Development of a Framework for the Manufacture of Customized Titanium Cervical Cage Implants Using Additive Manufacturing

by

Graziano Marcantonio

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Department of Industrial Engineering,
University of Stellenbosch,
Private Bag X1, Matieland 7602, South Africa.

Supervisors:

Prof. D.M. Dimitrov Prof. A.F. van der Merwe

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Declaration

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Abstract

Neck pain is a common phenomenon that occurs in a large percentage of the population every day. While many occurrences are not deemed critical such as those from muscle strain which can be treated with rest and pain medication, others due to sports injuries, whiplash from car accidents, bad posture or degeneration of the intervertebral disc can be quite severe. In extreme cases failure of the vertebra(e) or the intervertebral disc requires surgery and possibly the use of cervical implants.

Where intervertebral discs fail due to herniation or Degenerative Disc Disease (DDD), Anterior Cervical Discectomy and Fusion (ACDF) is a common surgical method used to remove the affected disc and replace it with a cervical cage implant. These implants are designed to restore the height between the vertebrae, allowing bone from both vertebrae to grow through them and mineralise. Additive Manufacturing (AM) technologies can produce parts with complex geometries not possible using conventional manufacturing methods. This design freedom, coupled with CT scans of a patient, allow for tailoring an implant to the specific anatomy of the affected vertebrae using CAD software.

Such an approach must be regulated and shown to be technically and commercially feasible before it can be implemented in industry. This study sought to develop a framework for manufacturing customized cervical cage implants using additive manufacturing. The efficacy of customization to reduce the risk of subsidence was investigated by means of non-destructive and destructive mechanical testing on six cadaver specimens, using readily available PEEK cage implants as a benchmark. The results showed that the customized implant was comparable to the PEEK, with no statistically significant difference between the two. In extreme cases, where PEEK implants cannot be used, customized implants could be a suitable alternative to reduce the risk of subsidence.

A manufacturing cost analysis was conducted to determine economic feasibility. The estimated cost and selling price of the customized implants under various utilization scenarios and mark-ups was compared to readily available PEEK implants. The estimated selling prices of the customized implants compared favourably to the PEEK verifying the economic viability of using AM.

Uittreksel

Nek pyn is 'n algemene verskynsel wat daagliks na tevore kom in die bevolking. Baie gevalle word nie as krities geklasifiseer nie soos byvoorbeeld spier pyn wat behandel kan word deur genoegsame rus en pyn medikasie. Pyn wat deur sportbeserings, sweepslag beserings 'whiplash' tydens motor ongelukke, verkeerde postuur, of deur slytasie van 'n intervertebrale skyf veroorsaak is, word dikwels as ernstig geklasifiseer. In ekstreme gevalle waar die werwel(s) of die inervertebrale skyf(we) faal, sal chirurgie en servikale inplantate moontlik nodig wees.

Waneer intervertebrale skywe faal weens herniatie of Degeneratiewe Skyf Siekte (DDD) kan 'n algemene chirurgiese metode, Anterieure Servikale Discectomie en Fusie (ACDF), gebruik word om die geaffekteerde skyf te verwyder en dit te vervang met 'n servikale samesmelting implantaat. Hierdie implantate herstel die hoogte tussen rugwerwels en is ontwerp sodat die been deur dit kan groei en mineraliseer. Komplekse geometrieë kan vervaardig word deur toevoegingsvervaardiging (AM) tegnologieë. Die ontwerp vryheid, gepaard met CT-skanderings en CAD-sagteware stel mens in staat om die geometrie van die implantaat aan te pas tot die spesefieke anatomie van die geaffekteerde vertebra.

So 'n benadering moet gereguleer word en eers tegnies en kommersieel uitvoerbaar bewys word voordat dit in die bedryf geïmplementeer kan word. Hierdie studie poog verder om 'n raamwerk vir die vervaardiging van persoonlike servikale implantate deur middel van toevoegingsvervaardiging te ontwikkel. Die doeltreffendheid van persoonlike implantate om te verhoed dat die chirurg die eind-plaat beskadig, en sodoende die risiko van insakking te verminder, is ondersoek deur middel van meganiese toetse op ses kadawer monsters. Hierdie toetse is gedoen met behulp van geredelik beskikbaar PEEK servikale implantate as 'n maatstaf.

Die resultate het getoon dat die persoonlike- en PEEK implantate vergelykbaar is. In moontlike gevalle waar PEEK implantate nie geskik sou wees nie, kan persoonlike implantate 'n alternatiewe opsie wees om die risiko van insakking te verminder.

Ekonomiese uitvoerbaarheid was bepaal deur 'n koste analise van die vervaardigingsproses. Die beraamde koste van verskeie benutting "scenario's" en winsgrense was vergelyk met die van kommersieel beskikbare PEEK implantate. Hierdie vergelykings was ten gunste van die persoonlike implantate en sodoende is die ekonomiese uitvoerbaarheid van AM bevestig.

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Finally, God for giving me the patience, strength and faith to tackle this project.

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List of Acronyms

ACD	Anterior Cervical Discectomy
ACDF	Anterior Cervical Discectomy and Fusion
ACDFI	Anterior Cervical Discectomy and Fusion and Instrumentation
AM	Additive Manufacturing
CAD	Computer Aided Design
CT	Computer Tomography
Co-Cr	Cobalt Chromium
CFR	Carbon-Fiber-Reinforced
DDD	Degenerative Disc Disease
DMLS	Direct Metal Laser Sintering
EBM	Electron Beam Melting
FDA	Food and Drug Administration
GHTF	Global Harmonization Task Force
ISO	International Standards Organization
MHRA	Medicines and Healthcare Products Regulatory Agency
MHW	Ministry of Health and Welfare
MRI	Magnetic Resonance Image
MIP	Medical Image Processing
PEEK	Polyetheretherketone
PLIF	Posterior Lumber Interbody Fusion
PMA	Pre-Market Approval

QMS	Quality Management System
RP	Rapid Prototyping
RM	Rapid Manufacturing
SAMED	South African Medical Device Industry Association
SLA	Stereolithography
SLM	Selective Laser Melting
TGA	Therapeutic Goods Administration
TDR	Total Disc Replacement
TLIF	Transforaminal Lumber Interbody Fusion
TDR	Total Disc Replacement
UV	Ultraviolet

Glossary

Allograft: Bone substitute where the bone comes from a donor (usually a cadaver).

Annulus fibrosus: The outer rim of an intervertebral disc.

Anterior Cervical Discectomy and Fusion (ACDF): A surgical procedure where an affected intervertebral disc is removed from the front and replaced with cage implant.

Autograft: Bone substitute where the bone comes directly from the patient from the iliac crest (hip) area.

Bone graft substitute Man made disc substitutes (often referred to as cages) made from either plastic, ceramic, titanium or bioresorbable materials. These implants are normally filled with either bone shavings or a bone substitute to stimulate bone growth.

Cranioplasty: The surgical repair of a defect or deformity of the skull.

Degenerative Disc Disease (DDD): A condition where the water content of the nucleus pulposus decreases over time and dries up, reducing the load carrying capacity of the intervertebral disc.

Disc herniation: Medical condition affecting the spine where the outer annulus fibrosis tears, allowing the soft inner nucleus pulposus to bulge out.

Nucleus Pulposus: Internal gelatinous fluid housed by the annulus fibrosus.

Osseintegration: Where living bone attaches onto the surface of a load-bearing implant.

Chapter 1

Introduction

1.1 Background

Back pain causes can be grouped into three categories (De Beer, 2011):

- Pinched nerves often due to herniated or deteriorated discs
- Musculoskeletal pain
- Infections occur in the vertebrae.

A common cause for patients requiring spinal surgery is Degenerative Disc Disease (DDD). DDD is a natural part of ageing where the water content of the nucleus fibrosus reduces over time. This causes the disc to dry up and lowers its load carrying capability. Various surgical techniques are available to treat back pain. Table 1.1 summaries the number of operative procedures listed by Eager *et al.* (2011) across 2069 cases. It is apparent that fusion is a common surgery that is carried out right across the spine. The use of cage devices for interbody fusion in the lumbar and cervical spine has rapidly increased in recent years (Subach *et al.*, 2011). Advantages of using a cage device in place of conventional fusion includes the restoration of disc height. Table 1.1 also indicates that the lumbar spine is the most affected. Extensive research however has already been conducted on the lumber spine to the extent that now there are disc devices available for Total Disc Replacement (TDR). De Beer (2011) investigated the possibility of a customized lumbar disc replacement with matching end-plate geometry. The cervical spine however has not been as extensively researched which leaves room to investigate aspects such as customized implants.

There are three types of anterior surgical interventions for the treatment of DDD: discectomy alone (ACD), discectomy with fusion (ACDF) and discectomy with fusion and instrumentation (ACDFI) (Xie and Hurlbert, 2007). Discectomy alone merely removes the affected herniated disc.

Table 1.1: Type of operative procedures, N=2069 (Eager *et al.*, 2011)

Procedure type	**No.**	**%**
ACDF	323	16%
Anterior/Posterior Cervical Fusion	59	3%
Anterior/Posterior Lumbar Fusion	59	3%
Spinal Decompression (any level, no fusion)	121	6%
Single-Level TLIF or PLIF	377	18%
Resection of Lesion (with or without fusion)	210	10%
Multi-Level Cervical or Cervicothoracic Fusion	203	10%
Multi-Level Thoracolumbar or Lumbar Fusion	532	26%
Thoracic Fusion	97	5%
Release of Tethered Cord	15	1%
Other	73	4%

In discectomy with fusion the entire disc is removed and the space between the vertebrae is maintained using either bone graft or a disc replacement such as a cage device. Discectomy with fusion and instrumentation is similar to ACDF but with an added plate that is secured anteriorly to the adjacent vertebrae using screws. Wang *et al.* (2009) showed that ACDF was the most common surgery carried out for the cervical spine between 1992 and 2005. Marawar *et al.* (2010) analysed that over three periods between 1990 to 2004, the number of estimated discharges of ACDF surgeries in North America increased from 59 952 between 1990-1994, to 260 804 between 1995-1999, to 451 166 between 2000-2004, making the total number of discharges over 15 years to be 771 932. Figure 1.1 shows the surgical trends of the cervical spine between 1992 and 2005 as researched by Wang *et al.* (2009). Hussain *et al.* (2012) suggests that the C5/6 region is the most frequently affected. Barsa and Suchomel (2007) also found that this region had the most number of surgeries carried out, followed by the C6/7 region (Figure 1.2).

Cervical cage devices are used in ACDF when the intervertebral disc needs to be removed due to myelopathy, herniation or DDD. Originally they were fabricated using titanium alloys, but the industry has shifted to Polyetheretherketone (PEEK) as the material of choice for mass production of standard implants. These devices are designed to fit rigidly between the vertebrae to restore its original spacing and promote osteointegration for successful fusion. Because they are standardized, they do not always ensure a perfect fit and could loosen after surgery. Surgeons often have to run through a few sizes to find the implant that fits best, sometimes at the expense of damaging the end-plates of the adjacent vertebrae (van Jonbergen *et al.*, 2005). The risk with using such cages however has been subsidence.

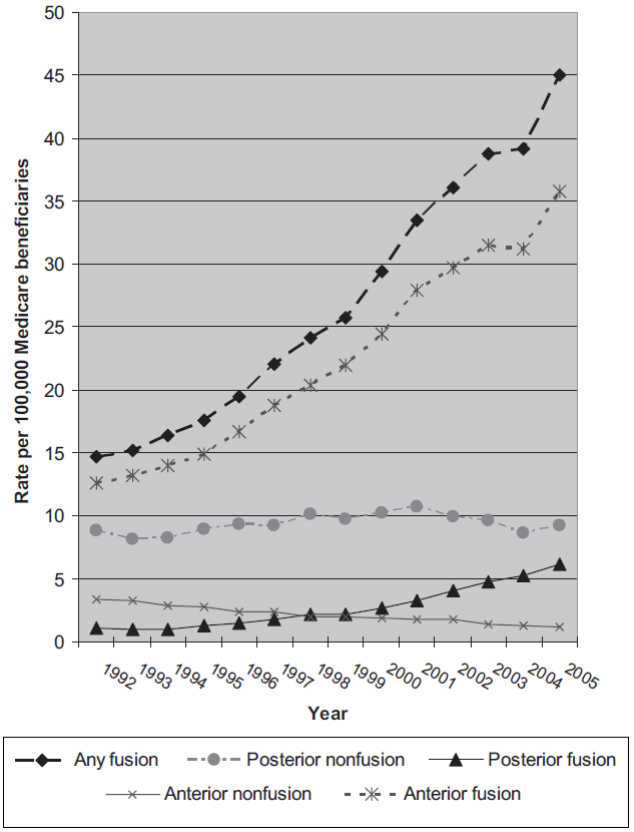


Figure 1.1: Trends in surgery for degenerative changes of the cervical spine: Medicare beneficiaries, 1992-2005 (Wang *et al.*, 2009)

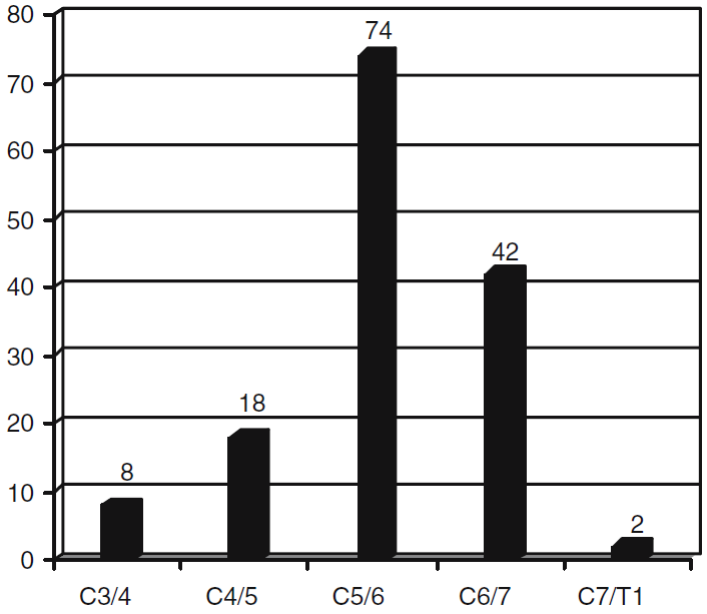


Figure 1.2: Anatomical distribution of implants in the 100 consecutive patients (Barsa and Suchomel, 2007)

1.2 Problem Statement

Subsidence is a phenomenon that occurs after intervertebral discectomy surgery, where the cage device collapses into the lower adjacent vertebra. In research conducted by van Jonbergen *et al.* (2005) and Barsa and Suchomel (2007), subsidence was defined as cage migration of 3mm or more into the adjacent vertebral body. Both performed radiographs directly post-surgery and 6 months post-surgery (Figure 1.3). Out of 100 patients, Barsa and Suchomel (2007) found 18 patients with subsided cages, while van Jonbergen *et al.* (2005) found 10 cages out of 106 implanted had subsided (9%). A problem statement can thus be defined that:

There is a need for a cage device which will lower the frequency of revision surgery due to post-operative complications such as subsidence.

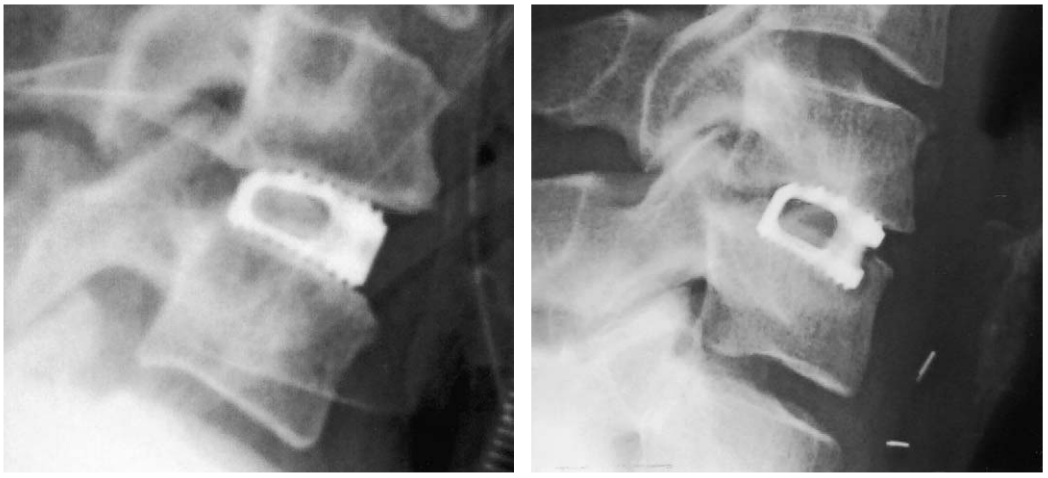


Figure 1.3: Radiograph of a SynCage C, a) directly postoperative and b) after 6 months follow-up showing subsidence into C7 (van Jonbergen *et al.*, 2005)

Cage design, end plate preparation (damage kept to a minimum) and stress distribution at the cage-end plate interface are suggested as the main factors of subsidence (van Jonbergen *et al.*, 2005; Gercek *et al.*, 2003; Barsa and Suchomel, 2007). Van Jonborgen goes on to suggest that a modified cage design with improved and extended lower contact surface could be expected to reduce subsidence.

1.3 Research Objectives

Additive Manufacturing (AM) methods such as Selective Laser Melting (SLM) enable the production of individual parts with complex geometries whilst maintaining the mechanical properties of standard parts manufactured by conventional methods such as casting (Bremem *et al.*, 2012). Because there is no need for part-specific tooling for each part, single piece and small batch production is possible and cost efficient. The geometric freedom also allows parts to be manufactured with functionalities such as hollow structures, graded porosity and/or surface structure (Bremem *et al.*, 2012). This makes AM a viable fabrication option for customized cervical implants.

For a customized cervical implant to be feasible, there must exist a strong working relationship between medicine and engineering, where Medical Image Processing (MIP), Computer Aided Design (CAD) and AM work to minimize time and cost, so that a complete framework exists as a proposed alternative to the current conventional ACDF surgical method. Such frameworks have already been introduced into cranioplasty applications (Hieu *et al.*, 2002), where a patient's data is obtained using a Computer Tomography (CT) scanner which is then transformed into a 3D model. The non-defected side of the skull is mirrored to the defected side using software such as MIMICS (Materialise NV, Belgium). CAD operations are performed to make further refinements and the new overall implant is then fabricated. Figure 1.4 shows the design flow processes for modeling cranioplasty implants which will be adapted for use in cervical cage implants.

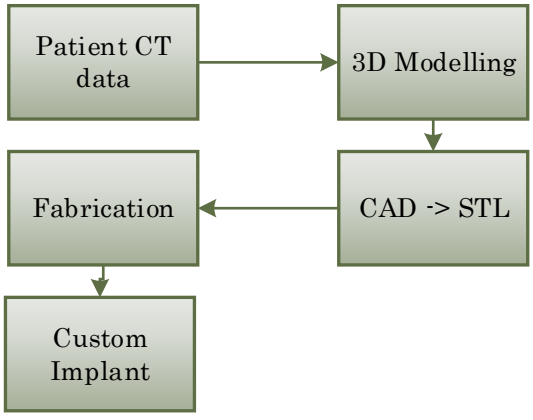


Figure 1.4: The design data flow for modeling cranioplasty implants

This study aims to develop a framework for manufacturing customized cervical cage implants using additive manufacturing. A process chain for implant development forms the kernel of the framework, while technical and commercial challenges are researched to determine feasibility. This study also makes provision for recommendations made by De Beer (2011) regarding research into customization of cage devices, the FDA regulatory approval system as well as the design of surgical tooling for insertion of the implants. The efficacy of customization to reduce the risk of subsidence due to factors such as cage design and end-plate preparation is investigated by means of mechanical testing on cadaver specimens.

1.4 Roadmap

The background, problem statement and research objectives have been identified in this chapter. Chapter 2 gives an overview of all the aspects applicable to this project such as spinal anatomy, causes of neck pain and the surgical method used to treat it. Fabrication methods used to develop customized medical prosthetics as well as the biomedically compatible materials that they make use of are listed and briefly explained. The international standards and guidelines applied for implant design with a focus on product development are discussed. Chapter 3 defines the framework proposed for developing the customized cervical implants and all the steps are explained. Technical and commercial challenges associated with implementing a new medical implant are investigated. The scope and limitations of this research is also defined here. Chapter 4 implements the steps of the framework defined in chapter 3 by means of mechanical experiments on cadaver specimens to help determine technical feasibility. Experimental results are given and discussed in Chapter 5. Finally Chapter 6 concludes the study by discussing whether the research objectives were adequately met and recommendations are made for future work.

Chapter 2

Bio-Fabrication: A Spine Related Overview

This chapter provides background on the anatomy of the spine, with a focus on the cervical spine. Causes of pain such as disc herniation and Degenerative Disc Disease (DDD) are briefly discussed, as well as the surgical means to treat them. Fabrication methods used in the medical field are reviewed as well as areas where customization is already being realized. Materials that are bio-compatible are investigated. The standards and guidelines used for the design and development of a medical device within a quality management system are defined, with a focus on meeting regulatory and customer requirements. All key elements are introduced, while product realization is explained in detail.

2.1 Spinal Anatomy Background

The vertebral column consists of 33 bones called vertebrae which articulate with one another at the anterior and posterior joints (Moore, 1992). It forms a strong yet flexible support for the torso, and extends from the base of the skull through the neck and the torso. The column is arranged in 5 regions (from top down): cervical, thoracic, lumber, sacral and coccygeal. Of the 33 vertebrae, 24 are movable (7 cervical, 12 thoracic and 5 lumber). When using a MRI, four curvatures are normally visible in adults (Moore, 1992). The primary curvatures are the thoracic and sacral because they develop during the fetal period. The secondary curvatures are the cervical and lumber regions, which begin to appear before birth but are not obvious until after (Moore, 1992).

2.1.1 The Cervical Spine

The cervical vertebrae are the smallest of the movable ones mentioned previously, and form the bony skeleton of the neck. They are numbered C1 through

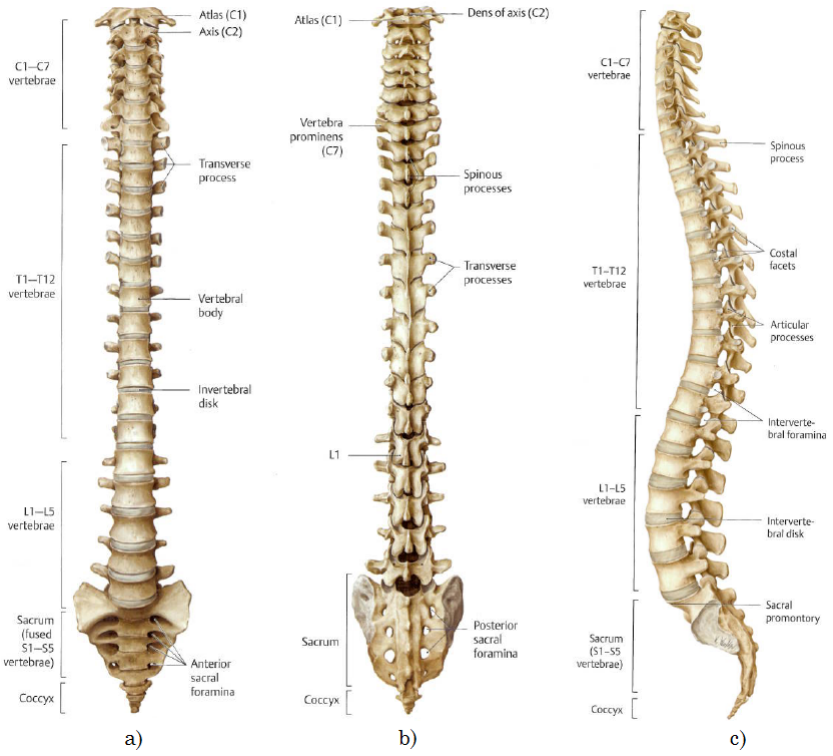


Figure 2.1: Bones of the vertebral column as shown from a) Anterior view b) Posterior view c) Lateral view (Gilroy *et al.*, 2008)

to C7. Bogduk *et al.* (2000) describes the cervical spine as consisting of four units, each of which have their own unique morphology that determine their kinematics. These are the cradle (C1), the axis (C2), the root (C2-C3 junction) and the column (C3-C7). C1 is called the **atlas**. It has a ring shape and supports the skull. C2 is called the **axis** because C1 rotates around it. It is also the strongest of the cervical vertebrae. C7, the lowest of the cervical vertebrae, is also known as the **vertebra prominens** because of its long spinous process. Figure 2.2 shows the bones of the cervical spine.

Housed between the vertebrae are intervertebral discs. These are cartilaginous joints which allow the vertebrae to move slightly. Their main role is mechanical, transmitting loads from body weight and muscle through the spinal column, providing flexibility, allowing bending, flexion and torsion (Urban *et al.*, 2003). Each disc consists of an internal gelatinous **nucleus pulposus** which is housed by an external **annulus fibrosus** (also referred to as the "rim" of the intervertebral disc), and is also sandwiched inferiorly (above) and superiorly (below) by **cartilage end-plates** (Moore, 1992; Urban *et al.*, 2003).

The nucleus pulposus consists of a proteoglycan and water, which is loosely held together by an irregular network of fine type II collagen and elastin fibers.

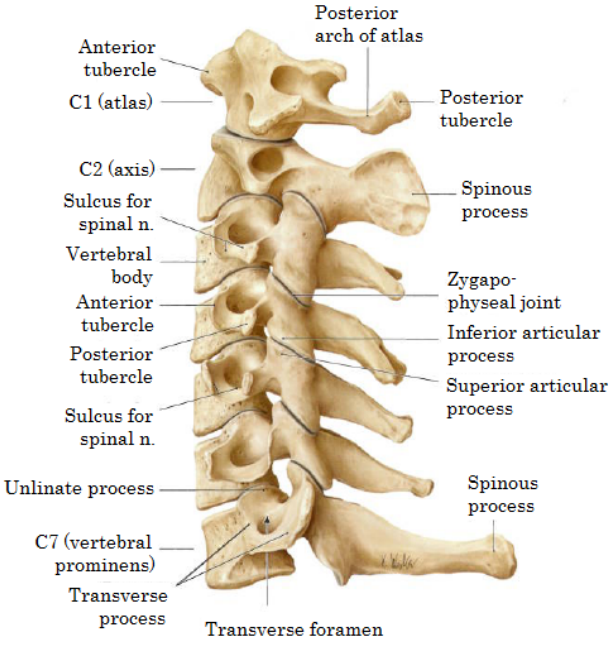


Figure 2.2: Bones of the cervical spine, left lateral view (Gilroy *et al.*, 2008)

It acts as the "shock absorber" for axial forces while during flexion, rotation and/or extension it acts like a "semifluid ball bearing" (Moore, 1992). The annulus fibrosus consists of concentric lamellae of collagen type I fibrocartilage, running obliquely from one vertebra to another. This provides very strong bonds between them. The main function of the fibres is to house the nucleus pulposus and to distribute pressure evenly across the disc. The cartilage end-plates are thin horizontal layers (usually less than 1mm thick) of hyaline cartilage. This layer links the disc and the vertebral body with collagen fibres within it that run horizontal and parallel to the vertebral bodies, with fibres continuing into the disc (Urban *et al.*, 2003). Figure 2.3 shows a schematic drawing of an intervertebral disc.

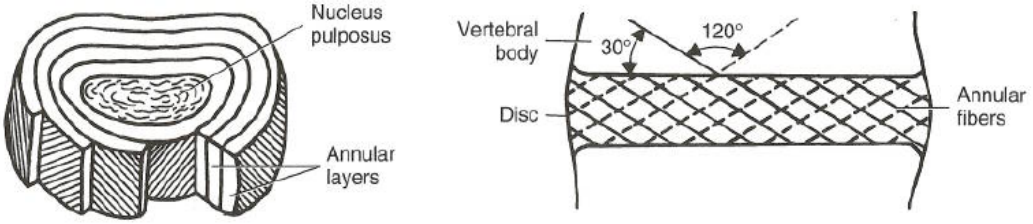


Figure 2.3: Schematic drawings of an Intervertebral disc showing the criss-cross arrangement of its fibers (Nordin and Frankel, 2001)

2.1.2 Disc Herniation

Disc herniation is caused by trauma or heavy lifting injuries, which in turn can cause the outer layer of the intervertebral disc to tear, allowing the inner nucleus pulposus to bulge out. There are three types of annulus tears: circumferential tears, peripheral rim tears and radial fissures (Adams and Roughley, 2006). The displacement of the nucleus pulposus can lead to the direct compression of the spinal cord or impingement of nerve roots. This type of herniation often leads to radiculopathy, where the nerve root is compressed and inflamed (Figure 2.4). The symptoms are ipsilateral (located on the same side) pain in the neck, or pain which radiates down the arm to the fingers (Yeung *et al.*, 2012). The cervical discs that are most commonly ruptured are between C5-C6 and C6-C7 (Hussain *et al.*, 2012; De Beer, 2011; Lunsford *et al.*, 1980). In general when a disc protrudes, it can compress the nerve roots inferior to (below) the disc i.e. nerve C6 by the C5 disc and nerve C7 by the C6 disc (De Beer, 2011).

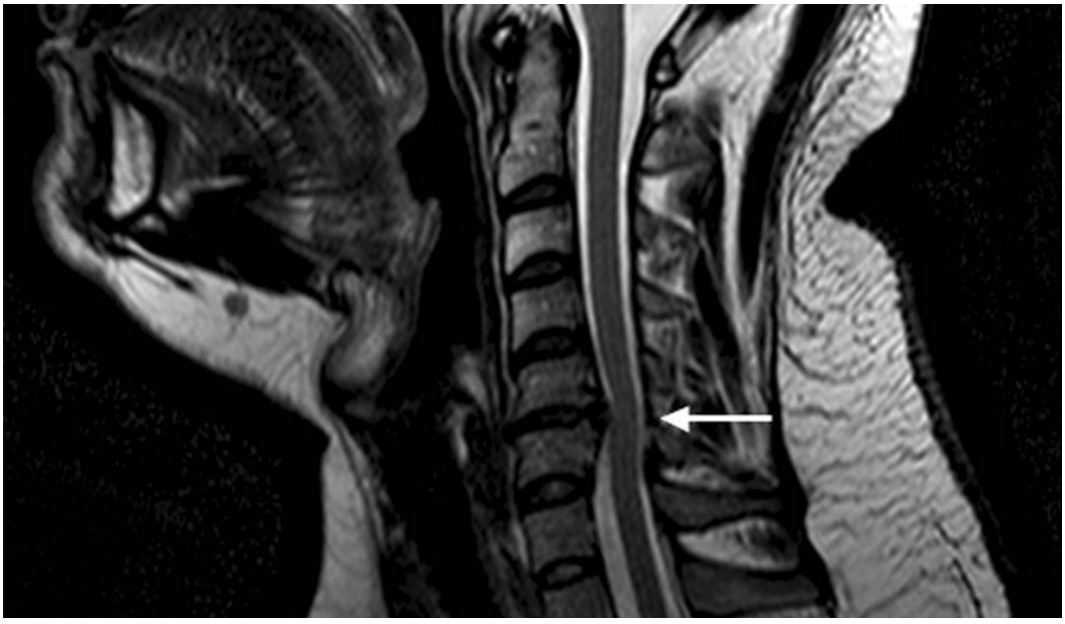


Figure 2.4: Pre-operative MRI scan. The arrow on the sagittal T1-weighted cervical spine image shows the central canal is severely narrowed (Yeung *et al.*, 2012)

2.1.3 Degenerative Disc Disease

As the water content of the nucleus pulposus begins to decrease over time, the annulus fibrosus begins to encroach on it. When this happens, the fine type II collagen fibres of the inner annulus begin to be replaced by the outer type I fibres, whilst these type I fibres also start to become coarser. If the proteoglycan fragments of the nucleus can remain entrapped in the disc by

the annulus and the vertebral end-plates, then they can still perform their role to a degree. Excessive mechanical loading or herniation can cause a disc to degenerate by disrupting its structure (Adams and Burton, 2006). Adams and Roughley (2006) state that:

The process of disc degeneration should be defined as an aberrant, cell-mediated response to progressive structural failure. Definitions of a degenerated disc and early degenerative changes should also refer to structural failure, whereas degenerative disc disease should apply to a degenerated disc, which is also painful. The underlying cause of disc degeneration is tissue weakening occurring primarily from genetic inheritance, aging, nutritional compromise, and loading history. The precipitating cause is structural disruption occurring from injury or fatigue failure.

Adams and Roughley (2006) also show the progression of degenerated discs in Figure 2.5, where **(A)** is a young disc (male, 35 years old), **(B)** is a mature disc (male, 47 years old), **(C)** is a disrupted young disc (male, 31 years old), **(D)** is a severely disrupted young disc (male 31, years old and **(E)** is a disc induced to prolapse in the laboratory (male, 40 years old).

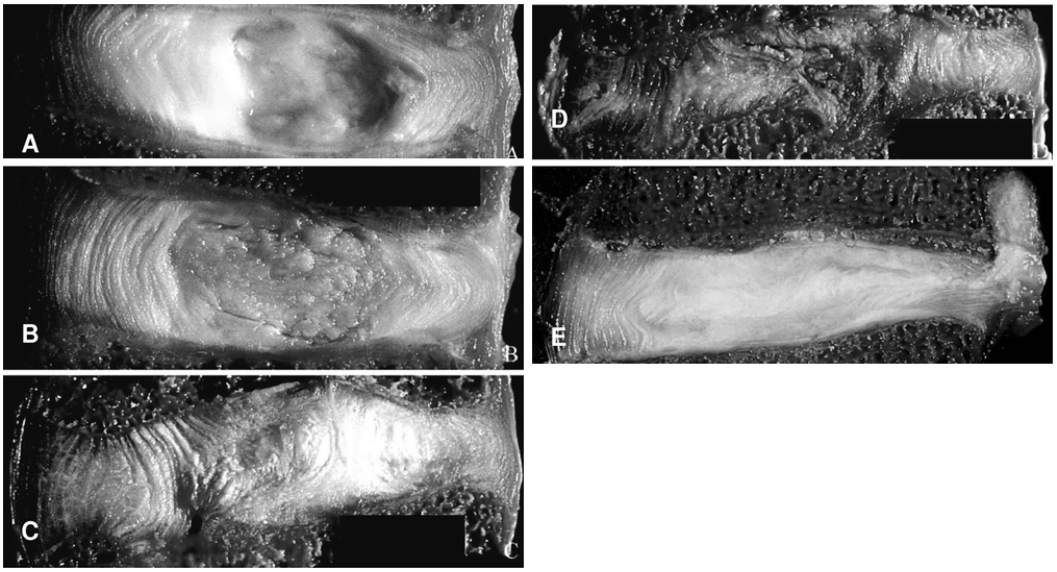


Figure 2.5: Cadaveric lumbar intervertebral discs sectioned in the midsagittal plane (anterior on left)(Adams and Roughley, 2006)

2.2 Anterior Cervical Discectomy and Fusion

Anterior Cervical Discectomy and Fusion (ACDF) is a surgical procedure that is performed to remove a disc that is either herniated or degenerated. The procedure is performed anteriorly (from the front), removing the disc and restoring height with either allograft, autograft or a cervical cage. After about 6 months, the vertebrae above and below should have fused successfully.

Patients who present with Degenerative Disc Disease (DDD) symptoms are normally diagnosed using a combination of radiographs, MRI and/or CT myelograms. Before surgery is considered, conservative treatment is explored with rest, pain medication, nonsteroidal anti-inflammatory medications, intermittent cervical traction and/or physical therapy (Cherry, 2002). Whilst many patients benefit from this, some do continue to have numbness or weakness and thus become candidates for surgical treatment (Cherry, 2002).

The patient is first prepared for surgery by being placed on his/her back after which anaesthesia is administered. Once under, the neck area is cleaned and prepped. A radiology technician operates a fluoroscope throughout the course of the surgery so that the surgeon has an inner view of the spine so as to check for positioning. The surgeon begins by making a transverse incision on either the right or left side of the neck over the surgical disc space (Cherry, 2002). To expose the bony vertebrae and discs, a pathway must be made by moving the muscles in the neck and retracting the trachea, oesophagus, arteries and finally by lifting the muscles that support the front of the spine (Figure 2.6).

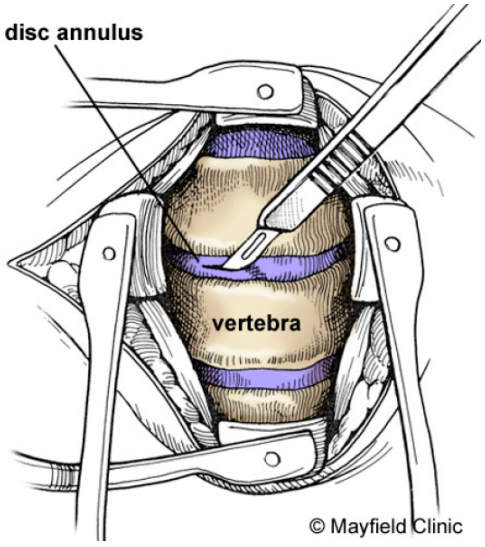


Figure 2.6: Retracted muscles to expose the vertebra. The disc annulus is cut open and the disc material is removed with grasping tools (©Mayfield Clinic)

Using gentle tension, the surgeon inserts a spreader into the body of each vertebra above and below the disc so as to separate each from the disc. The outer wall of the annulus is cut and disc material is removed in small fragments using a pituitary rongeur (grasping tool). If there is any disc material pressing on the nerve causing herniation such as bony spurs (osteophytes), then this is removed as well. Sometimes the foramen through which the spinal nerve exits will be enlarged using a drill to give the nerves more room.

A burr drill is used to remove the end-plates and outer cortical layer of each vertebra to expose the blood-rich canellous bone. This open space is now ready to receive some sort of graft or implant. Bone graft materials have three basic properties: **Osteoconductive** bone grafts materials provide a framework for the ingrowth of osteoblasts (the bone forming cells) from the vertebra. **Osteoinductive** bone graft materials stimulates the growth of new bone cells. Thus, **Osteogenic** bone grafts contain viable bone cells that have the ability to stimulate bone growth at the site of the graft (Cherry, 2002). There are various bone grafting options available for the surgeon to use, namely:

Autograft The bone comes directly from the patient from the iliac crest (hip) area. The advantage is high successful fusion rate. The disadvantage is pain in the hipbone area after surgery.

Allograft The bone comes from a donor (usually a cadaver). The advantage is not having to harvest the patient's own bone. Disadvantage is that it has no bone-growing cells or proteins. Surgeons thus use bone shavings from the burr drilling of the vertebra which are added to the allograft to stimulate bone growth.

Bone graft substitute These are man made disc substitutes (often referred to as cages) made from either plastic, ceramic, titanium or bioresorbable materials. These implants are normally filled with either bone shavings or a bone substitute to stimulate bone growth.

Once the graft has been secured in place and the position has been confirmed by fluoroscopy, the surgeon removes the vertebral body distractor. After this wound closure begins where the wound is irrigated copiously with a normal saline-antibiotic solution. The subcutaneous tissue is closed with an absorbable suture and the skin is approximated with skin staples. A sterile dressing is then applied to the closed wound. The patient's vital signs are monitored. In most cases the patient may return home the same day under certain instructions. A neck brace is recommended for sleep, walking and when riding a car.

2.3 Fabrication Methods Used in the Medical Field

Additive Manufacturing (AM) is a fabrication process whereby complex geometry can be produced using CAD and a layer by layer approach, without the need for specialised tooling or the need for Design for Manufacture principles (Hao *et al.*, 2010). AM is being increasingly used to produce parts that are topologically optimized to save material and costs. This saves a large amount of cost for producing one-off parts or a small volume thereof. There are various methods of fabrication which fall under AM, notably:

- Stereolithography (SLA)
- 3D Printing
- Electron Beam Melting (EBM)
- Selective Laser Melting (SLM).

2.3.1 Stereolithography

Stereolithography (SLA) is a form of Additive Manufacturing (AM) that creates a physical 3D object by using a liquid Ultraviolet (UV)-capable photopolymer resin and a UV laser. Figure 2.7 shows the SLA process. There is a pool of photopolymer resin within which a platform is lowered into. A UV laser beam traces a cross-sectional profile of the part onto the resin which causes it to cure. The platform is then lowered by one thickness where a resin-filled re-coater blade runs across the part to put a layer of fresh of resin on top. The process repeats itself until the part is completed.

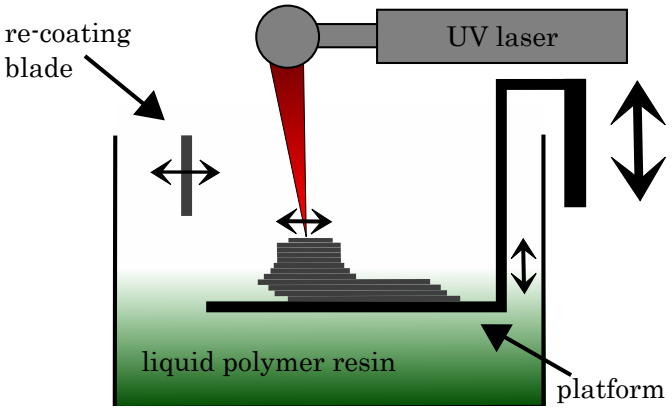


Figure 2.7: SLA process

2.3.2 3D Printing

3D Printing was invented and patented in December 1989 by Sachs et al. from Massachusetts Institute of Technology (MIT) and later licensed to the Z Corporation in 1994. In 1996, the first system, the Z402 was commercialized. In January 2012, the Z Corporation was acquired by 3D Systems. Another company that specializes in 3D printing is Objet Geometries. Founded in 1999, they completed a merger with Stratasys on December 3rd 2012 with a market capitalization of approximately $3.0 billion.

Figure 2.8 shows the printing process for the Z Corp 3D printer. There are two trays: a feeding tray which houses the powder supply and a building tray where the model is printed onto. First a layer powder is spread from the feeding tray across to the building tray. The printer head then prints a 2D cross section of liquid binder in the form of a preprogrammed slice from the CAD model on top of the powder. The building tray then moves down one layer, while the feeder tray moves up one level and the process begins again. This continues until the final 3D part is completed.

Figure 2.9 shows the printing process for the Objet 3D printer. It uses a printer head to deposit layers of photopolymer material onto a building platform. As each layer is completed, it is cured using ultraviolet light from lamps that are mounted on the side of the printing head (Rossiter *et al.*, 2009). Once hardened, the build platform is then lowered and the process repeats. Once the part is completed, it is removed from the build platform. If a support structure is needed for certain complex geometry, the printer can also deposit a gel-like material at the location where the support is needed. When the part is removed, the support material is washed away with a jet of water. If there are still traces of support material, it is soaked in a caustic soda solution until removed (Rossiter *et al.*, 2009).

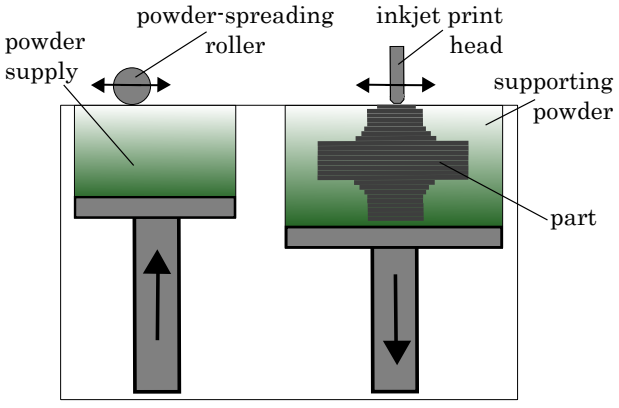


Figure 2.8: 3D Printing process (Z Corp)

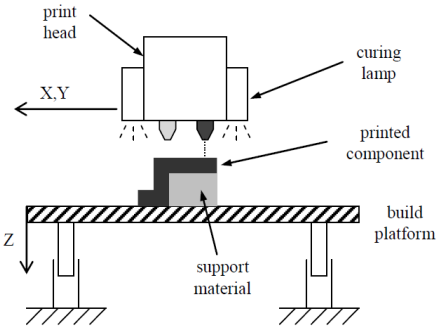


Figure 2.9: 3D Printing process (Objet) (Rossiter *et al.*, 2009)

2.3.3 Electron Beam Melting

Electron Beam Melting (EBM) is a solid freeform fabrication method that uses an electron beam to melt metal powder in a vacuum into a fully-dense material using a layer by layer approach (Petrovic *et al.*, 2012). The technology comes from the Swedish company Arcam AB. The process uses an electron beam which is formed by electrons emitted from a tungsten filament and is accelerated in a high voltage difference in the electron beam gun (Cronskär, 2011). Two magnetic fields focus the beam which welds consecutive layers of powder. Once a layer is completed, a new layer of powder (approximately 0.05-0.2mm thick) is spread over the previously welded layer by a rake. The powder is pre-heated before being melted to the geometry. To minimize residual stresses, the powder bed is kept warm throughout the build whilst being kept at a vacuum of 1×10^{-4} mbar (Cronskär, 2011). The part is left inside the chamber to cool down, after which a blast chamber is used to remove the excess the powder which gets sifted and reused. EBM uses Titanium Ti_6Al_4V-ELI, Titanium Grade 2 and Cobalt-Chrome standard powders. Figure 2.10 shows a schematic working of an EBM machine.

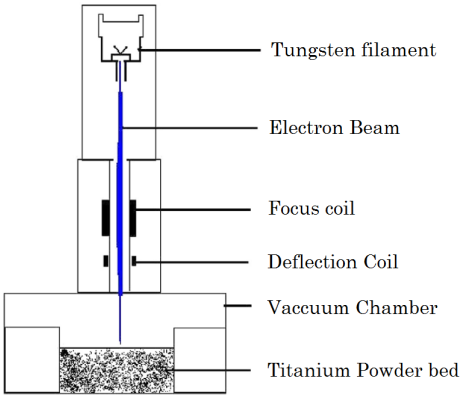


Figure 2.10: Schematic working of an EBM machine (Parthasarathy *et al.*, 2010)

2.3.4 Selective Laser Melting

Selective Laser Melting (SLM) is an additive technique that allows 3D parts to be made by selectively melting successive layers of metal powder on top of each other using thermal energy by a laser beam. It is a complex thermo-physical process that depends on material, laser, scan and environmental parameters (Vandenbroucke and Kruth, 2007). Two popular commercially available versions of this technology are LaserCUSING and Direct Metal Laser Sintering (DMLS). LaserCUSING is so named as the word Cusing refers to Fusing, and is derived from the company Concept Laser®. DMLS is a patented version of the SLM process developed by EOS INT ®.

The SLM process begins where a 3D volume model developed in CAD software is exported to a .stl file format. This file is then imported into the MAGICS software (©Materialise, Belgium) for pre-processing. Here any bad edges or surfaces can be corrected and support structures for manufacture can be put in. The model is also broken down into many layers which are then transferred to the machine. The metal powder can be fused in layer thicknesses between 20-50μm. A laser beam fuses the profile of the layer. After the layer solidifies, the machine lowers the substrate by one layer thickness. The powder material is then deposited by means of a roller blade which scrapes the powder across. This process repeats again and again until the part is fully fabricated. The fabricated part is then removed from the base plate using gentle force or by means of wire cutting. Figure 2.11 shows the basic principle of the SLM process.

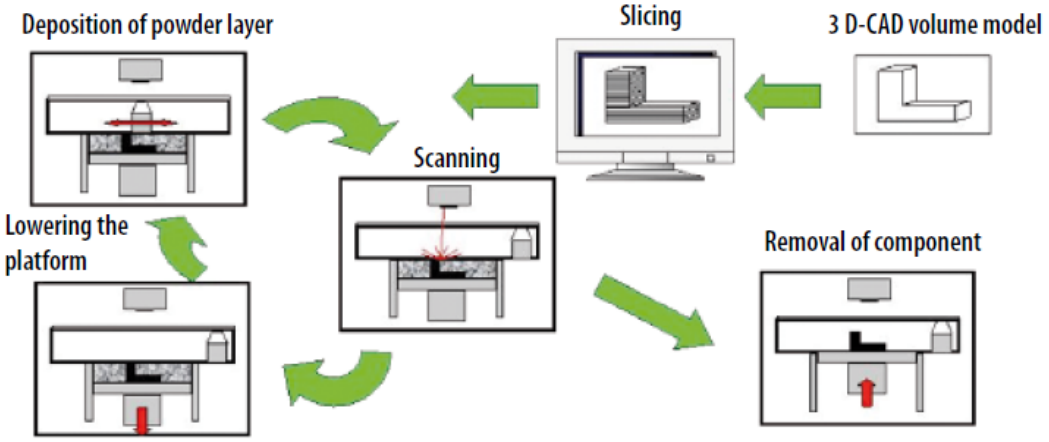


Figure 2.11: Principle of the SLM process (Bremem *et al.*, 2012)

The technical characteristics of the LaserCUSING and DMLS machines are given in Table 2.1. The main difference between these two systems is found in the laser building strategies (Herzog, 2009). DMLS (Figure 2.12a) uses a state-of-the-art melting method where a building section (commonly referred to as an "island") is completed fully before moving on to another section. Conversely, the patented melting strategy used in the LaserCUSING (Figure 2.12b) process starts with a single melting line in one section and moves to another section (not neighbouring "island") and so on, until it returns to the initial section to repeat the process until the build is complete. This subsequently reduces residual stresses resulting to form from the high temperature gradients due to rapid solidification. The technique is know as a "stochastic sequence selection strategy".

Table 2.1: Main technical characteristics of LaserCUSING and DMLS

Dimensions	**EOSINT M 280**	**M2 LaserCusing**
Building volume (mm)	250x250x325	250x250x280
Layer thickness (μm)	20-100	25-50
Laser type	Yb-fibre laser 200 or 400 W	
Scan speed	up to 7.0 m/s	
Variable focus diameter (μm)	100-500	70-200

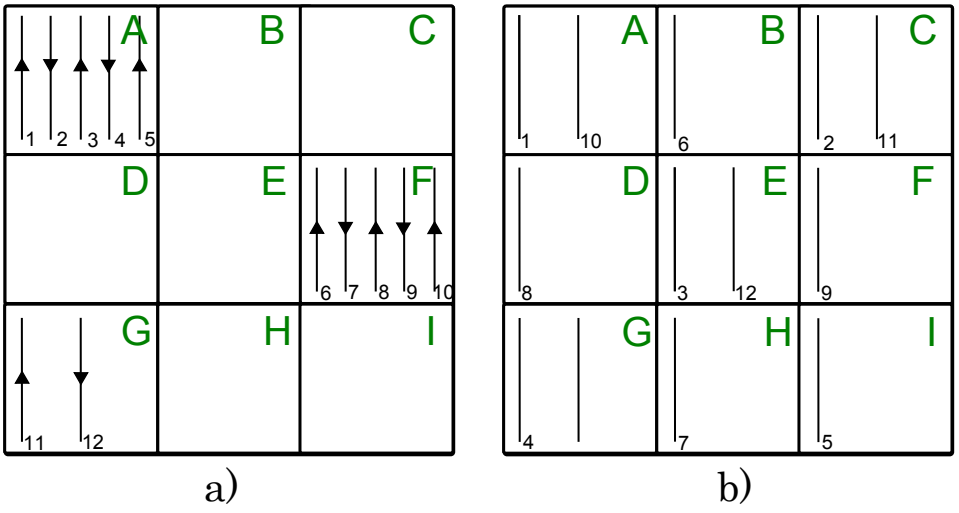


Figure 2.12: Implemented building strategies: a) DMLS b) LaserCUSING (Herzog, 2009)

2.4 Existing Applications of Customized Implants

Customized implants are still a relatively new field of study. Rapid Prototyping (RP) technologies which were once used only for surgical planning purposes are now being realized as proven manufacturing techniques in the form of Rapid Manufacturing (RM) through Additive Manufacturing (AM). Existing areas where RM is being utilized are:

Dental: Patient specific frameworks for complex dental prostheses can be manufactured by SLM enables efficient production of dental parts with a strong economic potential as well (Vandenbroucke and Kruth, 2007).

Hip: Acetabulum prototypes with smooth interior socket for minimal wear and rough exterior surface finish to aid in osseointegration are being realized using Arcam's EBM process (Truscott *et al.*, 2007).

Cranioplasty: Custom hydroxyapatite-based cranioplasty implants are created by using a model of the patient's skull which is created by SLA (De Beer *et al.*, 2008).

Oral Maxillofacial: Mandible reconstruction plates that were once produced by manual bending of a titanium plate can now be designed with CAD to fabricate a mould by SLA to produce the custom titanium part using investment casting (Singare *et al.*, 2006).

Tissue Engineering: Biodegradable implants or scaffolds act a a temporary skeleton to stimulate and accommodate new tissue growth (Bartolo *et al.*, 2012).

Spine: A customized Total Disc Replacement (TDR) implant with matching end-plate geometries has been researched and developed by De Beer (2011).

Surgical Planning: SLA gives accurate 3D models of an area to be operated on, allowing surgeons to plan the best approach for surgery (Honiball, 2010).

2.5 Biocompatible Materials

The choice of material for use in biocompatible implants is important. Geetha *et al.* (2009) indicate that materials used for orthopaedic implants (especially those for load bearing applications) should possess:

- Adequate mechanical properties
- Biocompatibility
- High corrosion and wear reistance
- Design for osseintegration.

The type of material chosen for a specific application depend on the mechanical properties. Of prime importance are the tensile strength, elongation and elastic modulus. Fatigue strength determines the response of the material to repeated cyclic loads and strains. If an implant fractures due to inadequate strength or a mismatch in the mechanical properties between the implant and the bone, then this fracture is referred to as biomechanical incompatibility (Geetha *et al.*, 2009). Bone has a modulus of between 4 and 30 GPa depending on the type of the bone as well as the direction of measurement. If the implant material has a higher stiffness than bone, then the needed stresses are not transferred across from the implant to the adjacent bone. This results in bone resorption around the implant and can lead to implant loosening. This phenomena is known as the *"stress shielding effect"* and is a derivative of Wolff's law, where, if the loading on the bone decreases, the density of the bone will decrease and become weaker because there is no stimulus for remodelling to maintain bone mass. Materials used in orthopaedic implants must thus have a combination of high strength and a low modulus which is closer to bone to avoid revision surgery.

The material used for implants should be biocompatible. Williams (2003) defines biocompatibility as: *"The ability of a material to perform with an appropriate host response in a specific application"*. This means that there must not be any inflammatory or allergic reaction from the material of the implant that would put the patient at risk. Metal ions such as Ni, Co, Cr, V and Al can be cytotoxic if released from the implant. The three most well known metallic biomaterials are stainless steel, cobalt chromium (Co-Cr) and titanium. The most popular non-metallic biomaterial is Polyetheretherketone (PEEK).

2.5.1 Stainless Steel

Whilst there are many types of stainless steel available for use in implants (including pins and screws), the most common is 316L grade 2. The "L" denotes

that it is a low-carbon alloy with less than 0.030% (wt.%) carbon (Ratner *et al.*, 2004). The alloy is predominately iron (Fe) with large additions of chromium (Cr) and nickel (Ni), and minor additions of nitrogen (N), manganese (Mn), molybdenum (Mo), silicon (Si), phosphorous (P) and sulphur (S). The modulus of elasticity is also high compared to Titanium alloys and much higher than cortical bone (Figure 2.13).

2.5.2 Cobalt Chromium

Cobalt Chromium (Co-Cr) based alloys are predominantly used in the medical field for dental implants and the head of artificial hip joints. There are two alloys of Co-Cr, cobalt nickel chromium molybdenum (Co-Ni-Cr-Mo) and cobalt chromium molybdenum (Co-Cr-Mo). They have greater wear resistance compared to stainless steels and titanium alloys (Niinomi, 2002). However the possible toxicity of released Ni ions as well as wear debris causing implant loosening has raised many concerns for its use in total joint arthroplasty (Nouri *et al.*, 2010). Also, the modulus of elasticity of Co-Cr, like stainless steel, is very high.

2.5.3 Titanium

Titanium is the newest of the three commonly used metallic biomaterials and is the most popular. This is due to its high strength, lower density, high immunity to corrosion, low modulus and high capacity to join with bone and other tissues. Titanium was first discovered as a biomaterial in the 1930's when it was found that it was well tolerated in cat femurs, like the other biomaterials of stainless steel and vitallium, a cobalt chromium alloy (Geetha *et al.*, 2009). Initially, commercially pure titanium (CP Ti with alloy type α) and Ti_6Al_4V (with alloy type $\alpha + \beta$) were the most used of the so called "first generation" titanium biomaterials. However, due to the elastic modulus still being much higher than bone, focus shifted to the so called "second generation" β type biocompatible titanium alloys.

Cytotoxicity is another reason for the shift to β-type alloys, as the release of metal ions from titanium alloy implants could generate an adverse biological effect or cause allergic reactions (Li *et al.*, 2010). Niinomi (2002) identifies the β-stabilizing element of Vanadium (V) to be cytotoxic, while Li *et al.* (2010) cites both Vanadium and Aluminium (A) to be potentially cytotoxic. Li goes on to suggest that, whilst the bulk forms of the titanium alloying elements, tantalum (Ta), niobium (Nb), zirconium (Zr), molybdenum (Mo), tin (Sn) and silicon (Si) are biocompatible, the powdered forms of Mo, Nb and Si show a certain degree of cytotoxicity. Table 2.2 lists the first and second generation biocompatible titanium materials along with their mechanical properties and standards.

Table 2.2: Mechanical Properties of Biomedical Titanium Alloys (Geetha *et al.*, 2009)

Material	Standard	Modulus (Gpa)	Tensile Strength (MPa)	Alloy Type
First-generation (1950-1990)				
Commercially Pure Ti (CP grade 1-4)	ASTM 1341	100	240-550	α
Ti-6Al-4V ELI Wrought (grade 23)	ASTM F136	110	860-965	$\alpha + \beta$
Ti-6Al-4V Standard grade (grade 5)	ASTM F1472	112	895-930	$\alpha + \beta$
Ti-6Al-7Nb Wrought	ASTM F1295	110	900-1050	$\alpha + \beta$
Ti-5Al-2.5Fe	-	110	1020	$\alpha + \beta$
Second-generation (1990-till date)				
Ti-13Nb-13Zr Wrought	ASTM F1713	79-84	973-1037	Metastable β
Ti-12Mo-6Zr-2Fe (TMZF)	ASTM F1813	74-85	1060-1100	β
Ti-35Nb-7Zr-5Ta (TNZT)		55	596	β
Ti-29Nb-13Ta-4.6Zr	-	65	911	β
Ti-35Nb-5Ta-7Za-0.40 (TNZTO)		66	1010	β
Ti-15Mo-5Zr-3Al		82		β
Ti-Mo	ASTM F2066			β

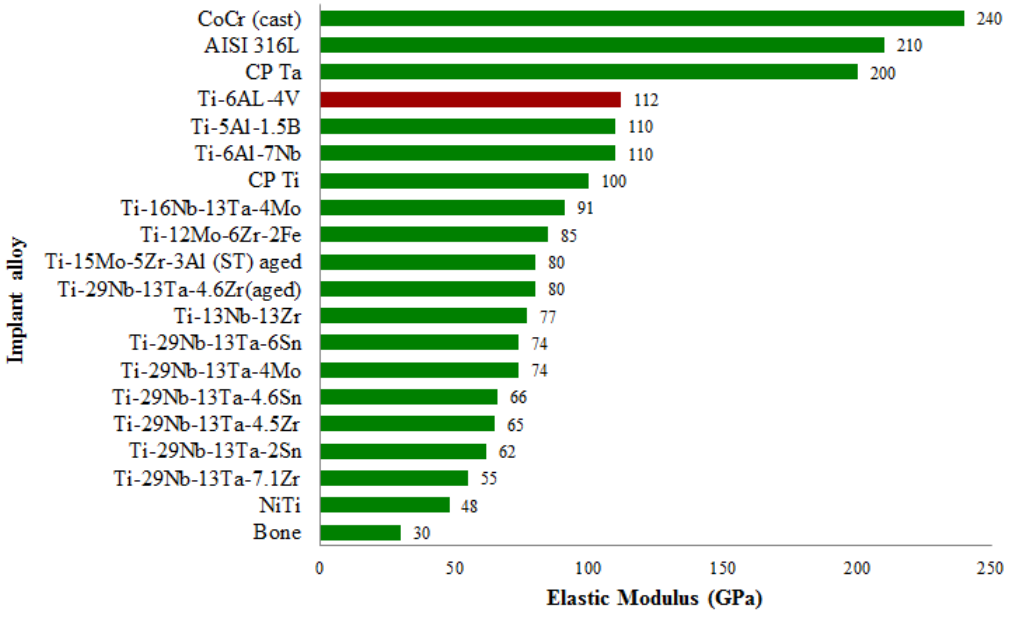


Figure 2.13: Modulus of elasticity of metallic biomedical alloys (Geetha *et al.*, 2009)

2.5.4 PEEK

Polyetheretherketone (PEEK) is a colourless organic polymer thermoplastic and is a derivative of polaryletherketone (PAEK). It is very popular in industry due to its stability at high temperatures, resistance to chemical loading and radiation change, compatibility with many reinforcing agents and greater strength (on a per mass basis) than many metals (Kurtz and Devine, 2007). The polymer is processed through conventional techniques such as injection molding, extrusion or machining (Toth *et al.*, 2006). The medical grade of PEEK is known as PEEK-OPTIMA (developed by Invibio ®).

One of the key features that make PEEK an attractive alternative to the metallic biomaterials is that it is radiolucent (cannot be seen on an x-ray). This aids surgeons in being able to detect whether a successful fusion has occurred. The other key feature is that it has a low modulus of elasticity, reducing the risk of stress shielding. It is however still subject to the same complications of other cage devices, such as subsidence, wear and fracture (Kurtz and Devine, 2007). Katzer *et al.* (2002) incubated PEEK fiber material with seven different genotype variants of salmonella bacterium and found no mutagenic or cytotoxic activity. Table 2.3 shows typical average properties of PEEK as well as Carbon-Fiber-Reinforced (CFR) PEEK composite biomaterials.

Table 2.3: Typical average physical properties of PEEK and CFR-PEEK structural composite biomaterials (Kurtz and Devine, 2007)

Property (ISO)	**Selected Invibio PEEK biomaterials (OPTIMA LT1)**		
	Unfilled (OPTIMA LT1)	**30% (w/w) chopped CFR (LT1CA30)**	**68% (v/v) continuous CFR (Endolign)**
Polymer type	Semi-crystalline	Semi-crystalline	Semi-crystalline
Molecular weight (10^6 g/mole)	0.08-0.12	0.08-0.12	0.08-0.12
Poisson's ratio	0.36	0.40	0.38
Specific gravity	1.3	1.4	1.6
Flexural modulus (GPa)	4	20	135
Tensile strength (MPa)	93	170	>2000
Tensile elongation (%)	30-40	1-2	1
Degree of crystallinity	30-55	30-35	30-35

2.6 International Standards and Guidelines for Implant Design

2.6.1 International Standards Organization

ISO 13485 is a stand-alone Quality Management System (QMS) standard that caters specifically for the design and manufacture of medical devices. Its fundamentals derive from its parent standard, ISO 9001. Though similar, it does not focus on continual improvement and customer satisfaction. Rather it focuses on meeting regulatory and customer requirements, as well as risk management and maintaining effective processes (Wichelecki, 2008). The five key sections of this standard are (ISO, 2003):

4. **Quality Management System Requirements**
5. **Management Responsibility**
6. **Resource Management**
7. **Product Realization**
8. **Measurement, Analysis & Improvement**

Section 4 covers the quality management system as a whole and establishes the general and documentation requirements to be implemented and maintained by an organization to provide medical devices that meet customer needs and regulatory requirements. It also states that any process that is outsourced must also be controlled by the organization.

Section 5 deals with management responsibility. Top management must provide evidence of its commitment to development and implementation of the quality management system, ensuring that customer requirements are understood and met, whilst being committed to maintaining the quality policy and adhering to the regulatory requirement. These aspects should be periodically reviewed for continued suitability.

Section 6 handles resource management. This includes the provision of resources where the organization (specifically top management mentioned in section 5) must determine and provide resources needed to implement the quality management system, maintain its effectiveness and meet customer and regulatory requirements. Humans, infrastructure and work environment are the resources cited as a prerequisite for an effective QMS.

Section 7 focuses entirely on product realization. Everything from the planning of product realization, customer-related processes, design and development, purchasing, production and service provision, and control of monitoring

and measuring devices is set out in this section. Section 7.3 is very similar to it's American counterpart, FDA 21 Code of Federal Regulations 820.30, which are the design controls for medical devices (discussed later on).

Finally section 8 discusses measurement, analysis and improvement. Monitoring and measurement processes are needed to ensure product conformance, as well as conformance of the QMS so as to maintain its effectiveness. Products and processes are included in this process. This enables feedback to be a key performance indicator (KPI) of the QMS, including:

- Customer related info
- Internal and external audit results
- Monitoring and measurement of processes (including QMS processes)
- Monitoring and measurement of the product.

The key sections of the standard are shown in Figure 2.14. What is evident is that product realization is the main focus of the standard and that the other aspects are in place to ensure consistent quality.

2.6.2 Product Realization

Section 7 of ISO 13485 focuses on product realization. As shown in Figure 2.14, this is the most important part of the entire quality management system. Without it, there is no product and thus no reason for implementing a QMS. There are 6 areas that ISO 13485 cite for product realization:

- Planning of product realization
- Customer-related processes
- Design and development
- Purchasing
- Production and service provision
- Control of monitoring and measuring devices

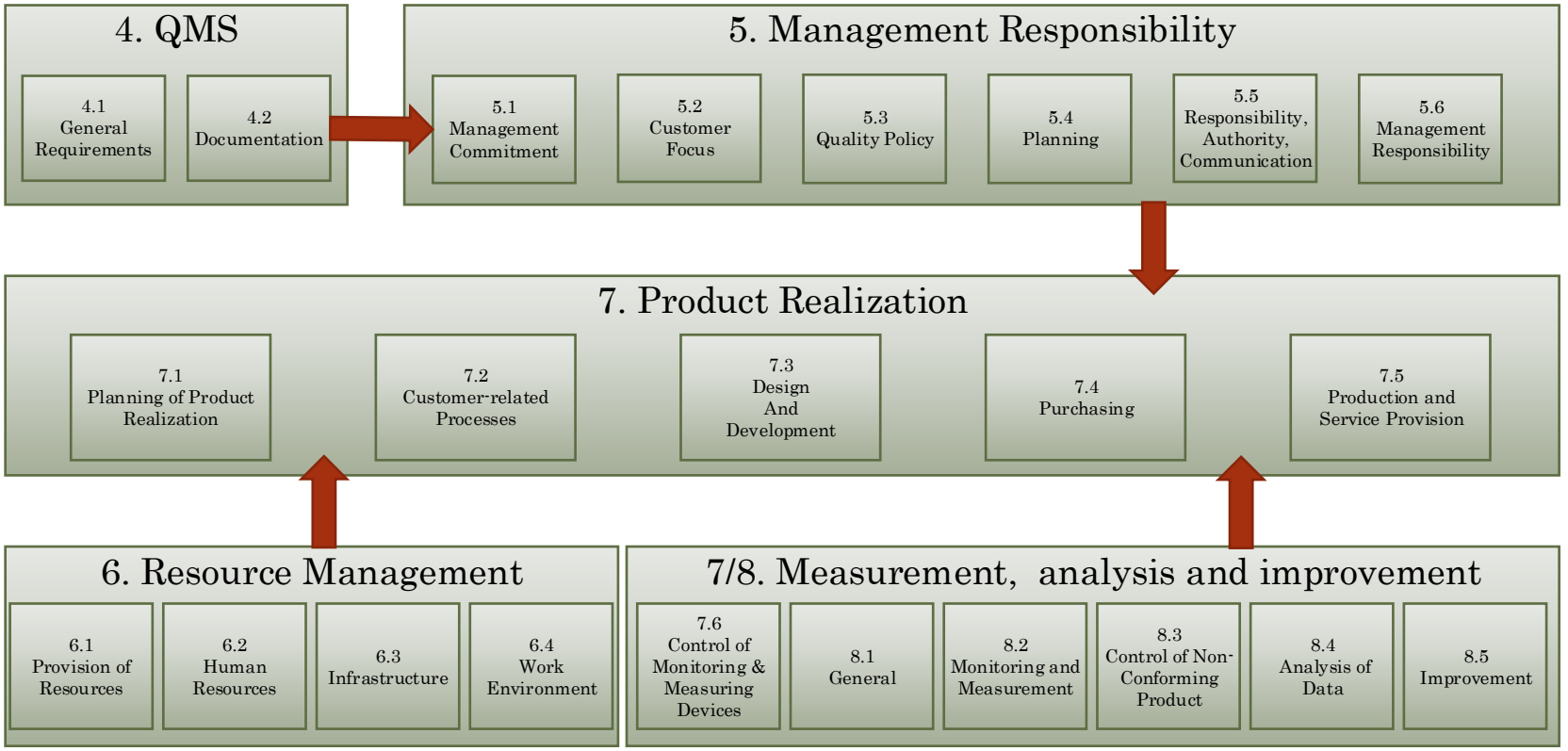


Figure 2.14: Quality Management System according to ISO 13485 (Li, 2012)

2.6.2.1 Planning of Product Realization

Before any product can be realized, proper planning needs to be done to determine:

- quality objectives and requirements for the product,
- the need to establish processes, documents and provide resources specific to the product; required verification, validation, monitoring, inspection and test activities specific to the product, and
- records needed to provide evidence that the realization processes and resulting product meet requirements. Risk management also needs to be planned for as part of the review process throughout product realization.

2.6.2.2 Customer-Related Processes

Customer-related processes focuses on the product and services to be supplied to the customer. These can be:

- the product requirements that are defined from the user-needs, which become the design inputs and later design outputs which must then be evaluated,
- contract or order requirements,
- regulatory or legal requirements,
- or any unspecified customer expectations.

Reviews must be conducted throughout product realization so as to ensure that there are not any discrepancies between the original user needs and the final product.

2.6.2.3 Design and Development

Once the initial planning and all customer-related processes have been completed, the design and development process can begin. Planning must be conducted to determine all the stages during the process, as well as review, verification, validation and design transfer activities, all of which must be document throughout the process. These design controls are very important within a QMS. FDA 21 Code of Federal Regulations 820.30 states that:

Design controls are an interrelated set of practises and procedures that are incorporated into the design and development process, i.e, a system of checks and balances. Design controls make systematic assessment of the design an

integral part of development. As a result, deficiencies in design input requirements, and discrepancies between the proposed designs and requirements, are made evident and corrected earlier in the development process. Design controls increase the likelihood that the design transferred to production will translate into a device that is appropriate for its intended use.

Both ISO 13485 and FDA 820.30 have similar design controls for product realization. The complexity of the product will determine what type of development model is adopted. For more complex designs which possibly involve assemblies, a concurrent engineering approach should be followed. For a simpler design (such as a stand-alone disc replacement), the traditional waterfall model can be adopted (Figure 2.15). Thus as one phase is completed, it is reviewed and then moves onto the next phase. The phases are explained below.

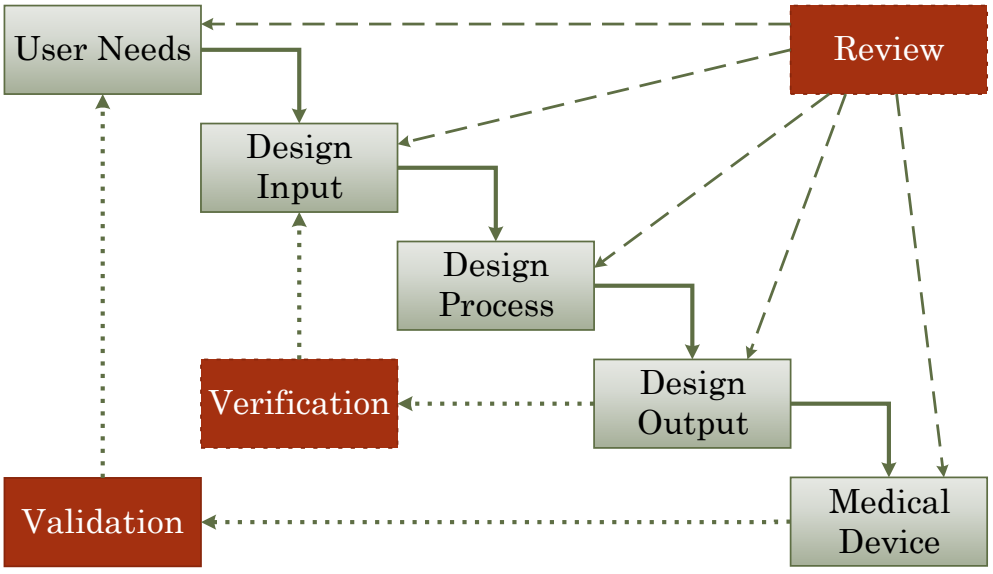


Figure 2.15: Application of Design Controls to Waterfall Design Process (FDA, 1997)

User Needs: List of requirements for what the product must do. These requirements apply to all those affected by the introduction of product, either through design, manufacturing or as the end-user.

Design Inputs: Are the physical and performance requirements of a device that are used as a basis for the device design, written to an engineering level of detail. It is the most important design control activity in the process, as it is the basis for performing subsequent tasks and is used to validate the design.

Design Outputs: Allow for an adequate evaluation of conformance to design input requirements and will contain or reference product acceptance criteria. It is in essence, the basis for the device master record. A total design output consists of the device, its packaging, labeling and master record.

Verification: Confirms that the design output meets the design input requirement. Verification activities are conducted at all stages and levels of the device design. They involve tests, inspections and analyses. Examples are biocompatibility testing of materials and/or comparing a design to a previous successful product.

Review: Is a documented, comprehensive and systematic examination of a design to evaluate the adequacy of its requirements, the capability of the design to meet these requirements and identify problems. Reviews are conducted at all stages of the design process from defining the user needs, down to the final produced device. A team of personnel should be established during the planning stage of the project to carry out the reviews.

Validation: Is the confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

2.6.2.4 Purchasing

Procedures must be established for the purchasing of products used to manufacture the designed product. Suppliers of these products must be evaluated and selected based on their ability to supply products in accordance with the organization's requirements. Records containing purchasing information such as specifications, quality and environment requirements, regulatory requirements and certification information must be kept where applicable. Inspection and/or other activities must be established to ensure that the purchased product meets the specified purchase requirements.

2.6.2.5 Production and Service Provision

Controlled conditions are required to control production and service. These conditions include:

- availability of information that gives characteristics of the product,
- availability of documented procedures, requirements, work instructions, reference materials and reference measurements,

- the use of suitable equipment; availability and use of monitoring and measuring equipment; implementation of the monitoring and measuring equipment (see below),
- implementation of release, delivery and post-delivery activities, and
- the implementation of defined operations for labeling and packaging.

Validation of processes for production and service is required when the resulting output cannot be verified by subsequent monitoring or measurement. It should help demonstrate the ability of the processes to achieve the planned results. Where applicable, arrangements must be made for these processes such as: defining criteria for review and approval of the process; approval of equipment and qualification of all involved personnel; the use of specific methods and procedures; requirements of records and revalidation. Any software used in the automated processes must also be validated. Throughout product realization, documentation must be established to identify the product. This leads to fault diagnosis in the event of quality problems for traceability. The history or location of a product must also be traceable by recorded identification. This includes records of all components, materials and work environment conditions.

2.6.2.6 Control of Monitoring and Measuring Devices

To provide evidence of conformity of the product, monitoring and measurements must be determined and established along with the equipment used to determine this evidence. Where necessary, the equipment must be calibrated or verified prior to use and/or at specific intervals against either national or international standards, be protected from damage or deterioration and be safeguarded from adjustments that would invalidate the measured result. Records of calibration and verification results must be kept. Records of the validity must be assessed when they do not conform to requirements.

2.7 Concluding Remarks

The cervical spine is the smallest of the movable vertebrae. Between each pair of vertebrae, there is one intervertebral disc, except between C1-C2, as C1 is the atlas which rotates aroung C2, the axis. Intervertebral discs are cartilaginous joints which allow slight movement. Their primary function is to transmit loads through the spinal column. Each disc has an inner gelatinous nucleus pulposus and an external annulus fibrosis, housed between two cartilage end-plates.

ACDF is a common surgical procedure used to remove and replace intervertebral discs that have failed due to herniation or DDD. To maintain height between the vertebrae, a cervical cage implant is inserted at the location of the removed disc. Cervical cage implants should have properties that are as close to bone as possible to promote a successful fusion. This is achieved by osseointregation of the bone into the implant. The material should be biocompatible so that no reaction occurs that would put the patient at risk. Table 2.4 summarises the material properties of bone, Ti_6Al_4V and PEEK.

Table 2.4: Material properties of bone, Ti_6Al_4V and PEEK

Property	**Bone**	**Ti6Al4V wrought**	**PEEK**
Elastic Modulus (GPa)	4-30	112	4-20
Tensile Strength (MPa)	80-150	895-930	93-170

AM technologies such as SLM are increasingly being researched for biomedical applications in many areas (as discussed in section 2.4). Two commercially available forms of SLM are LaserCUSING and DMLS. AM allows for parts with complex 3D geometries to be realised that were once not possible using conventional manufacturing methods such as CNC milling. It is also more cost effective for small batch production and saves on material usage by recycling any unused powder. A complex design with open channels can be design to aid in osseointegration and to reduce the elastic modulus, making it more comparible to bone.

For the development of customized titanium cervical cage implants, the aforementioned standards and guidelines should be adopted en route to achieving regulatory approval. The choice of which standard to adopt depends on the region for which the implant is to be sold. The European Union will require an ISO standard to be followed to obtain a CE mark, as will the United States require FDA principles for approval. The Global Harmonization Task Force (GHTF) itself has been developing its own guidelines for use across the globe, incorporating elements from both the ISO and the FDA. In the South

African context, striving towards either of the standards would be acceptable as they are very similar and consistent with the goals of the GHTF.

This project aimed to develop customized titanium cervical cage implants using Additive Manufacturing (AM). A reverse engineering approach was applied to develop the implant. An M2 LaserCUSING machine was readily available from the Rapid Product Development Laboratory (RPD) at the Department of Industrial Engineering, University of Stellenbosch and used to fabricate the implants using titanium Ti_6Al_4V powder (highlighted red in Figure 2.13). As shown in Table 2.4, it is one of the biocompatible materials commonly used. These implants were inserted into cadaver specimens by a surgeon to mimic the ACDF surgical method. After this the vertebral region housing the implants was removed and mechanically tested to investigate subsidence as well as the technical feasibility of the customized implants against implants that are currently being used in industry.

Chapter 3

A Framework for Manufacturing Customized Cervical Implants

This chapter discusses the framework proposed for the development of customized cervical cage implants. Each element within the framework is discussed in detail, such as the process chain which forms the kernel for the framework, and technical and commercial aspects that must be investigated to determine feasibility.

3.1 Scope and Limitations

The scope of this study includes outlining and defining the full framework for the development of customized cervical implants, using ISO 13845 as a guideline. Only section 7.3 (product design and development) however is applied and within this subsection (Figure 2.15) verification of the design controls are evaluated through mechanical testing (Chapter 4.7). Validation is excluded as no clinical studies on living patients are performed. The steps outlined in the experiment (Figure 4.1) aim to demonstrate the effectiveness of the framework both quantitatively (in the form of an economic analysis) and qualitatively (in terms of reporting the relationship between surgery, radiology and engineering). The experiment also seeks as a means to determine the technical feasibility of customized cervical implants.

3.2 Customized Implants Process Chain

With conventional cervical cage devices, a surgeon will merely determine the size needed and pick one that has already been procured. The prosthetic had already been developed through extensive research and clinical trials conducted long before it was needed by the surgeon. Customized cage devices are different in that they are developed "just in time" for use in surgery, using

data obtained directly from the patient in the form of a CT scan. The surgeon and radiologist are to a certain degree very much involved in the design process and can influence the final prosthetic produced. A process chain for developing customized implants is shown in (Figure 3.1) where the swimline columns indicate which of the three discipline is involved during its respective step. This brings together the three different disciplines, namely medicine, radiology and engineering, all of whom play a vital role in the development of the customized cage device.

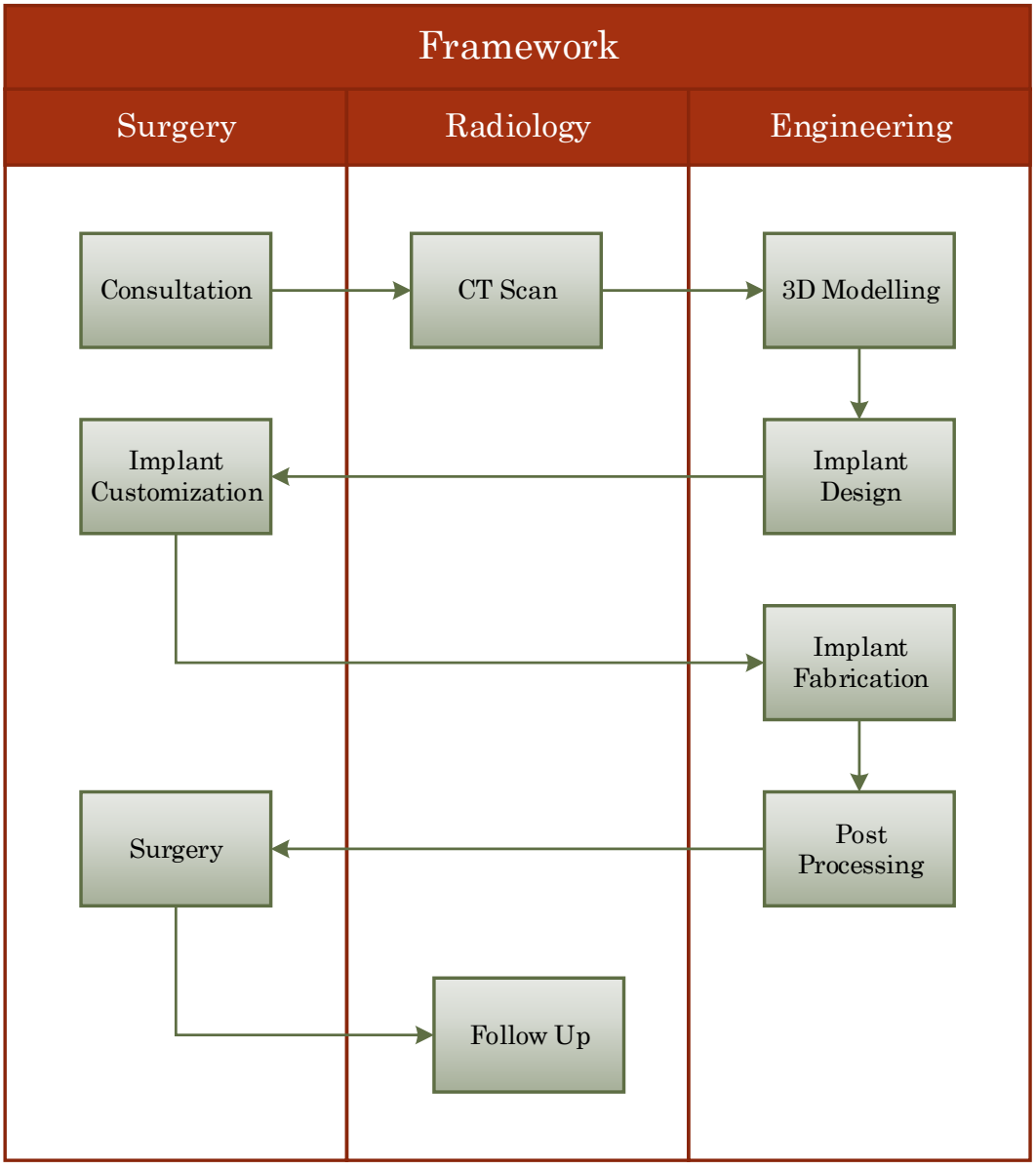


Figure 3.1: Process chain for developing customized cervical implants

3.2.1 Consultation

The patient will seek a consultation complaining of neck pain. Medication and possibly therapy will be prescribed to treat the pain. If the pain persists, an X-Ray could be taken to determine if something has failed. If not, then chronic pain management would be prescribed. If yes, then surgery must be carried out on the affected region. Imaging of the patient's spine is a very important step in diagnosing the cause of pain, the extent of the damage and what surgical procedure is required to treat it. If the vertebrae has failed, then a corpectomy is required. If there is pressure on the spinal cord, then a posterior laminectomy is required. If the cervical disc is herniated or has failed, then a either a discectomy or TDR is required. If a discectomy is required, the surgeon must decide whether a customized implant is necessary.

X-Rays are normally utilized in the initial stages of diagnosis. MRI's are generally used if the pain is more severe or in the case of a patient being involved in an accident, thus a CT scan is not always performed. The difference between a CT scan and an MRI is that a CT scan is better at obtaining anatomical images of the bones, whereas an MRI obtains soft tissue imaging. In the case of vertebrae or disc failure a CT scan is more suitable, whereas for pressure on the spinal cord an MRI is used.

3.2.2 Data Acquisition

Once it has been determined that the neck is the affected region, a CT scan will be performed to obtain anatomical images of the cervical spine. This is to first inspect the extent of damage in that area, as well as to generate a 3D model of the cervical spine that will be used in implant customization.

CT scanners use an X-Ray beam which moves in a circular path around the patient who must remain still. The information obtained is sent to a computer which generates a 2D "slice" of the scanned area. The scanner repeats this process by moving the beam a predetermined distance along the axis of the spine and repeating the circular scan to generate another slice. Once enough slices have been obtained, the scanned data is exported as DICOM CT images which form a volume. These images allow for viewing of the spine in the sagittal, coronal and transverse planes, the three standard planes of view.

The quality of the scan is proportional to the resolution of the scan obtained. The resolution is dependant on the scan time and intensity of the X-Rays. A longer scan time will yield a higher resolution scan but will also result in a higher radiation dose, while a shorter scan time will result in lower radiation doses but will return lower quality scans with noise and sharp edges. Thus a trade-off is required to obtain as high a quality scan as possible without

exposing the patient to an unnecessary dose of radiation. Originally CT scanners were single slice, requiring scan times in the minutes. Today multi slice scanners are used, where the scan is done in seconds and have special protocols written in to minimize radiation exposure, whilst still maintaining a high quality scan.

3.2.3 3D Modelling

The generated image slices can now be imported into the 3D modelling software for data transformation. Once all the images have been imported, parameters must first be set before the model is generated. Because a CT scan obtains all the types of organic matter found in the body, segmentation must be performed so as to isolate the bone matter from the surrounding tissue and the intervertebral discs. The most common form of image segmentation is thresholding. Thresholding assigns a domain to the original gray-scale image. If the value of the data falls within this threshold, then it is generated. If not, it is assigned a zero value and will not be generated.

The thresholding region is applied to the images by means of a mask. This mask runs through the data of the images within the specified threshold and eliminates everything that falls outside of it. The software is also capable of determining whether there are multiple parts within this threshold (such as multiple bones). Mask editing operations can be performed to separate the bones from each other. If there are holes in the generated model, local thresholding can be applied to that specific model to close them. If there are still holes after local thresholding then a "wrapping" function can be applied to close them.

After all parameters have been set, the 3D model of the cervical spine can be generated. This model is however exported as a surface and needs to be transformed into a volume so that it is suitable for use in a boolean operation required for implant customization (discussed below).

3.2.4 Implant Design and Customization

Chapter 2.6 discussed product realization of medical implants with an emphasis on the design controls that should be followed (Figure 2.15). These design controls can now be applied here by determining the user needs. These requirements can then be transformed into design inputs which are physical and performance requirements with engineering values. Note that a requirement such as biocompatibility can have or imply many sub-requirements which must be accounted for in the design inputs. Table 3.1 shows the user needs proposed and their respective design inputs. These design inputs become the basis with

which to design the implant.

Table 3.1: User needs and their respective design inputs for customized cervical implants

User Needs	**Design Inputs**
Biocompatibility	
- Not be poisonous	Use of material with known cytotoxic elements is prohibited
- Prevent stress shielding	Elastic modulus of material used must be < 90 GPa
As light as possible	Weight must not exceed 3g
Encourage osseointegration	Surface finish Ra $> 10\ \mu m$
Load as much of the vertebrae as possible	>30% surface area of vertebrae loaded
Rest on "flat" part of vertebrae only (not on osteophytes)	Implant may not rest on bone which lies at an angle > 70 degrees to the horizontal
Simple to insert surgically	Must have M2 threaded hole on anterior side for surgical tool

A customized implant design is a two-stage process. First a base model is designed in CAD software which has the necessary features and is of the correct width and length. As mentioned previously, off-the-shelf cage implants come in sets of standard sizes. The only difference between each implant in the set is the height, where the implant which fits the best is used. In the case of the base CAD model of the customized implant, the height is not a predetermined value. The base model can be kept in the database until a 3D model of the patient is obtained, both of which must be in the .stl format.

The second stage is the customization of the implant. The 3D model of the patient is imported into suitable software. At this stage the surgeon can suggest changes that need to be made with regards to the height and angle of the vertebrae to possibly correct for any misalignment or lordosis. The base model is then imported and placed in-between the superior (top) and inferior (bottom) vertebrae. A boolean subtraction is then performed which removes the vertebrae from the implant model at the end-plate interference. What remains is a new model with the custom end-plate geometry of the patient. The implant is now ready for fabrication.

3.2.5 Implant Fabrication

Additive Manufacturing (AM) is a suitable candidate for the manufacture of customized prosthetics. It allows designs with custom and complex geometries that are not possible using conventional machining operations to be fabricated without complications. There are many various systems available that fall under AM (see section 2.3). LaserCUSING is the chosen system for this study as discussed in section 2.7.

After the implant has been customized the .stl file must first be pre-processed before the LaserCUSING machine begins fabrication. MAGICS (©Materialise, Belgium) is a suitable pre-processing software tool that fixes bad edges and surfaces. It is also used to create support structures (if needed) and determine suitable slice thickness' for the LaserCUSING machine to execute. Once pre-processing is complete, the final file is exported to the machine for fabrication.

Fabrication time is dependent on part size and complexity. Utilization of the machine for other types of prosthetics such as hip or cranio replacements may take longer. Cervical cages however are quite small and can be fabricated within a day. This enables the patient to not be delayed unnecessarily waiting for an implant. The implant is now ready for post-processing.

3.2.6 Post Processing

For an implant to be inserted correctly, a surgeon makes use of special surgical tools that are supplied. These tools have a thread at the end of them which screw into a tapped hole in the implant. For the customized implant, a small hole can be fabricated, which can later be tapped to fit the surgical tool. The surface finish of the part is adequate as fabricated, however where support structures are removed there will be a very rough area that may require sand-blasting.

Sterilization of implants is a necessity. Sterilization can be done using steam, ethylene oxide or gamma rays. For metallic medical devices, steam sterilization is appropriate. The implant is exposed to saturated steam under pressure at 120°C. A typical steam sterilization process usually lasts around 15-30 minutes (Davis, 2003).

3.2.7 Surgery

Once post processing is complete, the implant can be surgically inserted into the affected area. The surgical procedure is Anterior Cervical Discectomy and Fusion (ACDF) (see section 2.2). An incision is made from the front with a blade. A pathway is made by moving the muscles and retracting the trachea,

esophagus, arteries and by lifting the muscles that support the front of the spine. A spreader is used to separate the disc from the superior and inferior vertebrae. The disc is removed and the implant is inserted.

3.2.8 Follow Up

After surgery, the patient will be moved to the recovery care unit area, all vital signs will be monitored and later the patient will be moved to a regular room. The patient can sometimes be sent home the same day, as well as be fitted with a neck brace. A follow up appointment should be scheduled and possible X-rays be taken a few weeks post-op.

3.2.9 Discussion

The aforementioned steps explain each process involved in developing customized cervical implants. Figure 3.1 also shows a working interdisciplinary relationship between medicine, radiology and engineering where all parties play a key role. The flow of information through the process chain is shown in Figure 3.2 (A full scale version is given in Appendix A). This process chain forms the kernel for the entire framework. Aspects surrounding the framework that must be investigated are:

- Technical Feasibility
  - Techincal Capabilities
  - Mechanical Capabilities
- Commercial Viability
  - Regulatory Approval
  - Product Risk Management
  - Economic viability.

If all of these aspects are satisfied, then the framework can be successfully implemented in a commercial business.

3.3 Technical Feasibility

This section focuses on the technical aspects of developing customized cervical implants. It applies all the necessary steps from the framework that are defined in section 3.2 in the form of a cadaver experiment. Technical and mechanical capabilities from undergraduate projects are also included as they investigate various aspects of the LaserCusing machine that was used to fabricate the implants.

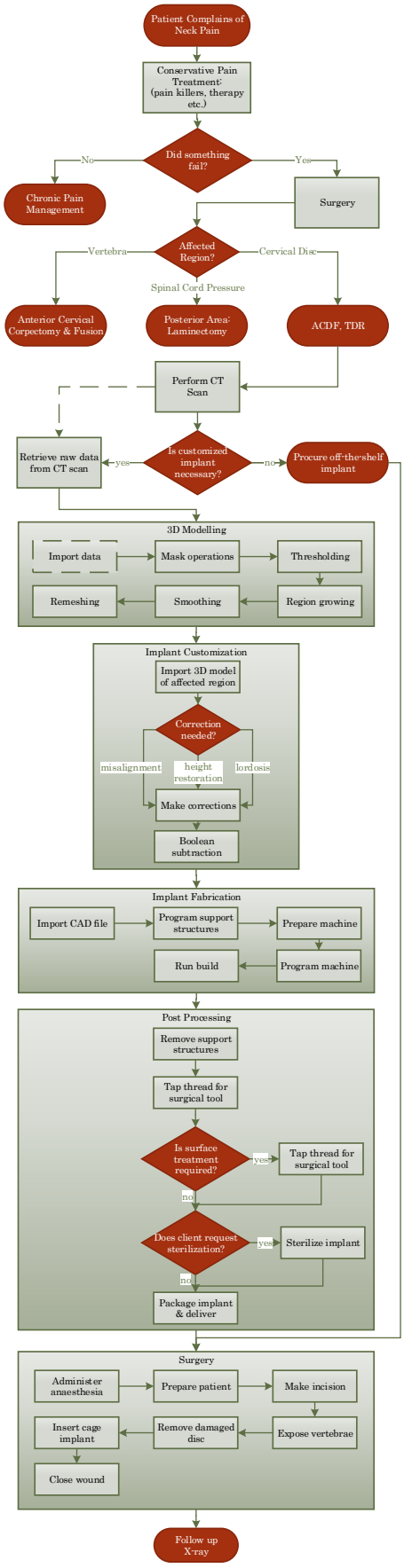


Figure 3.2: Decision tree showing the flow of information for the development of customized cervical cage implants

3.3.1 Technical Capabilities

A capability profile of the LaserCusing machine was developed using benchmark parts (Figure 3.3) with various features fabricated out of tooling steel using the standard settings. No post-manufacturing procedures were conducted on the built parts. No support structures were used at all. The benchmark part had an overall size 50×50×10mm. The features that were tested are listed in Table 3.2. These results were considered when designing the customized implant.

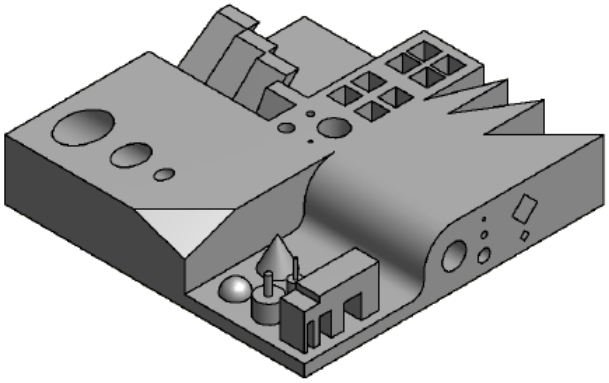


Figure 3.3: Benchmark part used in capability testing (van Zyl, 2012)

Table 3.2: Benchmark features tested for capability profile of LaserCusing machine (van Zyl, 2012)

Feature	**Successful build without support structures**		
	Horizontal plane	**Vertical plane**	**Critical dimension/tolerance**
Main dimensions	✓	✓	± 0.245mm
Wall thickness	✓	✗	> 0.5mm
Cylinders	✓	✗	> 2mm
Squares	✓	✗	> 1mm
Angles and overhangs	n/a	✓	> 40°
Sharp edges	✓	n/a	±1.6°
Curved and sloping areas	✓	n/a	n/a

3.3.2 Mechanical Capabilities

Two final year projects investigated the material characteristics of LaserCused Ti_6Al_4V. One part looked at the density, residual stress and tensile stress (van Rooyen, 2013), while the other looked at fatigue behavior and fracture toughness (De Jongh, 2013).

Comparing LaserCused Ti_6Al_4V to its wrought forms, van Rooyen (2013) found that LaserCused samples had better tensile strength, but fell short in terms of ductility and density. The elastic modulii of the samples were found to be slightly lower than the wrought forms. The samples were also compared to another type of SLM process using an SLM LM-Q machine (developed in-house by Vrancken *et al.* (2012) at KU Leuven). The results summarised in Table 3.3 show that the LasurCused samples have comparable material properties to those of wrought form.

De Jongh (2013) identified that the LaserCUSING process produces residual stresses in the as-built conditions. These can be reduced by a recrystallization annealing process, creating a greater resistance to fatigue. Compared to fatigue data, the annealed samples lie within the range (Figure 3.4). De Jongh (2013) goes on to suggest that post heat treatment should always be performed for improving fatigue behavior where necessary. Fracture toughness testing revealed that the LaserCused parts failed in a brittle matter, with no substantial deformation before failure.

The results of both of these projects which were obtained using the same LaserCUSING machine that the customized implants have been fabricated with, show favourable results when compared with the wrought form, both in an as-built as well as with a heat treated case. For medical applications which require elastic modulii as close to bone as possible, having values slightly lower than the wrought form is advantageous. The modulii of the overall implant can be reduced further by tailoring designs with open channels whilst maintaining strength. As mentioned previously, the fatigue properties of the LaserCused samples can be improved by a recrystallization annealing process. The results of these projects were only released after the customized cage implants used in the mechanical experiments were fabricated and thus could not be considered at the time. In future, the samples can be heat treated to reduce residual stresses and improve fatigue behavior.

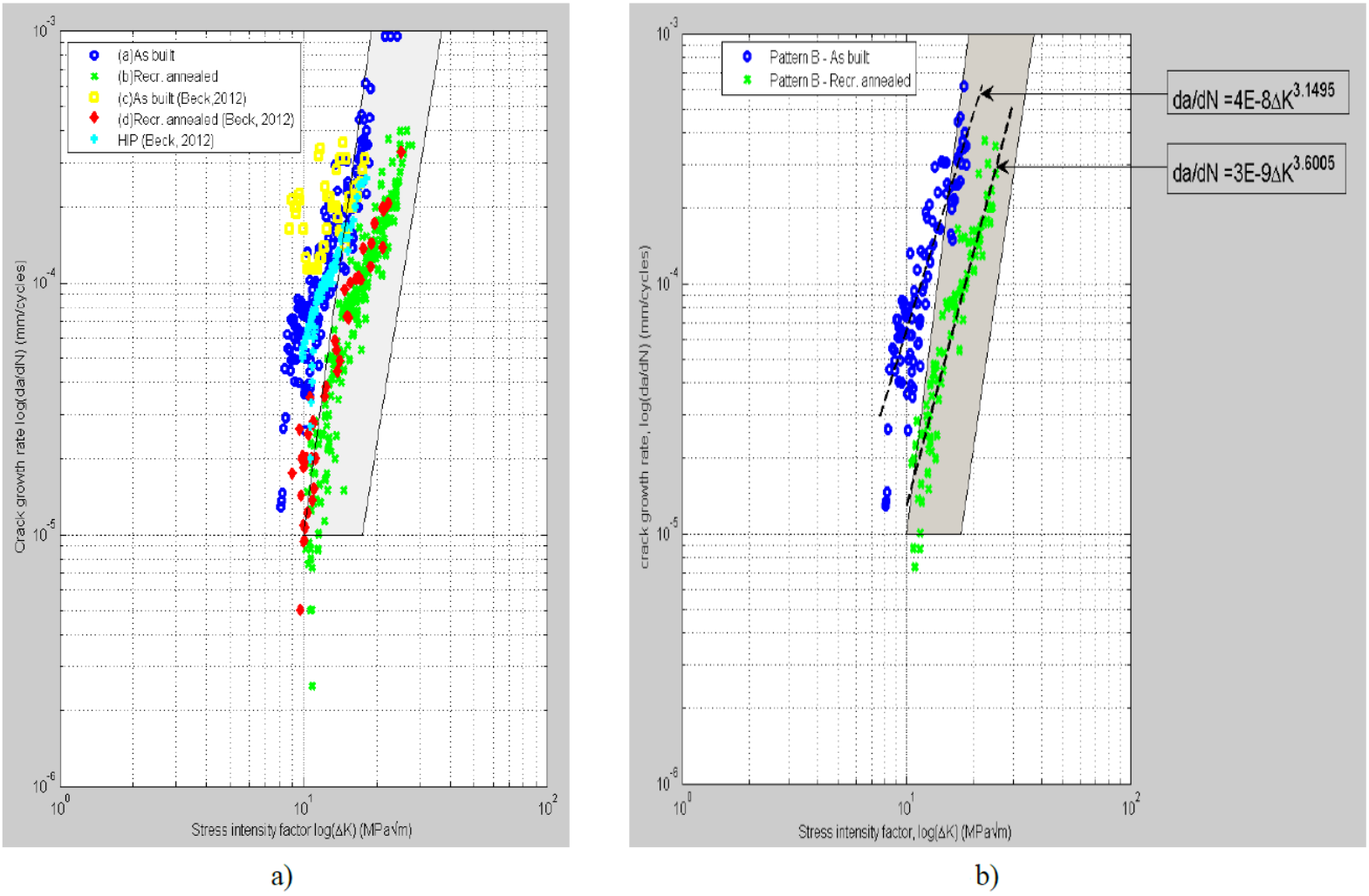


Figure 3.4: Crack growth curves of LaserCused and DMLS. The grey scatter band shows wrought Ti_6Al_4V data (Donachie, 2000). a) Comparison between different heat treatments. b) Fatigue behavior of specimens with hatch pattern B showing the Paris relationship (De Jongh, 2013)

Table 3.3: Comparison between properties of Ti_6Al_4V ELI produced through different processes (van Rooyen, 2013)

Type of Processing	**Yield strength (MPa)**	**UTS (MPa)**	**Elastic modulus (GPa)**	**Elongation at failure (%)**	**Density (g/cm3)**	**Source**
LaserCusing as-built	1100 - 1150	1211 - 1262	100.5 - 109	7.2 - 9	4.22 - 4.42	(van Rooyen, 2013)
Wrought	760 - 827	830 - 896	113.8	15	4.43	(Lampman, 1990)
SLM - LM-Q as-built	1110 $\pm$ 9	1267 $\pm$ 5	109.2 $\pm$ 3.1	7.28 $\pm$ 1.12	-	(Vrancken *et al.*, 2012)
LaserCusing - recrystallization anneal	890 - 1030	950 - 1060	105.6 - 111.9	6.5 - 11.7	-	(van Rooyen, 2013)
Wrought - recrystallization anneal	825	890	110	14	4.43	(Donachie, 2000)
LaserCusing - SLM tailored	956 - 980	1002 - 1031	102 - 109.9	9.2 - 10.7	-	(van Rooyen, 2013)
SLM - LM-Q SLM tailored	955 $\pm$ 6	1004 $\pm$ 6	114.7 $\pm$ 3.6	12.84 $\pm$ 1.36	-	(Vrancken *et al.*, 2012)

3.4 Commercial Viability

Whilst a new implant design may prove to be technically superior than those already available on the market, it must also be commercially viable so as to generate a return on investment. It must also meet certain regulatory requirements, which are especially important in the medical sector. This section discusses the challenges in obtaining regulatory approval, with an emphasis on product risk management. Thereafter an economic analysis is used to determine the cost price of fabricating a customized cage implant under different scenarios.

3.4.1 Regulatory Approval

Before a new medical device can be marketed and sold, it needs regulatory approval. Approval is gained through an application process to the relevant regulatory board of that country. The United States for example has the Food and Drug Administration (FDA), the United Kindom has the Medicines and Healthcare Products Regulatory Agency (MHRA), Australia the Therapeutic Goods Administration (TGA) and Japan the Ministry of Health and Welfare (MHW) (Graham and Peck, 2012). A thorough regulatory approach must address the total product life cycle, from inception through pre-market clearance to commercial sale (Hogan, 2006). South Africa currently does not have such regulations in place. The South African Medical Device Industry Association (SAMED) however has proposed a framework to:

"...control the manufacture, distribution and marketing of medical devices and in-vitro diagnostics (IVDs) to ensure that South African Patients have access to products that are safe, effective and of good quality."

As this was not yet been published at time of writing, international standards should be adopted. The FDA uses a "tiered" approach when regulating medical devices. Devices with the highest degree of risk are subjected to the highest level of regulation, while devices with a lesser degree of risk are subjected to a lesser degree of regulation (Hogan, 2006). Devices are placed in one of three classes, with class I representing the lowest level of risk and class III representing the highest level of risk. FDA approval is granted in two stages, premarket and postmarket regulation. Premarket approval is dependent of the type of class the device falls in. Class I and II devices require a 510(k) notice while class III devices require a Pre-Market Approval (PMA). Spinal implants generally fall into the class I or II category if the design is "substantially equivalent" to one or more "predicate devices". This means that if the device is similar to a previously approved version of the design in terms of intended use and technological features, then 510(k) clearance is granted. Mechanical testing and other types of non-clinical testing are generally used as means of

obtaining 510(k) clearance for spinal implants. Animal tests can be used to ascertain performance characteristics such as biocompatibility and biological response to wear debris (Hogan, 2006).

With physicians and patients seeking implants that are tailer-made to match each patient's anatomy, new challenges are being created for regulators and manufacturers. Within the federal food, drug and cosmetic act, two exemptions exist regarding the introduction of an adulterated device. The first is an investigational device (used as part of a clinical investigation) and the other a custom device, which then becomes exempt from the performance standards and premarket clearance requirements of 510(k). Manufacturers may use this as a means to avoid the waiting period by mislabeling their devices as custom. The FDA defines a "custom device" as a device that (Woodlee, 2011):

- necessarily deviates from devices generally available or from an application performance or Pre-Market Approval (PMA) requirement in order to comply with the order of an individual physician or dentist;
- is not generally available to, or generally used by, other physicians or dentists;
- is not generally available in finished form for purchase or for dispensing upon prescription;
- is not offered for commercial distribution through labeling or advertising; and
- is intended for use by an individual patient named in the order of physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practise.

With this in mind it is important to note that the FDA views patient-specific devices as customized implants. This falls outside the scope of "custom devices" and is still subject to premarket requirements. While these devices have a specific form for each patient, the processes used to manufacture them can be validated, and resulting implant feasibility can be studied as they do not deviate from the original specified performance criteria (point 1). A customized device cannot be custom if the basic design (with slight variations) and its method of production are generally used by other physicians (point 2). Point 4 is violated once a corporation attempts to make a profit by commercializing the patient-specific implant.

A recent example where approval of customized prosthesis was obtained was in 2012 (Perriello, 2013), where DePuy Orthopaedics obtained premarket approval for use of its TruMatch software in its Sigma RP knee prosthetics. CT scans are used to generate a 3D model of the knee which is used to develop custom guides that will be fitted to the patient. This shows that customized implants are no longer ideas, but have already become reality and that regulations have begun to accommodate them.

3.4.2 Product Risk Management

Risk is present in all areas of life, especially in bioengineering. Here the design, manufacturing and use of medical devices that are used by humans presents many factors of risk that can materialise, the consequences of which could be severe. Potential hazards must be identified and managed so as to ensure the safety of the end-user (in this case the patient). Minimization of risk in all sectors of product development is also a necessary step in obtaining regulatory approval. Within the FDA design controls 820.30, risk assessment is a requirement for design validation (Figure 2.15). Clause 7.1 of ISO 13485 requires risk management throughout product realization while clause 7.3.2 states that design and development inputs must include risk management outputs (section 2.6.2). ISO 14971 is recommended for implementation of product risk management and is recognized by the FDA.

ISO 14971 specifies a process for the identification of hazards associated with medical devices to estimate and evaluate the associated risks, the means to control them and the methods to monitor the effectiveness of the controls (ISO, 2007). There are 6 main areas in this standard that must be covered (Figure 3.5). These are explained below (O'Leary, 2007).

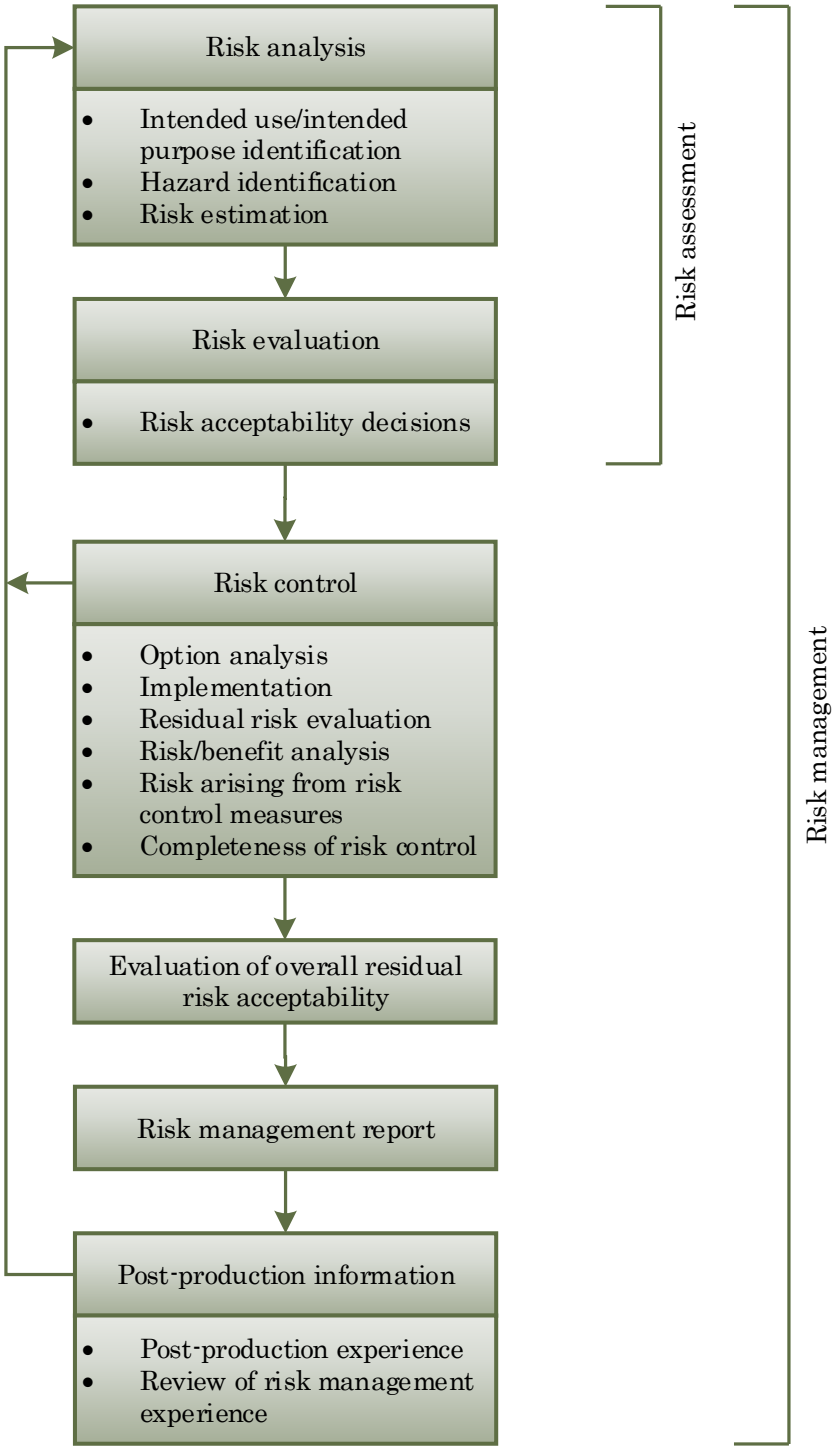


Figure 3.5: Schematic representation of the risk management process (ISO, 2007)

3.4.2.1 Risk Analysis

Intended use and foreseeable misuse of the device is documented so as to identify known and foreseeable hazards. Risk(s) for each hazardous situation is estimated. Risk is the product of the severity and the probability of harm caused by a sequence of hazardous events (Figure 3.6). Key questions that can be asked to determine risk are:

- What might go wrong? (hazardous situation)
- What is the likelihood it will go wrong? (probability)
- What are the consequences? (severity)

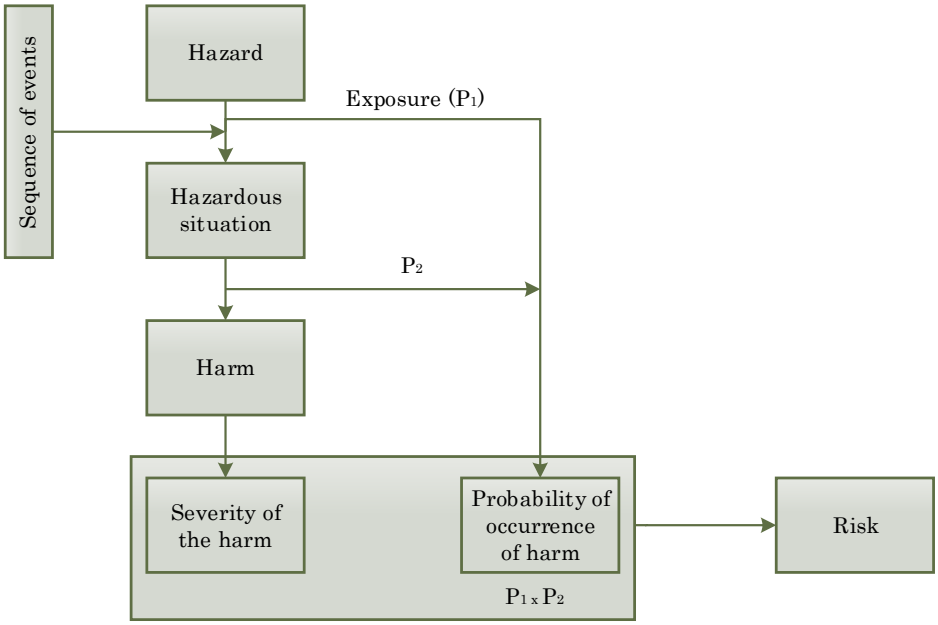


Figure 3.6: Pictorial representation of the relationship of hazard, sequence of events, hazardous situation and harm (ISO, 2007)

Using the aforementioned criteria, a basic risk assessment chart listing some of the hazards faced with developing customized implants is shown in Table 3.4.

Table 3.4: Risk assessment for development of customized implants

Step	**Event (Failure mode)**	**Effect**	**Probability**	**Probability factor**	**Severity**	**Risk factor**
Design	Corrupt CT data	Cannot design implant	<20%	1	2	2
	Inaccurate thresholding	Unable to fit implant	<20%	1	3	3
	Incorrect boolean operation	Misaligned implant	<20%	1	3	3
Manufacturing	LaserCUSING error	Delay in delivery	<40%	2	1.5	3
	Inaccurate part	Unable to fit implant	<20%	1	3	3
Post processing	Incorrect thread	Unable to insert implant	<20%	1	2	2
	Inadequate sterilization	Infection	<20%	1	4	4

3.4.2.2 Risk Evaluation

The risk management plan defines evaluation criteria for each hazardous situation, which are then evaluated individually against the original criteria in the risk management plan. Risk levels are defined calculated using severity and probability. The manufacturer must decide using this criteria whether risk reduction is required.

3.4.2.3 Risk Control

If a risk must be reduced, then control measures are implemented. The residual risk(s) are then evaluated to determine if new risk(s) have arised. Five steps (6.2-6.6) are outlined for control if risk reduction is required (Figure 3.7):

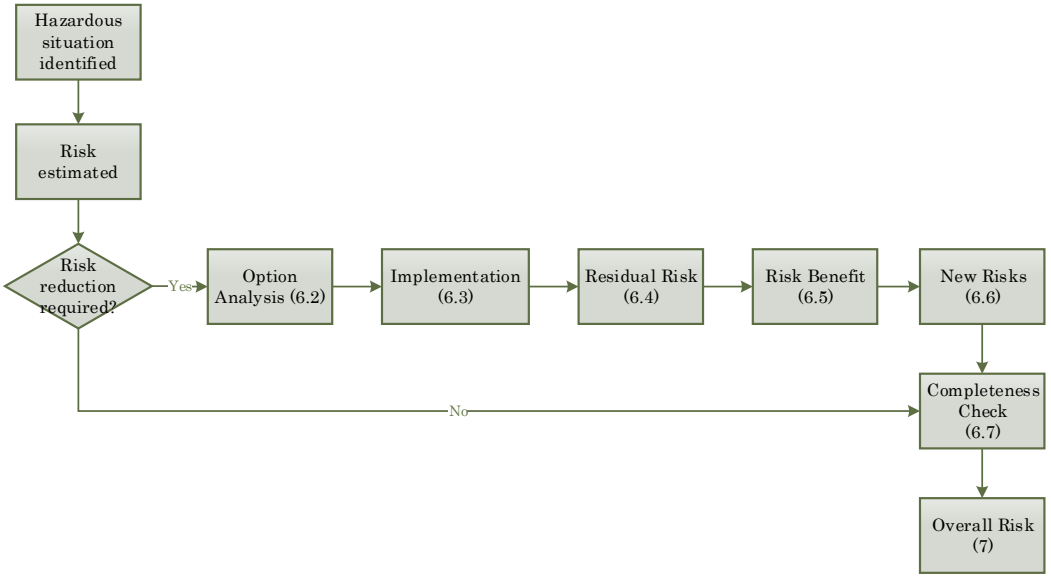


Figure 3.7: Control measures for risk reduction (O'Leary, 2007)

Examples of risk control options (6.2) are listed in priority order:

- inherent safety by design;
- protective measures in the medical device itself or in the manufacturing process;
- information for safety.

3.4.2.4 Residual Risk Evaluation

After control measures have been implemented and validated, the overall risk is reviewed. If the overall risk is unacceptable, then it must be determined if the medical benefits outweigh the overall residual risk.

3.4.2.5 Risk Management Report

The report must contain all the information of the risk management plan, including the scope and personnel responsible. It serves as a review to ensure that the plan has been implemented, that the overall risk is acceptable and that measures are in place to obtain production and post-production information.

3.4.2.6 Production and Post-Production Information

Information such as acceptance data during the production phase is collected; as well as information such as installation and servicing reports, customer complaints, new or revised standards and public information to be collected during the post-production phase.

3.4.3 Economic Analysis

The medical industry has become a special area of application for Additive Manufacturing (AM). Coupled with imaging equipment readily available at hospitals, AM is providing a new cost-effective way of producing anatomical models of patients used for surgical planning, as well as surgical tool prototypes. Peels *et al.* (2011) goes on to say that:

Some AM processes are lean, yet agile, allowing for the manufacture of low-volume batches of component parts with little manual intervention. In recent years, more companies have been using AM for production across a broad range of industrial sectors. Examples of AM production applications include parts for aerospace, medical implants, surgical guides, and hearing devices.

3.4.3.1 Cost Modelling Approach

A cost model for manufacturing using selective laser melting was setup by van Rooyen (2011) that can be used to determine the cost price of any item fabricated. The costs for AM can generally be put into 4 main categories:

Machine Costs: Depreciation and maintenance are the main factors calculated for machine costs. Depreciation is usually calculated using a straight line method.

Material Costs: Metal powder used for manufacturing. AM material costs are higher than conventional materials used due to small volume builds.

Labour Costs: Staff employed to prepare and operate the machine.

Overheads Costs: Can include auxiliary costs that are not large enough to be accounted for on their own.

Taking these into account, van Rooyen (2011) adapted these costs for LaserCUSING as follows:

Running Costs: Running costs include electricity and gas that are used in the running of the machine.

Material Costs: Powder used. The cost is determined by using the price per kg and converting it into a price per volume.

Labour Costs: Staff are paid regardless of whether the machine is running or not. A grade-A artisan (the highest level according to the Metal and Engineering Industries Bargaining Councel) would be assigned to operate the machine. The operator would only be directly involved with the machine during the preparation and removal stages. While the machine is running the operator would be utilized elsewhere such as CAD work.

Maintenance Costs: Three types of maintenance plans are available for LaserCUSING: basic, comfort and premium. The basic is a preventative maintenance plan involving annual visits for filter changes, cleaning and software actualization. The comfort plan add one additional 2-day service as well as fusible parts (filters, computer filters and joints. The premium plan is the comfort plan with all parts replaced if broken under normal use, an extra 2-day service and laser maintenance. The laser itself has a useful life of 10 000 hours.

Fixed Costs: Are costs that are worked into the cost price of the item so as to pay off the initial capital investment of the machine. An example of these costs in the case of the LaserCUSING machine can be found in Appendix C.

For machine utilization, van Rooyen (2011) estimated the total available hours per annum at 90% utilization to be 7 800. If the machine depreciates over 10 years, then the total useful life is 78 000 hours. The two input parameters necessary to accurately calculate the fabrication cost are the part volume and the build time. The part volume is used to determine the amount of material used in the build, while the build time is used against the hourly rates previously mentioned. The total fabrication cost was given by van Rooyen (2011) as:

$$\begin{aligned} Total\ fabrication\ cost\ [R] = {} & Part\ volume\ [cm^3] \times Material\ price\ \left[\frac{R}{cm^3}\right] + \\ & Build\ hours\ [h] \times \Big(Running\ cost\ \left[\frac{R}{h}\right] + \\ & Labour\ cost\ \left[\frac{R}{h}\right] + Maintenance\ cost\ \left[\frac{R}{h}\right] + \\ & Fixed\ cost\ \left[\frac{R}{h}\right]\Big) \end{aligned} \tag{3.4.1}$$

Another economic analysis was conducted to determine specifically the estimated cost of fabricating customized implants. This was done as part of a final year project by Hamman (2012), where single production and batch production conditions were investigated. Setup cost, prep work, post-processing, electricity, gas, direct labour and laser usage were constant as the build time was the same throughout all four scenarios. The total fabrication cost for single production was given by Hamman (2012) as:

$$\begin{aligned} Total\ fabrication\ cost\ = {} & Setup\ cost\ [R] + \\ & Preparatory\ work\ cost\ [R] + \\ & \Big(Part\ volume\ \left[cm^3\right] \times \\ & Material\ price\ \left[\frac{R}{cm^3}\right]\Big) + \\ & (Running\ cost\ per\ build\ [R] + \\ & Maintenance\ cost\ per\ build\ [R] + \\ & Depreciation\ cost\ per\ build\ [R] + \\ & Fixed\ cost\ per\ build\ [R] + \\ & Fungibles\ cost\ per\ build\ [R] + \\ & Software\ cost\ per\ build\ [R]\ ) + \\ & Post\ processing\ cost\ [R] \end{aligned} \tag{3.4.2}$$

There are some inconsistencies however. The electricity, maintenance, depreciation, laser and software costs were calculated on a per batch basis. These costs should rather be worked into an average to determine an hourly rate for the machine that is constant and used throughout as shown in the fabrication cost formula given by van Rooyen (2011), where the costs are better grouped together. This allows the formula to be applied in a more general way across all types of implants that are fabricated. No provision for rent expenses or

purchase value was made either. Post processing costs cannot be constant as they are project related and heat treatment has not been accounted for. The customer may also decide whether or not to perform their own sterilization. The results are however included as they do attempt to give some representation for the price of fabricating customized cervical implants.

The batch processing calculations give a more realistic approach to costing. Here the various costs were grouped as fixed and variable costs:

Unit Variable Cost

- Material costs
- Running costs
- Fungibles
- Preparatory costs
- Post processing costs

Fixed Costs

- Setup cost per batch
- Direct labour cost per month
- Uniform fixed cost per month
- Maintenance payments per month
- Depreciation payments per month
- Software licence costs per month

The total fabrication cost for batch processing was given by Hamman (2012) as:

$$Total\ fabrication\ cost\ per\ cage = \left[\frac{Fixed\ cost\ [R]}{Number\ of\ units\ [pc]}\right] + Unit\ variable\ cost\ per\ cage\ [R] \tag{3.4.3}$$

The equation used for batch processing is better adjusted for grouping the costs. However again these costs were calculated on a per batch basis for this specific case and not worked into a more general form that could be applied to all types of implants fabricated using the LaserCUSING machine. It is recommended that the formula given by van Rooyen (2011) be used in future when

investigating the cost of fabricating titanium prosthetics using the LaserCUSING machine. Using this model, the cost price for the implants is calculated for various scenarios. These scenarios were given by Hamman (2012) and van Rooyen (2011) as:

Hamman - Scenario 1

- The machine can run for 1960 hours per annum. This is when the machine is running one shift of 8 hours/day, 5 days a week for 49 weeks of the year.
- The total utilization of the machine is 80% per year due to down time, material handling, power shortages and setup time.

Hamman - Scenario 2

- The machine can run for 1960 hours per annum.
- The total utilization of the machine is 95% per year due to changeover times.

Hamman - Scenario 3

- The machine can work 5880 hours per annum. This is when the machine is running 3 shifts of 8 hours/day, 5 days/week for 49 weeks of the year
- The total utilization of the machine is 80% per year due to down time, material handling, power shortages and setup time.

Hamman - Scenario 4

- The machine can work 8232 hours per annum. This is when the machine runs 24/7 non-stop for 49 working weeks per year.
- The total utilization of the machine is 95% per year due to changeover times.

Van Rooyen

- The machine can work 8688 hours per annum. This is an estimate calculated from the average of the weekly and monthly annum values.
- The total utilization of the machine is 90% per year.

ConceptLaser (van Rooyen, 2011)

- The machine can work 8640 hours per annum. Their M3 machines are said to run 24 hours per day, 30 days a month.
- The total utilization of the machine was given as 97% per year.

Another scenario is given based on common manufacturing practise where the available hours per annum is calculated on 24 hours per day 365 days per year which is 8760 available hours per annum at a utilization of 80%. Using the following input parameters taken from the customized implants that were fabricated for the cadaver experiments we obtain the following cost prices (Table 3.5) for each scenario using the cost model spreadsheet developed by van Rooyen (2011):

Input parameters

- Build volume of 3.218623 cm^3
- Total build time of 4 hours
- Basic maintenance plan selected

Table 3.5: Estimated cost price for fabrication of the customized implants

Scenario	Available [hrs] p/a	Utilization [%]	Actual [hrs] p/a	Cost [R]
Hamman 1	1960	80%	1568	14045.11
Hamman 2	1960	95%	1862	14041.53
Hamman 3	5880	80%	4704	5265.03
Hamman 4	8232	95%	7820	4021.43
Van Rooyen	7800	90%	7020	4228.03
ConceptLaser	8640	97%	8381	3816.32
Common manfucturing	8760	80%	7000	3818.99

It is evident that scenarios 1 and 2 of Hamman (2012) are not practical in terms of utilization which is far too low and should be disregarded. Scenario 3 does not take into account that the machine could run into the weekend. The 49 week assumption is too low for machine down time as the aforementioned maintenance plans do not take longer than 2 days at a time. Scenario 4 is closest to a real scenario however again the assumption of 49 weeks is too low. The 97% utilization achieved by ConceptLaser is an extreme case, given that they are the suppliers of the LaserCUSING machine. This is an important point as they have direct access to replacement parts and dedicated staff to ensure minimal down time. In reality an everyday company would have to first schedule a call-out for a maintenance service. Replacement parts would also have to be ordered and received before they can be replaced. If the company is based overseas, then there is an added waiting period for customs clearance. The continuous manufacturing scenario is thus recommended as the 80% utilization over a full year takes these factors into account as well as closing of factories over the end of year holiday period.

3.4.3.2 Business Approach

As mentioned in Chapter 1, there is an increasing trend for the number of ACDF surgeries that are being performed. At the time of writing, the statistics for South Africa was not available. Therefore an estimate was determined by extrapolating the number of surgeries performed in the United States against its population to obtain a ratio. Using this ratio and estimate for the number of anterior fusion surgeries was obtained for South Africa, shown in Table 3.6 (*note this is for discussion purposes only, in future it is strongly recommended to attempt to obtain actual data). These extrapolated values show that even in South Africa there is a large enough avenue for customized cervical implants to make use of AM in the form of LaserCUSING.

Table 3.6: Number of anterior fusions performed in the United States with extrapolated estimates for South Africa (Patil *et al.*, 2005)

Year	**Anterior fusions performed**	
	USA	**SA**
1990	9 578	1 417*
2000	78 007	12 406*

The utilization of the machine need not be limited to fabricating cervical cage implants. The machine can be used for other medical prosthetics as well, namely those that are made from Titanium (as discussed in section 2.4):

- Lumbar Total Disc Replacement (TDR)
- Cranial plate
- Hip acetabulum
- Dental prosthetics

The possibility for custom surgical tool pieces designed to fit existing tools for once-off use is also an area that can be explored. Together these applications encourage full utilization so as to maximise efficiency and thus lower cost. Jobs are provided to artisans who can be trained to prepare and operate the machine and perform post-processing tasks. Specially trained biomedical engineers can perform the 3D modelling and implant customization tasks as outlined in section 3.2.

An added benefit from a business point of view is that CT scanners are readily available at most large government and private hospitals across the country, thus no investment is required and staff expenses for radiologists who are already trained are covered by the hospital. This also means that the customized

implants are made accessible across these hospitals as the data is available from many potential sources. The raw DICOM files of the CT scans for a cervical spine are roughly 350 MB in total. A secure cloud server could be established to transfer the files from the hospital where the scan was taken, to the office where the data is used to design the patient-specific implant. Schnetler, Corbett & Partners Incorporated (SCP Inc.) is based in the Western Cape, where they provide radiology services including CT scanning ([S.a], 2014). They have five CT facilities across the province situated at Panorama, Durbanville and Paarl Medi-Clinic, West Coast Private Hospital (Vredenburg) and Louis Leipoldt Medical Centre (Bellville). If the LaserCUSING machine located at Stellenbosch University is used as an example, it can be shown graphically in Figure 3.8 that the prosthetics can be accessible to all of these hospitals.

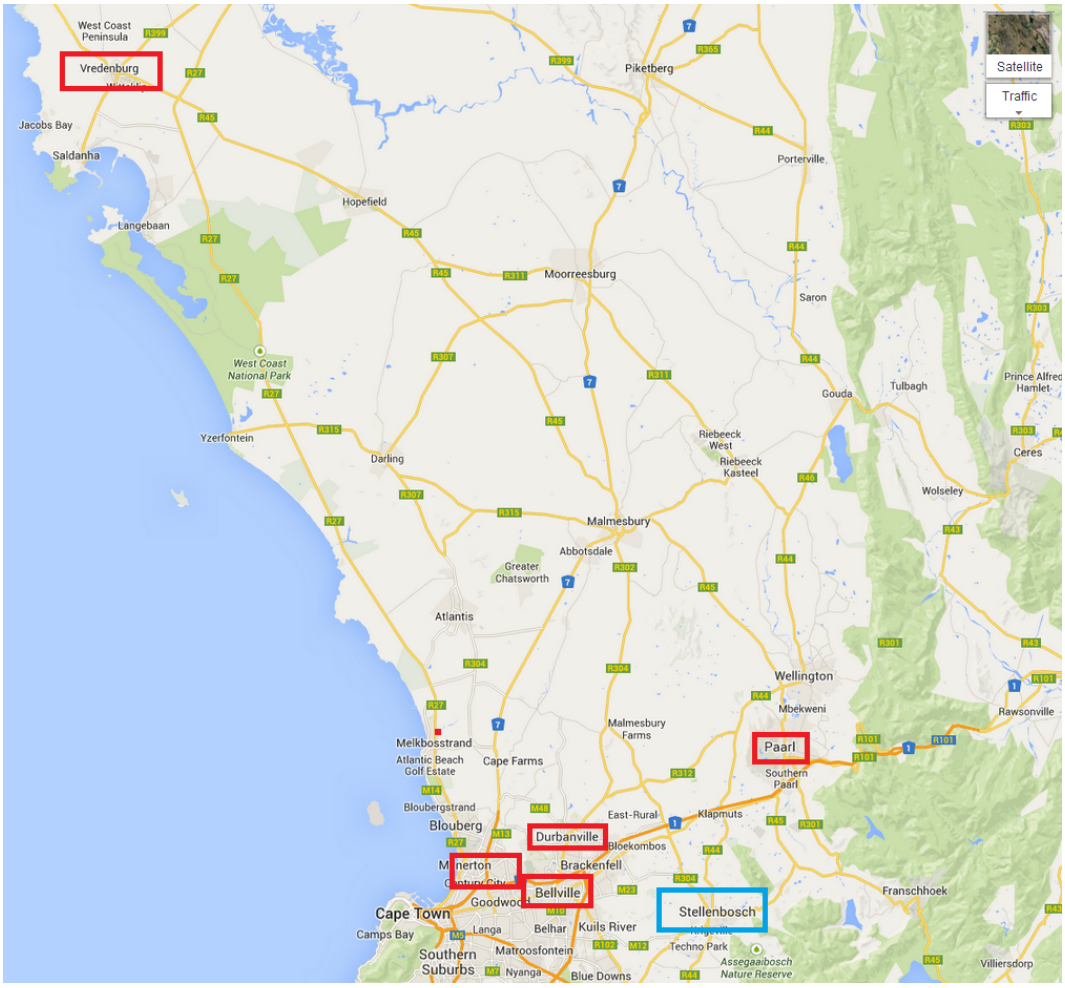


Figure 3.8: Example of possible fabrication site for supplying titanium prosthetics and neighbouring SCP Inc. CT centers (©Google Maps)

It should be noted however that in reality the LaserCUSING machine at Stellenbosch University is used for academic research into other types of metal such as tool and stainless steel. Each time a material is changed, the machine must be thoroughly cleaned out to ensure that there are no particles of the previous material powder used. The filters and the gas have to be changed as well and a different base plate installed. Once a filter has been removed, whether used fully or not, it must be discarded (as per requirements by Concept Laser), this means that a new one must be ordered for every change, triggering unnecessary costs. It is a lengthy process that is not practical for business purposes. This was experienced first hand during this study when the machine had to be changed to run on stainless steel for another project. This caused a two week delay in the study to fabricate the implants used in the cadaver experiments.

A better example is that of an EOS M280 Direct Metal Laser Sintering (DMLS) machine situated at the Central University of Technology. Here they have one machine that uses only titanium powder and is utilized only for research into medical applications. This machine runs up to 700 hours/month, a 97% utilization for a 30 day month (van Rooyen, 2011). The benefits of only using one type of material are:

No powder change: No risk of impurities from particles that were not properly cleaned out.

No gas change: No extra lines or rental of other gases required.

No unnecessary filter changes: No cost wasted due to premature discarding of filters.

Time saving: Unnecessary downtime is eliminated ensuring better utilization of machine.

For business purposes it is recommended to have one dedicated AM machine for medical purposes, located in an area central to most medium-large hospitals with access to CT scanner facilities, such as the example proposed for the Western Cape. Using only titanium ensures that, as is the case with the DMLS machine at CUT, the machine can run at optimal conditions. This is consistent with the scenarios tested in the cost model developed by van Rooyen (2011), where it was assumed that machine only produced medical prosthetics with titanium. Using mark-ups of 30% and 50%, the selling price (Table 3.7) of the customized implants can be estimated and compared against readily available PEEK implants (NB the Orhto-Sol price was obtained by Hamman (2012) and is possibly out of date, while the Medicrea IMPIX-C and EQOS cage prices were obtained on 16-01-2014). The selling price of the EQOS cage implant varies according to the type of customer, which could be a distributor, direct to surgeon, or a hospital group (Ten Napel, 2014).

Table 3.7: Selling price comparison

Device/Scenario	Selling price [R]		
	[30% mark-up]	[50% mark-up]	Market
Ortho-Sol ©			12229
Medicrea IMPIX-C ©			8250
EQOS ©			4500 - 11200
Hamman - S4	5227.86	6032.15	
Van Rooyen	5496.44	6342.05	
ConceptLaser	5094.75	5878.56	
Cont. manufacturing	4964.69	5728.49	

The results given in Table 3.7 show that the estimated selling price of the customized implants are favourable when compare to readily available PEEK implants. It is important to note that the selling price of the PEEK implants take costs such as certification, packaging and shipping into account.

3.5 Summary and Outlook

A framework for the development of customized cervical cage implants has been defined, with the process chain as the kernel surrounded by technical and commercial aspect that must be satisfied for successful implementation. The framework displays a working relationship between surgery, radiology and engineering. It is important to note that whilst the framework has been defined for developing cervical cage implants, it can be adapted for use in other areas where customized prosthetics are required such as cranioplasty, maxillofacial, hip and/or knee implants.

Additive Manufacturing (AM) coupled with reverse engineering techniques enables any of these prosthetics to be fabricated using the same personnel, software and machine. Data acquisition in the form of CT scanners is already available at most large-scale hospitals, making initial capital investment less. Mechanical properties and technical capabilities were investigated to determine the technical feasibility of using LaserCUSING. Commercial viability was evaluated by investigating regulatory approval, product risk management and by conducting an economic analysis to determine the cost price. The estimated cost and selling price of the customized implants compared favourably to readily available PEEK cages.

The framework is tested in the form of cadaver experiments that were conducted and are explained in Chapter 4. The results of these experiments are given in Chapter 5 to determine whether the customized implants are of the same standard as readily available PEEK cages, or are superior.

Chapter 4

Investigating Subsidence: Cadaver Testing

Six cadaver specimens were obtained from the Department of Anatomy and Histology at the Faculty of Medicine and Health Sciences, located at Stellenbosch University's Tygerberg campus. Permission was granted from the University's Health Research Ethics Committee (documentation can be found in Appendix B). These cadavers were used in non-destructive and destructive testing as a quantitative means of comparing the proposed customized implant to that of existing off-the-shelf implants (Medicrea IMPIX-C PEEK) supplied by NeoSpine (Pty) Ltd. Each cadaver would have one customized implant and one off-the-shelf implant. The two implants were compared at levels C3/4 and C5/6. The steps of the experiment are summarised in Figure 4.1 and are subsequently explained.

4.1 Data Acquisition

The cadaver specimens were scanned at Panorama hospital using a Siemens SOMATOM Definition AS+ 128 Multi-Slice CT scanner (Figure 4.2). User defined settings were set to bone, no gantry tilt was used and the CARE kV option was enabled. This allows the machine automatically adjusts the amount of radiation used by assessing the patient's overall size so as to obtain an accurate contrast to noise ratio which returns the best images possible. Each cadaver took no longer than 10 seconds to scan from level C2 through C7. The images were recorded in the DICOM format, the most common format used which is also compatible with 3D modelling software such as MIMICS (©Materialise, Belgium). The images were automatically recorded twice at different quality settings which are indicated by a "B" designation. This refers to the number of "body kernels" in the image. The scans were recorded at 30 and 60 respectively and were labeled as B30 and B60.

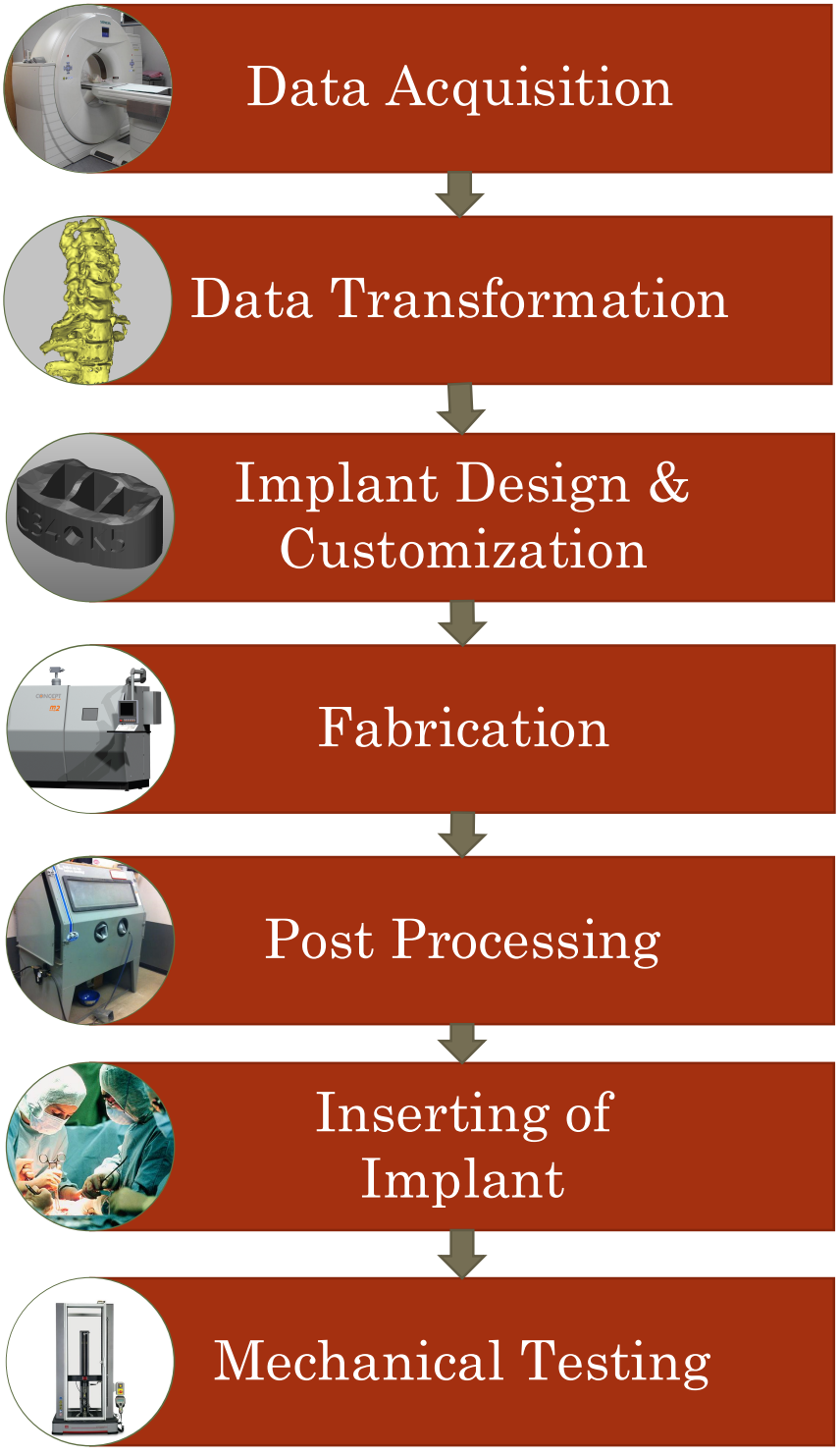


Figure 4.1: Diagram for the design and testing of the developed implant

Figure 4.2: Siemens SOMATOM Definition AS+ CT Scanner

4.2 Data Transformation

MIMICS (version 16.0) was used to process the DICOM files from the CT. The B60 set of DICOM images were used as they were of higher quality. Once the images were imported, thresholding was applied to filter out only the bone material from the set of images. The predefined threshold suggested by MIMICS was used with minimum of 1250 and a maximum of 3065 HU (Hunsfield Units) to generate a mask (Figure 4.3). The 3D model was then previewed using the "calculate 3D" tool to investigate the state of the model (Figure 4.4a). What is evident is that there is still loose bone material around the cervical spine. This was removed by use of the "region growing" tool where a reference point on the cervical spine was selected to retain only the spine (Figure 4.4b). The spine was then segmented using mask editing operations to eliminate all data outside the region on interest. This process was repeated to generate each vertebra separately (shown as the blue region in Figure 4.5).

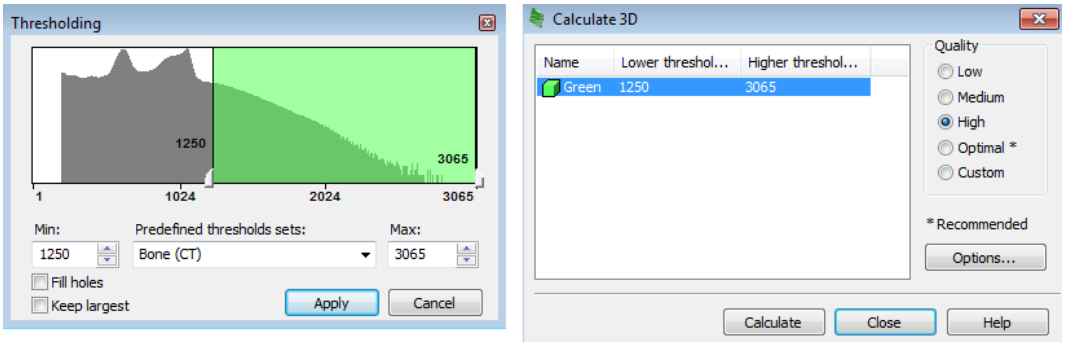
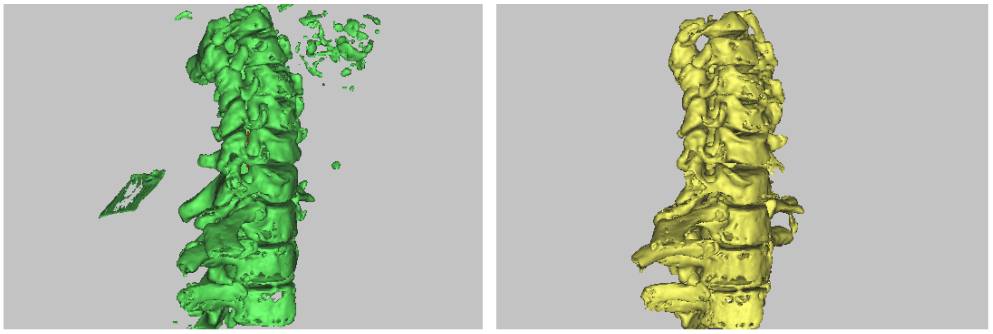


Figure 4.3: Thresholding and calculation of 3D settings



a) b)

Figure 4.4: Preview of 3D model a) after thresholding and b) after region growing

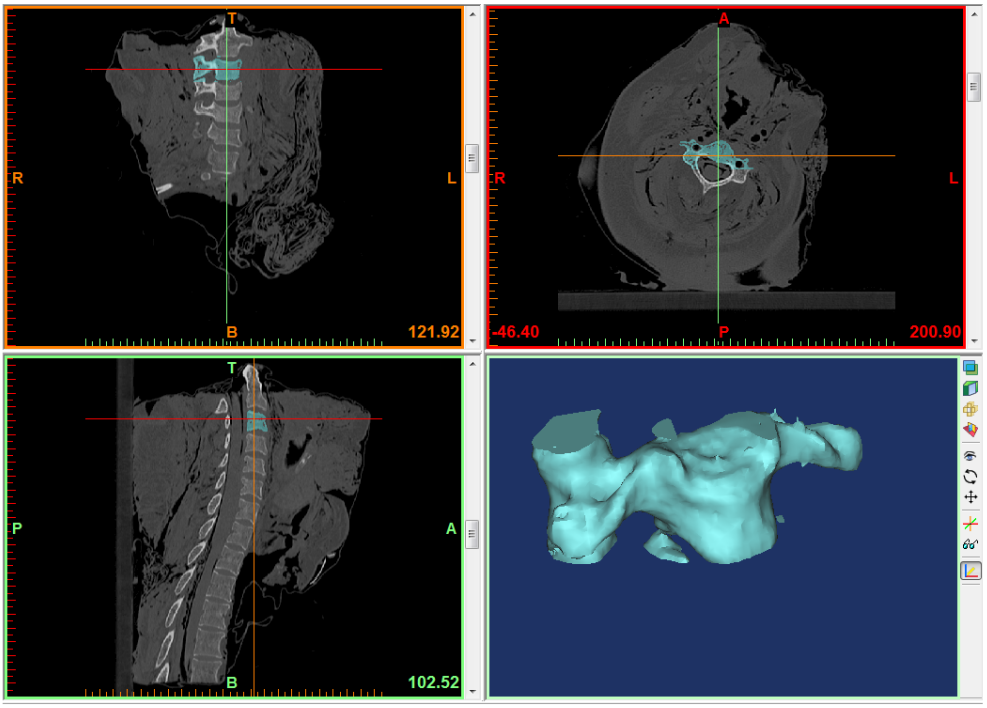


Figure 4.5: 3D model of vertebra after mask editing

Local thresholding was attempted, but the quality of the vertebrae models did not improve and this function was abandoned. The "wrapping" function was used to close any holes in the model and improve the quality of the models. The files were then taken over into 3Matic for final finishing. First a "smooth" function was applied with a factor of 0.7 using the first order Laplacian method. Thereafter the "reduce" tool was used to reduce the number of triangles with a threshold of 30 and a geometrical error of 0.5. An inspection scene was then conducted, giving a histogram showing the distribution of quality of the triangles with a minimum and maximum of 0 and 0.4. Within this region the bad triangles are identified in colour (Figure 4.6a). An auto-remesh is then applied using a shape quality threshold of 0.4 and a geometrical error of 0.05. Figure 4.6b shows the file with the new mesh. Finally another reduction was applied to reduce the number of triangles using the same parameters as those from the auto-remesh and the files were exported as .stl files.

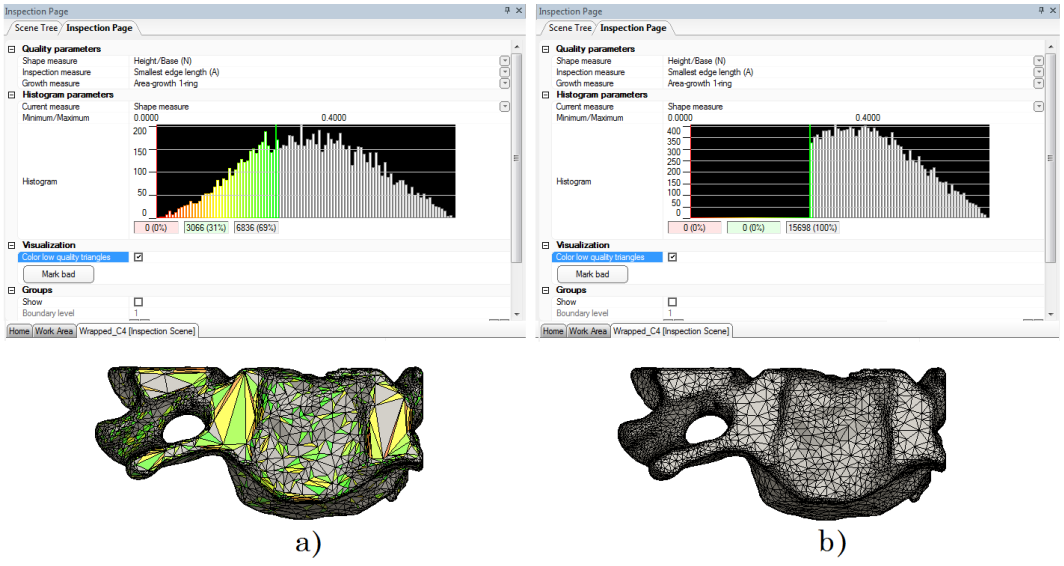
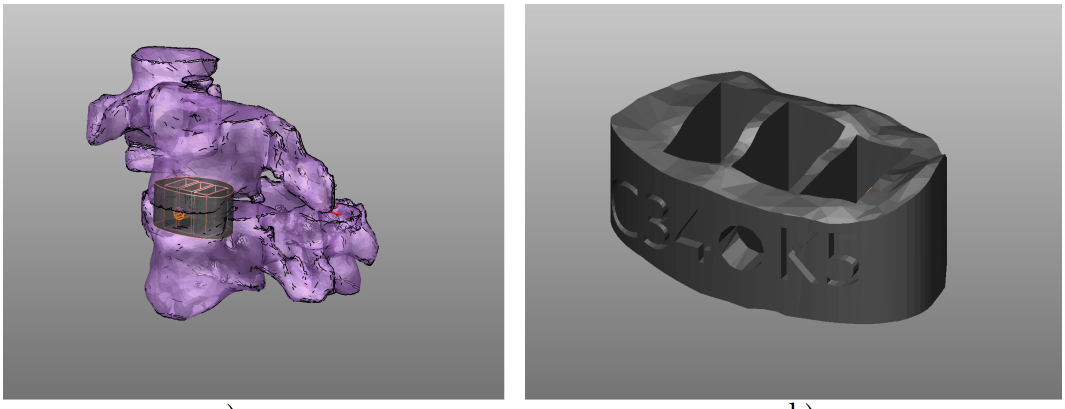


Figure 4.6: File quality a) before and b) after remeshing

4.3 Implant Design and Customization

The method used to design and customize the implants was discussed in detail in section 3.2.4. The base model was designed using CREO Parametric 2.0 (©PTC, MA USA) CAD software. The design used two ellipses to best approximate the surface area of the cervical vertebrae. Its height is more than that of an intervertebral disc so that it is suitable for boolean subtraction (in other words much higher than necessary). The file was then exported as a .stl file.

PowerSHAPE 2013 (©DELCAM, Birmingham UK) was used to conduct the Boolean operations for the customization of the implants. The superior and inferior vertebrae for each implant were imported. Where necessary, changes were made to correct for any misalignment or lordosis. The base implant file was then imported and placed between the two vertebrae (Figure 4.7a) in such a way that it only rested on the "flat" part (one of the design inputs listed in Table 3.1). Once aligned, the superior and inferior vertebrae were subtracted from the base implant yielding the now customized implant with specific contour geometry (Figure 4.7b). This process was repeated at levels C3/4 and C5/6 across all 6 cadavers, thereby producing 12 customized files ready for fabrication.



a) b)

Figure 4.7: Customization of implant: a) Base implant between superior and inferior vertebrae and b) generated implant after boolean subtraction

4.4 Fabrication

The laser parameters were standard settings supplied by Concept Laser® for CL40Ti. These parameters (shown in Table 4.1 and Figure 4.8) are:

Laser power: Controls the power [W] of the laser used in the fusing process.

Laser speed: Speed [mm/s] at which the laser scans across the powder bed.

Focus diameter: The assumed width [mm] of a melt track.

Hatching pattern: Every layer build layer is scanned in a checkerboard like layout. These checkerboards are referred to as "islands". There are many different patterns available to build within these islands.

Hatching spacing: Two distances can be changed; the distance between the scan vectors in the island and the overlap of the scan vectors between the islands.

Table 4.1: LaserCusing parameters used for fabrication of implants

Parameter	Value
Laser power [W]	100
Laser speed [mm/s]	600
Focus diameter [mm]	0.15
Hatching spacing: between [mm]	0.7 × d
Hatching spacing: overlap [mm]	0.15 × d

The machine first went through a thorough cleaning process as the powder was changed from steel to titanium. This involves a filter change as well as a change of gas for the build atmosphere. The LaserCUSING machine has two compartments. The left compartment is the construction module, where the base plate and powder were placed in separate chambers. The atmosphere was then flooded with Argon until the oxygen content reduced to under 2%. Once this was achieved, the chamber was transferred to the right compartment of the machine where the laser is situated for fabrication. Once completed, the base plate was removed from the machine with the parts still resting on their support structures (Figure 4.9). Gentle force was used to remove the implants from the base plate and the support structures were then removed from the implants.

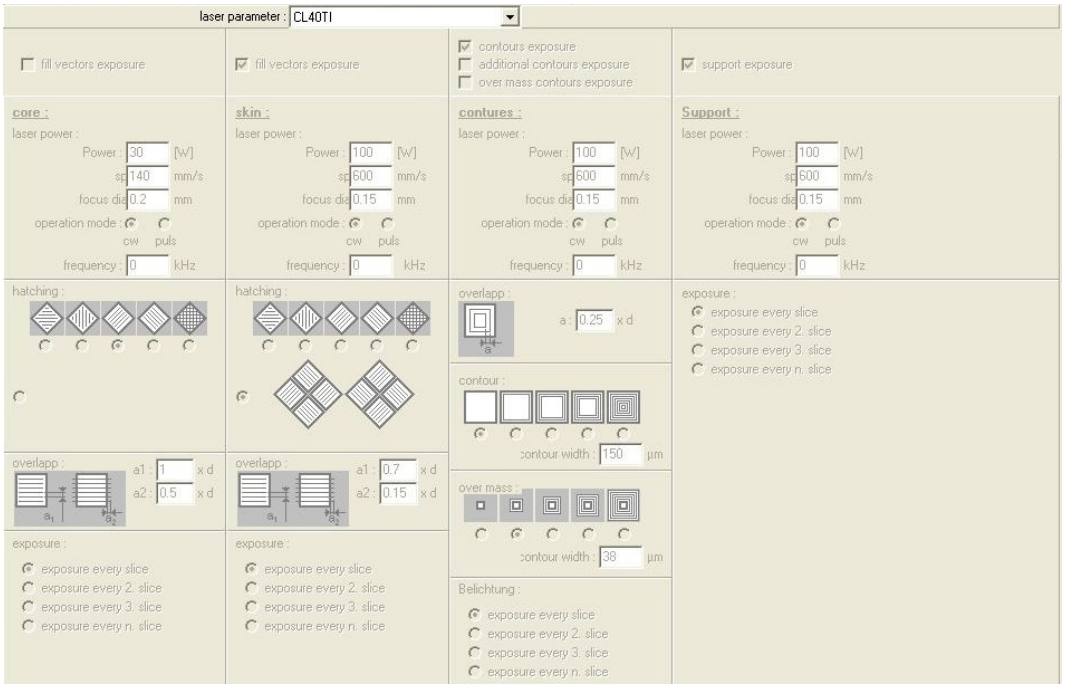


Figure 4.8: Machine parameters used in implant fabrication

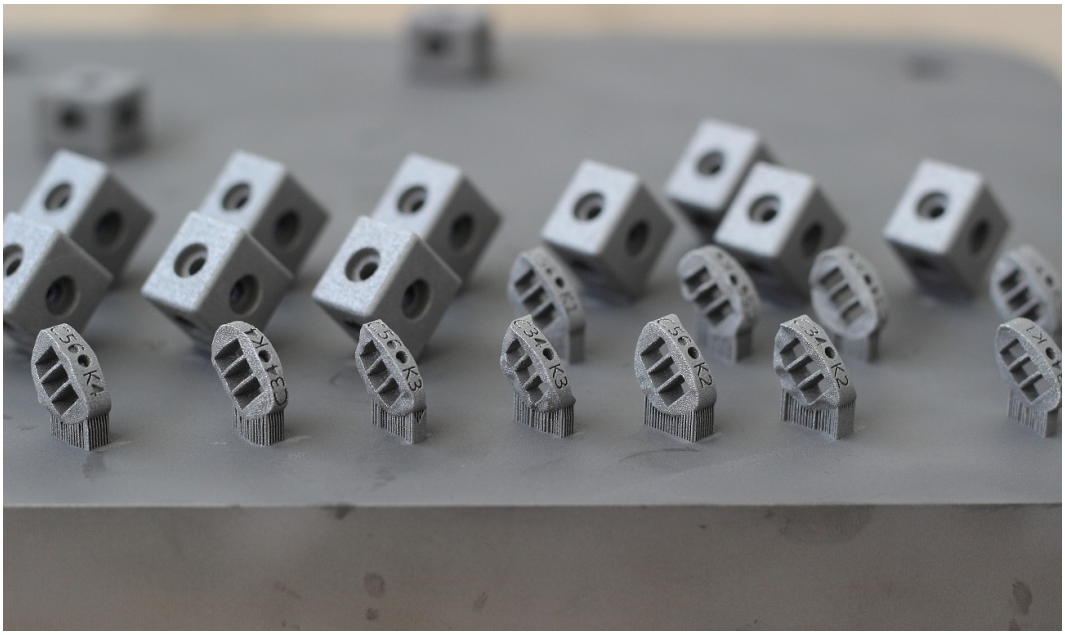


Figure 4.9: Fabricated parts on baseplate (cube specimens are part of another study)

4.5 Post Processing

The implants were removed from the base plate with their support structures still intact. Using a metal bristle brush, the supports were removed. The rough area left by the supports were sanded away using a polisher and thereafter gently sandblasted to ensure an even surface finish. The fabricated holes were bored to 2mm and then tapped into a M2.5 thread compatible with the surgical tool supplied by the consulting surgeon.

4.6 Surgery

The implants were inserted into the cadaver at the dissection lab at the Stellenbosch University's Medical Campus at Tygerberg by the consulting surgeon to mimic the surgical process. To try and eliminate variability caused by using different cadavers, half of the cadavers had the custom implants at level C3/4 with the off-the-shelf implants at level C5/6, while for the other half, the order was reversed. Table 4.2 shows the locations for each implant used. The custom implants are noted by the "Ti" label, while the off-the-shelf implants are labelled "PEEK". The regions were separated from each other and the surrounding tissue was then cleaned off to leave only the vertebrae and implants intact.

Table 4.2: Locations of implants at selected levels

Cadaver #	Level	
	C3/4	C5/6
K1	Ti	PEEK
K2	PEEK	Ti
K3	PEEK	Ti
K4	Ti	PEEK
K5	Ti	PEEK
K6	PEEK	Ti

4.7 Mechanical Testing

Before testing could commence the superior and inferior vertebrae at each level were potted in an epoxy resin (Prime 20 LV with slow hardener, AMT Composites). To orientate each vertebra horizontally, a support structure was designed and fabricated using the same boolean subtraction method as for the implants. These support structures were fabricated with a Z-Corp 3D printer (section 2.3.2). Each support structure was placed in a plastic container with the vertebra being gently placed on top of it. Then the resin mix was added till roughly half of the vertebra was left exposed (Figure 4.10). The pots were left overnight to set. The MTS Criterion Series 40 C44 machine was used for both the non-destructive and destructive testing. It has a built in load cell and cross-hair displacement sensor.

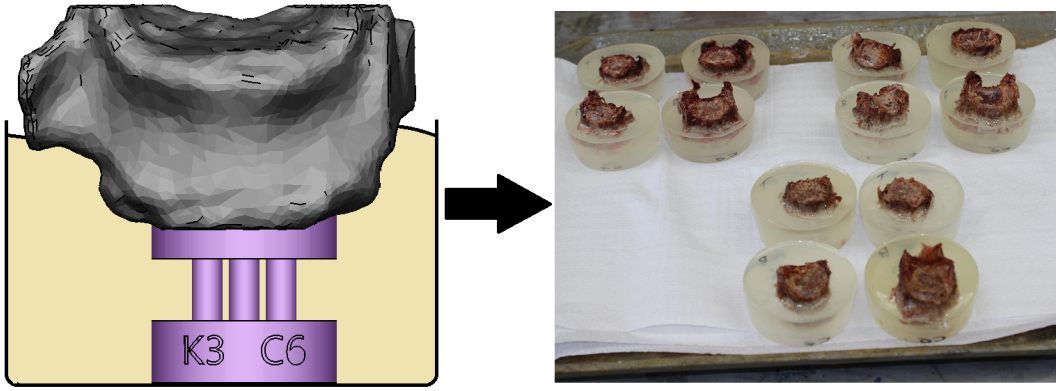


Figure 4.10: Vertebra on support structure to align horizontally in epoxy resin

4.7.1 Non-Destructive Testing

Non-destructive tests were performed to evaluate the contact load distribution of the implant on the inferior (lower) vertebra using an I-Scan pressure sensor (model 5051). The sensor is resistive based where a normal force applied to the sensor causes a change in the resistance of each element (called a sensel) inversely proportional to the force applied. A Tekscan data acquisition device collects the reading and sends it to the software to be recorded and displayed (Figure 4.11). The load distribution was recorded as a 2D area in mm^2. Loading was applied using the MTS machine. The inferior vertebra would be placed on the machine first, followed by the I-scan sensor, the implant and finally the superior vertebra. A preload of 50N was first applied and held for 15 seconds and then slowly increased to 200N, where it was held until the image stabilized. The load value was chosen to maintain consistency with a similar experiment conducted previously by De Beer (2011). The image was then recorded containing all the loading information.

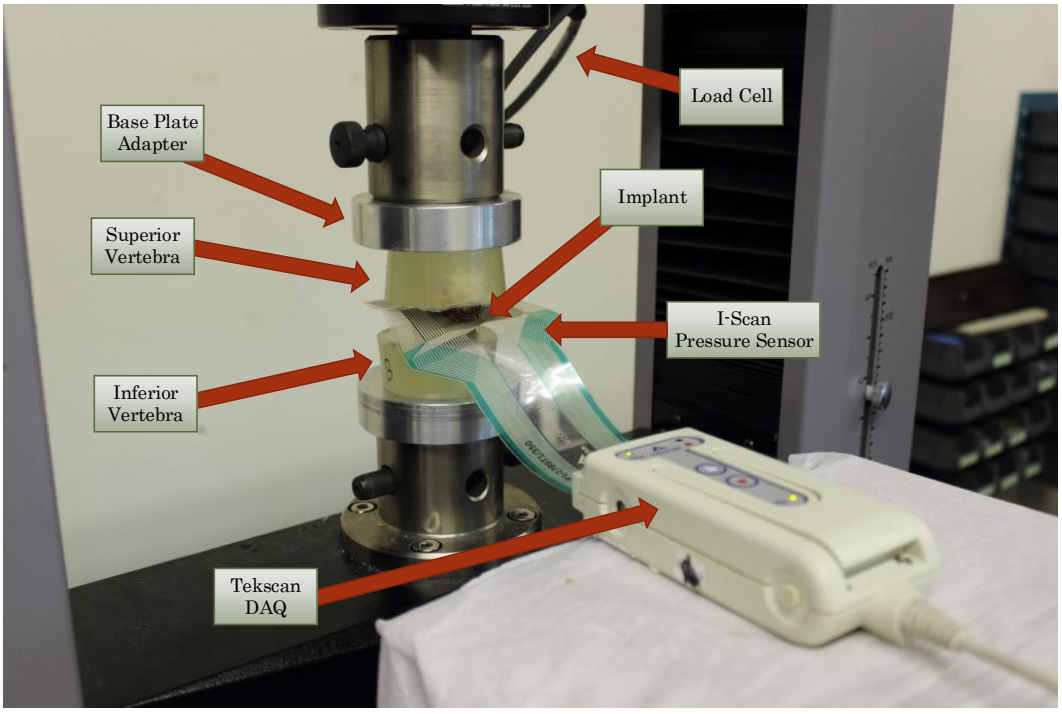


Figure 4.11: Non-destructive experimental setup

4.7.2 Destructive Testing

Destructive tests were performed to evaluate the failure of the implants. Again the MTS machine was used, which has built in load and displacement sensors that send the information back to the controlling PC. Both the force in newtons and the displacement in millimeters were recorded. A preload of 150N was first applied and held for 15 seconds. Thereafter a slow ramp was applied at 0.1mm/s using the built in controller. The slow ramp continued until the implant had fully subsided (i.e. was no longer visible) or until the machine reached its maximum displacement. All destructive tests were also recorded with a camera.

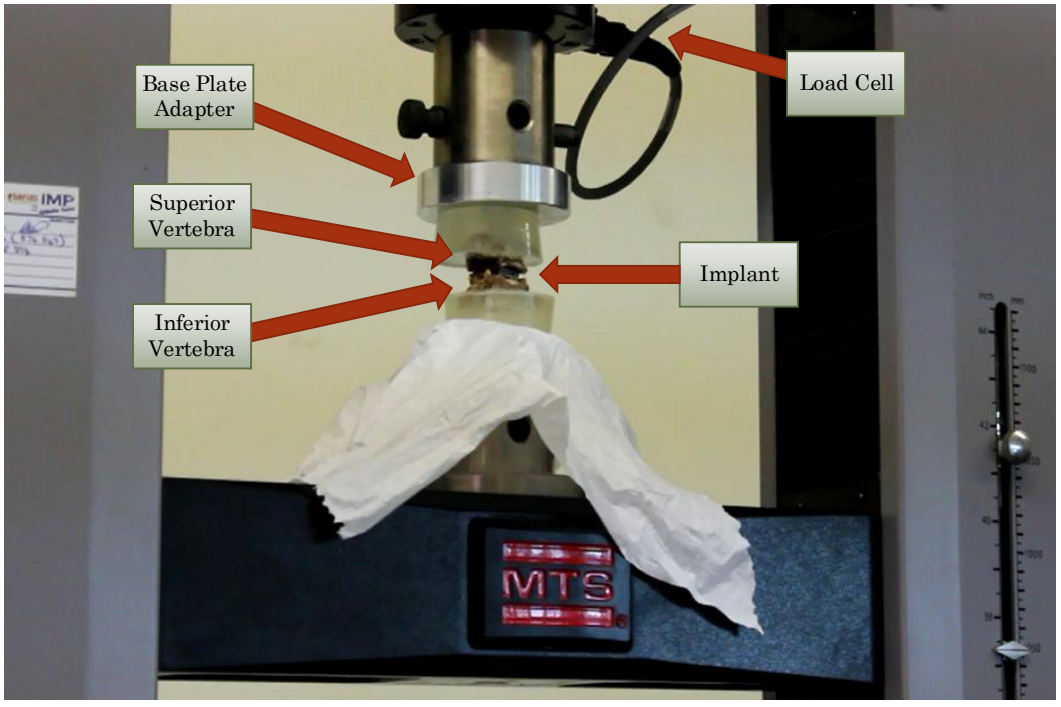


Figure 4.12: Destructive experimental setup

4.8 Summary

The technical feasibility of the development of customized cervical implants using additive manufacturing was investigated in the form of non-destructive and destructive testing. The relevant steps outlined in the framework (section 3.2) were followed and discussed. Where possible, the technical capabilities determined by van Zyl (2012) were used to aid the design process of the implant so as to achieve the desired characteristics (Table 3.2). The results are given and discussed in chapter 5.

Chapter 5

Experiment Results

This chapter discusses the results obtained from the destructive and non-destructive testing that was conducted on the cadaver specimens, explained in chapter 4.7. A statistical analysis was conducted on the results to determine validity.

5.1 Statistical Methods

A two-way analysis of variance (commonly known as an ANOVA) was the method used to evaluate the data from the non-destructive and destructive experiments. A quick summary of the method and formulae used is given below (Ramachandran and Tsokos, 2009).

A two-way ANOVA or *randomized block design*, consists of b blocks of k experimental units each. Treatments are assigned to the units in each block, with each treatment appearing once in every block. Thus the total number of observations in the randomized block design is $n = k \times b$. The reason for subdividing the experiments into blocks is to eliminate as much variability as possible (such as that arising from the use of different cadaver specimens).

The global mean from all $n = k \times b$ observations are:

$$\overline{y} = \frac{1}{n} \sum_{i=1}^{k} \sum_{j=1}^{b} y_{ij} \tag{5.1.1}$$

The total variation (SS is known as the sum of squares) of the combined measurements about the global mean $\overline{y}$ is defined by

$$SS_{Total} = \sum_{i=1}^{k} \sum_{j=1}^{b} (y_{ij} - \overline{y})^2 \tag{5.1.2}$$

Next we define the variation between the two treatments (in this case the two cage designs), which measures the total spread of the treatment group means $\overline{y_i}$ with respect to the grand mean $\overline{y}$ as

$$SS_{Treatment} = \sum_{i=1}^{k} b(\overline{y_{ki}} - \overline{y})^2 \tag{5.1.3}$$

Where the means of each treatment are

$$\overline{y_{ki}} = \frac{y_{1i} + y_{2i} + \cdots + y_{bi}}{b}$$

The variation between the conditions, also referred to as blocks (in this case, between the 6 cadavers or "blocks"), which measures the total spread of the condition group means $\overline{y_{jb}}$ with respect to the grand mean $\overline{y}$ is defined as

$$SS_{Condition} = \sum_{j=1}^{b} k(\overline{y_{jb}} - \overline{y})^2 \tag{5.1.4}$$

Where the means of each condition are

$$\overline{y_{jb}} = \frac{y_{j1} + y_{jk}}{k}$$

There is also and error term that must be compensated for. The total sum of squares is also the sum of the treatment, condition and error terms

$$SS_{Total} = SS_{Treatment} + S_{Condition} + SS_{Error}$$

Rearranging to solve for the error we have

$$SS_{Error} = SS_{Total} - SS_{Treatment} - S_{Condition} \tag{5.1.5}$$

The degrees of freedom for the total set ($n = k \times b$), treatments ($k = 2$), conditions ($b = 6$) and error (remainder) are

$$df_{Total} = n - 1$$
$$df_{Treatments} = k - 1$$
$$df_{Conditions} = b - 1$$
$$df_{Error} = df_{Total} - df_{Treatments} - df_{Conditions}$$

We now introduce the mean square term (MS) which is used to calculate the test statistic for use in the F-test, as

$$MS = \frac{sum\ of\ squares}{degrees\ of\ freedom} = \frac{SS}{df} \tag{5.1.6}$$

Thus we define the mean square of the total, treatment, condition and error as

$$MS_{Total} = \frac{SS_{Total}}{df_{Total}}$$
$$MS_{Treatment} = \frac{SS_{Treatment}}{df_{Treatment}}$$
$$MS_{Condition} = \frac{SS_{Condition}}{df_{Condition}}$$
$$MS_{Error} = \frac{SS_{Error}}{df_{Error}}$$

We use an F-test to determine whether there is a statistically significant difference between the means of the two cage designs (the treatments). We calculate our F statistic for the treatments as

$$F_{calculated} = \frac{MS_{Treatments}}{MS_{Error}} \tag{5.1.7}$$

If $F_{calculated} > F_{critical}$, then we reject the null hypothesis.

5.2 Results

5.2.1 Non-Destructive Testing

The data was recorded as a 2D contact area using the I-Scan sensor as explained in section 4.7.1. The contact area was then divided by the area of the vertebrae which was measured using the CAD software. This gave a percentage contact area for each cage implant that was loaded. The results are summarised in Table 5.1 and shown graphically in Figure 5.1.

The custom implant had a higher contact load for three out of the six cadavers with a margin no greater than 18%. Conversely for the cases where the PEEK implants fared better, the margins were greater (up to 23.79%). A box and whiskers plot (Figure 5.2) shows the range of each data set.

Table 5.1: Summary of Non-Destructive Testing Results

Cadaver	Level	Cage	Loaded Area [mm^2]	Total Area [mm^2]	% Contact
K1	C4	Ti	56	138.72681	40.37%
	C6	PEEK	126	228.77784	55.08%
K2	C4	PEEK	76	197.91858	38.40%
	C6	Ti	131	232.10705	56.44%
K3	C4	PEEK	115	139.53531	82.42%
	C6	Ti	105	179.09023	58.63%
K4	C4	Ti	81	181.26987	44.68%
	C6	PEEK	126	177.60414	70.94%
K5	C4	Ti	113	190.25799	59.39%
	C6	PEEK	111	210.18477	52.81%
K6	C4	PEEK	116	188.47918	61.55%
	C6	Ti	90	125.13244	71.92%

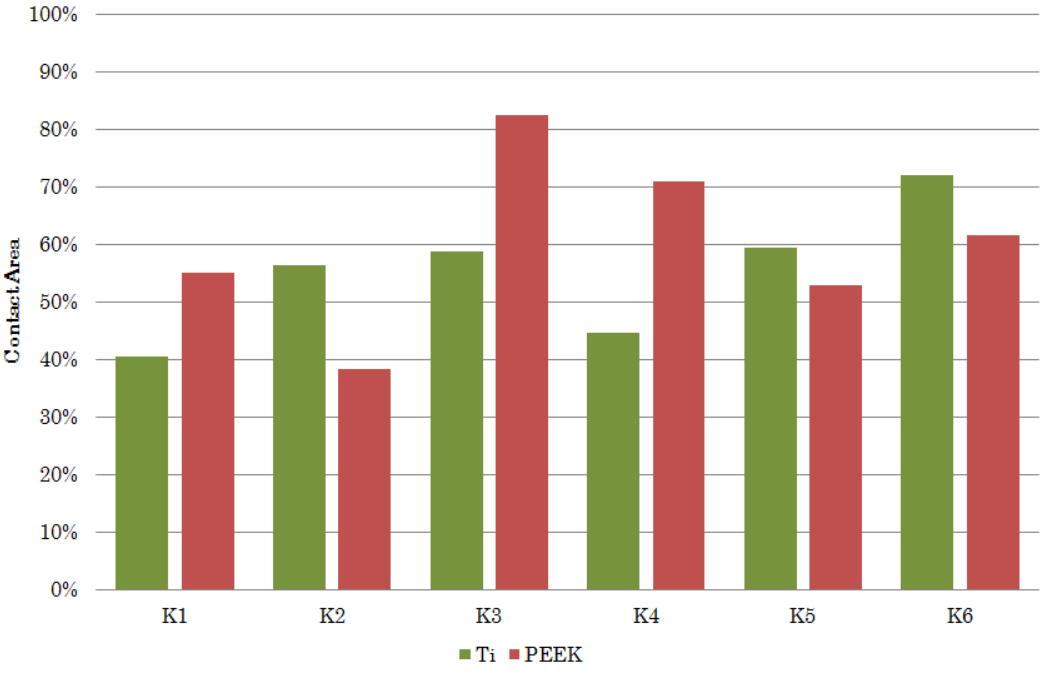


Figure 5.1: Percentage contact for Titanium and PEEK cage implants

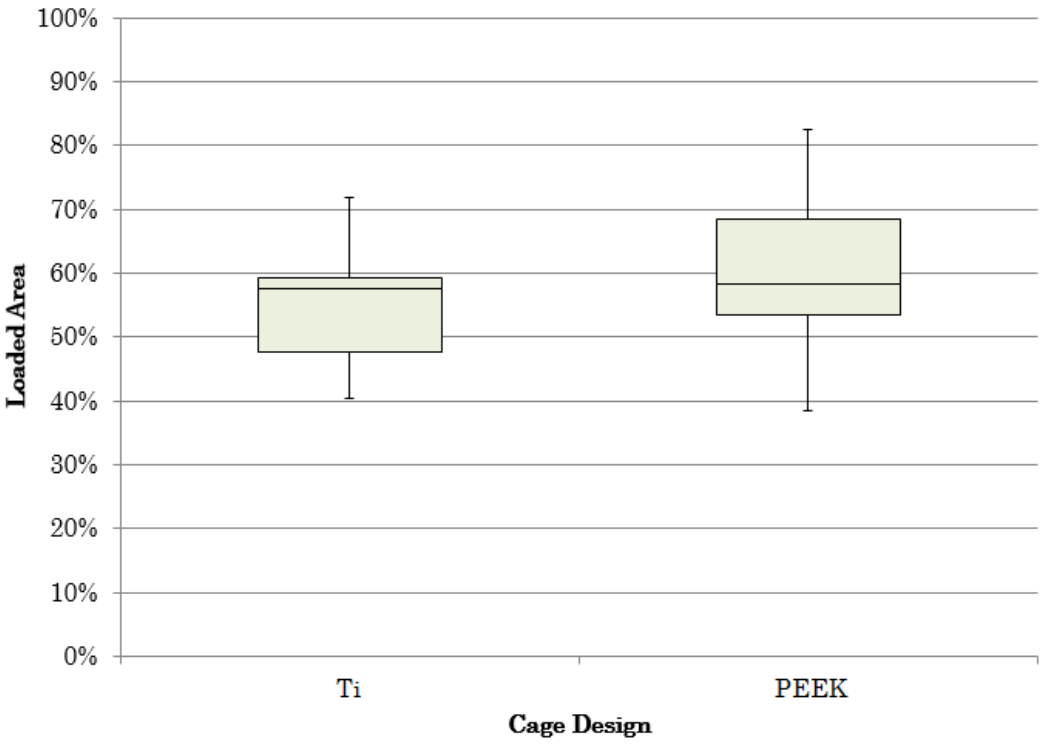


Figure 5.2: Box and whiskers plot comparing contact loading

It is evident that there is an overlap between the two regions and that the medians of each are in close proximity, indicating that the custom implants have comparable loading to the PEEK implants. A two-way ANOVA was conducted to determine whether there was a statistically significant difference between the two designs (See Appendix D for the full set of calculations without rounding as presented here). Let μ_1 and μ_2 represent the average contact area for the titanium and PEEK implants respectively. The null hypothesis for this test is

$$H_0 : \ \mu_1 = \mu_2$$

with an alternative hypothesis

$$H_1 : \ \mu_1 \neq \mu_2$$

Using equation 5.1.1 the global mean for the data set (where $k = 2$, $b = 6$ and $n = k \times b$) is

$$\overline{y} = \frac{1}{12} \sum_{i=1}^{2} \sum_{j=1}^{6} y_{ij} = 0.5772$$

The sum of squares for the total set, treatment, condition and error (equations 5.1.2 - 5.1.5) are

$$SS_{Total} = \sum_{i=1}^{2}\sum_{j=1}^{6}(y_{ij} - 0.5772)^2 = 0.1882$$

$$SS_{Treatment} = \sum_{i=1}^{2} 6(\overline{y_{ki}} - 0.5772)^2 = 0.0074$$

$$SS_{Condition} = \sum_{j=1}^{6} 2(\overline{y_{jb}} - 0.5772)^2 = 0.0908$$

$$SS_{Error} = SS_{Total} - SS_{Treatment} - S_{Condition} = 0.1882 - 0.0074 - 0.0908 = 0.0900$$

The mean squares of the treatment and the error are now calculated (equation 5.1.6)

$$MS_{Treatment} = \frac{SS_{Treatment}}{df_{Treatment}} = \frac{0.0074}{2-1} = 0.0074$$

$$MS_{Error} = \frac{SS_{Error}}{df_{Error}} = \frac{0.0900}{11-1-6} = 0.0180$$

The F statistic is calculated using equation 5.1.7

$$F_{calculated} = \frac{MS_{Calculated}}{MS_{Error}} = \frac{0.0074}{0.0180} = 0.4097$$

The critical F value was calculated using EXCEL's F.INV function with $\alpha = 0.05$

$$F_{critical} = 6.6078$$

Therefore $F_{Calculated} < F_{critical}$ and thus the null hypothesis is not rejected. This confirms what was seen in the box and whiskers plot (Figure 5.2), that there is no significant difference between the loading of two designs. These calculations were compared against EXCEL's built-in "ANOVA: Two-factor without replication" to check the validity of the answers and can be found in Appendix D.

5.2.2 Destructive Testing

Force and displacement values were recorded using the MTS' built in data sensors as explained in section 4.7.2 and are plotted in Appendix E. The stiffness was calculated using a linear regression of the elastic region, with the difference of the maximum and minimum values being divided by the corresponding change in displacement. The yield point was determined as the point where the elastic region was deemed to have ended by noting the change in slope. The results are summarised in Table 5.2.

Table 5.2: Summary of Destructive Testing Results

Cadaver	Level	Cage	Elastic Region min [N]	Elastic Region max [N]	Yield [N]	Stiffness [N/mm]
K1	C4	Ti	251.6968	632.9485	647.8198	279.9081
	C6	PEEK	281.8711	450.1080	573.3244	400.6402
K2	C4	PEEK	357.0426	708.2566	875.0595	405.5776
	C6	Ti	307.2702	460.7904	452.3158	143.4836
K3	C4	PEEK	346.3327	556.0136	643.5723	220.2460
	C6	Ti	420.0063	1313.8110	2088.1935	923.5143
K4	C4	Ti	822.4595	2000.5060	2108.6918	823.9874
	C6	PEEK	338.1806	1057.0600	1099.0660	604.2578
K5	C4	Ti	516.3210	1742.1650	2004.4980	785.9840
	C6	PEEK	308.5035	1020.8170	1241.0790	583.0033
K6	C4	PEEK	339.5022	1256.4340	1771.4160	441.3207
	C6	Ti	325.0802	811.2842	818.5447	472.1436

Figure 5.3 shows a comparison between the stiffness of each cage implant across the six cadavers. The custom implants had a higher stiffness in four of the six cases. Figure 5.4 compares the yield points between the implants. Again the custom implants fared better in four out of the six cadavers.

The box and whiskers plot (Figure 5.5) shows a large range for the custom implants while the PEEK implants have a much narrower range. Whilst there is an overlap, the median of the custom implants lies above that of the PEEK implants. The two-way ANOVA method was again used to determine if there is a statistically significant difference between the two designs.

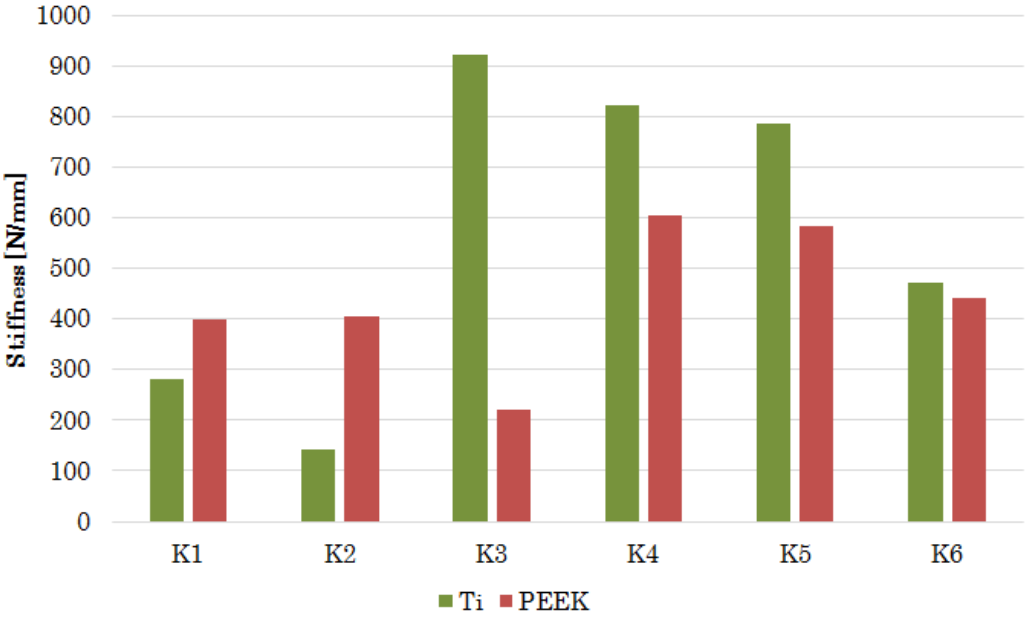


Figure 5.3: Stiffness for Titanium and PEEK cage implants

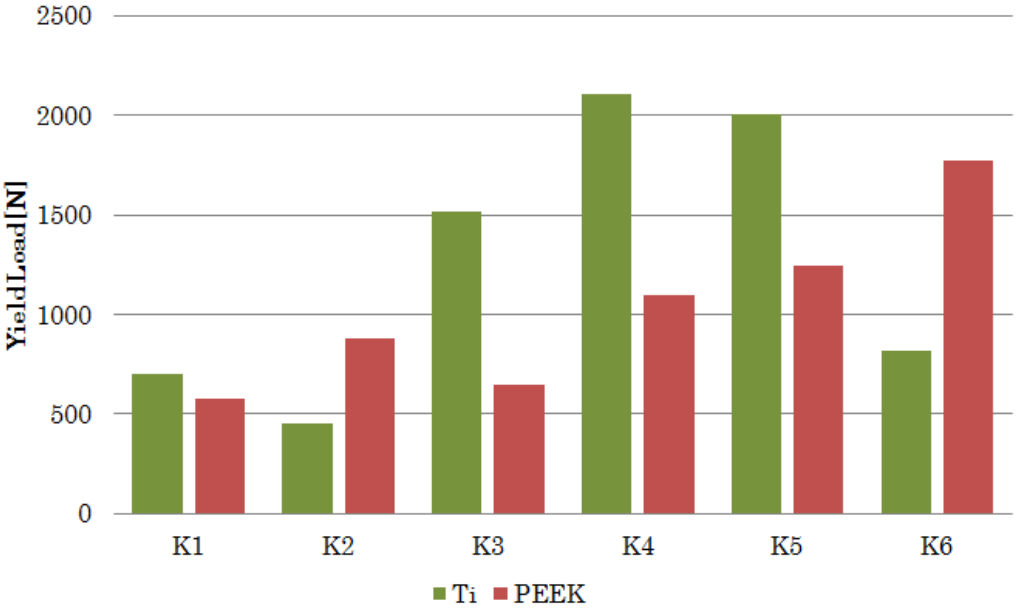


Figure 5.4: Yield points for Titanium and PEEK cage implants

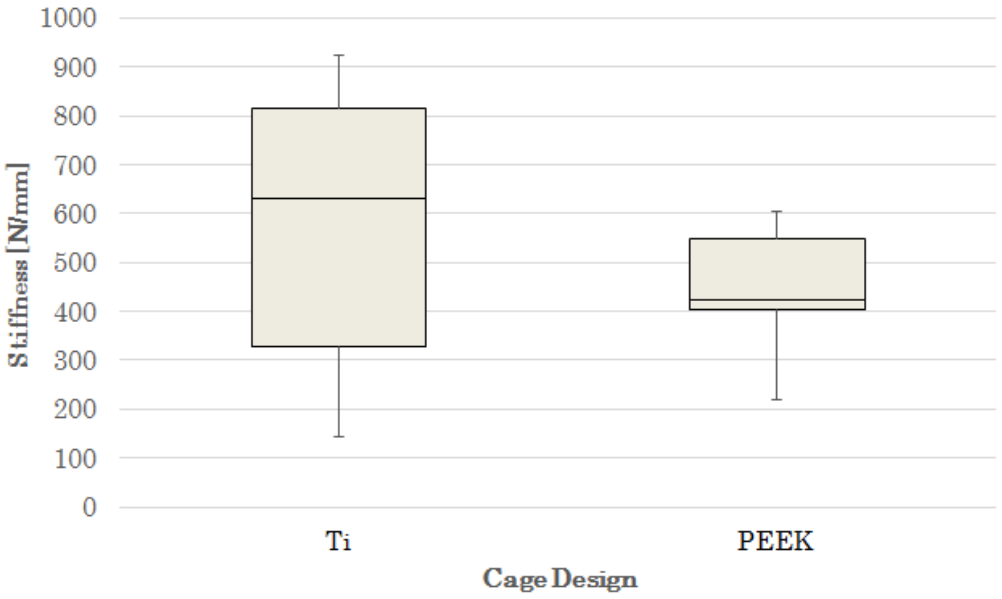


Figure 5.5: Box and whiskers plot comparing stiffness between implants

Let μ_1 and μ_2 represent the average stiffness for the titanium and PEEK implants respectively. The null hypothesis is

$$H_0 : \ \mu_1 = \mu_2$$

with an alternative hypothesis

$$H_1 : \ \mu_1 \neq \mu_2$$

Using equation 5.1.1 the global mean for the data set (where $k = 2$, $b = 6$ and $n = k \times b$) is

$$\overline{y} = \frac{1}{12} \sum_{i=1}^{2} \sum_{j=1}^{6} y_{ij} = 507.0056$$

The sum of squares for the total set, treatment, condition and error (equations 5.1.2 - 5.1.5) are

$$SS_{Total} = \sum_{i=1}^{2} \sum_{j=1}^{6} (y_{ij} - 507.0056)^2 = 660103.2370$$

$$SS_{Treatment} = \sum_{i=1}^{2} 6(\overline{y_{ki}} - 507.0056)^2 = 49919.8267$$

$$SS_{Condition} = \sum_{j=1}^{6} 2(\overline{y_{jb}} - 507.0056)^2 = 325959.1773$$

$$\begin{aligned} SS_{Error} &= SS_{Total} - SS_{Treatment} - S_{Condition} \\ &= 660103.2370 - 49919.8267 - 325959.1773 \\ &= 284224.2331 \end{aligned}$$

The mean squares of the treatment and the error are now calculated (equation 5.1.6)

$$MS_{Treatment} = \frac{SS_{Treatment}}{df_{Treatment}} = \frac{49919.8267}{2-1} = 49919.8267$$

$$MS_{Error} = \frac{SS_{Error}}{df_{Error}} = \frac{284224.2331}{11-1-6} = 58644.8466$$

The F statistic is calculated using equation 5.1.7

$$F_{calculated} = \frac{MS_{Calculated}}{MS_{Error}} = \frac{49919.8267}{56844.8466} = 0.878177$$

The critical F value was calculated using EXCEL's F.INV function with $\alpha = 0.05$

$$F_{critical} = 6.6078$$

Therefore $F_{Calculated} < F_{critical}$ and thus the null hypothesis is not rejected, meaning there is no statistically significant difference between the loading of two designs. As with the non-destructive data, these calculations were also compared against EXCEL's built-in "ANOVA: Two-factor without replication" to check the validity of the answers and can be found in Appendix D.

5.3 Discussion

The results from both experiments showed that the custom implants were within similar operating conditions as the PEEK implants. The hypothesis testing in both cases did not show a statistically significant difference in terms of both loaded area and stiffness. The reason for the large variation in the destructive testing, shown in the box and whiskers plot of Figure 5.5 could be due to the drying out of the cadaver specimens over the duration of the experiments. These cadaver specimens, treated with formaldehyde (a preserving agent), were kept sealed until they were potted in the epoxy resin. Once potted overnight, the non-destructive test was conducted, while the destructive testing was conducted the following day. This meant that by the second day of being exposed to air, the cadavers became more tough. In future it would be advised to try and acquire fresh-frozen cadavers and minimise the time exposed to air for destructive testing.

Chapter 6

Conclusion and Recommendations

A framework for developing customized titanium cervical cage implants using additive manufactured was defined. Customized implants that are patient-specific were designed using reverse engineering techniques and fabricated using additive manufacturing in the form of LaserCUSING. This was to investigate whether cage implants with matching end-plate geometry could perform better than readily available cage implants made from PEEK.

Whilst the original objective was to design an implant that performed better than readily available PEEK cage implants, it is important to note that they are at the very least comparable. For general use, the PEEK implants are already available and are the current state-of-the-art. However where PEEK cannot be used in extreme cases, the customized implants is a suitable candidate to fill the gap needed. The customized implants had higher contact loading in three of the six cadavers during non-destructive testing, while for destructive testing had higher stiffness and yield points in four of the six cadavers. Though as stated previously there were large variations in the destructive testing results, possibly due to the fact that the specimens were not fresh-frozen cadavers. The two-way ANOVA analysis showed no statistically significant difference between either designs. Clinical trials can further determine technical performance of the customized implants.

The study also investigated some of the recommendations proposed by De Beer (2011), namely the application of customization to cage implants, regulatory approval and surgical tooling. The LaserCused samples were tapped to produce threads that were suitable for use with existing surgical tools supplied by the consulting surgeon. The surgeon was pleased with the ease the tool went into the customized implants and reported that inserting it into the cadavers was no more different than with the PEEK implants. This means that existing surgical tools can be used, saving on the cost of having to design and fabricate new tools. Special attachments for existing tools can also be fabricated if needed.

A cost analysis was conducted using a model set up by van Rooyen (2011). The costs were updated to reflect the current economy. The estimated cost price was then determined for different scenarios with the build volume and build time from the fabricated implants used in the cadaver experiments. The selling price under various utilization scenarios was then estimated using mark-ups of 30% and 50% (Table 3.7). These prices compared favourably to two readily available PEEK implants. This verified the economic viability of the customized implants fabricated using AM.

Utilization of the LaserCUSING machine is not limited to fabricating cervical cage implants. The machine can be used for other medical prosthetics as well. Different prosthetics can be included in the same build, reducing waiting time. If a design is updated, it can be fabricated immediately as there is no tooling that needs to be changed. As discussed in section 3.4.3.2 it is recommended to have one dedicated AM machine, located in an area central to most medium-large hospitals with access to CT scanner facilities. Thus the only investments that need to be made is the purchase of the machine, employment of biomedical engineers for implant design and the training of staff to operate the machine.

For future research, the following recommendations are made:

- Investigate other types of cage design which only AM can produce. These designs could have more of a focus on tailored mechanical properties and/or lattice structures to aid in osseointegration. Such a design which has no variation can be more easily regulated and quality control measures could be implemented.
- Investigate other methods of AM fabrication such as Electron Beam Melting (EBM), which is showing promise in the fabrication of acetabulums, for use with hip implants.
- For future cadaver testing, especially destructive testing, attempts should be made to obtain fresh-frozen cadavers. This will ensure that there is a clean break when the vertebrae fail, producing more accurate data. It should also ensure that the intervertebral discs are removed more easily, as those from the cadavers used had dried and were brittle.
- Patentability of customized implants is an area that was not investigated in this research. This could be proposed as a future Bachelors or Masters thesis.

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Appendices

Appendix A

Decision tree for the development of customized cervical cage implants

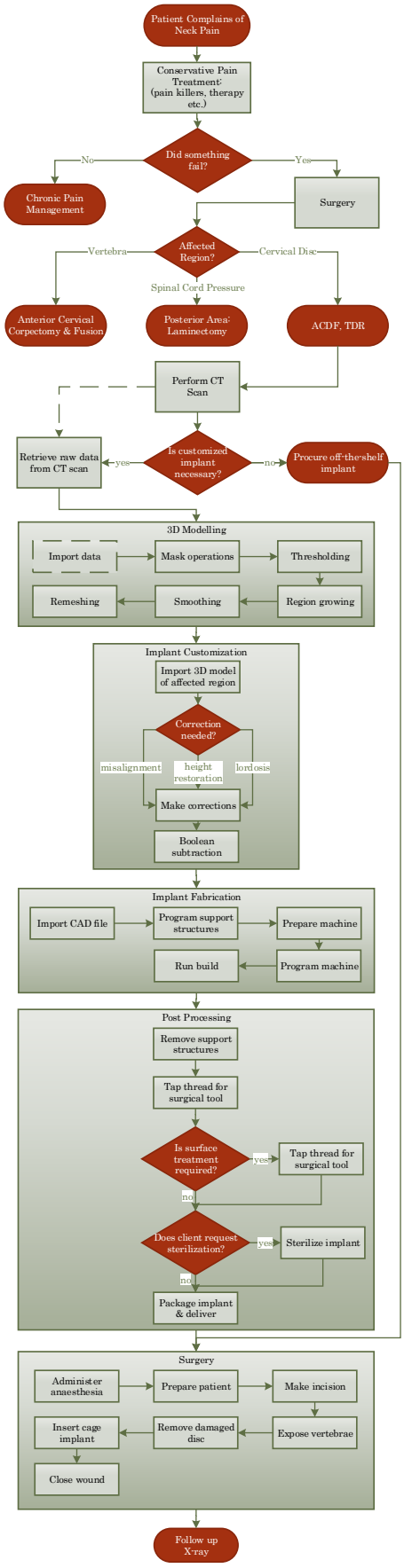

Figure A.1: Decision tree showing the flow of information for the development of customized cervical cage implants

Appendix B

Health Research Ethics Committee - Documentation for Use of Cadaver Specimens

STELLENBOSCH UNIVERSITY
FACULTY OF MEDICINE AND HEALTH SCIENCES

HEALTH RESEARCH ETHICS COMMITTEE 1 AND 2

APPLICATION FORM

(INFORMATION SHOULD BE TYPED)

SECTION 1: DETAILS OF APPLICANT/PRINCIPAL INVESTIGATOR		
Name: Graziano	**Surname: Marcantonio**	**SU number: 15163814**
Professional Status: BEng (Mechanical)		
University Division AND Department: Rapid Product Development Laboratory; Department of Industrial Engeering		
Complete Postal Address: Privaat Sak/Private Bag X1 Matieland 7602, Suid-Afrika/South Africa		
Telephone No: 021 808 4240	**Fax No: 021 808 4245**	**Cell No: 071 508 7717**
E-mail address: 15163814@sun.ac.za		
SECTION 2: TITLE OF STUDY		
Title of Research Project: Development of a Framework for the Manufacture of Customized Titanium Cervical Cage Implants using Additive Manufacturing		
Sponsor's Protocol No (if applicable)		
Sponsor's Details (if applicable)		
SECTION 3: STUDY FOR DEGREE PURPOSES	**Not applicable**	
Name of Degree: MEng (Research) Engineering Management	**Supervisor: Prof D. Dimitrov**	
Division/Department: Department of Industrial Engineering	**E-mail: dimitrov@sun.ac.za**	
Contact No: 021 808 3205		

OFFICE USE ONLY

PROJECT ID NUMBER

SECTION 4: DETAILS OF SUB-INVESTIGATORS		
Name and Title	**Position**	**Division/Department**
1. Dr AD Vlok	**Head of Tygerberg Spinal Service**	**Division of Neurosurgery**
2. Mr Brendan Boulle	**Laboratory Technician**	**Department of Mechanical Engineering, Stellenbosch University**
3.		
4.		
5.		

SECTION 5: DETAILS OF COLLABORATING INVESTIGATORS		
Name and Title	**Position**	**Division/Department**
1.		
2.		
3.		
4.		
5.		

SECTION 6: WHERE WILL THE STUDY BE CONDUCTED?	
1. Tygerberg Hospital	
2. Stikland Hospital	
3. Karl Bremer Hospital	
4. Faculty of Medicine and Health Sciences	
5. Other: Faculty of Engineering, University of Stellenbosch	**X**

SECTION 7: HUMAN SUBJECTS RESEARCH PROTECTION		
1. Does the Research involve Human Subjects who are Alive?		
Dead (includes identifiable tissues specimens)?		**X**
Medical records only?		
2. Will any medicine be tested during the investigation?	**Yes**	**No**
2.1 If Yes to question 2, is the medicine approved by the Medicines Control Council?		**X**
2.2 If yes to question 2.1, is the medicine registered for the dose which will be used in this specific project?		
2.3 If Yes to question 2.1, is the medicine registered for the indication(s) which will be used in this specific project?		
2.4 If No to question 2.1, is the medicine approved by the Medicines Control Council		

for your use in this specific project?		
2.5 If No to question 2.2 and/or 2.3, is the medicine approved by the Medicines Control Council for your use in this specific project?		
3. Will any radioactive material be administered to the patient during the investigation?		**X**
4. Is any biohazardous material (*) involved in the project?		**X**
5. Have you acquainted yourself with the code of conduct regarding the Ethics of research and this Institution and do you undertake to fully comply with it at all times?		**X**

(*) *"Biohazardous material" refers to recombinant DNA molecules, viruses, fungi, parasites, bacteria and all other potentially biohazardous material or products that are dangerous to both the experimental patient and the researcher, and which is patient to ct stricontainment specifications and safety measures.*

SECTION 8: STUDY TYPE

1. Industry Sponsored Clinical Trial		**2. Self Initiated Clinical Trial**	
3. Retrospective Record Review		**4. Laboratory-Based Research**	**X**
5. Qualitative Research		**6. Prospective Descriptive Study**	
7. Other		**8. Please state type if 'Other':**	

SECTION 9: HOW IS THIS RESEARCH FUNDED? STATE APROXIMATE TOTAL BUDGET

1. Industry	**R**	**2. NIH**	**R**
3. Internal/Self	**R**	**4. Other/ US Fed Agency**	**R**
5. External SA Grant	**R**	**6. Internat. Grant**	**R60 000**

SECTION 10: SIGNING OF APPLICATION

Applicant	Supervisor	Head of Division
G.MARCANTONIO	D. DIMITROV	C Schutte
Print name	Print name	Print name
Signature	Signature	Signature
13-08-2013	13.08.2013	13/8/13
Date	Date	Date

Kindly see overleaf for required documentation to accompany all applications.

Appendix C

LaserCUSING Machine Quotation

CONCEPTLASER
hofmann innovation group

Quotation Nr. M2 cusing / 012 / 11,
25.03.2011

Prices:

Pos.	Article	Price/part	Amount	Price
1	M2 Cusing Basic Machine	485.000,00 €	1	485.000,00 €
	Software			
2	Materialise Magics Software	14.760,00 €	1	14.760,00 €
	Materials			
3	CL 20 ES (1.4404 / 316 L) fine grade	95,00 €	20	1.900,00 €
4	CL 31 AL (GD-AlSi19Mg)	85,00 €	0	0,00 €
5	CL 41 TI ELI (TiAl6V4 ELI)	580,00 €	10	5.800,00 €
6	CL 50 WS (1.2709 / Maraging Steel)	175,00 €	80	14.000,00 €
7	CL 91	270,00 €	0	0,00 €
8	CL 100 NB	190,00 €	0	0,00 €
9	remanium star CL	400,00 €	0	0,00 €
	Installation & Training			
10	Installation	3.500,00 €	1	3.500,00 €
11	Training	5.000,00 €	1	5.000,00 €
12	CAD training	8.000,00 €	1	8.000,00 €
	Options			
13	Nitrogen Generator	8.950,00 €	0	0,00 €
14	Buffer vessel	1.750,00 €	0	0,00 €
15	Powder exchange container (Master)	2.800,00 €	0	0,00 €
16	Powder exchange container	2.500,00 €	0	0,00 €
17	Reference Clamping EROWA	7.950,00 €	0	0,00 €
18	Storage Cabinet	3.850,00 €	0	0,00 €
19	Ruwac Wet Scrubber	7.500,00 €	1	7.500,00 €
20	Titanium Plate 250 x 250 x 250 mm	2.450,00 €	1	2.450,00 €
21	Wear Parts	1.000,00 €	1	1.000,00 €
22	Blasting Cabinet (incl. blasting media)	5.400,00 €	0	0,00 €
23	QM System Meltpool	59.500,00 €	0	0,00 €
24	QM System Powder	22.500,00 €	0	0,00 €
	Total Price			**548.910,00 €**
	University discout			**108.910,00 €**
	Special price for University Stellenbosch			**440.000,00 €**

Figure C.1: Concept Laser quotation to Stellenbosch University for purchase of LaserCUSING machine

Appendix D

Statistical Calculations

Stats Calculations: Non-Destructive Testing

Data set

	Ti	PEEK	Mean
K1	0.403671074	0.550752648	0.477211861
K2	0.564394741	0.383996286	0.474195513
K3	0.586296633	0.824164149	0.705230391
K4	0.446847575	0.709442906	0.57814524
K5	0.593930378	0.528106778	0.561018578
K6	0.719237959	0.615452593	0.667345276
Mean	0.552396393	0.601985893	0.577191143

Hand-calcs

SS_Tot	0.188185473		
df_Tot	11		
MS_Tot	0.01710777		
SS_Col	0.007377355	F_Col	0.409709016
df_Col	1		
MS_Col	0.007377355		
SS_Row	0.090776471	F_Row	1.008272919
df_Row	5		
MS_Row	0.018155294		
		alpha	0.05
SS_err	0.090031646	F_Crit	6.607890974
df_err	5		
MS_err	0.018006329		

Anova: Two-Factor Without Replication

SUMMARY	*Count*	*Sum*	*Average*	*Variance*
Row 1	2	0.9544	0.477211861	0.010816495
Row 2	2	0.9484	0.474195513	0.016271801
Row 3	2	1.4105	0.705230391	0.028290478
Row 4	2	1.1563	0.57814524	0.034478154
Row 5	2	1.122	0.561018578	0.002166373
Row 6	2	1.3347	0.667345276	0.005385701
Column 1	6	3.3144	0.552396393	0.012822828
Column 2	6	3.6119	0.601985893	0.023338795

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Rows	0.090776471	5	0.018155294	1.008272919	0.496503358	5.050329058
Columns	0.007377355	1	0.007377355	0.409709016	0.550292343	6.607890974
Error	0.090031646	5	0.018006329			
Total	0.188185473	11				

Stats Calculations: Destructive Testing

Data set

	Ti	PEEK	Mean
K1	279.9081	400.6402	340.2742
K2	143.4836	405.5776	274.5306
K3	923.5143	220.2460	571.8802
K4	823.9874	604.2578	714.1226
K5	785.9840	583.0033	684.4937
K6	472.1436	441.3207	456.7322
Mean	571.5035	442.5076	507.0056

Hand-calcs

SS_Tot	660103.2370		
df_Tot	11		
MS_Tot	60009.3852		
SS_Col	49919.82665	F_Col	0.878177
df_Col	1		
MS_Col	49919.82665		
SS_Row	325959.1773	F_Row	1.146838
df_Row	5		
MS_Row	65191.83546		
		alpha	0.05
SS_err	284224.2331	F_Crit	6.607891
df_err	5		
MS_err	56844.8466		

Anova: Two-Factor Without Replication

SUMMARY	*Count*	*Sum*	*Average*	*Variance*
Row 1	2	680.5483	340.27415	7288.119985
Row 2	2	549.0612	274.5306	34346.63242
Row 3	2	1143.76	571.88015	247293.1509
Row 4	2	1428.245	714.1226	24140.54856
Row 5	2	1368.987	684.49365	20600.58229
Row 6	2	913.4643	456.73215	475.0255822
Column 1	6	3429.021	571.5035	102352.582
Column 2	6	2655.046	442.5076	19684.10011

ANOVA

Source of Varia	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Rows	325959.1773	5	65191.83546	1.146838092	0.442078211	5.050329058
Columns	49919.82665	1	49919.82665	0.87817682	0.391722788	6.607890974
Error	284224.2331	5	56844.84661			
Total	660103.237	11				

Appendix E

Load Displacement Curves