation**
7.1	Planning of product realisation
7.2	Customer-related processes
7.3	Design and development
7.4	Purchasing
7.5	Manufacturing
7.6	Control of monitoring and measuring equipment
8	**Measurement, analysis and improvement**
8.1	General
8.2	Monitoring and measurement
8.3	Control of nonconforming product
8.4	Analysis of data
8.5	Improvement

By way of introduction, paragraph one describes the objective of the BPO. A brief history of the AM company, its scope and legal identity and mission are explained in the second paragraph. Strategic objectives and the AM company's ethos must be reviewed on a regular basis to ensure that the AM company remains on track and maintains the standards set out in the objectives and remains relevant in the changing environment. It is important to list all products and services that will be rendered by the AM company and link them to a site description.

Human resource has a significant weight and effect on the realisation of the medical devices and meeting customer and regulatory requirements. Adequate resources necessary for the risk management activities must be allocated and ISO 13485 presents a method to analyse, plan and determine the human resources. The AM company must ensure that personnel performing work that affects the quality and conformity of the product are competent and have acquired the adequate

skills. Furthermore, it is essential to map out the BMS linking the personnel to specific business processes. The model is divided into the main business-, management- and support business processes, as shown in Figure A1.2.

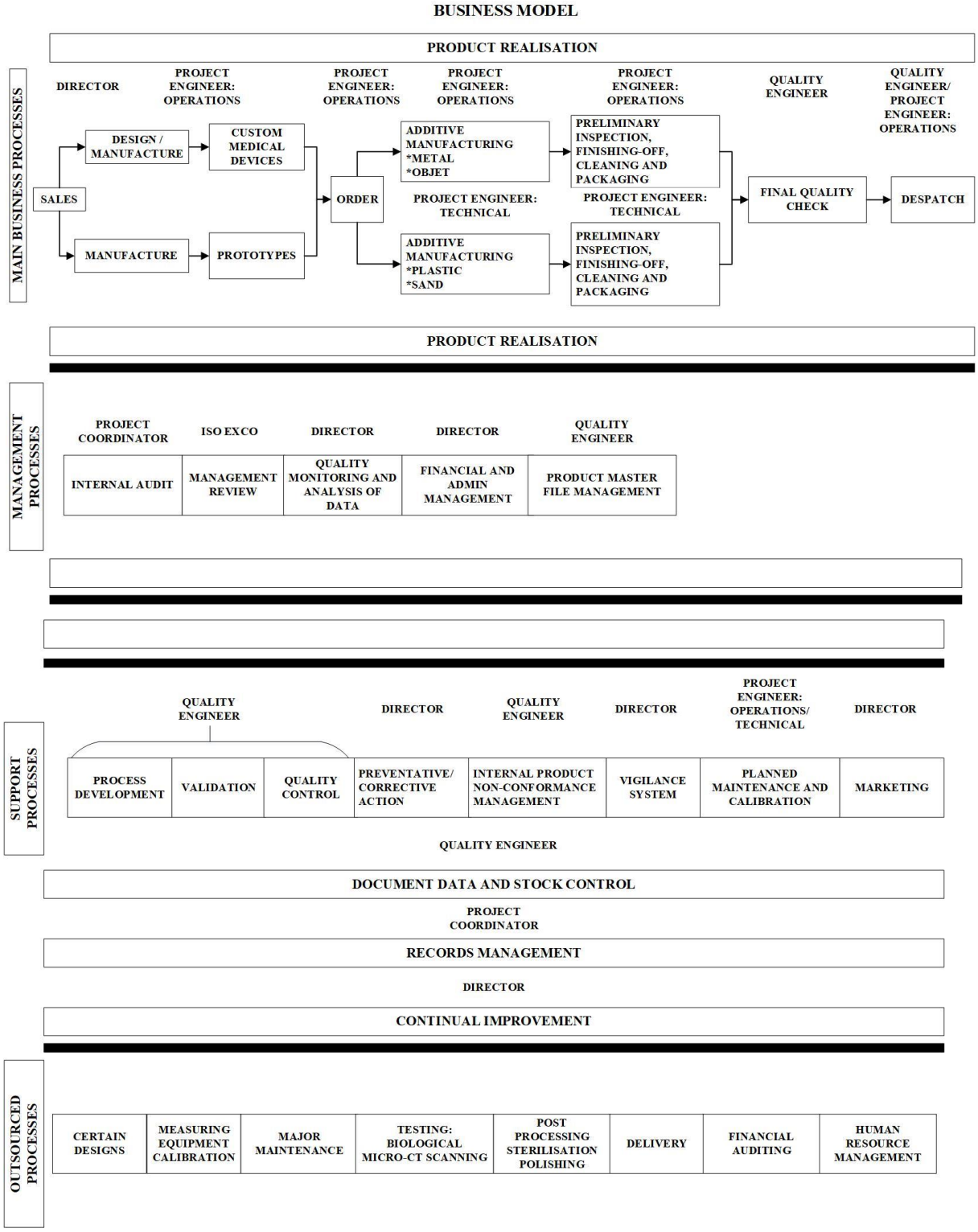

Figure A1.2: The Key Business Model Processes Flow Diagram (CRPM ISO 13485: 2016 Quality Management System)

The flow diagram details the person responsible for each process in the manufacturing of a product. However, not all the processes are carried out by the AM company – some are outsourced to other companies, as shown in Figure A1.2. Outsourced processes that affect product conformity to the requirements must be monitored to ensure control over these processes. It is important to note that the AM company retains responsibility for conformity to ISO 13485, the South African Medical Device Regulations, to customers and applicable regulatory requirements for outsourced processes. The controls are proportionate to the risk involved and the ability of the external party to meet the purchasing and supply requirements. Supplier Agreements and/or Service Level Agreements are established with all critical outsourced suppliers and subcontractors.

The BMS is based on the principle of process ownership, where specific processes have been identified and allocated to process owners for effective operation thereof. These process owners are also responsible for continual improvement of these processes. A key tool in ensuring conformance with the standard and managing the system is the Process Ownership Matrix, as shown in Table 4.13 in chapter 4. This document summarises responsibilities, authorities and accountabilities within the management system which are communicated by means of policies, procedures, work instructions and job profile/key performance indices to each employee. The Process Ownership Matrix is divided into the following process descriptions:

- Product/Process development
- Product Master File
- Risk Assessment
- Installation-, Operation-, Process Qualification and Validation of Equipment and Processes
- Preventive Actions
- Concessions and Deviations
- Customer Complaints, Vigilance & Recall
- Maintenance and Calibration
- Document Control, Change Management, Back-Up Management
- Control of Records
- Analysis of Data
- Continual Improvement

In the delegation of authority, the following role players are critical for the smooth operation of the system. They are accountable for the management of the system.

Director

The Director ensures the effective management of the AM company. The Director has the authority and carries the final overall responsibility for all of the facility's operations and quality assurance. The Director is also the appointed Authorised Representative for the licence obtained from SAHPRA.

The ISO Administrator/Project Coordinator

The ISO Administrator has the authority to ensure that the facility establishes-, implements- and maintains a quality system that meets ISO 13485 and the South Africa Medical Device Regulation (16.03).

Project Engineer: Operations

The Project Engineer: Operations must implement all design and additive-manufacturing-related policies, processes and procedures, and oversees all activities pertaining to the manufacturing of the medical devices.

Design Personnel

Design personnel must be trained in design for additive manufacturing (DfAM), deemed competent and authorised to perform design activities, understand the medical anatomical interface and medical operational procedures.

Additive Manufacturing Personnel

Additive manufacturing personnel must be trained, deemed competent and authorised to perform all activities related to the 3D printing, testing, packing, labelling and sterilisation of the medical devices.

Paragraph 3 of ISO 13485 speaks to the applicable documents required to administer the system. The BMS document further demonstrates how the requirements of the acts and standards are met, as shown in Table A1.2. The focus of this study is on patient-specific implants and therefore the system must conform to MDD/93/42/EEC (Annex I – List of Essential Requirements). The standard stipulates that a list of all medical devices manufactured by the AM company must be specified.

Table A1.2: The following documents are used as guidelines in establishing a documented management system

1	European Council Directive concerning medical devices as amended M5	93/42/EEC	2008
2	Medical Devices – Quality Management Systems – Requirements for regulatory purposes	ISO 13485	2016
3	Acts, Regulations, Standards and Guidelines	CUT-19-01	02
4	Guideline for a Licence to Manufacture, Import, Export or Distribute Medical Devices & IVD'S	16.03	2016
5	Medical Device Establishments: Licence Requirements	9.79	2016
6	Guideline For Medical Device Quality Manual	8.07	2010

Quality Management System

Paragraph 4 of the BMS describes the QMS. The processes, as set out in the QMS, must be adhered to and monitored to ensure conformity. A key document is the Quality Policy, an important tool to benchmark the AM company in all aspects of quality control.

Quality Policy

A Quality Policy sets out the general guidelines, intentions, and goals of the AM company referring to quality. The policy is defined and published by top management and lays the foundations for the definition of quality objectives. There are two main goals that must be implemented regarding the quality objectives, namely meeting customer and regulatory requirements. It is key that top management informs all employees related to the QMS about the policy. Not only must employees be familiar with the main principles of the policy, but they must fully understand their position in the QMS and the impact of their activities on the product. Documentation requirements are prescribed in the standard.

Control of Documents

All documents within the management system are controlled according to a Procedure for Document- Data Control and Change Management. This procedure creates a method to review, update and approve all documents in the system. Educational, promotional and recruitment materials must be controlled and records retained to ensure that claims made in advertising are supported by scientific evidence. The control of documents to prevent the use of obsolete documents is of importance, as are the steps to prevent the loss and deterioration of documents. At least one copy of obsolete documents is electronically retained in the archive. All documents must be available for at least the lifetime of the medical devices plus five years, but not less than the retention period of any resulting record, or as specified by applicable regulatory requirements.

Control of Records

A Procedure for Records and the Records Matrix stipulates how records are maintained to provide evidence of conformity to requirements and of the effective operation of the QMS. The controls are defined for the identification, storage, security and integrity, retrieval, retention time and disposition of records. Furthermore, methods for protecting confidential health information contained in records must be defined and implemented. This includes ensuring that the records remain legible, readily identifiable and retrievable. Records must be retained for at least the lifetime of the medical devices plus five years, or as specified by applicable regulatory requirements.

Management Responsibility

Management commitment

Top management provides evidence of its commitment to the development and improvement of the QMS by communicating to the employees the importance of meeting customer- as well as regulatory- and statutory requirements and standards in terms of the safety and performance of the medical devices being developed and manufactured. A critical function of top management is to establish the Quality Policy Statement and Quality Objectives. Management Reviews are conducted to track performance of the AM company and to identify corrective actions where non-compliance is found. The review is also used to improve the systems, plan for the future, and be proactive in gauging the market trends. Management is responsible to ensure the availability of necessary human resources and financial resources.

Customer focus

As the customer is the reason for the AM company's existence, top management must ensure that customer requirements, needs and expectations are determined, converted into requirements and fulfilled with the aim of achieving safe medical devices. The AM company must aims at one hundred percent safe medical devices and one hundred percent customer satisfaction. To track customer satisfaction, a Post-Market Surveillance System and a Feedback System is used for evaluation and analysis at the Management Review Meetings.

Planning

Top management ensures that quality objectives are established, including those needed to meet applicable regulatory requirements and requirements for the product. These are established at relevant functions and levels within the organisation. The quality objectives shall be measurable (where possible) and consistent with the Quality Policy.

Top management ensures the availability of resources needed to achieve the identified and planned quality objectives. The output of the planning is documented by means of an Annual Budget. A quality plan for each "custom-made product" is developed and called the Patient File.

Responsibility, authority and communication

Responsibility and authority

The Human Resource Manual defines the functions and their interrelations within the organisation, including responsibilities and authorities. The interrelationship between all personnel who manage, perform and verify work affecting quality must be communicated to ensure the independence and authority necessary to perform these task. As indicated in the Functional Organisation Structure, Quality Assurance and Quality Control reports directly to the Director and is independent of Production.

Management Representative

A vital part of management's responsibility is the appointment of the company Management Representative, who has the responsibility and corresponding authority to ensure that processes needed for the management system are established, implemented and maintained. A South African Authorised Representative must be appointed for registration at the SAHPRA to obtain a licence to

manufacture. The AM company is also required to appoint a company Medical Device Safety Representative, who has the responsibility and corresponding authority to manage customer complaints, the vigilance and the recall system and make recall and notification decisions.

Internal communication

The organisation must ensure internal communication between its various levels and functions regarding the processes of the QMS and their effectiveness by means of formal meeting structures such as the Management Review, ISO EXCO and Factory Meetings. The effective use of the Preventive and Corrective Action System ensures effective communication flow and all employees are encouraged to participate in the system.

Management Review

As mentioned, the Management Review forms the crux of the ISO 13485 reviewing process. During an audit, this document is reviewed first as it gives a snapshot of the AM company and its progress towards the ultimate goals of all regulatory processes.

Review input

Management Review inputs include current performance and improvement opportunities related to the following:

a) Outstanding actions from the previous review;
b) Feedback (customer feedback and vigilance information);
c) Complaint handling;
d) Reporting to regulatory authorities;
e) Audits;
f) Monitoring and measurement of processes;
g) Monitoring and measurement of product;
h) Corrective action;
i) Preventive action;
j) Follow-up actions from previous Management Reviews;
k) Changes that could affect the QMS;
l) Recommendations for improvement; and
m) Applicable new or revised regulatory requirements.

Review output

The output from management reviews is recorded and includes the input reviewed and any decisions and actions related to:

a) Improvement needed to maintain the suitability, adequacy, and effectiveness of the QMS and its processes;
b) Improvement of product-related customer requirements;
c) Changes needed to respond to applicable new or revised regulatory requirements;
d) Resource needs.

Resource Management

Abuhav (2012:14), states that the resources required for the establishment of a QMS and the maintenance of its effectiveness are to be determined. The standard considers the allocation of appropriate resources as a key factor in realizing an effective quality system. The manufacturer is expected to analyse its needs for resource while considering certain organisational aspects. A correlation between the resources and the Quality Policy is essential. The standard requires specification of what resources are needed to assist and support in achieving these strategic aspects and to determine the resources: human resources, infrastructures, work environments, tools and equipment, information systems, suppliers and partners, natural resources, and financial resources.

Human Resources

Personnel performing work affecting product quality must be proven to be competent on the basis of appropriate education, training, skills and experience. The processes for establishing competence, providing needed training, and ensuring awareness of personnel are documented in a Procedure for Training.

A key element in conforming to the standards and regulatory bodies is to define the level of qualifications and skills that workers need to perform their tasks. Furthermore, personnel who train customers on medical devices must have adequate experience and training to carry out the task. All records of education, training, skills and experience must be maintained.

Executive management is included in the training programme for quality management and the rules and regulations on medical devices, because training of personnel in quality-related aspects is not restricted to those solely concerned with quality responsibilities. Education of all personnel on the

organisation's Quality Policy, Objectives and concepts of customer satisfaction must be done on a regular basis, at least annually. The methodology used to check effectiveness is proportionate to the risk associated with the work for which the training is being provided.

Infrastructure

The infrastructure needed to achieve conformity to product requirements which prevents product mix-up and ensures orderly handling of product must be documented.

Infrastructure includes, where appropriate:

a) Buildings, workspace and associated utilities;
b) Process equipment (both hardware and software);
c) Supporting services (such as X-ray, heat treatment, transport, communication, or information systems).

Maintenance activities of all infrastructure is kept in a Maintenance File. Planning of maintenance must take into account the interval of these maintenance activities, particularly when such maintenance activities, or lack thereof, can affect product quality. These requirements apply to equipment used in production, the control of the work environment and monitoring and measurement.

Work environment and contamination control

The health of all personnel working in the manufacturing area is of primary concern to the AM company and medical screening, before employment and at least annually, is essential. SOPs describe the procedures to be followed while working in the manufacturing and cleaning areas.

Sterile manufacturing

Documented requirements for control of contamination with micro-organisms or particulate matter, and maintenance of the required cleanliness during additive manufacturing, cleaning of devices and preservation is mandatory. Routine bioburden monitoring of both the environment and the devices must be carried out. The clean-air rooms must be maintained and kept validated in accordance with ISO 14644. It must be ensured that the outsourced sterilisation facility is maintained and kept validated in accordance with EN ISO 11137-1.

Product Realisation

Product realisation effects the day-to-day operations in the AM company, much more than manufacturing and it covers everything that is required to realise a product, from customer needs to design and manufacturing, installation and support of a medical device.

Planning of product realisation

In her overview of the ISO 13485 Medical Device Quality Management System requirements, Lane (2017) states, “Planning is an essential part of a functioning QMS, and in planning for product realisation the company is required to establish processes for all phases of product realisation, from how they obtain customer requirements, design products, purchase supplies and materials, make, install and service a device. There is risk associated with everything that we do, but in making medical devices these can include the risk to a person's life”. The standard requires that documented requirements for risk management throughout product realisation be established. Broadly stated, risk management includes assessment of the risk and identifying all risks. Following this, an analysis of the risk is conducted by determining the severity and probability of all hazardous situations. From this information, risk reduction processes are followed to eliminate the risk as much as possible or practical.

Risk management applies to all QMS processes and most importantly, to device design, manufacturing and support processes. This is such an important process that ISO 13485 requires that risk management be done according to ISO 14971, the international standard for medical device risk management.

To this end, the AM company must develop a Procedure for Risk Assessment (see Appendix 2), based on the requirements of EN ISO 14971, the Essential Principles (8.02) and the Essential Requirements (MDD 93/42/EEC, Annex I). The Life Cycle Risk Assessment Matrices are updated based on post-market surveillance information, early warnings, customer complaints and internal non-conformances.

Furthermore, Lane states that planning for product realisation begins with establishing processes for handling customer requirements and how to communicate with the customer throughout the lifecycle of the device. Requirements may be as simple as processing orders to as complex as requirements to design a complex device from a general concept.

Where product or process designs are done, the requirements for design controls as per the standard must be followed. Lane mentions that where regulatory agencies reported adverse events of medical devices, they found that most often, the problems were caused by poor design. A controlled design process that follows the design control requirements begins with establishing design requirements, and goes through validation and transfer to manufacturing.

It is important to ensure that the materials being used in the manufacture of the device are correct. The standard specifies that purchasing requirements covering purchases from qualified suppliers, according to pre-established specifications, must meet these specifications.

In the manufacture and production of the devices, there must be controls to assure that the manufactured device meets all of its specifications. This includes not only controlling the production processes, but control of how material and devices are identified, stored and used. Documented processes must cover receiving, warehouse, production, testing, shipping right through to the parameters set in the Instructions for Use document supplied to the customer.

Processes that cannot or will not be fully verified must be validated to assure that they always meet specifications, and once validated, must be controlled and performed by trained personnel. All identified risks must be minimised or eliminated by implementing actions, and records of these actions are maintained.

Design and development

Developing a new product to comply with the regulatory bodies is a rigorous process. Throughout the process, records are kept, as stipulated in the BMS.

Design and development planning

Firstly, it must be noted that it is the AM company's responsibility to plan and control the design and development of products. Design and development planning documents are maintained and updated as the design and development progresses.

Design and development inputs

When the product requirements are determined, the factors to be considered are functional, performance, usability and safety requirements, taking into account the regulatory requirements, standards and the outputs of risk management and where relevant, information derived from previous similar developments/design. These factors are, therefore, the inputs used to design and develop a new product.

Design and development outputs

Design and development outputs are reviewed to meet the input requirements for design and development and provide appropriate information for purchasing and production. The characteristics of the product that are essential for its safe and proper use must be specified.

Design and development review

Systematic reviews of design and development are performed at suitable stages during the design and development process. Specialist personnel are included in the reviews.

Design and development verification

Design and development verification are performed to ensure that the design and development outputs have met the design and development input requirements. Typically, these are tests conducted at accredited laboratories against standards and internal specifications. It is the responsibility of the AM company to develop documented verification plans that include methods, acceptance criteria and, where appropriate, statistical techniques with rationale for sample size. If the intended use requires that the custom-made device will be connected to, or have an interface with other medical devices, verification includes confirmation that the design outputs meet design inputs when connected or interfaced, e.g. dental implants.

Design and development validation

Design and development validation is performed in accordance with planned and documented arrangements to ensure that the resulting product meets the requirements for the specified application or its intended use.

All software used in medical device additive design and manufacturing is documented and Procedures for Software Validation must be developed. These software applications are validated prior to initial use of the product and where appropriate, after changes to the software or its application. The specific approach and activities associated with software validation and revalidation is taken-up in the risk assessment as shown in a Validation Master Plan and the Procedure for Risk Assessment.

The documented validation plans should include methods, acceptance criteria and, where appropriate, statistical techniques with rationale for sample size. Design validation is conducted on a representative product and the rationale for the choice of product used for validation is recorded. As part of design and development validation, the AM company performs clinical evaluations or performance evaluations of the medical device in accordance with applicable regulatory requirements, as stipulated in a Procedure for Clinical Evaluations.

If the intended use requires that the medical device be connected to, or have an interface with, other medical devices, validation must include confirmation that the requirements for the specified application or intended use have been met when connected or interfaced.

Design and development transfer

Once the design and development of the product has been completed, the outputs must be verified as suitable for additive manufacturing before becoming final production specifications. Results and conclusions of the transfer are recorded as stipulated in the Procedure for Product- and Process Development.

Control of design and development changes

Should any changes be made to the function, performance, usability, safety and applicable regulatory requirements for the medical device and its intended use, the AM company must determine the significance of the change and document procedures to control design and

development changes as set out in a Procedure for Document- and Data Control and Change Management. In terms of the procedure, before implementation of any changes, they must be reviewed verified, validated, where appropriate and approved. The review of design and development changes includes evaluation of the effect of the changes on constituent parts and product in process or already delivered, inputs or outputs of risk management and product realisation processes.

Design and Development Files

A Design and Development File for each custom-made medical device must be kept. This file includes or references records generated to demonstrate conformity to the requirements for design and development and records for design and development changes.

Medical Device Files

It must be mentioned that an AM company focused on design and manufacturing of custom-made medical devices does not need a comprehensive Medical Device File as the focus would be on a Patient File as each patient's device is a custom design. For custom-made medical devices, abbreviated Medical Device Files for each patient are established to ensure that the Essential Requirements are always satisfied and this includes the complete design documentation and a comprehensive risk assessment.

For each medical device family manufactured (one design manufactured in production quantities), the AM company has to establish and maintain Medical Device Files for each product which contains documents generated to demonstrate conformity to ISO 13485 and compliance with applicable regulatory requirements.

Purchasing

Purchasing process

The AM company needs to document procedures to ensure that purchased product conforms to specified purchasing information. Criteria for the evaluation and selection of suppliers must be established based on the supplier's ability to provide product that meets the organisation's requirements and the performance of the supplier. The effect of the purchased product on the quality of the medical device and the proportionate risk associated with the medical device must be

determined. Supplier performance is monitored and re-evaluated to ensure that the requirements for the purchased product are met and recorded during the Annual Management Review Meeting.

Purchasing information

The AM company must ensure the adequacy of the specified purchasing requirements prior to forwarding this information to the supplier. Purchasing information includes a written agreement with critical suppliers stating that the supplier will notify the organisation of changes in the purchased product prior to implementation of any changes that will affect the ability of the purchased product to meet the specified purchase requirements. Purchasing information in the form of documents and records are maintained to the extent required for traceability.

Verification of purchased product

The AM company needs to establish and implement inspection, testing or any other activities necessary to ensure that the purchased product meets the specified purchasing requirements based on the supplier evaluation results and proportionate to the risks associated with the purchased product.

When the AM company becomes aware of any changes to the purchased product, it must be determined whether these changes affect the product realisation process or the custom-made devices.

Materials management

The AM company identifies and provides adequate materials and consumables to perform, verify and manage all activities performed in the facility. The AM company needs to implement a system that evaluates and qualifies critical supplies to ensure that purchased materials conform to the specified requirements as captured in a Procedure for Purchasing and Supplier Management. The AM company must ensure that suppliers of critical materials are qualified and selected based on the supplier's ability to meet specified requirements, including training and qualifications of personnel who perform activities related to the provision of materials and supplies. The AM company needs to monitor the performance of critical suppliers as needed based on the nature of the material and the impact on the quality of the custom-made medical devices. The AM company must take corrective action and report to management when a supplier fails to meet the specified requirements. A procedure is implemented where the AM company notifies a supplier when materials are received in an unacceptable condition and a Supplier Complaint Form will be send out to the supplier.

Manufacturing

All procedures affecting the manufacturing process are contained in the Manufacturing Manual.

Control of manufacturing

Manufacturing is planned, carried out, monitored and controlled to ensure that the process conforms to specification.

Manufacturing controls include:

a) Documentation of procedures and methods for the control of manufacturing;
b) Qualification of infrastructure as per a Validation Master Plan;
c) Monitoring and measurement of process parameters and product characteristics;
d) Availability and use of monitoring and measuring equipment;
e) Defined operations for labelling and packaging; and
f) Product release, delivery and post-delivery activities.

A record for each custom-made device must be established and maintained to provide traceability and to identify the input design criteria, manufacturing input material, etc. The custom-made patient records must be verified and approved.

Cleanliness of the product

The AM company needs to document requirements for cleanliness of product or contamination control of product if the product has to be maintained in a clean environment prior to sterilisation or any process agents that need to be removed from product during manufacture.

Particular requirements for sterile medical devices

Records of the sterilisation process parameters used for each sterilisation run of medical devices manufactured are maintained. This ensures that sterilisation records are traceable to each batch number. The sterilisation processes are maintained and validated in accordance with ISO 11137-1.

Validation of processes for medical device manufacturing and preservation

The AM company must validate any processes for medical device manufacturing and preservation where the resulting output cannot be, or is not verified by subsequent monitoring or measurement. Validations demonstrate the ability of these processes to achieve the planned results consistently.

Particular requirements for validation of processes for sterilisation and sterile barrier systems

Documentation of procedures for the validation of processes for sterilisation and sterile barrier systems must be implemented. Processes for sterilisation and sterile barrier systems are validated prior to implementation and following product or process changes, where appropriate. Records of the results and, conclusion of validation and necessary actions from the validation are maintained.

Identification

A procedure for the suitable means of product identification throughout product realisation must be established. Identification of product status is maintained throughout manufacturing and storage of medical devices to ensure that only medical devices that have passed the required tests or released under an authorised concession are dispatched.

Traceability

The AM company must document procedures for traceability starting from the input material received, throughout the additive manufacturing process and packaging and sterilisation used to the final product identification. Where medical devices are implanted, traceability is more complex and it is vital that records of materials and conditions for the work environment used are recorded to ensure conformity to the specified safety and performance requirements of each custom-made implantable device.

Users of the devices, such as hospitals and surgeons, must maintain records of the implants to allow traceability and these records must be available for inspection.

Customer property

Patients' X-rays and CT scans must be protected throughout the process to maintain confidentiality.

Preservation of product

Preservation of the conformity of medical devices to requirements during additive manufacturing, storage, handling, and supply is of the utmost importance. The AM company must protect the product from alteration, contamination or damage when exposed to expected conditions and hazards during additive manufacturing, storage, handling, and delivery. This must be done by designing and constructing suitable collection, packaging and shipping containers. Documentation of requirements for special conditions needed if packaging alone cannot provide preservation must be drawn up and adhered to.

Equipment management

Adequate equipment must be provided to perform, verify and manage all activities performed in the facility. Furthermore, the AM company needs to establish and maintain policies, processes and procedures to identify, control, maintain and monitor critical equipment.

Elements of control are required to define equipment specifications before purchase and it is essential to qualify all equipment for its intended use and ensure all equipment has unique identification.

Equipment repairs and upgrades are evaluated and equipment requalified, where appropriate, based on a Validation Master Plan and manufacturers' recommendations. Equipment is always installed as per the manufacturer's specifications and validated thereafter. The functionality of each piece of equipment is verified before actual use and must meet the manufacturer's operational specifications (IQ). The AM company needs to demonstrate that equipment performs as expected for its intended use (OQ and PQ). The AM company needs to document each identified piece of equipment with the appropriate maintenance and monitoring schedule that, at a minimum, is in accordance with the manufacturer's written instructions. It is essential to identify equipment that is to be maintained in a calibrated state and to define the process for the calibration of equipment, including details of equipment type, unique identification, locations, frequency of checks, check method, acceptance criteria and limitations. The equipment must be safeguarded from adjustments that would invalidate the calibration setting. A procedure must be implemented when equipment is found to be out of calibration or specification. When this occurs, the validity of previous inspection and services to the specifications must be assessed.

Records must be maintained of equipment use in a manner that permits tracing of custom-made medical devices to all equipment associated with the manufacturing, sterilisation, storage and distribution of the product. It must also be possible to identify any medical devices associated with a specific piece of equipment.

This equipment is maintained in accordance with the documented requirements for the maintenance activities, including the interval of these maintenance activities, and when such maintenance activities, or lack thereof, can affect product quality. These requirements apply to equipment used in production, the control of the work environment and monitoring and measurement. All inspection, measuring and test equipment is calibrated on an annual basis in accordance with the Procedure for Maintenance and Calibration. Validation of the equipment is vital to prove the repeatability of the manufacturing process and are managed through a validation master plan.

Control of monitoring and measuring equipment

All inspection, measuring and test equipment is calibrated on an annual basis in accordance with a Procedure for Maintenance and Calibration against measurement standards traceable to international or national measurement standards. When no such standards exist, the basis used for calibration or verification needs to be recorded.

Measurement, analysis and improvement

Monitoring and measurement

The ISO 13485 standard is very clear that the product requirements defined by the customer are met. Where the product does not meet with the customer's expectations, processes must be set in motion to capture the complaint and determine the root cause and steps taken by preventive or corrective actions to rectify the problem and where applicable, improve the process. Recall of a product is triggered when a problem is identified, either internally or via a customer complaint, that is deemed to be a high risk. Customer feedback is requested on an ongoing basis and the data is formally evaluated and reported in the Annual Management Review.

Feedback

The AM company needs to document procedures for the feedback process. This feedback process includes gathering data from manufacturing as well as post-production activities. The information gathered in the feedback process serves as potential input into risk management for monitoring and maintaining the product requirements as well as the product realisation or improvement processes.

Complaint handling

The AM company needs to document procedures for timely complaint handling in accordance with applicable regulatory requirements. If any complaint is not investigated, justification is documented. Any correction or corrective action resulting from the complaint-handling process is documented. If an investigation determines activities outside the organisation contributed to the complaint, relevant information is exchanged between the organisation and the external party involved.

Reporting to regulatory authorities

If a regulatory authority requires notification of complaints that meet their reporting criteria, the AM company needs to have documented procedures for providing notification to the appropriate regulatory authorities, such as SAHPRA and where devices are sold in Europe. Records of reporting to regulatory authorities shall be maintained.

Internal audit

The AM company conducts internal audits at planned intervals to determine whether the QMS conforms to planned and documented arrangements, requirements of ISO 13485, South African Medical Device Regulations and MDD 93/42/EEC, QMS requirements established by the organisation, and applicable regulatory requirements. It must also be determined whether the QMS is effectively implemented and maintained.

An Audit Programme is an essential part of the QMS. In planning the programme, the audit criteria, scope, interval and methods are to be defined and recorded. Once the audit has been completed, the management responsible for the area being audited must ensure that any corrections and corrective actions are taken without undue delay.

Monitoring and measurement of medical devices

The AM company must monitor and measure the characteristics of the custom-made medical devices to verify that all requirements have been met. This is carried out at relevant stages of the process of medical device realisation. To achieve this, the Clinical Advisor conducts follow-up consultations with the patients using records and photos as verification and evidence of conformity to the acceptance criteria are maintained on the patient file. Medical devices may not be released until the planned and documented arrangements have been satisfactorily completed.

Control of non-conforming product

General

The AM company must ensure that products that do not conform to specifications are identified and controlled to prevent their unintended use or delivery. A procedure to define the controls and related responsibilities and authorities for the identification, documentation, segregation, evaluation and disposition of non-conforming product must be developed.

Actions in response to non-conforming product detected before delivery

The AM company needs to deal with non-conforming product by one or more of the following ways:

a) Taking action to eliminate the detected non-conformity;
b) Taking action to preclude its original intended use or application;
c) Authorising its use, release or acceptance under concession.

The AM company ensures that non-conforming product is accepted by concession only if the justification is provided, approval is obtained and applicable regulatory requirements are met.

Actions in response to non-conforming product detected after delivery

When non-conforming product is detected after delivery or use has started, the AM company takes action appropriate to the effects, or potential effects, of the non-conformity. The procedures for issuing of advisory notices in accordance with regulatory requirements must be in place and they must be capable of being put into effect at any time.

Rework

The AM company only performs rework in accordance with documented procedures that take into account the potential adverse effect of the rework on the product. These procedures must undergo the same review and approval as the original procedure. After the completion of rework, the product is verified to ensure that it meets applicable acceptance criteria and regulatory requirements.

Analysis of data

The AM company needs to document procedures to determine, collect and analyse appropriate data to demonstrate the suitability, adequacy and effectiveness of the QMS as per a Procedure for Quality Monitoring and the Process Ownership Matrix. The analysis of data includes data generated as a result of monitoring and measurement and from other relevant sources and include, at a minimum, input from:

a) Feedback;
b) Conformity to medical devices requirements;
c) Characteristics and trends of processes and product, including opportunities for improvement;
d) Suppliers;
e) Audits; and
f) Service reports, where appropriate.

If the analysis of data shows that the QMS is not suitable, adequate or effective, the AM company must use this analysis as input for improvement.

Improvement

General

The AM company needs to identify and implement any changes necessary to ensure and maintain the continued suitability, adequacy and effectiveness of the QMS as well as medical device safety and performance through the use of the Quality Policy, Quality Objectives, Audit Results, Post-Market Surveillance, analysis of data, corrective actions, preventive actions and Management Review.

Corrective action

The AM company takes action to eliminate the cause of non-conformities to prevent recurrence. Any corrective actions taken due to non-conformities must be taken without undue delay. Corrective actions must be proportionate to the effects of the non-conformities encountered.

The AM company must document a procedure to define requirements for reviewing non-conformities (including complaints). The causes of non-conformities must be determined and the need for action must be planned and evaluated to ensure that non-conformities do not recur. This should include updating documentation. A further step is to verify that the corrective action does not adversely affect the ability to meet applicable regulatory requirements or the safety and performance of the medical device. Thereafter, the effectiveness of corrective action taken must be reviewed. Records of the results of any investigation and of action taken must be maintained and captured in a Preventive and Corrective Action Request.

Preventive action

The AM company must determine action to eliminate the causes of potential non-conformities in order to prevent their occurrence. Preventive actions must be proportionate to the effects of the potential problems. Procedures should be documented to describe requirements determine potential non-conformities and their causes. Evaluation, planning and documentation of actions needed and implementation of the actions must be documented. Thereafter verification that the action does not adversely affect the ability to meet applicable regulatory requirements or the safety and performance of the medical device. Reviewing the effectiveness of the preventive action taken is of utmost importance.

Appendix 2: Procedure for Conducting a Product Risk Assessment (CRPM ISO 13485: 2016 Quality Management System)

PROCEDURE FOR CONDUCTING A PRODUCT RISK ASSESSMENT

DESCRIPTION
PURPOSE AND SCOPE PURPOSE SCOPE DEFINITIONS AND ABBREVIATIONS DEFINITIONS ABBREVIATIONS APPLICABLE DOCUMENTS PROCEDURE RISK MANAGEMENT FILE RISK ASSESSMENT ESTIMATION/QUANTIFICATION OF RISKS FOR EACH HAZARD RISK CONTROL OVERALL RISK EVALUATION RISK MANAGEMENT REPORT POST-PRODUCTION AND POST-MARKETING INFORMATION REVIEW

AMENDMENT RECORD		
01		
02		
03		
04		

APPROVAL		
	SIGNATURE	**DATE**
COMPILED BY: PROJECT COORDINATOR		
ACKNOWLEDGEMENT AND ACCEPTANCE MANAGEMENT REPRESENTATIVE: ISO 13485		
APPROVAL: DIRECTOR		

DISTRIBUTION		
COPY NUMBER	**POSITION**	**ADDRESS**
MASTER	PROJECT COORDINATOR	
1.	AUTHORISED REPRESENTATIVE	
2.		

Purpose and scope

Purpose

The purpose of this document is to define the procedure followed by the AM company in performing a product risk assessment on a medical device by making use of a scientific method.

Scope

This document is applicable to all risk assessments conducted on medical devices for the AM company.

Definitions and abbreviations

Definitions

The Risk Assessment Team shall consist of the following persons, when necessary:

- Director
- Project Engineer: Operation
- Quality Engineer
- Medical Device Consultant; and
- Co-opted members such as medical doctors, nurses, etc., as required.

The members of the Risk Assessment Team shall have sufficient knowledge and experience in risk assessment and management techniques and application of the device. Records of qualification and experience shall be maintained.

Abbreviations

None

Applicable documents

The documents that were used as guidelines in the establishing of this procedure within the AM company, is shown in Table A2.1.

Table A2.1: Guideline documents to establish procedure

1.	Medical Device Regulation	EU 2017/745	2017
2.	Medical devices - Quality management systems – Requirements for regulatory purposes	ISO 13485	2016
3.	Medical devices — Application of risk management to medical devices	EN ISO 14971	2012
4.	Implementation of risk management principles and activities within a Quality Management System	GHTF/SG3/N15R8	2005
5.	List of Standards	CUT-19-01	02
6.	European Council Directive concerning medical devices	93/42/EEC	2007

Procedure

The Risk Management Flow Diagram is shown in Figure A2.1.

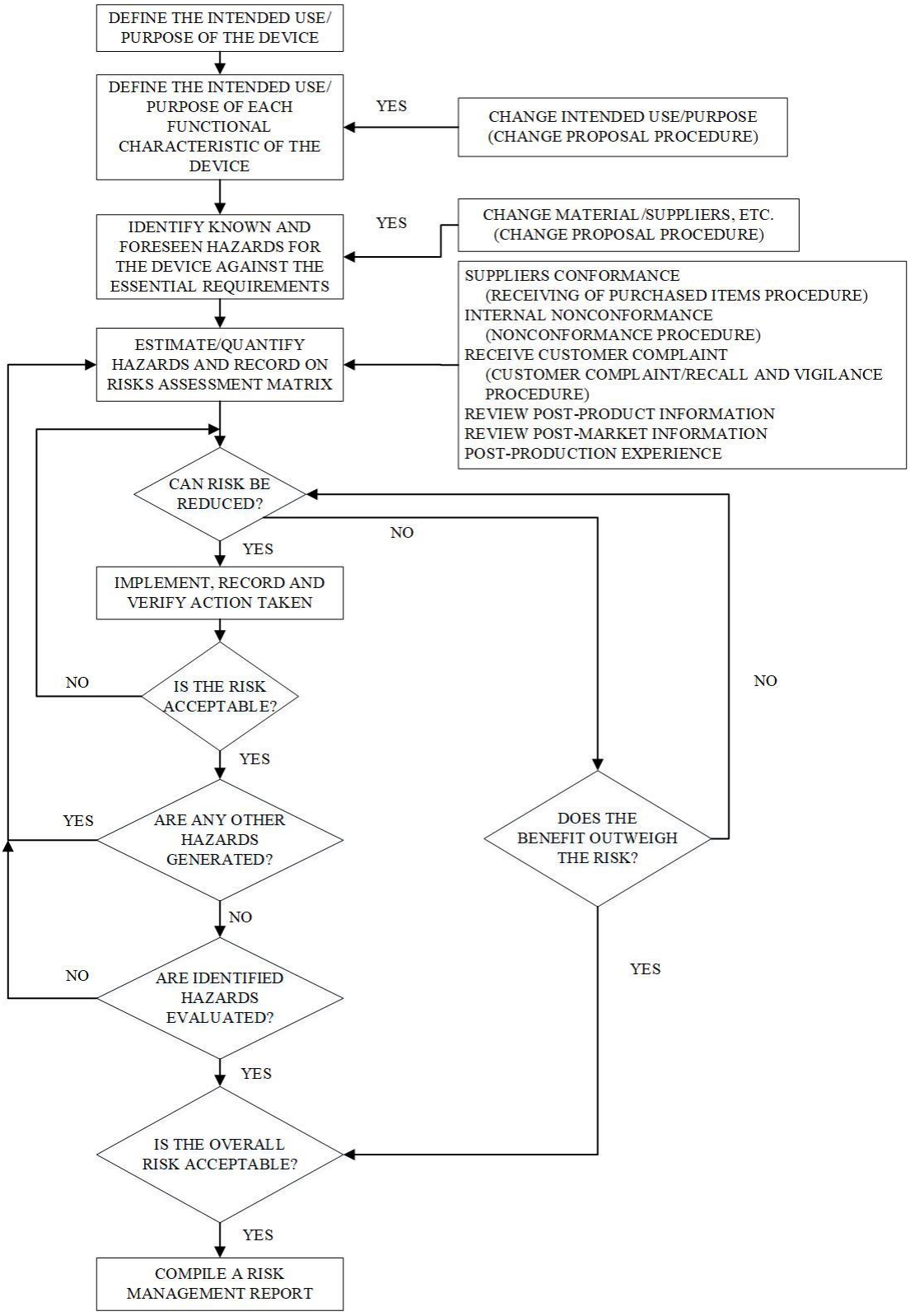

Figure A2.1: Risk management flow diagram

Figure A2.2 shows a flow diagram explaining the risk analysis, evaluation and control steps in order to end up with post-production and marketing information.

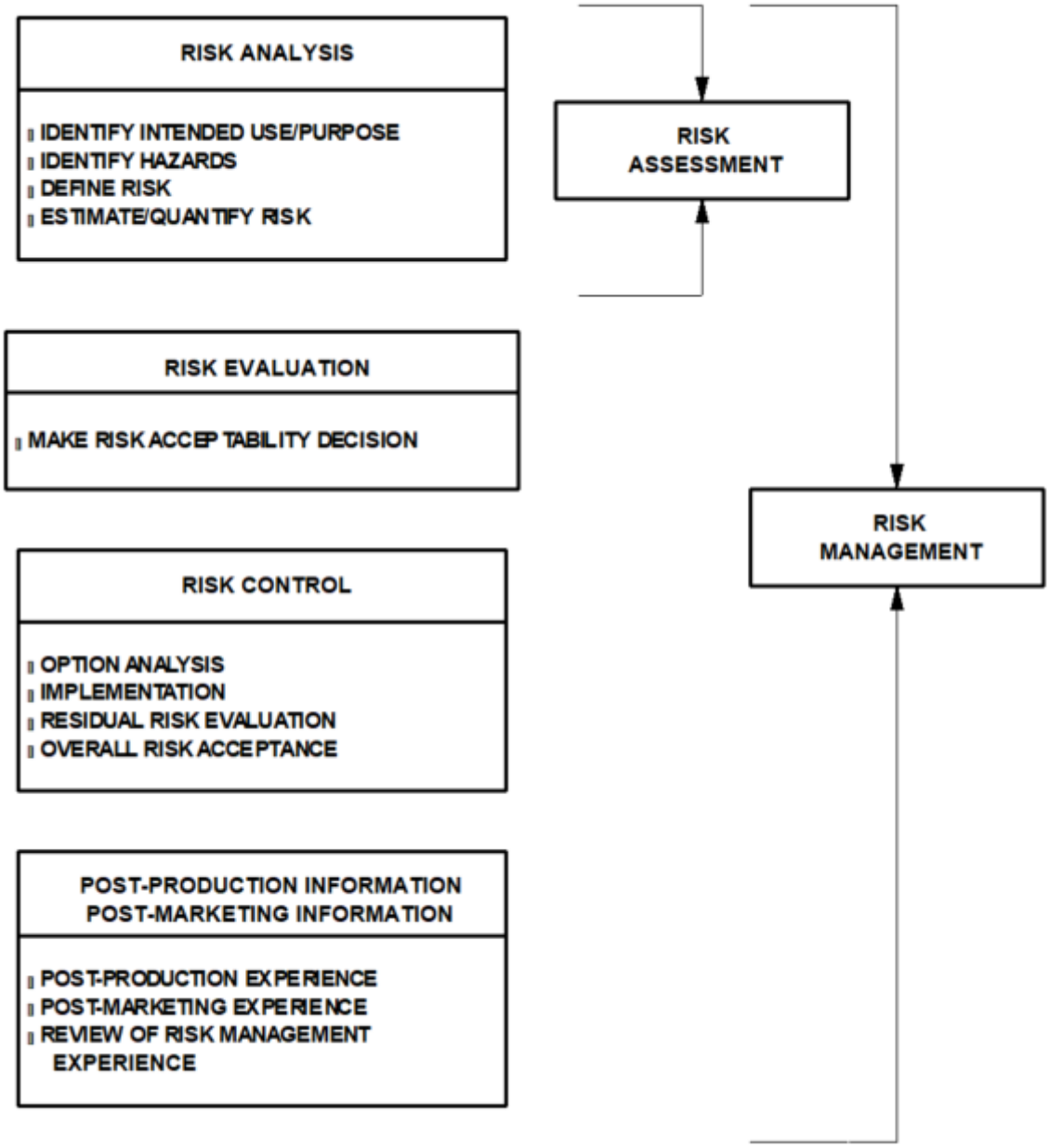

Figure A2.2: Risk assessment and management flow diagram

Risk Management File

The Quality Engineer shall establish a Risk Management File at the beginning of the design and development phase of a product, or for existing product, retrospectively.

The Risk Management File shall at least consist of the following:

- Risk Management Plan;
- Risk Assessment Matrix against the Essential Requirements;
- Checklist against the Essential Requirements;
- Risk Verification Plan;
- Any post-production information that influences the Risk Management Plan;
- Any post-marketing information that influences the Risk Management Plan; and
- Risk Management Report.

Risk assessment

Define the intended use/purpose of the device and characteristics. The intended use/purpose of the device and/or accessories and its characteristics shall be defined. The following shall be used as input into the definition:

- Required skill and training of the user;
- Ergonomic factors;
- Role the device will play in diagnosis, prevention, monitoring, treatment or alleviation of disease, compensation for injury or handicap, replacement or modification of anatomy, etc.;
- Is the device sustaining or life supporting?

Identification of known and foreseen hazards

The following will be considered at least in the identification of known and foreseen hazards:

- Is the device intended to have contact with the patient or other persons?
- What materials and/or components are incorporated in the device or are used with, or are in contact with the device?
- Is energy delivered to and/or extracted from the patient?
- Are substances delivered to and/or extracted from the patient?
- Are biological materials processed by the device for subsequent re-use?
- Is the device supplied sterile or intended to be sterilised by the user or are other microbiological controls applicable?

- Is the device intended to be routinely cleaned and disinfected by the user?
- Is the device intended to modify the patient environment?
- Are measurements taken?
- Is the device interpretative?
- Is the device intended to control or to interact with other devices or drugs?
- Are there any unwanted outputs of energy or substances?
- Is the device susceptible to environmental influences?
- Does the device influence the environment?
- Are there essential consumables or accessories associated with the device?
- Is maintenance and/or calibration necessary?
- Does the device have a restricted shelf life?
- Are there any possible delayed and/or long-term use effects?
- To what mechanical forces will the device be subjected?
- What determines the lifetime of the device?
- Is the device intended for single use?
- Is safe decommissioning or disposal of the device necessary?
- Does installation of the device require special training?
- Will new manufacturing processes need to be established or introduced?
- Is successful application of the device critically dependent on human factors such as the user interface?
    - Connecting parts and accessories
    - Control interface
    - Display information
    - Controlled by a menu
- Is the device intended to be mobile or portable?

Estimation/quantification of risks for each hazard

The Risk Assessment Team shall conduct a risk assessment in accordance with this procedure and ISO 14971 as baselines. The worst-case scenario/single fault condition shall be predicted and an evaluation of the risk made. The Risk Analysis Table shall be completed based on the Essential Requirements Checklist and the Risk Analysis Table and Essential Requirements Checklist.

Table A2.2 shows the Risk Evaluation Criteria that could be used during a risk assessment.

Table A2.2: Risk Evaluation Criteria

		LEVEL OF RISK				
		Negligible	Limited	Moderate	Severe	Critical/fatal
PROBABILITY OF OCCURRENCE		1	2	3	4	5
Frequent (1 per week)	40	40	80	120	160	200
Probable (1 per month)	15	15	30	45	60	75
Remote (1 per annum)	13	13	26	39	52	65
Unlikely (1 per 3 years)	9	9	18	27	36	45
Improbable (1 in 5 years)	6	6	12	18	24	30
Incredible (1 in 10 years)	3	3	6	9	12	5
Not possible	1	1	2	3	4	5

Any figure above **27** shall receive attention to determine methods to minimise or eliminate the risk. Where the residual risk cannot be reduced or eliminated and the benefits outweigh the risk a warning will be issued.

Risk control

Action plans to eliminate the risk or reduction in the risk shall be assessed and implemented. The risk associated with the risk reduction/elimination action shall be verified to determine if it has created an alternative or additional risk. Implement risk reduction/elimination plans shall be verified to ensure that it is effective. The verifications shall be recorded in the Risk Management File.

Each risk shall be weighed to decide if the risk is acceptable and if the risk is residual and if necessary, warning are given (provided that the residual risk outweighs the medical benefits of the device).

Overall risk evaluation

The Risk Assessment Team shall evaluate the identified risks and risk reduction/elimination plans and will issue a statement that the overall risks of the device is acceptable. This is done by means of the Declaration of Conformity by the Director.

Risk management report

A Risk Assessment Report shall be documented and shall provide traceability for each hazard to the risk analysis, the risk evaluation, the risk implementation and verification of the risk control measures, and that the residual risk/s is acceptable. The Risk Management Report shall be filed in the Risk Management File.

Post-production and post-marketing information

The Risk Assessment Matrix, Risk Management Report and Risk Management File shall be updated where indications of new or amended risks are obtained from the following:

- Internal non-conformances;
- Customer Complaints;
- Input from product development activities during new product development;
- Input from the Post-Market Surveillance System;
- Where major changes are done to the product characteristics;
- Where the class of the medical device is changed due to a new application;
- Where raw materials or packaging materials are changed;
- Where the sterilisation process is changed; and
- Where raw material suppliers or subcontractors are changed.

Monitoring of the products in the field will be an ongoing activity monitoring the results and feedback of devices deployed in the field. All events involving the device which result in some adverse effect on the patient or operator must be recorded, analysed, and action taken where necessary. If the analysis of the event shows some defect in the design or manufacture of the device, design changes must be made to resolve these defects.

Annual Post-Market Surveillance Process Check Meetings

The ISO Administrator proactively checks on a quarterly basis that all issues arising in the field are indeed being reported, recorded and handled appropriately. Any events identified must be reported at the next ISO EXCO meeting.

Manufacture and servicing

The AM company manufactures, maintains and services medical products with the same personnel in the same location. As such any defects are tracked and resolved.

If any risks become apparent that were previously not identified, the Risk Analysis Process will be followed to analyse and mitigate these risks.

Notified Body relationship

A close relationship will be maintained with the Notified Body responsible for certifying the AM company's medical products so as to provide complete support in identifying, tracking and resolving any incidents that may possibly occur in the field. The AM company will contact the Notified Body immediately if they discover such a failure or incident that causes significant harm to a patient or user.

Handling of a "Notifiable Incident"

- A notifiable incident is an event where a patient was exposed to risk, or injured, or a death occurred. In terms of the requirements for CE marking, such events are to be reported to the Notified Body that approved the product for CE marking.

- The purpose of the report is to ensure that the occurrence of such an event is not repeated – not only by the AM company's products, but by any similar medical products.

- The definition of incidents to be reported is given in the document "Guidelines on a Medical Devices Vigilance System", MEDDEV 2.12.1.

- These steps are to be followed by the Director in submitting the report.

- Further to the initial report, an investigation will be conducted, and the matter resolved in co-operation with the Competent Authority.

Review

The Risk Assessments shall at least be reviewed annually as part of the Annual Management Review.

Appendix 3: Draft SLA for Micro-CT Scanning

SERVICE LEVEL AGREEMENT

PARTIES:-

CLIENT – *PLEASE ADD NAME*

AND

SERVICE PROVIDER – *PLEASE ADD NAME*

DEFINITIONS:-

In this Agreement, unless clearly inconsistent with or otherwise indicated by the context:-

"Agreement" means the agreement set out in this document.

"Business Day" means a day, other than a Saturday, a Sunday or a Public Holiday in the Republic of South Africa.

“Service Provider” means ***PLEASE ADD NAME***, he being duly authorised thereto.

“Client” means ***PLEASE ADD NAME***, duly authorized thereto and acting by virtue of delegated authority.

“AM Medical Devices” means the devices set out in Annexure “A” hereto.

"Parties" means the Client and Service Provider and "Party" means any one of them as the context may indicate.

"Signature Date" means the date of signature of this Agreement by the Party signing last in time.

In this Agreement, unless clearly inconsistent with or otherwise indicated by the context:-

Any reference to a singular includes the plural and *vice versa*.

Any reference to natural persons include legal persons and *vice versa*.

Any reference to a gender includes the other genders.

Where appropriate, meanings ascribed to define words and expressions in this clause, shall impose substantive obligations on the Parties.

The clause headings in this Agreement have been inserted for convenience only and shall not be taken into account in its interpretation.

Where any term is defined in this Agreement within the context of any particular clause or sub-clause, the term so defined shall, unless it appears clearly from such clause or sub-clause that such term has limited application to the relevant clause or sub-clause only, bear the meaning ascribed to it for all purposes in terms of this Agreement, notwithstanding that such term has not been defined in this clause.

Where this Agreement requires a Party to use "best endeavours", in relation to an act or omission that Party shall do all such things as are or may be necessary or desirable so as to achieve that act or to omit taking an action, unless the Parties agree that it is not reasonable to take the action or to omit taking an action.

The use of the word "including" followed by a specific example or examples shall not be construed or interpreted as limiting the meaning of the general working preceding it and the *euisdem generis* rule shall not be applied in the interpretation of such general wording and /or such specific example or examples.

Since this Agreement is the product of negotiations between the Parties, the *contra proferentem* rule of construction shall not apply nor shall this Agreement be construed in favour of or against any Party by reason of the extent to which any Party or its professional advisors participated in the preparation of this Agreement.

This Agreement shall be governed by and construed and interpreted in accordance with the law of the Republic of South Africa.

INTRODUCTION:-

Client needs to produce the AM Medical Devices.

Client has the capacity to manufacture the AM Medical Devices.

Client requires the Service Provider to determine the mechanical properties of the AM Medical Devices according to certain standards as specified in the attached Annexure A and within certain time frames.

The Parties have agreed on the terms of their Agreement and wish to record same in writing.

AGREEMENT TO MANUFACTURE:-

Client undertakes to manufacture the AM Medical Devices to be assessed by the Service Provider.

Client undertakes to manufacture the AM Medical Devices according to the quality and specifications set out in Annexure B, whilst the Service Provider undertakes to assess the mechanical characteristics of said AM Medical Devices according to the specifications set out in Annexure A.

DURATION OF AGREEMENT:-

This Agreement shall commence on the Signature Date and shall endure for twelve (12) months.

After the initial period of twelve (12) months, the Agreement shall continue indefinitely subject to either Parties' right to terminate the Agreement by giving the other Party twenty (20) business days' written notice of its intention to terminate the Agreement.

SCOPE OF WORK:-

The scope of the work to be undertaken by Service Provider in terms of this Agreement is to assess the mechanical characteristics of the AM Medical Devices according to the set specifications and within the time frames stipulated by Client.

PAYMENT:-

Client shall pay Service Provider strictly thirty (30) days from date of invoice.

Payment shall be made by way of Electronic Funds Transfer directly into Service Provider's bank account, the details of which are as follows:-

Account name: …….
Bank: …….
Branch: …….
Account number: ……

Save where expressly provided otherwise, where any payment or sum of money due from Client to the Service Provider in terms of the Agreement is not paid within thirty (30) days from date of invoice, it shall bear interest thereon at the maximum annual finance rate applicable from time to time in terms of the National Credit Act 34 of 2005.

COMMUNICATION AND CONTACT:-

All communication regarding this Agreement shall be conducted by and between the Parties' duly authorised representatives as set out in this clause.

The duly authorised representative for Client is ***PLEASE ADD NAME***, his contact details are set out in Annexure C hereto.

The duly authorised representative for Client is ***PLEASE ADD NAME*** whose contact details are set out in Annexure D hereto.

In the event that either Party wishes to change its contact representative, it shall forthwith in writing notify the other Party of the identity and contact details of its representative and such representative shall thereafter represent that Party in all transactions.

DUTIES OF SERVICE PROVIDER:-

Service Provider shall adhere strictly to the specifications and quality set out in Annexure A or as indicated to it in writing from time to time by Client.

Service Provider shall not, without prior written approval of Client change:

Any of the procedures specified in the quotation, order or the specifications;

Any of the equipment or machinery to be used as specified in the quotation and subsequent order;

The facility or the site within the facility where the assessment is to take place;

The test part provided to Service Provider for purposes of quality control.

Service Provider shall as quickly as possible, but in any event, within twenty four (24) hours of becoming aware thereof, report to Client:

Any manufacturing defects;

Any safety issues in respect of the materials used in manufacturing the AM Medical Devices.

Service Provider shall forthwith, on becoming aware of it, report to Client any issue that may delay testing or result in late delivery of the AM Medical Devices assessed in terms of a specific order.

Service Provider shall ensure that all work done in terms of this Agreement is performed and supervised by competent and suitably qualified personnel.

DUTIES OF CLIENT:-

Client shall ensure that all orders are placed timeously and that Service Provider is given adequate time to complete orders.

Client shall provide Service Provider with adequate notice of any variations to the specifications or time periods of a specific order.

Client shall pay Service Provider all amounts due to strictly as specified in this Agreement.

INTELLECTUAL PROPERTY:-

All intellectual property in and to the AM Medical Devices shall vest in Client or such third parties who may have authorised Client to use the intellectual property.

Nothing in this Agreement shall entitle Service Provider to use, or give Service Provider any right to the intellectual property.

If, at any time during the duration of this Agreement, Service Provider becomes aware of an attempt to infringe on the intellectual property, it shall forthwith advise Client who shall be entitled to take such steps as may be required to protect its right and in an interest to the intellectual property.

NO WARRANTY

The Service Provider gives no warranty or undertaking of whatever nature as to the fitness for any purpose, functionality or appropriateness of the specifications of the AM Medical Devices.

INDEMNITY AND LIMITATION OF LIABILITY

Client indemnifies the Service Provider against any claim, injury and/or damage, incidental damages or any loss caused as a result of the utilisation of a Device assessed by the Service Provider for any purpose whatsoever, except where such Device was not assessed in accordance with the specifications provided by Client to Service Provider.

Notwithstanding any provision to the contrary in this Agreement, no Party shall be entitled to institute any delictual, contractual or other claim against the other Party for any indirect or consequential losses or damages (including without limitation, loss of profit, loss of use, loss of production, loss of business, or loss of business opportunity) due to any cause whatsoever.

CONFIDENTIALITY:-

Client acknowledges that, during the currency of this Agreement, Client will disclose information regarding the AM Medical Devices, their use, Client's customers and systems to Service Provider.

Service Provider acknowledges that such information is a valuable, special and unique asset proprietary to Client.

Service Provider agrees that it shall not, during the course of this Agreement, or at any time thereafter, disclose the confidential information to any third party for any reason or purpose whatsoever and that any such disclosure may cause irreparable loss, harm and damage to Client.

Service Provider agrees that it will protect the information disclosed to it by Client pursuant to the provisions of this Agreement and that it will use the same standard of care that it uses to safeguard its own propriety, secret and confidential information and that the information will be stored and handled in such a way as to prevent any unauthorised disclosure thereof.

The confidential information shall not include-

information which was known to the Service Provider prior to its receipt from Client;

information which is or lawfully becomes generally available to the public;

information which is lawfully acquired from third parties who have a right to disclose such information;

information which by mutual agreement is released from confidential status; and

information which is required to be disclosed in response to a valid order of court or other governmental agency or if disclosure is otherwise required by law, and the Service Provider will provide Client with prompt written notice if such disclosure is required, and shall limit the disclosure to the minimum necessary to comply with the law.

On termination of the Agreement, for whatsoever reason, Service Provider shall return to Client all material containing, pertaining to or relating to information disclosed to it pursuant to the terms of this Agreement. Client may require Service Provider to provide it with written proof that it has complied with the provisions of this sub-clause. Client may also require Service Provider to destroy any items of intellectual property in its possession or under its control, in which case Service Provider shall forthwith carry out the required destruction and advise Client thereof.

BREACH:-

Should any Party breach a provision of this Agreement and remain in breach thereof for seven (7) business days after having received notice from the other Party to remedy such breach, then the innocent Party shall be entitled to:-

Hold the guilty party to the provisions of this Agreement or;

Cancel the Agreement;

Nothing in clause **BREACH** aforesaid shall compromise a Party's right to claim such damages as it may be entitled to.

ARBITRATION AND JURISDICTION:-

Any dispute, question or difference arising at any time between the Parties with regard to:

any matter arising out of;

the rights and obligations of either Party under;

the interpretation of;

the termination or cancellation of;

any matter arising out of the termination or cancellation of; or

the rectification of;

this Agreement between the parties must be submitted to and decided by arbitration on notice given by either Party to the other.

The arbitration shall be held in Bloemfontein under the auspices of and subject to the rules and procedures of the Arbitration Foundation of South Africa ("AFSA"), except that:

The arbitration must be informal and must be conducted in the most expeditious and inexpensive manner possible; and

The arbitrator will have the fullest and freest discretion to determine the procedure to be adopted, subject only to clause **ARBITRATION AND JURISDICTION** and to the rules of natural justice;

It being the agreed intention that the arbitration must be held and concluded within twenty-one (21) business days after it has been demanded.

The arbitrator must be:
An independent chartered accountant of not less than ten (10) years' standing agreed upon between the Parties, if the question in dispute is primarily an accounting matter;

A practising advocate or attorney of not less than ten (10) years' standing agreed upon between the Parties, if the question in dispute is primarily a legal matter;

An independent and suitably qualified person agreed upon between the Parties, in the case of any other matter.

If the Parties are unable to reach agreement as contemplated in clause **ARBITRATION AND JURISDICTION** above within three (3) business days after the arbitration has been demanded, then the senior executive officer for the time being of AFSA must determine the nature of the dispute and appoint an arbitrator within seven (7) business days after the Parties have failed to reach agreement, with the intention that the arbitration be held and concluded within the twenty-one (21) day period referred to in clause **ARBITRATION AND JURISDICTION**.

This clause **ARBITRATION AND JURISDICTION** will constitute each Party's irrevocable consent to the arbitration proceedings, and neither Party will be entitled to withdraw from the provisions of this clause or to claim at such arbitration proceedings that such Party is not bound by this clause.

Each of the Parties irrevocably agree that the decision of the arbitrator (including any costs awarded):

Will be final and binding on each of them;

Will be carried into effect; and

May be made an order of court on application by either Party.

Nothing contained or implied in this Agreement will preclude either Party from applying to court for a temporary interdict or any other relief of an urgent and temporary nature, pending the decision or award of the arbitrator.

The provisions of this clause **ARBITRATION AND JURISDICTION** are separate and severable from the rest of this Agreement and will remain in effect despite the termination, cancellation or invalidity for any reason of this Agreement.

DOMICILIUM CITANDI ET EXECLIENTANDI:-

The Parties hereby choose their respective domicilia citandi et exeClientandi as follows:-

Client - Please add address and contact person
Fax no:
E-mail:
Service provider - Please add address and contact person

Fax no:
E-mail:

Each of the Parties shall be entitled from time to time, by written notice to the other, to vary his domicilium to any other address within the Republic of South Africa, which is not a post office box or a post restante.

Any notice given by any Party to the other (the addressee) which:-

is delivered by hand during the normal business hours at the addressee's domicilium for the time being, shall be presumed, unless the contrary is proved by the addressee, to have been received by the addressee at the time of delivery;

is posted by pre-paid registered post from an address within the Republic of South Africa to the addressee at the addressee's domicilium within the Republic of South Africa, as the case may be, shall be presumed, unless the contrary is proved by the addressee, to have been received by the addressee on the fifth day after the date of posting;

has been transmitted by facsimile, shall, unless the contrary is proved, be deemed to have been received on week-days six (6) hours after the time of transmission and, on week-ends, on the first working day after the week-end.

has been transmitted by e-mail, shall, unless the contrary is proved, be deemed to have been received on weekdays six (6) hours after the time of transmission and, on weekends, on the first working day after the weekend.

VARIATIONS/AMENDMENTS:-

No variation or amendment of the terms and provisions of this Agreement shall have any force or effect unless same are reduced to writing and such amending document is signed by both Parties.

LATITUDE:-

Any latitude or extension of time granted by one Party to the other in respect of any provision in this Agreement shall not be deemed to be a waiver of any right that the aggrieved Party may have in terms of this Agreement.

ENTIRE AGREEMENT:-

This Agreement shall constitute the entire agreement between the Parties and no other conditions, warranties, stipulations or representations shall be binding on the Parties.

SIGNATORIES:-

The signatories to this Agreement warrant that they are duly authorised to bind their respective employers, Client and Service Provider.

COUNTERPARTS:-

This Agreement may be signed in more than one counterpart, which counterparts read together will constitute an Agreement.

DATED at _____ this the_____ day of_____ 20__

AS WITNESSES:-

1 _____

2 _____ _____

Client - Please add name

DATED at _____ this the_____ day of_____ 20__

AS WITNESSES:-

1 _____

2 _____ _____

Service provider - Please add name

ANNEXURE A

DETAILS OF PROCEDURE TO BE FOLLOWED FOR MICRO-CT SCANNING OF PATIENT-SPECIFIC AM MEDICAL DEVICES

Patient-specific devices manufactured by the Client will be sent to the Client for micro-CT scanning according to the procedure outlined below:

Mounting procedure

Each implant must be mounted in an appropriate fixture of low density and fixed to the mount to prevent any possible movement during scan, using single or double-sided sticky tape.

Scanning procedure

The micro-CT scans are performed in a General Electric Phoenix V|Tome|X L240 micro-CT scanner, which allows X-ray energies up to 240 kV to be generated in a direct/reflection type target.

Each implant is scanned individually for best results. The sample is positioned such that its widest points in the scan volume covers roughly half of the available pixels in the detector; this determines the scan resolution based on the width of the sample, the distance from source to sample and from source to detector.

Once the resolution is selected, the X-ray penetration is optimized by varying the X-ray accelerating voltage, current and beam filters in order to allow approximately 10% penetration at the densest part of the sample in linear absorption.

Dynamic range is also optimised to reduce noise, i.e. detector sensitivity is increased when possible, or image acquisition time is increased. In the optimisation procedure the settings must also be kept low enough to ensure the X-ray spot size is smaller than the scan resolution, which is crucial in obtaining the required resolution in the final images.

Rules of thumb include: at least 0.6 mm copper beam filter is suggested for titanium parts, to reduce image artefacts; at least 1600 images are suggested to reduce reconstruction artefacts, with up to 3200 images in one rotation. Typical image acquisition time is 500 ms, averaging increases the data quality and can be up 3 images averaged per position, and finally a skip function is activated, which results in improved detector clarity for each new position (reducing shadowing effects).

Once parameters are selected, the sample is moved out of the field of view and background calibration is done to ensure a homogeneous background X-ray intensity across the entire detector.

Once this is completed, the sample is moved into place, a region of interest is selected (which corrects for X-ray flux variations during scan) and the scan is initiated.

The scan data is reconstructed using system-supplied Datos reconstruction software and the 3D data set is analysed with Volume Graphics VGStudioMax 2.2 (or the latest available software).

ANNEXURE B

SPECIFICATIONS

Machine:	General Electric Phoenix V
Model:	Tome|X L240
Facility:	
X-ray energy	Up to 240 kV
Software:	Volume Graphics VGStudioMax 2.2
Shipping:	Client will arrange collection

QUALITY

Activities by Regulators, Notified Bodies, or Certification Bodies

Service Provider shall promptly notify Client of any inspections, audits or formal visits of any Regulator, Notified Body or Certification Body, acting in a formal capacity.

Environmental control

If environmental conditions could reasonably be expected to have adverse effects on the product quality and safety, Service Provider shall establish and maintain procedures to adequately control these environmental conditions.

Equipment

Service Provider shall ensure that all equipment used in the CT scanning process for the AM Medical Devices is appropriately placed and installed.

Service Provider shall establish and maintain schedules for the calibration, adjustment, cleaning and other maintenance of the equipment or machinery to ensure that Heat Treatment Specifications are met.

Packaging

AM Medical Devices shall be placed in the box in which the device arrived at the Scanning facility upon removal by Service Provider.

Validation

Service Provider will supply Client with an STL file of the device that was scanned in order to do a 3D CAD-to-Part comparison to verify the part geometrical accuracy.

Cleaning

No additional cleaning of AM Medical Devices shall be done once removed from the oven.

Storage and shipment

Service Provider shall establish and maintain procedures to control storage areas and stockrooms to prevent mix-ups, damage, deterioration, contamination or other adverse effects.

Record retention

Service provider shall keep records of all quality control activities and make them available to Client upon request.

Records will be maintained for a period of five (5) years from the termination of this Agreement.

Audits

Regulators, notified bodies or certification bodies may from time-to-time require quality control audits.

Service Provider shall allow Client, or its authorised representatives, to perform audits of the facilities, systems, documents, and other requirements related to this Agreement.

Audits shall be conducted at mutually agreed dates and times.

ANNEXURE C

CONTACT DETAILS CLIENT

Full name	
Tel (Office)	
Cell phone	
E-mail	
Physical Address	
Postal Address	

ANNEXURE D

CONTACT DETAILS CLIENT

Full name	
Tel (Office)	
E-mail	
Physical Address	
Postal Address	

Appendix 4: Material Data Sheets

(EOS GmbH-Electro Optical System. EOSINT M280 Data Sheet Available https://www.eos.info)

Material data sheet

EOS Titanium Ti64

EOS Titanium Ti64 is a titanium alloy powder which has been optimized especially for processing on EOSINT M systems.

This document provides information and data for parts built using EOS Titanium Ti64 powder (EOS art.-no. 9011-0014) on the following system specifications:

- EOSINT M 270 Installation Mode *Xtended*
  with PSW 3.4 and default job Ti64_30_030_default.job
- EOSINT M 270 Dual Mode
  with PSW 3.5 and Original EOS Parameter Set Ti64_Performance 2.0
- EOSINT M 280
  with PSW 3.5 and Original EOS Parameter Set Ti64_Speed 1.0

Description

Parts built in EOS Titanium Ti64 have a chemical composition corresponding to ISO 5832-3, ASTM F1472 and ASTM B348.

This well-known light alloy is characterized by having excellent mechanical properties and corrosion resistance combined with low specific weight and biocompatibility.

This material is ideal for many high-performance engineering applications, for example in aerospace and motor racing, and also for the production of biomedical implants (note: subject to fulfilment of statutory validation requirements where appropriate).

Due to the layerwise building method, the parts have a certain anisotropy, which can be reduced or removed by appropriate heat treatment - see Technical Data for examples.

EOS GmbH - Electro Optical Systems
Robert-Stirling-Ring 1
D-82152 Krailling / München
Telephone: +49 (0)89 / 893 36-0
Telefax: +49 (0)89 / 893 36-285
Internet: www.eos.info

Technical data

General process and geometric data

Typical achievable part accuracy [1]	± 50 µm
Min. wall thickness [2]	approx. 0.3 – 0.4 mm approx. 0.012 – 0.016 inch
Surface roughness, as built [3]	
Ti64_30_030_default.job Ti64 Performance (30 µm)	R_a 9 - 12 µm, R_z 40 - 80 µm R_a 0.36 – 0.47 x 10^{-3} inch, R_z 1.6 – 3.2 x 10^{-3} inch
Ti64 Speed 1.0 (60 µm)	R_a 6 - 10 µm, R_z 35 - 40 µm R_a 0.23 – 0.39 x 10^{-3} inch, R_z 1.37 –1.57 x 10^{-3} inch
Volume rate [4]	
Ti64_30_030_default.job Ti64 Performance (30 µm)	3.75 mm³/s (13.5 cm³/h) 0.82 in³/h
Ti64 Speed 1.0 (60 µm)	9 mm³/s (32.4 cm³/h) 1.98 in³/h

[1] Based on users' experience of dimensional accuracy for typical geometries. Part accuracy is subject to appropriate data preparation and post-processing, in accordance with EOS training.

[2] Mechanical stability is dependent on geometry (wall height etc.) and application

[3] Due to the layerwise building, the surface structure depends strongly on the orientation of the surface, for example sloping and curved surfaces exhibit a stair-step effect. The values also depend on the measurement method used. The values quoted here given an indication of what can be expected for horizontal (up-facing) or vertical surfaces.

[4] Volume rate is a measure of build speed during laser exposure. The total build speed depends on the average volume rate, the recoating time (related to the number of layers) and other factors such as DMLS-Start settings.

EOS GmbH - Electro Optical Systems
Robert-Stirling-Ring 1
D-82152 Krailling / München

Physical and chemical properties of parts

Material composition	Ti (balance) Al (5.5 – 6.75 wt.-%) V (3.5 – 4.5 wt.-%) O (< 2000 ppm) N (< 500 ppm) C (< 800 ppm) H (< 150 ppm) Fe (< 3000 ppm)
Relative density	approx. 100 %
Density	4.41 g/cm³ 0.159 lb/in³

Mechanical properties of parts

	As built	Heat treated [6]
Tensile strength [5]		
- in horizontal direction (XY)	typ. 1230 ± 50 MPa typ. 178 ± 7 ksi	min. 930 MPa (134.8 ksi) typ. 1050 ± 20 MPa (152 ± 3 ksi)
- in vertical direction (Z)	typ. 1200 ± 50 MPa typ. 174 ± 7 ksi	min. 930 MPa (134.8 ksi) typ. 1060 ± 20 MPa (154 ± 3 ksi)
Yield strength ($R_{p0.2}$) [5]		
- in horizontal direction (XY)	typ. 1060 ± 50 MPa typ. 154 ± 7 ksi	min. 860 MPa (124.7 ksi) typ. 1000 ± 20 MPa (145 ± 3 ksi)
- in vertical direction (Z)	typ. 1070 ± 50 MPa typ. 155 ± 7 ksi	min. 860 MPa (124.7 ksi) typ. 1000 ± 20 MPa (145 ± 3 ksi)
Elongation at break [5]		
- in horizontal direction (XY)	typ. (10 ± 2) %	min. 10 % typ. (14 ± 1 %)
- in vertical direction (Z)	typ. (11 ± 3) %	min. 10 % typ. (15 ± 1 %)
Modulus of elasticity [5]		
- in horizontal direction (XY)	typ. 110 ± 10 GPa typ. 16 ± 1.5 Msi	typ. 116 ± 10 GPa typ. 17 ± 1.5 Msi
- in vertical direction (Z)	typ. 110 ± 10 GPa typ. 16 ± 1.5 Msi	typ. 114 ± 10 GPa typ. 17 ± 1.5 Msi
Hardness [7]	typ. 320 ± 12 HV5	

[5] Tensile testing according to ISO 6892-1:2009 (B) Annex D, proportional test pieces, diameter of the neck area 5 mm (0.2 inch), original gauge length 25 mm (1 inch).

[6] Specimens were treated at 800 °C (1470 °F) for 4 hours in argon inert atmosphere. Mechanical properties are expressed as minimum values to indicate that mechanical properties exceed the minimum requirements of material specification standards. ASTM F1472-08. By fulfilling these minimum values, also the specifications of standards ASTM B348-09 and ISO 5832-3:2000 are meet.

[7] Vickers hardness measurement (HV) according to EN ISO 6507-1 on polished surface. Note that measured hardness can vary significantly depending on how the specimen has been prepared.

Material data sheet

Thermal properties of parts

Maximum long-term operating temperature	approx. 350 °C approx. 660 °F

Abbreviations

typ.	typical
min.	minimum
wt.	weight
approx.	approximately

Notes

The data are valid for the combinations of powder material, machine and parameter sets referred to on page 1, when used in accordance with the relevant Operating Instructions (including Installation Requirements and Maintenance) and Parameter Sheet. Part properties are measured using defined test procedures. Further details of the test procedures used by EOS are available on request.

The data correspond to our knowledge and experience at the time of publication. They do not on their own provide a sufficient basis for designing parts. Neither do they provide any agreement or guarantee about the specific properties of a part or the suitability of a part for a specific application. The producer or the purchaser of a part is responsible for checking the properties and the suitability of a part for a particular application. This also applies regarding any rights of protection as well as laws and regulations. The data are subject to change without notice as part of EOS' continuous development and improvement processes.

EOS®, EOSINT® and DMLS® are registered trademarks of EOS GmbH.

EOS GmbH - Electro Optical Systems
Robert-Stirling-Ring 1
D-82152 Krailling / München

Appendix 5: ISO Certificates

TÜV SÜD South Asia Private Limited
●1st & 4th Floor, No: 11 & 13, Origin Towers- Type 2 ●Dr. Vikram Sarabhai Instronic Estate ●Thiruvanmiyur ●Chennai – 600 041 ●India
Tel: +91 44 22548500 • Fax: +91-044 - 22548529

South Asia

Choose certainty.
Add value.

Our reference: Project No. IND2016003
May 21, 2016

Whomsoever it may concern

This is to state that the quality management system of **Centre for Rapid Prototyping and Manufacturing, Central University of Technology,** located at **20 President Brand Street, Bloemfontein, 9300, South Africa**, has been assessed by us as certification process during the period from 2016-02-24 - 2016-02-26 in accordance with the requirements of **EN ISO 13485:2012** for the scope as mentioned below:

EN ISO 13485:2012

"Design, Development and Production of Patient Specific Custom Made Titanium Implants by means of 3D Printing/Additive Manufacturing

Design, Development and Production of Patient Specific Custom Made Preoperative Models, Jigs, Cutting Guides in Nylon by means of 3D Printing/Additive Manufacturing

Contract Production of Titanium Implants by means of 3D Printing/Additive Manufacturing.

Contract Production of Preoperative Models, Jigs, Cutting Guides in Nylon by means of 3D Printing/Additive Manufacturing"

It is confirmed that the implemented & maintained quality management system complies with the above said requirements and recommended for issuance of certificates.

However, the decision for issuance of certificates will be made after successful review of audit documents by certification body / notified body of TUV SUD Product Service Gmbh, Germany.

For TÜV SÜD South Asia

N. Sridharan

Senior Manager
Medical and Health Services

PAN No.: AABCT0716G
TAN No.: MUMT09385F
Service Tax Code No.:
AABCT0716GSD004
CST No. : 27150828488C

Registered Office:
TÜV SÜD South Asia Pvt. Ltd.
TÜV SÜD House,
Off Saki Vihar Road,
Saki Naka, Andheri (East),
Mumbai – 400072, India.

Corporate Office:
TÜV SÜD South Asia Pvt. Ltd.
Solitaire, 4th Floor,
ITI Road, Aundh,
Pune – 411007, India.

Email: info@tuv-sud.in
www.tuv-sud.in

ZERTIFIKAT ◆ CERTIFICATE ◆ 認証書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Product Service

CERTIFICATE

No. Q1N 16 02 94449 001

Holder of Certificate: **Centre for Rapid Prototyping and Manufacturing, Central University of Technology, Free State**

20 President Brand Street
Bloemfontein
9300 SOUTH AFRICA

CRPM

Facility(ies):

Centre for Rapid Prototyping and Manufacturing,
Central University of Technology, Free State
20 President Brand Street, Bloemfontein, 9300
SOUTH AFRICA

Certification Mark:

Scope of Certificate:

Design, Development and Production of Patient Specific Custom Made Titanium Implants by means of 3D Printing/Additive Manufacturing.
Design, Development and Production of Patient Specific Custom Made Preoperative Models, Jigs, Cutting Guides in Nylon by means of 3D Printing/Additive Manufacturing.
Contract Production of Titanium Implants by means of 3D Printing/Additive Manufacturing.
Contract Production of Preoperative Models, Jigs, Cutting Guides in Nylon by means of 3D Printing/Additive Manufacturing.

Applied Standard(s):

EN ISO 13485:2012 + AC:2012
Medical devices - Quality management systems - Requirements for regulatory purposes
(ISO 13485:2003 + Cor. 1:2009)
DIN EN ISO 13485:2012

The Certification Body of TÜV SÜD Product Service GmbH certifies that the company mentioned above has established and is maintaining a quality management system, which meets the requirements of the listed standard(s). See also notes overleaf.

Report No.: IND2016003
Valid from: 2016-06-20
Valid until: 2019-06-19

Date, 2016-06-20

Stefan Preiß

Page 1 of 1

DAkkS Deutsche Akkreditierungsstelle D-ZM-11321-01-00

TÜV SÜD Product Service GmbH · Zertifizierstelle · Ridlerstraße 65 · 80339 München · Germany

DAkkS CRT2 / 10.13

TÜV SÜD ZERTIFIKAT ◆ CERTIFICATE ◆ 認證證書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

DAkkS Deutsche Akkreditierungsstelle D-ZM-11321-01-00

TÜV SÜD Product Service

Certificate

No. Q5 094449 0004 Rev. 00

Holder of Certificate: **Centre for Rapid Prototyping and Manufacturing, Central University of Technology, Free State**
20 President Brand Street
Bloemfontein
9300 SOUTH AFRICA

CRPM

Facility(ies): Centre for Rapid Prototyping and Manufacturing, Central University of Technology, Free State
20 President Brand Street, Bloemfontein, 9300 SOUTH AFRICA

Certification Mark:

TÜV SÜD EN ISO 13485 tuv-sud.com/ps-cert

Scope of Certificate: Design, Development and Production of Patient Specific Custom Made Titanium Implants by means of 3D Printing/ Additive Manufacturing.
Design, Development and Production of Patient Specific Custom Made Preoperative Models, Jigs, Cutting Guides in Nylon by means of 3D Printing/Additive Manufacturing.
Contract Production of Titanium Implants by means of 3D Printing /Additive Manufacturing.
Contract Production of Preoperative Modles, Jigs, Cutting Guides in Nylon by means of 3D Printing/Additive Manufacturing.

Applied Standard(s): EN ISO 13485:2016
Medical devices - Quality management systems - Requirements for regulatory purposes
(ISO 13485:2016)
DIN EN ISO 13485:2016

The Certification Body of TÜV SÜD Product Service GmbH certifies that the company mentioned above has established and is maintaining a quality management system, which meets the requirements of the listed standard(s). See also notes overleaf.

Report No.: IND2018008

Valid from: 2018-08-29
Valid until: 2019-06-19

Date, 2018-08-29

Stefan Preiß

A4 / 07.17

TÜV SÜD Product Service GmbH • Certification Body • Ridlerstraße 65 • 80339 Munich • Germany

TÜV®